SECTION 4

RESPIRATORY SYSTEM DRUGS

Chapter 16 Drugs for Cough and Bronchial Asthma

DRUGS FOR COUGH

Cough is a protective reflex, its purpose being expulsion of respiratory secretions or foreign particles from air passages. It occurs due to stimulation of mechano- or chemoreceptors in throat, respiratory passages or stretch receptors in the lungs. Cough may be useful or useless. Useless (nonproductive) cough should be suppressed. Useful (productive) cough serves to drain the airway, its suppression is not desirable, may even be harmful, except if the amount of expectoration achieved is small compared to the effort of continuous coughing. Apart from specific remedies (antibiotics, etc. *see* box), cough may be treated as a symptom (nonspecific therapy) with:

1. *Pharyngeal demulcents* Lozenges, cough drops, linctuses containing syrup, glycerine, liquorice.

2. *Expectorants (Mucokinetics)*
   (a) *Bronchial secretion enhancers:* Sodium or Potassium citrate, Potassium iodide, Guaiphenesin (Glyceryl guaiacolate), balsum of Tolu, Vasaka, Ammonium chloride.
   (b) *Mucolytics:* Bromhexine, Ambroxol, Acetyl cysteine, Carbocisteine

3. *Antitussives (Cough centre suppressants)*
   (a) *Opioids:* Codeine, Ethylmorphine, Pholcodeine.
   (b) *Nonopioids:* Noscapine, Dextromethorphan, Chlophedianol.
   (c) *Antihistamines:* Chlorpheniramine, Diphenhydramine, Promethazine.
   (d) *Peripherally acting:* Prenoxdiazine.

4. *Adjuvant antitussives*
   Bronchodilators: Salbutamol, Terbutalin.

DEMULCENTS AND EXPECTORANTS

Pharyngeal demulcents sooth the throat and reduce afferent impulses from the inflamed/irritated pharyngeal mucosa, thus provide symptomatic relief in dry cough arising from throat.

Expectorants (Mucokinetics) are drugs believed to increase bronchial secretion or reduce its viscosity, facilitating its removal by coughing.

Sodium and potassium citrate are considered to increase bronchial secretion by salt action. Potassium iodide is secreted by bronchial glands and can irritate the airway mucosa. Prolonged use can affect thyroid function and produce iodism. It is not used now. Guaiphenesin, vasaka, tolu balsum are plant products which are supposed

Specific treatment approaches to cough

Etiology of cough	*Treatment approach*
• Upper/lower respiratory tract infection	Appropriate antibiotics
• Smoking/chronic bronchitis/bronchiectasis	Cessation of smoking/avoidance of pollutants, steam inhalation, postural drainage
• Pulmonary tuberculosis	Antitubercular drugs
• Asthmatic cough	Inhaled β_2 agonists/corticosteroids/ipratropium
• Cough in pulmonary eosinophilia	Diethyl carbamazine citrate, inhaled corticosteroids
• Postnasal drip due to sinusitis	Antibiotic, nasal decongestant, H_1 antihistaminic
• Postnasal drip due to allergic/perennial rhinitis	Avoidance of precipitating factor(s), corticosteroid nasal spray, H_1 antihistaminic
• Gastroesophageal reflux	Bed head elevation, light dinner, diet modification, H_2 blocker, proton pump inhibitor, mosapride
• ACE inhibitor associated cough	Substitute ACE inhibitor by losartan, NSAIDs may reduce cough
• Post-viral cough	No specific treatment, subsides by itself.

to enhance bronchial secretion and mucociliary function while being secreted by tracheobronchial glands. Ammonium salts are nauseating—reflexly increase respiratory secretions. A variety of expectorant formulations containing an assortment of the above ingredients, often in combination with antitussives/antihistaminics are marketed and briskly promoted, but objective evidence of efficacy of these is non-conclusive. The US-FDA has stopped marketing of all expectorants, except guaiphenesin. Steam inhalation and proper hydration may be more helpful in clearing airway mucus.

Mucolytics

Bromhexine A derivative of the alkaloid *vasicine* obtained from *Adhatoda vasica* (Vasaka), is a potent mucolytic and mucokinetic, capable of inducing thin copious bronchial secretion. It depolymerises mucopolysaccharides directly as well as by liberating lysosomal enzymes—network of fibres in tenacious sputum is broken. It is particularly useful if mucus plugs are present. *Side effects* are rhinorrhoea and lacrimation, nausea, gastric irritation, hypersensitivity.

Dose: adults 8 mg TDS, children 1–5 years 4 mg BD, 5–10 years 4 mg TDS.

BROMHEXINE 8 mg tablet, 4 mg/5 ml elixir.

Ambroxol A metabolite of bromhexine having similar mucolytic action, uses and side effects.

Dose: 15–30 mg TDS.

AMBRIL, AMBROLITE, AMBRODIL, MUCOLITE 30 mg tab, 30 mg/5 ml liquid, 7.5 mg/ml drops.

Acetylcysteine It opens disulfide bonds in mucoproteins present in sputum—makes it less viscid, but has to be administered directly into the respiratory tract.

MUCOMIX 200 mg/ml inj in 1,2,5 ml amps; injectable solution may be nebulized/instilled through trachiostomy tube.

Carbocisteine It liquefies viscid sputum in the same way as acetylcysteine and is administered orally (250–750 mg TDS). Some patients of chronic bronchitis have been shown to benefit. It may break gastric mucosal barrier; is contraindicated in peptic ulcer patients. Side effects are gastric discomfort and rashes.

MUCODYNE 375 mg cap, 250 mg/5 ml syr.

It is available in combination with amoxicillin or cephalexin for treatment of bronchitis, bronchiectasis, sinusitis, etc.

CARBOMOX: Carbocisteine 150 mg + amoxicillin 250 or 500 mg caps. CARBICEF: Carbocisteine 150 mg + cephalexin 250 or 500 mg caps.

ANTITUSSIVES

These are drugs that act in the CNS to raise the threshold of cough centre or act peripherally in the respiratory tract to reduce tussal impulses, or both these actions. Because they aim to control rather than eliminate cough, antitussives should be used only for dry nonproductive cough or if cough is unduly tiring, disturbs sleep or is hazardous (hernia, piles, cardiac disease, ocular surgery).

Opioids

Codeine (*see* Ch. 34) An opium alkaloid, qualitatively similar to and less potent than morphine, but is more selective for cough centre. Codeine is regarded as the standard antitussive; suppresses cough for about 6 hours. The antitussive action is blocked by naloxone indicating that it is exerted through opioid receptors in the brain. Abuse liability is low, but present; constipation is the chief drawback. At higher doses respiratory depression and drowsiness can occur, especially in children. Driving may be impaired. Like morphine, it is contraindicated in asthmatics and in patients with diminished respiratory reserve; should be avoided in children.

Dose: 10–30 mg; children 2–6 years 2.5–5 mg, 6–12 years 5–10 mg, frequently used as syrup codeine phos. 4–8 ml. CODINE 15 mg tab, 15 mg/5 ml linctus.

Ethylmorphine It is closely related to codeine which is methylmorphine, and has antitussive, respiratory depressant properties like it, but is believed to be less constipating.

Dose: 10–30 mg TDS; DIONINDON 16 mg tab.

Pholcodeine It has practically no analgesic or addicting property, but is similar in efficacy as antitussive to codeine and is longer acting—acts for 12 hours; dose: 10–15 mg.

Nonopioids

Noscapine (Narcotine) An opium alkaloid of the benzoisoquinoline series (*see* Ch. 34). It depresses cough but has no narcotic, analgesic or dependence inducing properties. It is nearly equipotent antitussive as codeine, especially useful in spasmodic cough. Headache and nausea occur occasionally as side effect. It can release histamine and produce bronchoconstriction in asthmatics.

Dose: 15–30 mg, children 2–6 years 7.5 mg, 6–12 years 15 mg. COSCOPIN 7 mg/5 ml syrup, COSCOTABS 25 mg tab.

Dextromethorphan A synthetic central NMDA (N-methyl D-aspartate) receptor antagonist; the *d*-isomer has antitussive action while *l*-isomer is analgesic. Dextromethorphan does not depress mucociliary function of the airway mucosa and is practically devoid of constipating action. Though considered nonaddicting, some drug abusers indulge in it. The antitussive action of dextromethorphan has been rated equivalent to codeine, but some clinical studies have found it to be no better than placebo.

Side effect: Dizziness, nausea, drowsiness; at high doses hallucinations and ataxia may occur.

Dose: 10–20 mg, children 2–6 years 2.5–5 mg, 6–12 years 5–10 mg. It is a common ingredient of many proprietary cough formulations (*see* antitussive combinations below).

Chlophedianol It is a centrally acting antitussive with slow onset and longer duration of action.

Side effect: Dryness of mouth, vertigo, irritability.

Dose: 20–40 mg; DETIGON, TUSSIGON 20 mg/5 ml linctus with Ammon. chloride 50 mg and menthol 0.25 mg.

Antihistamines

Many H_1 antihistamines have been conventionally added to antitussive/expectorant formulations (*see* below). They afford relief in cough due to their sedative and anticholinergic actions, but lack selectivity for the cough centre. They have no expectorant property, may even reduce secretions by anticholinergic action. They have been specially promoted for cough in respiratory allergic states, though their lack of efficacy in asthma is legendary.

Chlorpheniramine (2–5 mg), Diphenhydramine (15–25 mg) and Promethazine (15–25 mg; PHENERGAN 5 mg/5 ml elixir) are commonly used. Second generation antihistamines like fexofenadine, loratadine, etc. are ineffective.

Peripherally acting antitussives

Prenoxdiazine In contrast to other antitussives, it acts peripherally; desensitizes the pulmonary stretch receptors and reduces tussal impulses originating in the lungs. It is indicated in cough of bronchial origin. Efficacy, however, is not impressive. Though an old drug developed in Hungary, it has been introduced recently in India.

Dose: 100–200 mg TDS-QID; PRENOXID 100, 200 mg tab.

Bronchodilators Bronchospasm can induce or aggravate cough. Stimulation of pulmonary receptors can trigger both cough and bronchoconstriction, especially in individuals with

bronchial hyperreactivity. Bronchodilators relieve cough in such individuals and improve the effectiveness of cough in clearing secretions by increasing surface velocity of airflow during the act of coughing. They should be used only when an element of bronchoconstriction is present and not routinely. Their fixed dose combinations with antitussives are not satisfactory because of differences in time course of action of the components and liability for indiscriminate use.

Fixed dose combinations of a centrally acting antitussive with a bronchodilator or with an antihistaminic having high atropinic activity have been banned in India, but many are still marketed.

Aeromatic chest rub is widely advertized as a cough remedy. Though it has been shown to reduce experimentally induced cough in healthy volunteers, there is no evidence of benefit in pathological cough.

SOME ANTITUSSIVE-EXPECTORANT COMBINATIONS

ASTHALIN EXPECTORANT: Salbutamol 2 mg, guaiphenesin 100 mg per 10 ml syr; dose 10–20 ml.

ASCORIL-C: Codeine 10 mg, chlorpheniramine 4 mg per 5 ml syr.

AXALIN: Ambroxol 15 mg, guaiphenesin 50 mg, salbutamol 1 mg, menthol 1 mg per 5 ml syr.

BRONCHOSOLVIN: Guaiphenesin 100 mg, terbutalin 2.5 mg, bromhexine 8 mg per 10 ml susp.

CADICOFF, GRILINCTUS: Dextromethorphan 5 mg, chlorpheniramine 2.5 mg, guaiphenesin 50 mg, Amm. chloride 60 mg per 5 ml syr.

BENADRYL COUGH FORMULA: Diphenhydramine 14 mg, amm. chlor. 138 mg, sod. citrate 57 mg, menthol 1.1 mg per 5 ml syrup; dose 5–10 ml, children 2.5–5 ml.

BRO-ZEDEX: Bromhexine 8 mg, guaiphenesin 100 mg, terbutaline 2.5 mg, menthol 5 mg per 10 ml syrup; dose 10 ml.

CADISTIN EXPECTORANT: Chlorpheniramine 2 mg, glyceryl guaiacolate 80 mg, amm. chlor. 100 mg, sod. citrate 44 mg, menthol 0.8 mg, terpin hydrate 4 mg, tolu balsum 6 mg, Vasaka syrup 0.13 ml per 5 ml syrup; dose 10 ml.

CHERICOF: Dextromethorphan 10 mg, chlorpheniramine 2 mg, phenylpropanolamine 12.5 mg per 5 ml liq.

CLISTIN: Carbinoxamine 4 mg, amm. chlor. 240 mg, sod. citrate 240 mg per 10 ml syrup.

COREX: Chlorpheniramine 4 mg, codeine phos. 10 mg, menthol 0.1 mg per 5 ml syrup; dose 5 ml, children 1.25–2.5 ml.

COSCOPIN LINCTUS: Noscapine 7 mg, chlorpheniramine 2 mg, citric acid 29 mg, sod. citrate 3 mg, amm. chlor. 28 mg, per 5 ml syrup; dose 10–20 ml.

COSOME: Dextromethorphan 10 mg, phenylpropanolamine 25 mg, chlorpheniramine 4 mg per 10 ml syr; dose 10 ml.

GRILINCTUS: Dextromethorphan 5 mg, chlorpheniramine 2.5 mg, guaiphenesin 50 mg, ammon. chlor. 60 mg/5 ml syr; dose 5–10 ml.

GRILINCTUS SOFTCAPS: Dextromethorphan 10 mg, chlorpheniramine 2 mg, phenylpropanolamine 12.5 mg softcaps.

SOLVIN EXPECTORANT: Bromhexine 4 mg, pseudoephedrine 30 mg tablet and in 10 ml liquid; dose 1 tablet/5 ml liquid.

TOSSEX: Codeine phos 10 mg, chlorpheniramine 4 mg. menthol 1.5 mg, sod. citrate 75 mg per 5 ml liquid; dose 5 ml.

VENTORLIN EXPECTORANT: Salbutamol 2 mg, guaiphenesin 100 mg per 10 ml syrup; dose 10 ml, children 2.5–7.5 ml.

ZEET LINCTUS: Dextromethorphan 10 mg, guaiphenesin 50 mg, phenylpropanolamine 25 mg per 5 ml syr; dose 5 ml.

DRUGS FOR BRONCHIAL ASTHMA

Bronchial asthma is characterised by hyperresponsiveness of tracheobronchial smooth muscle to a variety of stimuli, resulting in narrowing of air tubes, often accompanied by increased secretion, mucosal edema and mucus plugging. Symptoms include dyspnoea, wheezing, cough and may be limitation of activity.

Asthma is now recognized to be a primarily inflammatory condition: inflammation underlying hyperreactivity. An allergic basis can be demonstrated in many adult, and higher percentage of pediatric patients. In others, a variety of trigger factors (infection, irritants, pollution, exercise, exposure to cold air, psychogenic) may be involved:

Extrinsic asthma: It is mostly episodic, less prone to status asthmaticus.

Intrinsic asthma: It tends to be perennial, status asthmaticus is more common.

Mast cells (present in lungs) and inflammatory cells recruited as a result of the initial reaction produce a multitude of mediators by the following processes:

- Release of mediators stored in granules *(immediate):* histamine, protease enzymes, TNFα.

- Release of phospholipids from cell membrane followed by mediator synthesis *(within minutes):* PGs, LTs, PAF.
- Activation of genes followed by protein synthesis *(over hours):* Interleukins, TNFα.

These mediators together constrict bronchial smooth muscle, cause mucosal edema, hyperemia and produce viscid secretions, all resulting in reversible airway obstruction. The inflammation perpetuates itself by cell-to-cell communication and recruitment of more and more inflammatory cells. Bronchial smooth muscle hypertrophy, increase in the population of mucus secreting cells and blood vessels occurs over time and damage to bronchial epithelium accentuates the hyperreactivity. Vagal discharge to bronchial muscle is enhanced reflexly. Airway remodeling progressively worsens the disease.

Chronic obstructive pulmonary disease (COPD) is also an inflammatory disease of the lungs characterized by progressive emphysema (alveolar destruction) and bronchiolar fibrosis in variable proportions. Loss of bronchiolar elasticity leads to closure of smaller air tubes during expiration. The airway obstruction is accentuated during exercise causing shortness of breath. The expiratory airflow limitation does not fluctuate markedly over long periods of time, but there are exacerbations precipitated by respiratory infections, pollutants, etc. It is clearly related to smoking and characteristically starts after the age of 40. Quiting smoking reduces the rate of decline in lung function. Bronchodilators prevent closure of peripheral air tubes during expiration and afford symptomatic relief in COPD patients, but improvement in forced expiratory volume in 1st second (FEV_1) following inhalation of a shortacting β_2 agonist is generally <15%. An increasing part of airway obstruction is irreversible.

APPROACHES TO TREATMENT

1. *Prevention of AG:AB reaction*—avoidance of antigen, hyposensitization—possible in extrinsic asthma and if antigen can be identified.
2. *Neutralization of IgE (reaginic antibody)*—Omalizumab.
3. *Suppression of inflammation and bronchial hyperreactivity*—corticosteroids.
4. *Prevention of release of mediators*—mast cell stabilizers.
5. *Antagonism of released mediators*—leukotriene antagonists, antihistamines, PAF antagonists.
6. *Blockade of constrictor neurotransmitter*—anticholinergics.
7. *Mimicking dilator neurotransmitter*—sympathomimetics.
8. *Directly acting bronchodilators*—methylxanthines.

CLASSIFICATION

I. *Bronchodilators*

A. *β_2 Sympathomimetics:* Salbutamol, Terbutaline, Bambuterol, Salmeterol, Formoterol, Ephedrine.

B. *Methylxanthines:* Theophylline (anhydrous), Aminophylline, Choline theophyllinate, Hydroxyethyl theophylline, Theophylline ethanolate of piperazine, Doxophylline.

C. *Anticholinergics:* Ipratropium bromide, Tiotropium bromide.

II. *Leukotriene antagonists*

Montelukast, Zafirlukast.

III. *Mast cell stabilizers*

Sodium cromoglycate, Ketotifen.

IV. *Corticosteroids*

A. *Systemic:* Hydrocortisone, Prednisolone and others.

B. *Inhalational:* Beclomethasone dipropionate, Budesonide, Fluticasone propionate, Flunisolide, Ciclesonide.

V. *Anti-IgE antibody*

Omalizumab

SYMPATHOMIMETICS (*see* Ch. 9)

Adrenergic drugs cause bronchodilatation through β_2 receptor stimulation → increased cAMP formation in bronchial muscle cell → relaxation. In addition, increased cAMP in mast cells and other inflammatory cells decreases mediator release. Since β_2 receptors on inflammatory cells desensitize quickly, the contribution of this action to the beneficial effect of β_2 agonists in asthma where airway inflammmation is chronic, is uncertain, and at best minimal. Adrenergic drugs are the mainstay of treatment of reversible airway

obstruction, but should be used cautiously in hypertensives, ischaemic heart disease patients and in those receiving digitalis. They are the most effective and fastest acting bronchodilators when inhaled.

Though adrenaline ($\beta_1+\beta_2+\alpha$ receptor agonist) and isoprenaline ($\beta_1+\beta_2$ agonist) are effective bronchodilators, it is the selective β_2 agonists that are now used in asthma to minimize cardiac side effects.

Salbutamol (Albuterol) A highly selective β_2 agonist; cardiac side effects are less prominent. Selectivity is further increased by inhaling the drug. Inhaled salbutamol delivered mostly from pressurized metered dose inhaler (pMDI) produces bronchodilatation within 5 min and the action lasts for 2–4 hours. It is, therefore, used to abort and terminate attacks of asthma, but is not suitable for round-the-clock prophylaxis. Muscle tremors are the dose related side effect. Palpitation, restlessness, nervousness, throat irritation and ankle edema can also occur. Hypokalaemia is a possible complication. Salbutamol undergoes presystemic metabolism in the gut wall, oral bioavailability is 50%. Oral salbutamol acts for 4–6 hours, is longer acting and safer than isoprenaline, but not superior in bronchodilator efficacy.

Because of more frequent side effects, oral β_2 agonist therapy is reserved for patients who cannot correctly use inhalers or as alternative/adjuvant drugs in severe asthma.

Dose: 2–4 mg oral, 0.25–0.5 mg i.m./s.c., 100–200 µg by inhalation.

ASTHALIN 2, 4 mg tab., 8 mg SR tab., 2 mg/5 ml syrup, 100 µg metered dose inhaler; 5 mg/ml respirator soln., 200 µg rota caps; CROYSAL 0.5 mg/ml inj, SALOL 2.5 mg/3 ml inj; VENTORLIN 2 mg/5 ml syr, 4 mg, 8 mg CR caps; DERIHALER 100 µg metered dose inhaler.

Single enantiomer preparation of R(–) salbutamol has also been marketed, because it is the active β_2 agonist and more potent bronchodilator which may produce fewer side effects than the racemate.

Terbutaline It is similar to salbutamol in properties and use.

Dose: 5 mg oral, 0.25 mg s.c., 250 µg by inhalation.

TERBUTALINE, BRICAREX 2.5, 5 mg tab., 3 mg/5 ml syrup, 0.5 mg/ml inj; MISTHALER 250 µg/metered dose, 10 mg/ml nebulizing soln.; BRICANYL 0.5 mg/ml inj, 2.5 mg, 5 mg tabs, 1.5 mg/5 ml syr.

Inhaled salbutamol and terbutaline are currently the most popular drugs for quick reversal or bronchospasm, but should not be used on any regular schedule. Regular use does not reduce bronchial hyperreactivity: may even worsen it. This may be responsible for the diminished responsiveness seen after long-term use of these drugs. Regular use also down regulates bronchial β_2 receptors. It is advised that patients requiring regular medication should be treated with inhaled steroids, with or without inhaled long acting β_2 agonists (e.g. salmeterol), while short acting β_2 agonist inhalers should be restricted to symptomatic relief of wheezing.

Bambuterol This biscarbamate ester prodrug of terbutaline is slowly hydrolysed in plasma and lungs by pseudocholinesterase to release the active drug over 24 hours. Reversible inhibition of pseudocholinesterase occurs in a dose dependent manner. It is indicated in nocturnal and chronic asthma as a single evening dose of 10–20 mg oral.

BAMBUDIL 10 mg, 20 mg tabs, 5 mg/5 ml oral soln; BETADAY 10, 20 mg tabs.

Salmeterol It is the first long acting selective β_2 agonist with a slow onset of action; used by inhalation on a twice daily schedule for maintenance therapy and for nocturnal asthma, but not for acute symptoms. It is more β_2 selective than salbutamol, as well as more lipophilic which probably accounts for its longer duration of action. Concern of asthma worsening due to regular use of inhaled β_2 agonists applies to salmeterol also. Recent epidemiological studies indicate that risk of life-threatening asthma attacks may be increasd by regular use of long acting β_2 agonists. Concurrent inhaled steroid appears to limit this risk. Excess mortality among asthmatics treated continuously with long acting β_2 agonist inhalations has been reported. However, clinical studies have shown sustained improvement in asthma symptoms and lung function in majority of patients. Concurrent use of inhaled salmeterol with inhaled glucocorticoid produces effects equivalent to double dose of the corticoid alone. It is

advocated that long-acting β_2 agonists should be used only in combination with an inhaled steroid; combined formulations are available.

COPD: Long-acting β_2 agonists are superior to short-acting ones, and equivalent to inhaled anticholinergics in COPD. They reduce breathlessness by preventing expiratory closure of peripheral airways and abolishing the reversible component of airway obstruction.

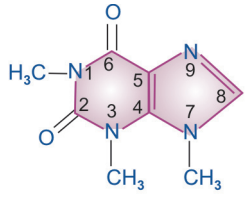
SALMETER, SEROBID 25 µg per metered dose inhaler; 2 puffs BD; severe cases 4 puffs BD; also SEROBID ROTACAPS 50 µg; 1–2 caps BD by inhalation.
SEROFLO—100/250/500 ROTACAPS: Salmeterol 50 µg + fluticasone 100 µg/250 µg/500 µg per rotacap
SEROFLO—125/250 INHALERS, COMBITIDE INHALER: Salmeterol 25 µg + fluticasone 125 µg/250 µg per puff.

Formoterol Another long-acting selective β_2 agonist which acts for 12 hrs when inhaled. In comparison to salmeterol, it has a faster onset of action. It is used on a regular morning-evening schedule for round-the-clock bronchodilatation.
Dose: 12–24 µg by inhalation twice daily.
FORATEC 12 µg rotacaps.

Ephedrine This oral sympathomimetic has $\alpha + \beta_1 + \beta_2$ actions; causes mild slowly developing bronchodilatation lasting for 3–5 hours. It is a constituent of older combination formulations and is used for mild to moderate chronic asthma. Because of low efficacy and frequent side effects, it is not preferred now.

METHYL XANTHINES

Theophylline and its compounds have been extensively used in asthma, but are not considered first line drugs any more. They are used more often in COPD. Theophylline is one of the three naturally occurring methylated xanthine alkaloids *caffeine, theophylline* and *theobromine*. The chemical relation between the three is depicted below:



THEOPHYLLINE
(1,3, Dimethylxanthine)

THEOBROMINE
(3,7, Dimethylxanthine)

CAFFEINE
(1,3,7, Trimethylxanthine)

They are consumed as beverages. The sources and average alkaloid contents of the beverages, as they are usually prepared are given below.

Source	Alkaloid content in beverage	
1. *Thea sinensis* (Tea leaves)	Caffeine Theophylline	50 mg in an average 1 mg cup of tea
2. *Coffea arabica* (Coffee seeds)	Caffeine	75 mg in an average cup of coffee
3. *Theobroma cacao* (Cocoa, chocolate)	Theobromine Caffeine	200 mg in an average 4 mg cup of cocoa
4. *Cola acuminata* (Guru nuts)	Caffeine	30 mg in 200 ml bottle of cola drink

All three alkaloids have qualitatively similar actions, but there are marked quantitative (Table 16.1) and pharmacokinetic differences.

TABLE 16.1 Comparative pharmacological actions of caffeine and theophylline

ACTION	CAFF.	THEO.
1. CNS—stimulation (low dose)	+++	++
—toxicity	++	+++
2. Heart—stimulation	++	+++
3. Blood vessel—relaxation	+	++
4. Bronchi—dilatation	+	+++
5. Kidney—diuresis	+	++
6. Sk. muscle—increased contractility	+++	++
7. Gastric mucosa—irritation	+	++
8. Phosphodiesterase inhibition	++	+++
9. Adenosine antagonism	++	+++

CAFF—Caffeine; THEO—Theophylline
Theobromine is of no therapeutic importance.

Pharmacological actions

1. *CNS* Caffeine and theophylline are CNS stimulants, primarily affect the higher centres. Caffeine 150–250 mg produces a sense of well-being, alertness, beats boredom, allays fatigue, thinking becomes clearer even when dullness has tended to prevail after a sustained intellectual effort. It tends to improve performance and increase motor activity. Caffeine is more active than theophylline in producing these effects. Higher doses cause nervousness, restlessness, panic, insomnia and excitement. Still higher doses produce tremors, delirium and convulsions.

Theophylline has greater propensity to produce these adverse effects at higher doses and is definitely more toxic than caffeine.

These alkaloids also stimulate medullary vagal, respiratory and vasomotor centres. Vomiting at high doses is due to both gastric irritation and CTZ stimulation.

2. *CVS* Methylxanthines directly stimulate the heart and increase force of myocardial contractions. They tend to increase heart rate by cardiac action, but decrease it by causing vagal stimulation—net effect is variable. Tachycardia is more common with theophylline, but caffeine generally lowers heart rate. Cardiac output and cardiac work are increased. At high doses cardiac arrhythmias may be produced.

While consumption of > 9 cups of coffee per day has been found to be associated with increased incidence of arrhythmias, moderate ingestion of caffeine (upto 500 mg/day) does not increase frequency or severity of cardiac arrhythmias even in patients with ischaemic heart disease or preexisting ventricular extrasystoles.

Methylxanthines, especially theophylline, dilate systemic blood vessels, including coronaries, by direct action: peripheral resistance is reduced. However, cranial vessels are constricted, especially by caffeine; this is one of the basis of its use in migraine.

Effect on BP is variable and unpredictable—

- Vasomotor centre and direct cardiac stimulation—tends to raise BP.
- Vagal stimulation and direct vasodilatation—tends to lower BP.

Usually a rise in systolic and fall in diastolic BP is observed.

3. *Smooth muscles* All smooth muscles are relaxed, most prominent effect is exerted on bronchi, especially in asthmatics. Theophylline is more potent than caffeine. Slow and sustained dose-related bronchodilatation is produced, but the effect is much less marked compared to inhaled β_2 agonists. Vital capacity is increased. Biliary spasm is relieved, but effect on intestines and urinary tract is negligible.

4. *Kidney* Methylxanthines are mild diuretics; act by inhibiting tubular reabsorption of Na^+ and water as well as increased renal blood flow and g.f.r. Theophylline is more potent, but action is brief.

5. *Skeletal muscles* Caffeine enhances contractile power of skeletal muscles. At high concentrations it increases release of Ca^{2+} from sarcoplasmic reticulum by direct action. At low doses, twitch response to nerve stimulation is augmented, while at toxic doses contracture is produced.

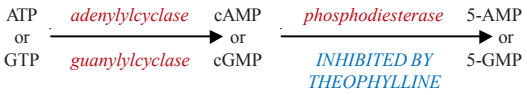
In addition, caffeine facilitates neuromuscular transmission by increasing ACh release. Its central action relieves fatigue and increases muscular work. Enhanced diaphragmatic contractility noted with theophylline in the therapeutic concentration range probably contributes to its beneficial effects in dyspnoea and COPD.

6. *Stomach* Methylxanthines enhance secretion of acid and pepsin in stomach, even on parenteral injection. They are also gastric irritants—theophylline more than caffeine.

7. *Metabolism* Caffeine and to a smaller extent theophylline increase BMR: plasma free fatty acid levels are raised. Release of endogenous catecholamines appears to be partly responsible for these effects.

8. *Mast cells and inflammatory cells* Theophylline decreases release of histamine and other mediators from mast cells and activated inflammatory cells. This may contribute to its therapeutic effect in bronchial asthma.

Mechanism of action Three distinct cellular actions of methylxanthines have been defined—
(a) Release of Ca^{2+} from sarcoplasmic reticulum, especially in skeletal and cardiac muscle.
(b) Inhibition of phosphodiesterase (PDE) which degrades cyclic nucleotides intracellularly.



The concentration of cyclic nucleotides is increased. Bronchodilatation, cardiac stimulation and vasodilatation occur when cAMP level rises in the concerned cells.

Several isoenzymes of the PDE superfamily exist in different tissues. Theophylline is a subtype nonselective and weak PDE inhibitor, but PDE4 inhibition is mainly responsible for bronchodilatation. However, some selective PDE4 inhibitors like *Cilomilast* and *Roflumilast* have been disappointing clinically in efficacy as well as side effects.

(c) Blockade of adenosine receptors: adenosine acts as a local mediator in CNS, CVS and other organs—contracts smooth muscles, especially bronchial; dilates cerebral blood vessels, depresses cardiac pacemaker and inhibits gastric secretion. Methylxanthines produce opposite effects.

Action (a) is exerted only at concentrations much higher than therapeutic plasma concentrations of caffeine and theophylline (ranging from 5–20 µg/ml). Action (b) and action (c) are exerted at concentrations in the therapeutic range and appear to contribute to bronchodilatation. Raised cAMP levels in inflammatory cells may attenuate mediator release and promote eosinophil apoptosis adding to the therapeutic effect of theophylline in asthma. Adenosine A_1 receptor antagonism is considered responsible for cardiac arrhythmias and seizures occurring in theophylline toxicity.

Recent evidence suggests that low concentations of theophylline ehnace histone deacetylation in airway inflammatory cells, suppressing proinflammatory gene transcription. Thus, even sub-bronchodilator doses of theophylline may exert some beneficial effect in asthma.

(Pharmacokinetics, adverse effects and uses of caffeine are described in Ch. 35)

Theophylline

Pharmacokinetics Theophylline is well absorbed orally; rectal absorption from suppositories is erratic. It is distributed in all tissues—crosses placenta and is secreted in milk, (V 0.5 l/kg), 50% plasma protein bound and extensively metabolized in liver by demethylation and oxidation primarily by CYP1A2. Only 10% is excreted unchanged in urine. Its elimination rate varies considerably with age. At therapeutic concentrations, the t½ in adults is 7–12 hours. Children eliminate it much faster (t½ 3–5 hours) and elderly more slowly. In premature infants also the t½ is prolonged (24–36 hours). There are marked interindividual variations in plasma concentrations attained with the same dose.

Theophylline metabolizing enzymes are saturable, t½ is prolonged with higher doses (to as much as 60 hours) as kinetics changes from first to zero order. Plasma concentrations, therefore, increase disproportionately with dose.

Factors which need dose reduction are— age > 60 yr (× 0.6), CHF (× 0.6), pneumonia (× 0.4), liver failure (× 0.2–0.4).

Adverse effects Theophylline has a narrow margin of safety. Dose-dependent toxicity starts from the upper part of therapeutic concentration range (Fig. 16.1). Adverse effects are primarily referable to the g.i.t., CNS and CVS. Headache, nervousness and nausea are early symptoms. Children are more liable to develop CNS toxicity.

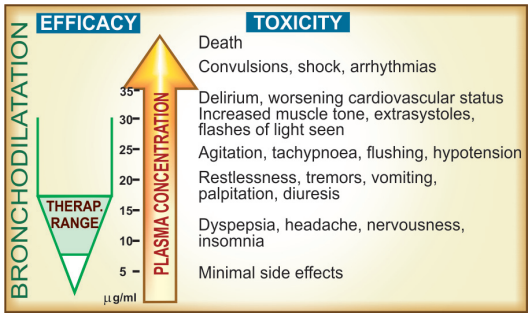


Fig. 16.1: Relationship between efficacy and toxicity of theophylline with its plasma concentration. The depicted concentration ranges are approximate

The irritant property of theophylline is reflected in gastric pain (with oral), rectal inflammation (with suppositories) and pain at site of i.m. injection. Rapid i.v. injection causes precordial pain, syncope and even sudden death—due to marked fall in BP, ventricular arrhythmias or asystole.

Interactions

1. Agents which enhance theophylline metabolism primarily by inducing CYP1A2 lower its plasma level: dose has to be increased by the factor given in parenthesis.

Smoking (1.6), phenytoin (1.5), rifampicin (1.5), phenobarbitone (1.2), charcoal broiled meat meal (1.3).

2. Drugs which inhibit theophylline metabolism and increase its plasma level are—erythromycin, ciprofloxacin, cimetidine, oral contraceptives, allopurinol; dose should be reduced to 2/3.
3. Theophylline enhances the effects of—furosemide, sympathomimetics, digitalis, oral anticoagulants, hypoglycaemics.
4. Theophylline decreases the effects of—phenytoin, lithium.
5. Aminophylline injection should not be mixed in the same infusion bottle/syringe with—ascorbic acid, chlorpromazine, promethazine, morphine, pethidine, phenytoin, phenobarbitone, insulin, penicillin G, tetracyclines, erythromycin.

Preparations and dose

(i) *Theophylline (Anhydrous)* Poorly water soluble, cannot be injected. 100–300 mg TDS (15 mg/kg/day) THEOLONG 100, 200 mg SR cap., DURALYN-CR 400 mg continuous release cap, UNICONTIN 400 mg, 600 mg CR tabs, THEOBID 200 mg, 300 mg SR tabs.
Only sustained release (SR) tab./caps. are used, because fast release tabs. produce high peak and low trough plasma concentrations.

Because solubility of theophylline is low, a number of soluble complexes and salts have been prepared, particularly for parenteral use.

(ii) *Aminophylline (Theophylline-ethylenediamine; 85% theophylline)* water soluble, can be injected i.v. but not i.m. or s.c.—highly irritating. 250–500 mg oral or slow i.v. injection; children 7.5 mg/kg i.v.; AMINOPHYLLINE 100 mg tab, 250 mg/10 ml inj.

(iii) *Hydroxyethyl theophylline (Etophylline, 80% theophylline)* water soluble; can be injected i.v. and i.m. (but not s.c.), less irritating; 250 mg oral/i.m./i.v.; DERIPHYLLIN 100 mg tab., 300 mg SR tab., 220 mg/2 ml inj.

(iv) *Choline theophyllinate (Oxtriphylline; 64% theophylline)* 250–500 mg oral, CHOLIPHYLLINE 125 mg cap., 125 mg/5 ml elixir.

(v) *Theophylline ethanolate of piperazine* 250–500 mg oral or i.v.; CADIPHYLLATE 80 mg/5 ml elixir, ETOPHYLATE 125 mg/5 ml syrup.

Doxophylline A long-acting oral methylxanthine that is claimed not to interfere with sleep or stimulate gastric secretion.
Dose: 400 mg OD or BD, children 12 mg/kg/day; OXYPUR 400 mg tab, DOXORIL 400 mg tab, 100 mg/5 ml syr.

The double salts/derivatives of theophylline are claimed to be less gastric irritant and better absorbed. However, anhydrous theophylline is completely absorbed and gastric irritancy of the salts is the same in terms of theophylline content.

Uses

1. *Bronchial asthma and COPD*: Theophylline benefits by causing bronchodilatation as well as by decreasing release of inflammatory mediators, promoting eosinophil apoptosis, improved mucociliary clearance, stimulation of respiratory drive and by augmenting diaphragmatic contractility. However, because of narrow margin of safety and limited efficacy, its use has declined. Sustained release theophylline can be used in mild-to-moderately severe asthma, as a 3rd line or alternative/adjuvant drug, especially in patients with nocturnal asthma. It is more useful in COPD; is often added to other drugs.

Use of intravenous aminophylline in status asthmaticus is outmoded.

2. *Apnoea in premature infant*: Theophylline reduces the frequency and duration of episodes of apnoea that occur in some preterm infants in the first few weeks of life. Closely monitored oral or i.v. treatment is employed for 1–3 weeks. Caffeine is equally effective.

ANTICHOLINERGICS (*see* Ch. 8)

Atropinic drugs cause bronchodilatation by blocking M_3 receptor mediated cholinergic constrictor tone; act primarily in the larger airways (Fig. 16.2) which receive vagal innervation. However, some recent evidence points to presence of M_3 receptors on peripheral bronchiolar muscles as well, though they are not vagally innervated.

Ipratropium bromide is a short acting (duration 4–6 hours) inhaled anticholinergic bronchodilator, while *tiotropium bromide* is long acting (duration 24 hours). Both are less efficacious than inhaled β_2 sympathomimetics in bronchial asthma. However, patients of asthmatic bronchitis, COPD and psychogenic asthma respond better to

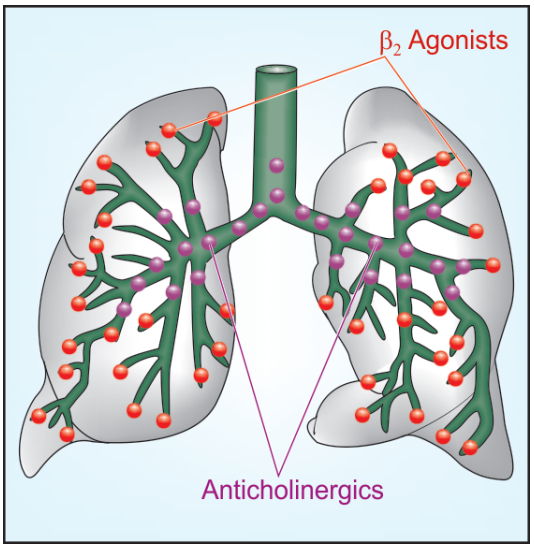


Fig. 16.2: Primary sites of bronchodilator action of inhaled adrenergic β_2 agonists and inhaled anticholinergics. Salbutamol mainly relaxes bronchiolar smooth muscle; Ipratropium blocks bronchoconstriction mainly in the larger airways

anticholinergics. They are the bronchodilators of choice in COPD. Reflex cholinergic tone appears to be the major reversible component of airway obstruction in COPD. Tiotropium is rated more effective than ipratropium in COPD; more suitable for severe cases (FEV_1<50% of predicted). No decline in its clinical efficacy has been noted over a period of 4 years. The inhaled anticholinergics produce slower response than inhaled β_2 sympathomimetics and are better suited for regular prophylactic use (ipratropium 2–4 puffs 6 hourly or tiotropium 1 rotacap OD) than for quick relief of breathlessness. Combination of inhaled ipratropium with β_2 agonist produces more marked and longer lasting bronchodilatation; since their effects are additive. This can be utilized in severe asthma or COPD. Nebulized ipratropium mixed with salbutamol is employed in refractory asthma. Combined formulations are available.

Salbutamol + Ipratropium

DUOLIN INHALER, 100 µg + 20 µg per metered dose
COMBIMIST INHALER
DUOLIN ROTACAP: 200 µg + 40 µg per rotacap
DUOLIN RESPULES, 2.5 mg + 500 µg in 2.5 ml solution
COMBIMIST RESPULES

LEUKOTRIENE ANTAGONISTS

Since it was realized that cystenyl leukotrienes ($LT\text{-}C_4/D_4$) are important mediators of bronchial asthma, efforts were made to develop their antagonists and synthesis inhibitors. Two *cys*LT_1 receptor antagonists *montelukast* and *zafirlukast* are available.

Montelukast and Zafirlukast Both have similar actions and clinical utility. They competitively antagonize *cys*LT_1 receptor mediated bronchoconstriction, airway mucus secretion, increased vascular permeability and recruitment of eosinophils. Bronchodilatation, reduced sputum eosinophil count, suppression of bronchial inflammation, mucus and hyperreactivity are noted in asthma patients. Parameters of lung function show variable improvement. Some studies have found that certain patients are 'responders' while others are 'nonresponders' to anti-LT therapy. This may reflect differing extent of involvement of LTs as asthma mediators.

Montelukast and zafirlukast are indicated for prophylactic therapy of mild-to-moderate asthma as alternatives to inhaled glucocorticoids. Though efficacy is low, they may obviate need for inhaled steroids, and may be more acceptable in children. In severe asthma, they have additive effect with inhaled steroids, may permit reduction in steroid dose and need for rescue β_2 agonist inhalations, but the additive effect of long-acting β_2 agonists is greater. They are not to be used for terminating asthma episodes. *cys*LT_1 antagonists are modestly effective in aspirin-induced asthma and exercise induced asthma, but are of no value in COPD.

Both montelukast and zafirlukast are very safe drugs; produce few side effects like headache and rashes. Eosinophilia and neuropathy are infrequent. Few cases of Churg-Strauss syndrome (vasculitis with eosinophilia) have been reported.

They are well absorbed orally, highly plasma protein bound and metabolized by CYP2C9 (montelukast by CYP3A4 as well). The plasma t½ of montelukast is 3–6 hours, while that of zafirlukast is 8–12 hours.

Montelukast: 10 mg OD; children 2–5 yr 4 mg OD, 6–14 yr 5 mg OD; in the evening.
EMLUKAST, MONTAIR, VENTAIR 4 mg, 5 mg, 10 mg tabs
Zafirlukast: 20 mg BD; children 5–11 yr 10 mg BD;
ZUVAIR 10 mg, 20 mg tabs.

Zileuton It is a 5-LOX inhibitor, blocks LTC_4/D_4 as well as LTB_4 synthesis. It therefore has the potential to prevent all LT induced responses including those exerted by activation of *cys*LT_1 receptor. However, clinical efficacy in asthma is similar to montelukast. The duration of action of zileuton is short and it has hepatotoxic potential. These limitations have restricted its use.

MAST CELL STABILIZERS

Sodium cromoglycate (Cromolyn sod.)

It is a synthetic chromone derivative which inhibits degranulation of mast cells (as well as other inflammatory cells) by trigger stimuli. Release of mediators of asthma like histamine, LTs, PAF, interleukins, etc. is restricted. The basis of this effect is not well understood, but may involve a delayed Cl^- channel in the membrane of these cells. Chemotaxis of inflammatory cells is inhibited. Long-term treatment decreases the cellular inflammatory response; bronchial hyperreactivity is reduced to variable extents. Bronchospasm induced by allergens, irritants, cold air and exercise may be attenuated. It is also not a bronchodilator and does not antagonize constrictor action of histamine, ACh, LTs, etc. Therefore, it is ineffective if given during an asthmatic attack.

Pharmacokinetics Sod. cromoglycate is not absorbed orally. It is administered as an aerosol through metered dose inhaler delivering 1 mg per dose: 2 puffs 4 times a day. Only a small fraction of the inhaled drug is absorbed systemically; this is rapidly excreted unchanged in urine and bile.

Uses

1. *Bronchial asthma:* Sod. cromoglycate is a long-term prophylactic in mild-to-moderate asthma. Decrease in the frequency and severity of attacks is more likely in extrinsic (atopic) and exercise-induced asthma, especially in younger patients. Therapeutic benefit (when it occurs) develops slowly over 2–4 weeks and lasts 1–2 weeks after discontinuing. However, it is less effective than inhaled steroids and is seldom used now.
2. *Allergic rhinitis:* Cromoglycate is not a nasal decongestant, but regular 4 times daily use as a nasal spray produces some symptomatic improvement in many patients after 4–6 weeks. The need for nasal decongestants may be reduced.
3. *Allergic conjunctivitis:* Regular use as eye drops is beneficial in some chronic cases.

FINTAL inhaler: 1 mg and CROMAL 5 mg/puff metered dose inhaler; 2 puffs 4 times daily.
FINTAL nasal spray: 2% CROMAL AQ 2.8 mg/dose; 2 squeezes in each nostril QID.
FINTAL eye drops: 2% CROMAL 2% and 4% eye drops; 1 drop in each eye QID.

Adverse effects Because of poor aqueous solubility, absorption of cromoglycate is negligible; systemic toxicity is minimal. Bronchospasm, throat irritation and cough occurs in some patients, especially with fine powder inhalation. Rarely nasal congestion, headache, dizziness, arthralgia and rashes have been reported.

Ketotifen It is an antihistaminic (H_1) with some cromoglycate like action; stimulation of immunogenic and inflammatory cells (mast cells, macrophages, eosinophils, lymphocytes, neutrophils) and mediator release are reduced. It is not a bronchodilator; produces sedation.

After prolonged use, modest symptomatic relief may occur in some patients of bronchial asthma, atopic dermatitis, perennial rhinitis, conjunctivitis, urticaria and food allergy. Thus, it may be tried in patients with multiple allergic disorders.

Adverse effects Generally well tolerated. Sedation and dry mouth are common. Other side effects are dizziness, nausea, weight gain.
Dose: 1–2 mg BD; children 0.5 mg BD.
ASTHAFEN, 1 mg tab, 1 mg/5 ml syrup; KETOVENT 1 mg tab, KETORID 0.25% eye drops.

CORTICOSTEROIDS

Glucocorticoids are not bronchodilators. They benefit by reducing bronchial hyperreactivity, mucosal edema and by suppressing inflammatory response to AG:AB reaction or other trigger stimuli. Their mechanism of action is detailed in Ch. 20.

The realization that asthma is primarily an inflammatory disorder which, if not controlled, accentuates with time, and the availability of inhaled steroids that produce few adverse effects has led to early introduction and more extensive use of glucocorticoids in asthma. Corticosteroids afford more complete and sustained symptomatic relief than bronchodilators or cromoglycate; improve airflow, reduce asthma exacerbations and may influence airway remodeling, retarding disease progression. They also increase airway smooth muscle responsiveness to β_2 agonists and reverse refractoriness to these drugs. Inhaled corticosteroids have thus markedly changed the outlook on asthma therapy. However, long-term systemic steroid therapy has its own adverse effects which may be worse than asthma itself.

SYSTEMIC STEROID THERAPY

Systemic steroid therapy is resorted to in asthma under the following two situations:

(i) *Severe chronic asthma:* not controlled by bronchodilators and inhaled steroids, or when there are frequent recurrences of increasing severity; start with prednisolone 20–60 mg (or equivalent) daily; attempt dose reduction after 1–2 weeks of good control and finally try shifting the patient onto an inhaled steroid. Only few patients require long term oral steroids—in them dose should be kept at minimum.

In patients requiring long-term glucocorticoid therapy, alternative treatment with immunosuppressants like methotrexate (low dose) or cyclosporine has been tried.

(ii) *Status asthmaticus/acute asthma exacerbation:* Asthma attack not responding to intensive bronchodilator therapy: start with high dose of a rapidly acting i.v. glucocorticoid which generally acts in 6–24 hours—shift to oral therapy for 5–7 days and then discontinue abruptly or taper rapidly.

COPD A short course (1–3 week) of oral glucocorticoid may benefit some patients of COPD during an exacerbation.

INHALED STEROIDS

These are glucocorticoids with high topical and low systemic activity (due to poor absorption and/or marked first pass metabolism). *Beclomethasone dipropionate*, *Budesonide* and *Fluticasone* have similar properties. *Ciclesonide* is a later addition. Because airway inflammation is present in early mild disease as well, and bronchial remodeling starts developing from the beginning, it has been advocated that inhaled steroids should be the 'step one' for all asthma patients. However, currently inhaled steroids are not considered necessary for patients with mild and episodic asthma. They are indicated in all cases of persistent asthma when inhaled β_2 agonists are required almost daily or the disease is not only episodic. Start with 100–200 µg BD, titrate dose upward every 3–5 days; max. 400 µg QID, beyond which no further benefit generally occurs.

Inhaled steroids suppress bronchial inflammation, increase peak expiratory flow rate, reduce need for rescue β_2-agonist inhalations and prevent episodes of acute asthma. However, they have no role during an acute attack or in status asthmaticus. Peak effect is seen after 4–7 days of instituting inhaled steroids and benefit persists for a few weeks after discontinuation. They can be started in patients who in the past have required oral steroids as well as in those with no such history. Patients who are to be switched over from oral steroid should receive inhaled steroid in addition for 1–2 weeks before oral steroid is tapered, otherwise steroid withdrawal may manifest (precipitation of asthma, muscular pain, lassitude, depression, hypotension). This confirms lack of systemic activity of inhaled steroids (at doses < 600 µg/day). Long-term experience has shown that efficacy of inhaled steroids is maintained and reinstitution of oral steroids is seldom needed. Short courses of oral steroids may be added during periods of exacerbation. Some patients who remain well controlled for long periods can even stop inhaled steroids without worsening of asthma.

COPD: The airway inflammation in COPD is not very responsive to corticosteroids. As such, only high dose inhaled steroids are beneficial in advanced COPD with frequent exacerbations; should not be used in early/mild cases. There is no proof that they slow disease progression.

Adverse effects Hoarseness of voice, dysphonia, sore throat, asymptomatic or symptomatic oropharyngeal candidiasis are the most common side effects. These can be minimized by the use of a spacer, gargling after every dose (to wash off the drug deposited on oral and pharyngeal mucosa) and prevented as well as treated by topical nystatin/clotrimazole. There is no evidence of mucosal damage or increased incidence of chest infections, even on prolonged use.

Systemic effects of long-term inhaled glucocorticoids are clinically relevant only at doses > 600 µg/day. The significant ones are—mood changes, osteoporosis, growth retardation in

children, bruising, petechiae, hyperglycaemia and pituitary-adrenal suppression; several reports of adrenal crisis have appeared, especially in children, during stress (of an infection, etc).

Inhaled steroids are safe during pregnancy.

Beclomethasone dipropionate

BECLATE INHALER 50 µg, 100 µg, 200 µg per metered dose, 200 doses inhaler, BECORIDE 50, 100, 250 µg per puff inhaler.
BECLATE ROTACAPS (with rotahaler) 100, 200, 400 µg powder per cap.
AEROCORT INHALER 50 µg/metered aerosol dose with salbutamol 100 µg.
AEROCORT ROTACAPS 100 µg with salbutamol 200 µg rotacaps (with rotahaler).

Intranasal spray (50 µg in each nostril BD–TDS) is effective in perennial rhinitis.

Budesonide A nonhalogenated glucocorticoid with high topical: systemic activity ratio (greater first pass metabolism than beclomethasone). Small fraction that is absorbed is rapidly metabolized; less systemic effects, may be preferred in more severe cases.

Dose: 200–400 µg BD–QID by inhalation in asthma; 200–400 µg/day by intranasal spray for allergic rhinitis.
PULMICORT 100, 200, 400 µg/metered dose inhaler, BUDECORT 100 µg/metered dose inhalation.
FORACORT: Formoterol 6 µg + Budesonide 100 µg/200 µg rotacaps.
RHINOCORT 50 µg per metered dose nasal spray; BUDENASE AQ 100 µg metered dose aqueous nasal spray; for prophylaxis and treatment of seasonal and perennial allergic or vasomotor rhinitis, nasal polyposis; initially 2 puffs in each nostril every morning, maintenance 1 puff in each nostril in the morning.

Nasal irritation, sneezing, crusting, itching of throat and dryness may occur, especially in the beginning. Contraindicated in presence of infection or nasal ulcers.

Fluticasone propionate This inhaled glucocorticoid has high potency (about double of beclomethasone); longer duration and negligible oral bioavailability. The dose swallowed after inhalation has little propensity to produce systemic effects. At high doses, systemic effects may be due to absorption from the lungs. The inhalational dose is 100–250 µg BD (max 1000 µg/day). May be preferred in patients requiring higher doses.

FLOHALE INHALER 25 µg, 50 µg, 125 µg per actuation.
FLOHALE ROTACAPS 50 µg, 100 µg, 250 µg rotacaps.
FLOMIST 50 µg per actuation nasal spray.

Flunisolide This topical steroid is available for prophylaxis and treatment of seasonal and perennial rhinitis.

SYNTARIS 25 µg per actuation nasal spray; one spray in each nostril 2–3 times daily.

Ciclesonide This inhalational steroid utilizes a novel approach to improve topical: systemic activity ratio. It is a prodrug that is cleaved by esterases in the bronchial epithelium to release the active moiety. Though it is absorbed from the lungs, oral bioavailability is <1%. In the circulation it is extensively bound to plasma proteins, further minimizing exposure of tissue cells to the free and active drug.

Dose: 80–160 µg by inhalation OD, preferably in the evening.
CICLEZ 80 µg and 160 µg per metered dose inhaler with HFA propellant.

ANTI-IgE ANTIBODY

Omalizumab It is a humanized monoclonal antibody against IgE. Administered s.c., it neutralizes free IgE in circulation without activating mast cells and other inflammatory cells. On antigen challenge, little IgE is available bound to the mast cell surface receptors ($F_{\varepsilon}R1$) to trigger mediator release (*see* Fig. 11.2) and cause bronchoconstriction. In severe extrinsic asthma, omalizumab has been found to reduce exacerbations and steroid requirement. No benefit has been noted in nonallergic asthma. It is very expensive; use is reserved for resistant asthma patients with positive skin tests or raised IgE levels who require frequent hospitalization. It is being tried in other allergic diseases as well.

INHALED ASTHMA MEDICATION

Four classes of antiasthma drugs, *viz*. β_2 agonists, anticholinergics, cromoglycate and glucocorticoids are available for inhalational use. They are aimed at delivering the drug to the site of action so that lower dose is needed and systemic side effects are minimized. Faster action of bronchodilators can be achieved compared to oral administration. Most asthma patients are now maintained on inhaled medication only. Aerosols are of two types:

(i) use drug in solution: pressurized metered dose inhaler (pMDI), nebulizers.
(ii) use drug as dry powder: spinhaler, rotahaler

Pressurized metered dose inhalers use chlorofluorocarbon (banned now for their effect on ozone layer) or hydrofluroalkane (HFA) propellants and deliver a specified dose of the drug in spray form per actuation. Device actuation

has to be properly coordinated with deep inspiration, which many patients are unable to learn. A large volume 'spacer' (chamber interposed between the inhaler and the patient's mouth) can be used to improve drug delivery by obviating the need for precise coordination. Moreover, larger particles settle on the walls of the spacer reducing the fraction that deposits in the throat and is later swallowed. Local complications (candidiasis with inhaled steroids) as well as systemic exposure are reduced. Jet nebulizers produce a mist of the drug solution generated by pressurized air or oxygen which can be inhaled through a mouth piece, face mask or in a tent. Ultrasonic nebulizers use electrically vibrated crystals; pressurized air/oxygen is not needed. Metered dose inhalers are convenient hand-held devices which can be carried along, while nebulizers are used at patient's bed side. Nebulizers are preferred for severe episodes of asthma as well as for children and elderly. More than one drug can be nebulized simultaneously.

Dry powder inhalers are also portable devices in which the capsule (rotacap) containing the drug is punctured/cut across and the powder is aerosolized by the inspiratory air flow of the patient. It requires high velocity inspiration which children, elderly and the very sick may not be capable of. The dry powder is also more likely to irritate the air passage—producing cough and bronchoconstriction.

Efficacy of aerosolized drug depends on the particle size: 1–5 µm diameter particles deposit on the bronchioles and effectively deliver the drug. Larger particles settle on the oropharynx, while very fine particles do not settle anywhere and are exhaled out. On an average only ~10% of the inhaled drug reaches the site of action. A considerable fraction is swallowed. Therefore, to minimize systemic action, the drug should have low oral bioavailability. Spacer devices improve inhaled to swallowed drug ratio. Slow and deep inbreathing after device actuation and holding the breath after inhalation also enhances efficacy of the inhaler. Greater proportion of smaller particles in a relatively narrow band width of 1-2 µM can be generated using the newer HFA propellant based pMDIs. This improves delivary of the drug to the smaller bronchioles. However, systemic absorption from the peripheral lungs is also more.

CHOICE OF TREATMENT

The severity of asthma symptoms ranges from transient respiratory difficulty to incapacitating breathlessness and characteristically fluctuates over time. A stepwise guideline to the treatment of asthma as per needs of the patient has been recommended. After the asthma is under control for 3–6 months, an attempt to reduce medication should be made in stepwise manner.

1. *Mild episodic asthma* (symptoms less than once daily, normal in between attacks): Inhaled short-acting β_2 agonist at onset of each episode. Since asthma is intermittent, it does not require continuous prophylactic therapy (Step-1).

2. *Seasonal asthma* Start regular low-dose inhaled steroid (200–400 µg/day) or cromoglycate 3–4 weeks before anticipated seasonal attacks and continue till 3–4 weeks after the season is over. Treat individual episodes with inhaled short-acting β_2 agonist.

3. *Mild chronic (persistent) asthma with occasional exacerbations* (symptoms once daily or so, subnormal ventilatory performance). Regular low-dose (100–500 µg/day) inhaled steroid (Step-2). Alternatively, inhaled cromoglycate or oral theophylline, but these are less effective. Episode treatment with inhaled short-acting β_2 agonist.

4. *Moderate asthma with frequent exacerbations* (attacks affect activity, occur > 1 per day or mild baseline symptoms) Increasing doses of inhaled steroid (up to 800 µg/day) + inhaled long-acting β_2 agonist (Step-3). In view of the potential risk of prolonged treatment with long-acting β_2 agonists, attempt should be made to discontinue it after maintaining asthma control over few months. Leukotriene antagonists may be tried in place of long-acting β_2 agonists, but their additive effect is less marked. Sustained release theophylline may be used as alternative additional drug to long-acting β_2 agonists, especially in nocturnal asthma.

5. *Severe asthma* (continuous symptoms; activity limitation; frequent exacerbations/hospitalization) Regular high dose inhaled steroid (800–2000 µg/day) through a large volume spacer device + inhaled long-acting β_2 agonist (salmeterol) twice daily. Additional treatment with one or more of the following (Step-4):

Leukotriene antagonist/sustained release oral theophylline/oral β_2 agonist/inhaled ipratropium bromide.

Rescue treatment with short-acting inhaled β_2 agonist.

In patients not adequately controlled or those needing frequent emergency care—institute oral steroid therapy (Step-5). Efficacy of oral steroids is proven, but should be the last resort. Attempt to withdraw it should be made periodically. The British guidelines recommend continuing high dose inhaled steroids along with oral steroids.

6. *Status asthmaticus/Refractory asthma*

Any patient of asthma has the potential to develop acute severe asthma which may be life-threatening. Upper respiratory tract infection is the most common precipitant.

(i) Hydrocortisone hemisuccinate 100 mg (or equivalent dose of another glucocorticoid) i.v. *stat,* followed by 100–200 mg 4–8 hourly infusion; may take upto 6 hours to act.

(ii) Nebulized salbutamol (2.5–5 mg) + ipratropium bromide (0.5 mg) intermittent inhalations driven by O_2.

(iii) High flow humidified oxygen inhalation.

(iv) Salbutamol/terbutaline 0.4 mg i.m./s.c. may be added, since inhaled drug may not reach smaller bronchi due to severe narrowing/plugging with secretions.

(v) Intubation and mechanical ventilation, if needed.

(vi) Treat chest infection with intensive antibiotic therapy.

(vii) Correct dehydration and acidosis with saline + sod. bicarbonate/lactate infusion.

Aminophylline 250–500 mg diluted in 20–50 ml glucose (5%) solution injected i.v. over 20–30 min had been routinely used, but recent evidence shows that it does not afford additional benefit; may even produce more adverse effects; use is restricted to resistant cases.

Some antiasthma combinations

BRONKOPLUS: Salbutamol 2 mg, anhydrous theophylline 100 mg tab., also per 5 ml syrup.
BRONKOTUS: Bromhexine 8 mg, salbutamol 2 mg tab., also syrup—bromhexine 4 mg, salbutamol 2 mg per 5 ml.
TERPHYLIN: Terbutaline 2.5 mg, etophylline 100 mg tab, and per 10 ml syr.
THEO ASTHALIN: Salbutamol 2 mg, theophylline anhydrous 100 mg tab, and per 10 ml syr.
THEO ASTHALIN-SR: Salbutamol 4 mg, theophylline 300 mg SR tab.
THEO BRIC: Terbutaline 2.5 mg, theophylline 100 mg tab.
THEOBRIC SR: Terbutaline 5 mg, theophylline 300 mg SR tab.
DURASALYN-CR: Salbutamol 4 mg, theophylline 200 mg CR cap.

☞ PROBLEM DIRECTED STUDY

16.1 A 60-year-old male patient of moderately severe chronic obstructive pulmonary disease (COPD) with FEV_1 45% of predicted, who has quit smoking for the last 5 years, and is maintained on—Ipratropium br. 20 µg/puff metered dose inhaler, 2 puffs 3 times a day, and Theophylline 400 mg SR tab. twice a day, developed sore throat and fever. He was prescribed—

Tab Erythromycin 250 mg, one tab 4 times a day for 5 days

Tab Paracetamol 500 mg 3 times a day till fever persists.

After 3 days he presented with pain in epigastrium, restlessness, irritability, inability to sleep, palpitation, tremor of fingers and hand, and had vomited twice. His fever had subsided and throat was better.

(a) What could be the reason for his recent illness?

(b) Could this illness be prevented, if so, how?

(see Appendix-1 for solution)

SECTION 5

HORMONES AND RELATED DRUGS

Chapter 17a Introduction

Hormone (Greek *hormaein*—to stir up) is a substance of intense biological activity that is produced by *specific cells* in the body and is transported *through circulation* to act on its target cells.

Hormones regulate body functions to bring about a programmed pattern of life events and maintain homeostasis in the face of markedly variable external/internal environment.

Body function	Major regulator hormone(s)
1. Availability of fuel	: Insulin, Glucagon, Growth hormone
2. Metabolic rate	: Triiodothyronine, Thyroxine
3. Somatic growth	: Growth hormone, Insulin-like growth factors
4. Sex and reproduction	: Gonadotropins, Androgens, Estrogens, Progestins
5. Circulating volume	: Aldosterone, Antidiuretic hormone
6. Adaptation to stress	: Glucocorticoids, Adrenaline
7. Calcium balance	: Parathormone, Calcitonin, Vitamin D

Hormones are secreted by the *endocrine* or *ductless* glands. These are:

1. *Pituitary*

(a) *Anterior* Growth hormone (GH), Prolactin (Prl),
Adrenocorticotropic hormone (ACTH, Corticotropin),
Thyroid stimulating hormone (TSH, Thyrotropin),
Gonadotropins—Follicle stimulating hormone (FSH) and Luteinizing hormone (LH).

(b) *Posterior*—Oxytocin,
Antidiuretic hormone (ADH, Vasopressin).

2. *Thyroid* Thyroxine (T_4), Triiodothyronine (T_3), Calcitonin.
3. *Parathyroid* Parathormone (PTH).
4. *Pancreas* (*Islets of Langerhans*) Insulin, Glucagon.
5. *Adrenals*

(a) *Cortex* Glucocorticoids (hydrocortisone)
Mineralocorticoids (aldosterone)
Sex steroids (dehydroepiandrosterone)

(b) *Medulla* Adrenaline, Noradrenaline

6. *Gonads* Androgens (testosterone)
Estrogens (estradiol)
Progestins (progesterone)

In addition, hypothalamus, which is a part of the CNS and not a gland, produces many releasing

Hypothalamic hormone/factor	Chemical nature
1. Thyrotropin releasing hormone (TRH)	Tripeptide
2. Corticotropin releasing hormone (CRH)	Peptide (41 AAs)
3. Gonadotropin releasing hormone (GnRH, LH-RH/FSH-RH), Gonadorelin	Decapeptide
4. Prolactin release inhibitory hormone (PRIH)	Dopamine
5. Growth hormone releasing hormone (GHRH)	Peptide (40, 44 AAs)
6. Somatostatin (Growth hormone release inhibitory hormone)	Peptide (14 AA)

and inhibitory hormones which control the secretion of anterior pituitary hormones. Some important ones of these are given in the box.

Placenta also secretes many hormones:

Chorionic gonadotropin	Prolactin
Estrogens	Progesterone
Placental lactogen	Chorionic thyrotropin

The natural hormones and in many cases their synthetic analogues which may be more suitable therapeutically, are used as drugs for substitution therapy as well as for pharmacotherapy. In addition, hormone antagonists and synthesis/release inhibitors are of therapeutic importance.

Sites and mechanisms of hormone action

The hormones act on their specific receptors located on or within their target cells. Receptor activation by the hormones is translated into response in a variety of ways.

1. *At cell membrane receptors*

a. Through alteration of intracellular cAMP concentration → alteration of protein kinase A→ regulation of cell function: Ca^{2+} acting as third messenger in some situations.	Adrenaline, Glucagon, TSH, FSH, LH, PTH, Calcitonin, ACTH, some hypothalamic releasing hormones, Vasopressin (V_2)
b. Through IP_3/DAG generation: release of intracellular Ca^{2+} and protein kinase C activation.	Vasopressin (V_1), Oxytocin
c. Direct transmembrane activation of tyrosine protein kinase → phosphorylation cascade → regulation of various enzymes.	Insulin, Growth hormone Prolactin

2. *At cytoplasmic receptors*

Penetrating cell membrane, hormone combines with a cytoplasmic receptor → exposes its DNA binding domain → migrates to nucleus and binds to specific genes → DNA mediated mRNA synthesis → synthesis of functional proteins.	Steroidal hormones: Glucocorticoids Mineralocorticoid Androgens Estrogens Progestins; Calcitriol

3. *At nuclear receptor*

The hormone penetrates the nucleus → combines with its receptor → alters DNA- RNA mediated protein synthesis.	Thyroid hormones: Thyroxine, Triiodothyronine

Chapter 17b Anterior Pituitary Hormones

Anterior pituitary (adenohypophysis), the master endocrine gland, elaborates a number of important regulatory hormones. All of these are peptide in nature and act at extracellular receptors located on their target cells. Their secretion is controlled by the hypothalamus through *releasing* and *release-inhibitory* hormones that are transported *via* hypothalamohypophyseal portal system, and is subjected to feedback inhibition by the hormones of their target glands. Each anterior pituitary hormone is produced by a separate group of cells, which according to their staining characteristic are either acidophilic or basophilic.

The *acidophils* are either somatotropes → GH; or lactotropes → Prolactin.

The *basophils* are gonadotropes → FSH and LH; thyrotropes → TSH; and corticotrope-lipotropes → ACTH. The latter in addition to ACTH also produce two melanocyte stimulating hormones (MSHs) and two lipotropins, but these are probably not important in man.

GROWTH HORMONE (GH)

It is a 191 amino acid, single chain peptide of MW 22000.

Physiological functions GH promotes growth of bones and all other organs by inducing hyperplasia. In general, there is a proportionate increase in the size and mass of all parts, but in the absence of gonadotropins, sexual maturation does not take place. The growth of brain and eye is independent of GH. It promotes retention of nitrogen, calcium and other tissue constituents: more protoplasm is formed. The positive nitrogen balance results from increased uptake of amino acids by tissues and their synthesis into proteins. GH promotes utilization of fat and spares carbohydrates: uptake of glucose by muscles is reduced while its output from liver is enhanced; fat is broken down.

GH acts on cell surface JAK-STAT binding protein kinase receptors (*see* p. 50) which are present on practically all cells. Binding of one GH molecule to the extracellular domain of a GH-receptor diamer results in the formation of a ternary complex which undergoes a conformational change and activates the intracellular domain to associate with cytoplasmic JAK-STAT tyrosine-protein kinase resulting in metabolic effects as well as regulation of gene expression.

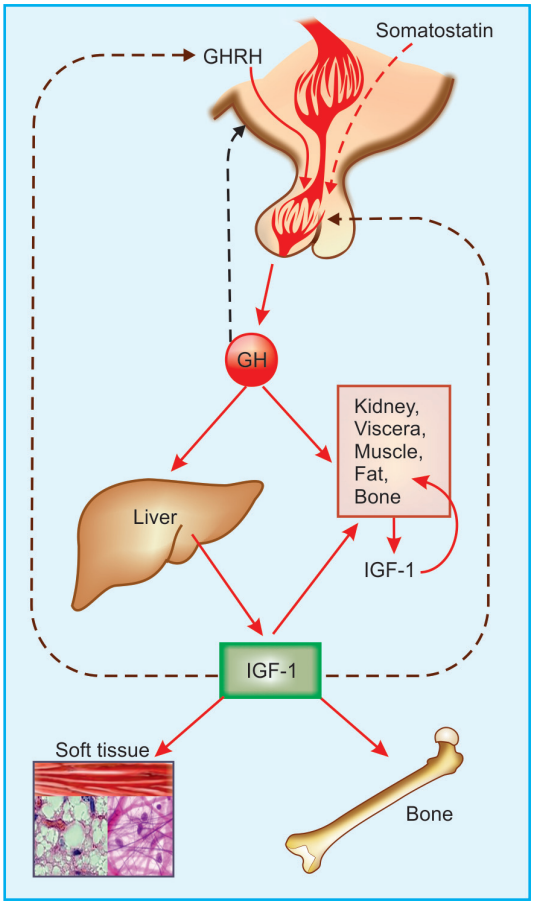


Fig. 17.1: Action of growth hormone (GH) and regulation of its secretion
GHRH—Growth hormone releasing hormone; IGF-1: Insulin like growth factor-1; Stimulation (——→); Inhibition (- - - -→)

The growth promoting, nitrogen retaining and certain metabolic actions of GH are exerted *indirectly* through the elaboration of peptides called *Somatomedins* or *Insulin-like growth factors (*mainly *IGF-1,* also *IGF-2)* which are extracellular mediators of GH response (Fig. 17.1). Liver is the major source of circulating IGF-1, while IGF-1 produced by other target cells acts locally in a paracrine manner. Like insulin, IGF-1 promotes lipogenesis and glucose uptake by muscles. The IGF-1 receptor also is structurally and functionally analogous to the insulin receptor (*see* p. 261).

GH acts directly as well to induce lipolysis in adipose tissue, gluconeogenesis and glycogenolysis in liver and decreased glucose utilization by muscles. These effects are opposite to those of IGF-1 and insulin. As such, GH accentuates the metabolic derangement in diabetes.

Regulation of secretion The hypothalamus produces GH releasing (GHRH) as well as release inhibitory (*somatostatin*) hormones. Both are peptides. *Somatostatin* is also produced by D cells of islets of Langerhans in the pancreas and by few other tissues. Receptors for GHRH and somatostatin are G protein coupled receptors (GPCRs) which enhance or inhibit GH secretion by increasing or decreasing cAMP formation respectively in pituitary somatotropes. Somatostatin has also been shown to inhibit Ca^{2+} channels and open K^{+} channels.

Stimuli that cause GH release are—fasting, hypoglycaemia, exercise, stress and i.v. infusion of arginine. GH secretion is inhibited by rise in plasma free fatty acid levels and by high doses of glucocorticoids. Dopaminergic agents cause a brief increase in GH release in normal subjects but paradoxically depress it in acromegalics. IGF-1 causes feedback inhibition of GH secretion. Short-loop feedback inhibition of secretion by GH itself has also been described.

Pathological involvements Excess production of GH is responsible for *gigantism* in childhood and *acromegaly* in adults. Hyposecretion of GH in children results in *pituitary dwarfism*. Adult GH deficiency is rare, but when it occurs, it results in low muscle and bone mass, lethargy, decreased work capacity, hyperlipidaemia and increased cardiovascular risk.

Preparations and use The primary indication for GH is *pituitary dwarfism*—0.03–0.06 mg/kg daily in the evening or on alternate days, upto the age of 20 years or more. Human GH produced by recombinant DNA technique (*rhGH*) *somatropin* (191AA) is available for clinical use. Somatropin causes IGF-1 to appear in plasma after a delay of several hours. IGF-1 then remains detectable for upto 48 hours. Early diagnosis and institution of GH therapy restores stature to near normal. rhGH can also be used in *Turner's syndrome* and in children with *renal failure.*

Somatropin has been tried in children with *constitutional short stature* (only if epiphyses are open) with encouraging results. Commercial interests are promoting it for accelerating growth in children without GH deficiency, but medical, ethical, cost-benefit and social objections have been raised.

In *adult GH deficient* patients, rHGH 150–300 µg/day s.c. adjusted later according to response increases lean body mass, decreases body fat, improves energy and mentation and may reudce excess morbidity and mortality, but stature is unaffected. Benefits of rHGH therapy in GH deficient adults are now well recognized. Unlimited availability of recombinant GH has provided opportunity for its trial in *catabolic states* like severe burns, bedridden patients, chronic renal failure, osteoporosis, etc. It is now approved for *AIDS-related wasting*: higher dose (0.05–0.1 mg/kg/day) is needed. However, it should not be given to postoperative, trauma, cancer and other critically ill patients. Somatropin is also being promoted for ageing, but benefits are uncertain. Its abuse by athletes is banned, and it is one of the drugs included in 'dope testing'.

Somatropin: NORDITROPIN 5, 10, 15 mg inj, HUMATROPE 6 mg, 12 mg cartridges, 1.33 and 5.33 mg vials.

Adverse effects Somatropin has low immunogenicity; allergic reactions or resistance to treatment are not a problem. Pain at injection site, lipodystrophy, glucose intolerance, hypothyroidism (due to unmasking of TSH deficiency), salt and water retention, hand stiffness, myalgia, headache are the possible adverse effects. Rise in intracranial tension occurs in few cases.

GH Inhibitors

Somatostatin

This 14 amino acid peptide inhibits the secretion of GH, prolactin, and TSH by pituitary; insulin and glucagon by pancreas, and of almost all gastrointestinal secretions including that of gastrin and HCl. The g.i. action produces steatorrhoea, diarrhoea, hypochlorhydria, dyspepsia and nausea as side effect. Somatostatin constricts splanchnic, hepatic and renal blood vessels. The decreased g.i. mucosal blood flow can be utilized for controlling bleeding esophageal varices and bleeding peptic ulcer, but octreotide is preffered now due to longer duration of action. Its antisecretory action is beneficial in pancreatic, biliary or intestinal fistulae; can also be used to reduce complications after pancreatic surgery. It also has adjuvant value in diabetic ketoacidosis (by inhibiting glucagon and GH secretion).

Use of somatostatin in acromegaly is limited by its short duration of action (t½ 2–3 min), lack of specificity for inhibiting only GH secretion and GH rebound on discontinuation. Surgical removal of pituitary adenomas is the preferred treatment modality, but somatostatin analogues are being increasingly used.

Dose: (for upper g.i.bleeding) 250 µg slow i.v. injection over 3 min followed by 3 mg i.v. infusion over 12 hours.

STILMEN, SOMATOSAN, SOMASTAT 250 µg and 3 mg amps.

Octreotide This synthetic octapeptide surrogate of somatostatin is 40 times more potent in suppressing GH secretion and longer acting ($t_{½}$ ~90 min), but only a weak inhibitor of insulin secretion. It is preferred over somatostatin for acromegaly and secretory diarrhoeas associated with carcinoid, AIDS, cancer chemotherapy or diabetes. Control of diarrhoea is due to suppression of hormones which enhance intestinal mucosal secretion.

Dose: Initially 50–100 µg s.c. twice daily, increased upto 200 µg TDS; for acromegaly maintain with 10-30 mg i.m. of microsphere formulation every 4 weeks.

Adverse effects are abdominal pain, nausea, steatorrhoea, diarrhoea, and gall stones (due to biliary stasis).

Octreotide injected i.v. (100 µg followed by 25–50 µg/hr) reduces hepatic blood flow and helps stop esophageal variceal bleeding.

SANDOSTATIN, OCTRIDE 50 µg, 100 µg in 1 ml amps.
SANDOSTATIN LAR (microsphere formulation) 20 mg/5 ml inj.

Lanreotide Another long-acting analogue of somatostatin, very similar in actions and specificity to octreotide, which on i.m. injection acts for 10–15 days. It is indicated for pharmacotherapy of acromegaly.

Pegvisomant This polyethylene glycol complexed mutant GH binds to the GH receptor but does not trigger signal transduction: acts as a GH antagonist. It is approved for treatment of acromegaly due to small pituitary adenomas.

PROLACTIN

It is a 199 amino acid, single chain peptide of MW 23000; quite similar chemically to GH. It was originally described as the hormone which causes secretion of milk from crop glands of pigeon and later found to be of considerable importance in human beings as well.

Physiological function Prolactin is the primary stimulus which in conjunction with estrogens, progesterone and several other hormones, causes growth and development of breast during pregnancy. It promotes proliferation of ductal as well as acinar cells in the breast and induces synthesis of milk proteins and lactose. After parturition, prolactin induces milk secretion, since the inhibitory influence of high estrogen and progesterone levels is withdrawn.

Prolactin suppresses hypothalamo-pituitary-gonadal axis by inhibiting GnRH release. Continued high level of prolactin during breastfeeding is responsible for lactational amenorrhoea, inhibition of ovulation and infertility for several months postpartum. Prolactin may affect immune response through action on T-lymphocytes.

A specific prolactin receptor is expressed on the surface of target cells, which is structurally and functionally analogous to GH receptor: action is exerted by transmembrane activation of JAK—cytoplasmic tyrosine protein kinases and STAT. Placental lactogen and GH also bind to prolactin receptor and exert similar effects, but prolactin does not bind to GH receptor.

Regulation of secretion Prolactin is under predominant inhibitory control of hypothalamus through PRIH which is dopamine that acts on pituitary lactotrope D2 receptor. Dopaminergic agonists (DA, bromocriptine, cabergoline) decrease plasma prolactin levels, while dopaminergic antagonists (chlorpromazine, haloperidol, metoclopramide) and DA depleter (reserpine) cause hyperprolactinemia.

Though TRH, prolactin releasing peptide and VIP can stimulate prolactin secretion, no specific prolactin releasing factor has been identified. Endogenous opioid peptides may also be involved in regulating prolactin secretion, but no feedback regulation by any peripheral hormone is known. Prolactin levels in blood are low in childhood, increase in girls at puberty and are higher in adult females than in males. A progressive increase occurs during pregnancy, peaking at term. Subsequently, high prolactin secretion is maintained by suckling: it falls if breast feeding is discontinued. Stress, exertion and hypoglycaemia also stimulate prolactin release.

Physio-pathological involvement Hyperprolactinaemia is responsible for the galactorrhoea–amenorrhoea–infertility syndrome in women. In males it causes loss of libido and depressed fertility. The causes of hyperprolactinaemia are:

(i) Disorders of hypothalamus removing the inhibitory control over pituitary.
(ii) Antidopaminergic and DA depleting drugs—these are a frequent cause now.
(iii) Prolactin secreting tumours—these may be microprolactinomas or macroprolactinomas.
(iv) Hypothyroidism with high TRH levels—also increases prolactin secretion.

Use There are no clinical indications for prolactin.

Prolactin inhibitors

Bromocriptine

This synthetic ergot derivative 2-bromo-α-ergocryptine is a potent dopamine agonist; most of its actions are based on this property. It has greater action on D2 receptors, while at certain dopamine sites in the brain it acts as a partial agonist or antagonist of D1 receptor. It is also a weak α adrenergic blocker but not an oxytocic.

Actions

1. Decreases prolactin release from pituitary by activating dopaminergic receptors on lactotrope cells: is a strong antigalactopoietic.
2. Increases GH release in normal individuals, but decreases the same from pituitary tumours that cause acromegaly.
3. Has levodopa like actions in CNS—anti-parkinsonian and behavioral effects.
4. Produces nausea and vomiting by stimulating dopaminergic receptors in the CTZ.
5. Hypotension—due to central suppression of postural reflexes and weak peripheral a adrenergic blockade.
6. Decreases gastrointestinal motility.

Pharmacokinetics Only 1/3 of an oral dose of bromocriptine is absorbed; bioavailability is further lowered by high first pass metabolism in liver. Even then, it has higher oral: parenteral activity ratio than ergotamine. Metabolites are excreted mainly in bile. Its plasma t½ is 3–6 hours.
PROCTINAL, PARLODEL, SICRIPTIN, BROMOGEN 1.25 mg, 2.5 mg tabs.

Uses Bromocriptine should always be started at a low dose, 1.25 mg BD and then gradually increased till response occurs otherwise side effects become limiting.

1. *Hyperprolactinemia* due to microprolactinomas causing galactorrhoea, amenorrhoea and infertility in women; gynaecomastia, impotence and sterility in men. Bromocriptine and cabergoline are the first line drug for most cases. Relatively lower doses (bromocriptine 2.5–10 mg/day or cabergoline 0.25–1.0 mg twice weekly) are effective. Response occurs in a few weeks and serum prolactin levels fall to the normal range; many women conceive. Bromocriptine should be stopped when pregnancy occurs, though no teratogenic effect is reported. Most (60–75%) tumours show regression during therapy and neurological symptoms (visual field defects, etc.) due to pressure on optic chiasma ease. However, response is maintained only till the drug is given—recurrences occur in many, but not all patients.

2. *Acromegaly* due to small pituitary tumours and inoperable cases. Relatively higher doses are required (5–20 mg/day) and it is less effective than octreotide/lanreotide. Oral administration and lower cost are the advantages..

3. *Parkinsonism* Bromocriptine, if used alone, is effective only at high doses (20–80 mg/day) which produce marked side effects. However, response is similar to that of levodopa. It is now recommended in low dose only, as an adjunct to levodopa in patients not adequately benefited and in those showing marked 'on-off' effect.

4. *Diabetes mellitus (DM)* A new use of bromocriptine based on its dopamine D2 agonistic action in the hypothalamus has been found in type 2 DM, and it has been approved by US-FDA as an adjunctive drug.

5. *Hepatic coma:* Bromocriptine may cause arousal.

6. Bromocriptine suppresses lactation and breast engorgement in case of neonatal death, but is not recommended due to unfavourable risk: benefit ratio.

Side effects: Side effects are frequent and dose related.

Early: Nausea, vomiting, constipation, nasal blockage. Postural hypotension may be marked at initiation of therapy—syncope may occur if starting dose is high. Hypotension is more likely in patients taking antihypertensives.

Late: Behavioral alterations, mental confusion, hallucinations, psychosis—are more prominent than with levodopa.
Abnormal movements, livedo reticularis.

Cabergoline

It is a newer D2 agonist; more potent; more D2 selective and longer acting (t½ > 60 hours) than

bromocriptine; needs to be given only twice weekly. Incidence of nausea and vomiting is also lower; some patients not tolerating or not responding to bromocriptine have been successfully treated with cabergoline. It is preferred for treatment of hyperprolactinemia and acromegaly. Some patients who achieve total regression of prolactinoma and normalization of prolactin levels can stop cabergoline without recurrence.

Dose: Start with 0.25 mg twice weekly; if needed increase after every 4–8 weeks to max. of 1 mg twice weekly.

CABERLIN 0.5 mg tab, CAMFORTE 0.5, 1 mg tabs.

GONADOTROPINS (Gns)

The anterior pituitary secretes two Gns *viz.* FSH and LH. Both are glycoproteins containing 23–28% sugar and consist of two peptide chains. The α-chain (92AA) is common between FSH and LH, but their β-chains are different: FSH (111 AA), LH (121 AA). Paradoxically the MW of FSH (~33KD) is greater than that of LH (~30 KD), because of the sugar moieties.

Physiological functions FSH and LH act in concert to promote gametogenesis and secretion of gonadal hormones.

FSH In the female it induces follicular growth, development of ovum and secretion of estrogens. In the male it supports spermatogenesis and has a trophic influence on seminiferous tubules. Ovarian and testicular atrophy occurs in the absence of FSH.

LH It induces preovulatory swelling of the ripe graafian follicle and triggers ovulation followed by luteinization of the ruptured follicle and sustains corpus luteum till the next menstrual cycle. It is also probably responsible for atresia of the remaining follicles. Progesterone secretion occurs only under the influence of LH. In the male LH stimulates testosterone secretion by the interstitial cells and is designated interstitial cell stimulating hormone (ICSH).

Distinct LH and FSH receptors are expressed on the target cells. Both are G protein coupled receptors which on activation increase cAMP production. This in turn stimulates gametogenesis and conversion of cholesterol to pregnenolone—the first step in progesterone, testosterone and estrogen synthesis. In the testes FSH receptor is expressed on seminiferous (Sertoli) cells while LH receptor is expressed on interstitial (Leydig) cells. In the ovaries FSH receptors are present only on granulosa cells, while LH receptors are widely distributed on interstitial cells, theca cells, preovulatory granulosa cells and luteal cells.

Regulation of secretion A single releasing factor (decapeptide designated GnRH) is produced by the hypothalamus which stimulates synthesis and release of both FSH and LH from pituitary. It is, therefore, also referred to as FSH/LH-RH or simply LHRH or gonadorelin. It has been difficult to explain how hypothalamus achieves a divergent pattern of FSH and LH secretion in menstruating women through a single releasing hormone. Since GnRH is secreted in pulses and the frequency as well as amplitude of the pulses differs during follicular (high frequency, low amplitude) and luteal (lower frequency, higher amplitude) phases, it is considered that frequency and amplitude of GnRH pulses determines whether FSH or LH or both will be secreted, as well as the amount of each. Further, the feedback regulation of FSH and LH may be different. In general, feedback inhibition of LH is more marked than that of FSH. In females estradiol and progesterone inhibit both FSH and LH secretion mainly through hypothalamus, but also by direct action on pituitary. However, the marked and sustained preovulatory rise in estrogen level paradoxically stimulates LH and FSH secretion. In addition there are other regulatory substances, e.g. *Inhibin*—a peptide from ovaries and testes, selectively inhibits FSH release, but not LH release. *Dopamine* inhibits only LH release. Testosterone is weaker than estrogens in inhibiting Gn secretion, but has effect on both FSH and LH. GnRH acts on gonadotropes through a G-protein coupled receptor which acts by increasing intracellular Ca^{2+} through PIP_2 hydrolysis.

The Gn secretion increases at puberty and is higher in women than in men. In men, the levels of FSH and LH remain practically constant (LH > FSH) while in menstruating women they fluctuate cyclically. During the follicular phase, moderate levels of FSH and low levels of LH prevail. There is a midcycle surge of both, but more of LH, just before ovulation, followed by progressive fall during the luteal phase. Gn levels are high in menopausal women due to loss of feedback inhibition by sex steroids and inhibin.

Pathological involvement Disturbances of Gn secretion from pituitary may be responsible for delayed puberty or precocious puberty both in girls and boys.

Inadequate Gn secretion results in amenorrhoea and sterility in women; oligozoospermia, impotence and infertility in men. Excess production of Gn in adult women causes polycystic ovaries.

Preparations

All earlier gonadotropin preparations were administered by i.m. route. The newer more purified preparations can be

given s.c. They are partly metabolized, but mainly excreted unchanged in urine: t½ 2–6 hours.

1. *Menotropins (FSH + LH):* is a preparation obtained from urine of menopausal women:
PREGNORM, PERGONAL, GYNOGEN 75/150; 75 IU FSH + 75 IU LH activity per amp, also 150 IU FSH + 150 IU LH per amp.

2. *Urofollitropin or Menotropin (pure FSH):* METRODIN, FOLGEST, FOLICULIN, PUREGON 75 IU and 150 IU per amp. This preparation has been preferred over the combined FSH + LH preparation for induction of ovulation in women with polycystic ovarian disease: these patients have elevated LH/FSH ratio; use of FSH alone is considered advantageous. It is also claimed to improve chances of obtaining good quality ova for *in vitro* fertilization.

3. *Human chorionic gonadotropin (HCG):* is derived from urine of pregnant women.
CORION, PROFASI, PUBERGEN 1000 IU, 2000 IU, 5000 IU, 10,000 IU, all as dry powder with separate solvent for injection.
The foetal placenta secretes HCG which is absorbed in maternal circulation and maintains corpus luteum of pregnancy. It is a glycoprotein with 33% sugar and 237 amino acids in two chains, MW 38000. It is excreted in urine by the mother from which it is commercially obtained. HCG binds to LH receptor with equal avidity; action of HCG is indistinguishable from that of LH.

Recombinant human FSH (rFSH: *Follitropin* α and *follitropin* β) and recombinant human LH (rLH: *Lutropin*) as well as recombinant HCG (rHCG: Choriogonadotropin α) have become available. These are more purified and have vertually replaced the urine derived preparations in the developed countries. They are more expensive.

Recombinant human LH (rhLH) is marketed as LUVERIS 75 IU inj.; indications and use is similar to HCG.

Uses

1. *Amenorrhoea and infertility* When it is due to deficient production of Gns by pituitary. Gns are generally tried when attempts to induce ovulation with clomiphene have failed or when nonovulation is due to polycystic ovaries. The procedure is to give 1 injection of menotropins (75 IU FSH + 75 IU LH or 75 IU pure FSH)) i.m. daily for 10 days followed the next day by 10,000 IU of HCG. Ovulation occurs within the next 24–48 hours in upto 75% cases and the woman may conceive. However, rates of abortion and multiple pregnancy are high, but not of teratogenesis.

To improve predictability of time of ovulation (controlled ovarian hyperstimulation) most experts now concurrently suppress endogenous FSH/LH secretion either by continuous pretreatment with a superactive GnRH agonist or by a GnRH antagonist.

2. *Hypogonadotrophic hypogonadism in males* manifesting as delayed puberty or defective spermatogenesis → oligozoospermia, male sterility. Generally, sexual maturation is induced by androgens and therapy with HCG is started when fertility is desired. Start with 1000–4000 IU of HCG i.m. 2–3 times a week (to stimulate testosterone secretion), add FSH 75 IU + LH 75 IU after 3–4 months (to stimulate spermatogenesis) and reduce dose of HCG; continue treatment for 6–12 months for optimum results, which nevertheless are not always impressive.

3. *Cryptorchidism* Since undescended testes can cause infertility and predispose to testicular cancer, medical/surgical treatment is imperative. Descent of testes can be induced by androgens whose production is stimulated by LH. Treatment with HCG can be tried at the earliest after the age of 1 year, preferably before 2 years if there is no anatomical obstruction; 1000–2000 IU is given i.m. 2–3 times a week till the testes descend. If 2–6 week treatment does not induce descent, surgery should be performed.

4. *To aid in vitro fertilization* Menotropins (FSH + LH or pure FSH) have been used to induce simultaneous maturation of several ova and to precisely time ovulation so as to facilitate their harvesting for *in vitro* fertilization.

Adverse effects and precautions

Ovarian hyperstimulation—polycystic ovary, pain in lower abdomen and even ovarian bleeding and shock can occur in females.
Precocious puberty is a risk when given to children.
Allergic reactions have occurred and skin tests are advised. Hormone dependent malignancies (prostate, breast) must be excluded.
Other side effects are edema, headache, mood changes.

GONADOTROPIN RELEASING HORMONE (GnRH): GONADORELIN

Synthetic GnRH injected i.v. (100 µg) induces prompt release of LH and FSH followed by elevation of gonadal steroid levels. It has a short plasma t½ (4–8 min) due to rapid enzymatic degradation; has been used for testing pituitary-gonadal axis in male as well as female hypogonadism.

Since only pulsatile exposure to GnRH induces FSH/LH secretion, while continuous exposure desensitizes pituitary gonadotropes resulting in loss of Gn release, therapy with GnRH or its analogues is not useful in the treatment of hypogonadism.

Superactive / long-acting GnRH agonists

Many analogues of GnRH, e.g. Goserelin, Leuprolide, Nafarelin, Triptorelin, have been developed which are 15-150 times more potent than natural GnRH and longer acting (t½ 2–6 hours) because of high affinity for GnRH receptor and resistance to enzymatic hydrolysis. Because physiological release of GnRH is in pulses, whereas these agonists act continuously; they only initially increase Gn secretion. After 1–2 weeks they cause desensitization and down regulation of GnRH receptors → inhibition of FSH and LH secretion → suppression of gonadal function. Spermatogenesis or ovulation cease and testosterone or estradiol levels fall to castration levels. Recovery occurs within 2 months of stopping treatment.

The superactive GnRH agonists are used as nasal spray or injected s.c. Long-acting preparations for once a month s.c. injection have been produced (triptorelin, goserelin depot). The resulting reversible pharmacological oophorectomy/orchidectomy is being used in precocious puberty, prostatic carcinoma, endometriosis, premenopausal breast cancer, uterine leiomyoma, polycystic ovarian disease and to assist induced ovulation. They also have potential to be used as contraceptive for both males and females.

Nafarelin This long-acting GnRH agonist is 150 times more potent than native GnRH. It is used as intranasal spray from which bioavailability is only 4–5%.

NASAREL 2 mg/ml soln for nasal spray; 200 µg per actuation.

Down regulation of pituitary GnRH receptors occurs in10 days but peak inhibition of Gn release occurs at one month. It is broken down in the body to shorter peptide segments; plasma t½ is 2–3 hours. Uses are:

Assisted reproduction: Endogenous LH surge needs to be suppressed when controlled ovarian hyperstimulation is attempted by exogenous FSH and LH injection, so that precisely timed mature oocytes can be harvested. This is achieved by 400 µg BD intranasal nafarelin, reduced to 200 µg BD when menstrual bleeding occurs.

Uterine fibroids: Nafarelin 200 µg BD intranasal for 3–6 months can reduce the size of leiomyoma and afford symptomatic relief.

Endometriosis: 200 µg in alternate nostril BD for upto 6 months. As effective as danazol, but second course cannot be given due to risk of osteoporosis.

Central precocious puberty: 800 µg BD by nasal spray; breast and genital development is arrested in girls and boys. The effect is reversible; pubertal changes resume when therapy is discontinued.

Adverse effects: Hot flashes, loss of libido, vaginal dryness, osteoporosis, emotional lability.

Goserelin Another long-acting GnRH agonist available as a depot s.c./i.m. injection to be used both for endogenous Gn suppression before ovulation induction, as well as for endometriosis, carcinoma prostate, etc. To achieve pituitary desensitization before ovulation induction with exogenous Gns: 3.6 mg of the depot injection is given once in the anterior abdominal wall 1–3 weeks earlier.

For endometriosis and carcinoma prostate 3.6 mg is injected in the same way every 4 weeks or 10.8 mg is injected every 3 months. An androgen antagonist (bicalutamide) is given concurrently for 3–4 weeks when goserelin is used for carcinoma prostate.

ZOLADEX 3.6 mg prefilled syringe, ZOLDEX L-A 10.8 mg vial depot injection.

Triptorelin: This long acting GnRH agonist is formulated as a regular release daily s.c. injection for short term indications, such as female infertility, and as a depot i.m. monthly injection for long-term Gn suppression in the treatment of carcinoma prostate, endometriosis, precocious puberty and uterine leiomyoma. For prostate cancer, it is combined with an androgen antagonist flutamide or bicalutamide to prevent the initial flare up of the tumour that occurs due to increase in Gn secretion for the first 1–2 weeks.

Continuous treatment with any GnRH agonist is not advised beyond 6 months due to risk of osteoporosis and other complications.

Fibroids, endometriosis, carcinoma prostate: 3.75–7.5 mg i.m. every 4 weeks.
Precocious puberty: 50 µg/kg i.m. of depot inj. every 4 weeks.
Assisted reproduction: 0.1 mg s.c. daily for 10 days from 2nd day of cycle.
DECAPEPTYL DAILY 0.1 mg inj., DECAPEPTYL DEPOT 3.75 mg inj.

Leuprolide This long acting GnRH agonist is injected s.c./i.m. daily or as a depot injection once a month for palliation of carcinoma prostate alongwith an androgen antagonist, as well as for other conditions needing long term Gn suppression.
LUPRIDE 1 mg inj., 3.75 mg depot inj., PROGTASE 1 mg/ml inj.

GnRH antagonists Some more extensively substituted GnRH analogues act as GnRH receptor antagonists. They inhibit Gn secretion without causing initial stimulation. The early GnRH antagonists had the limitation of producing reactions due to histamine release. Later agents like *ganirelix* and *cetrorelix* have low histamine releasing potential and are being clinically used as s.c. inj. in specialized centres for inhibiting LH surges during controlled ovarian stimulation in women undergoing *in vitro* fertilization. Their advantages over long-acting GnRH agonists include:

- They produce quick Gn suppression by competitive antagonism, need to be started only from 6th day of ovarian hyperstimulation.
- They carry a lower risk of ovarian hyperstimulation syndrome.
- They achieve more complete suppression of endogenous Gn secretion.

However, pregnancy rates are similar or may even be lower.

THYROID STIMULATING HORMONE (TSH, THYROTROPIN)

It is a 210 amino acid, two chain glycoprotein (22% sugar), MW 30000.

Physiological function TSH stimulates thyroid to synthesize and secrete thyroxine (T_4) and triiodothyronine (T_3). Its actions are:

- Induces hyperplasia and hypertrophy of thyroid follicles and increases blood supply to the gland.
- Promotes trapping of iodide into thyroid by increasing Na^+: Iodide symporter (NIS).
- Promotes organification of trapped iodine and its incorporation into T_3 and T_4 by increasing peroxidase activity.
- Enhances endocytotic uptake of thyroid colloid by the follicular cells and proteolysis of thyroglobulin to release more of T_3 and T_4. This action starts within minutes of TSH administration.

The TSH receptor present on thyroid cells is a GPCR which utilizes the adenylyl cyclase-cAMP transducer mechanism (by coupling to Gs protein) to produce its effects. In human thyroid cells high concentration of TSH also induces PIP_2 hydrolysis by the linking of TSH receptor to Gq protein. The resulting increase in cytosolic Ca^{2+} and protein kinase C activation may also mediate TSH action, particularly generation of H_2O_2 needed for oxidation of iodide and iodination of tyrosil residues.

Regulation of secretion Synthesis and release of TSH by pituitary is controlled by hypothalamus primarily through TRH, while somatostatin inhibits TSH secretion. Dopamine also reduces TSH production induced by TRH. The TRH receptor on pituitary thyrotrope cells is a GPCR which is linked to Gq protein and activates PLC–IP_3/DAG–cytosolic Ca^{2+} pathway to enhance TSH synthesis and release. The negative feedback for inhibiting TSH secretion is provided by the thyroid hormones which act primarily at the level of the pituitary, but also in the hypothalamus. T_3 has been shown to reduce TRH receptors on the thyrotropes.

Pathological involvement Only few cases of hypo- or hyperthyroidism are due to inappropriate TSH secretion. In majority of cases of myxoedema TSH levels are markedly elevated because of deficient feedback inhibition. Graves' disease is due to an immunoglobulin of the IgG class which attaches to the thyroid cells and stimulates them in the same way as TSH. Consequently, TSH levels are low. Contrary to earlier belief, TSH is not responsible for exophthalmos seen in Graves' disease because TSH levels are low.

Use Thyrotropin has no therapeutic use. Thyroxine is the drug of choice even when hypothyroidism is due to TSH deficiency. The diagnostic application is to differentiate myxoedema due to pituitary dysfunction from primary thyroid disease.

ADRENOCORTICOTROPIC HORMONE (ACTH, CORTICOTROPIN)

It is a 39 amino acid single chain peptide, MW 4500, derived from a larger peptide *pro-opio melanocortin* (MW 30,000) which also gives rise to endorphins, two lipotropins and two MSHs.

Physiological function ACTH promotes steroidogenesis in adrenal cortex by stimulating cAMP formation in cortical cells (through specific cell surface GPCRs) → rapidly increases the

availability of cholesterol for conversion to pregnenolone which is the rate limiting step in the production of gluco, mineralo and weakly androgenic steroids. Induction of steroidogenic enzymes occurs after a delay resulting in 2nd phase ACTH action. The stores of adrenal steroids are very limited and rate of synthesis primarily governs the rate of release. ACTH also exerts trophic influence on adrenal cortex (again through cAMP): high doses cause hypertrophy and hyperplasia. Lack of ACTH results in adrenal atrophy. However, zona glomerulosa is little affected because angiotensin II also exerts trophic influence on this layer and sustains aldosterone secretion.

Regulation of secretion Hypothalamus regulates ACTH release from pituitary through corticotropin-releasing hormone (CRH). The CRH receptor on corticotropes is also a GPCR which increases ACTH synthesis as well as release by raising cytosolic cAMP. Secretion of ACTH has a circadian rhythm. Peak plasma levels occur in the early morning, decrease during day and are lowest at midnight. Corticosteroids exert inhibitory feedback influence on ACTH production by acting directly on the pituitary as well as indirectly through hypothalamus.

A variety of stressful stimuli, e.g. trauma, surgery, severe pain, anxiety, fear, blood loss, exposure to cold, etc. generate neural impulses which converge on median eminence to cause elaboration of CRH. The feedback inhibition appears to be overpowered during stress—rise in ACTH secretion continues despite high plasma level of cortisol induced by it. Arginine vasopressin (AVP) enhances the action of CRH on corticotropes and augments ACTH release. AVP release and augmentation of ACTH action appears to be important during stress.

Pathological involvement Excess production of ACTH from basophil pituitary tumours is responsible for some cases of Cushing's syndrome. Hypocorticism occurs in pituitary insufficiency due to low ACTH production. Iatrogenic suppression of ACTH secretion and pituitary adrenal axis is the most common form of abnormality encountered currently due to the use of pharmacological doses of glucocorticoids in nonendocrine diseases.

Use ACTH is used primarily for the diagnosis of disorders of pituitary adrenal axis. Injected i.v. 25 IU causes increase in plasma cortisol if the adrenals are functional. Direct assay of plasma ACTH level is now preferred.

For therapeutic purposes, ACTH does not offer any advantage over corticosteroids and is more inconvenient, expensive as well as less predictable.

Chapter 18 Thyroid Hormones and Thyroid Inhibitors

THYROID HORMONE

The thyroid gland secretes 3 hormones—thyroxine (T_4), triiodothyronine (T_3) and calcitonin. The former two are produced by thyroid follicles, have similar biological activity and the term 'thyroid hormone' is restricted to these only. *Calcitonin* produced by interfollicular 'C' cells is chemically and biologically entirely different. It is considered along with parathormone, (Ch. 24) with which it regulates calcium metabolism.

The physiological significance of thyroid gland was recognized only after Graves and Basedow (1835, 1840) associated the clinical features of the 'Graves' disease' with swelling of thyroid gland and Gull (1874) correlated myxoedema with its atrophy. Kendall (1915) obtained crystalline thyroxine and postulated its chemical formula which was confirmed in 1926. Thyroxine was the first hormone to be synthesized in the laboratory. Since, T_4 could not account for all the biological activity of thyroid extract, search was made and more potent T_3 was discovered in 1952.

CHEMISTRY AND SYNTHESIS

Both T_4 and T_3 are iodine containing derivatives of *thyronine* which is a condensation product of two molecules of the amino acid *tyrosine*. *Thyroxine*; is 3, 5, 3′, 5′–tetraiodothyronine while T_3 is 3, 5, 3′ triiodothyronine.

The thyroid hormones are synthesized and stored in the thyroid follicles as part of *thyroglobulin* molecule—which is a glycoprotein synthesized by thyroid cells, MW 660 KDa, contains 10% sugar. The synthesis, storage and release of T_4 and T_3 is summarized in Fig. 18.1 and involves the following processes.

1. *Iodide uptake* The total body content of I_2, obtained from food and water, is 30–50 mg, out of which about 1/5 is present in the thyroid. Concentration of iodide in blood is low (0.2–0.4 µg/dl) but thyroid cells have an active transport process Na^{+}: *iodide symporter (NIS)* to concentrate this anion; this trapping is stimulated by TSH to exceed a gradient of more than 100 fold by inducing and activating NIS. The I_2 content of thyroid gland somehow regulates the uptake mechanism: meagre store activating and large store inhibiting it. The iodide concentrating mechanism is not peculiar to thyroid. Skin, salivary glands, gastric mucosa, intestine, mammary glands and placenta also possess it, but uptake in these organs is not stimulated by TSH.

2. *Oxidation and iodination* Iodide trapped by follicular cells is carried across the apical membrane by another transporter termed '*pendrin*' and oxidized by the membrane bound thyroid peroxidase enzyme to iodinium (I^{+}) ions or hypoiodous acid (HOI) or enzyme-linked hypoiodate (E-OI) with the help of H_2O_2. These forms of iodine combine avidly with tyrosil residues of thyroglobulin, apparently without any enzymatic intervention, to form monoiodotyrosine (MIT) and diiodotyrosine (DIT) while these residues are still attached to the thyroglobulin chains.

3. *Coupling* Pairs of iodinated tyrosil residues couple together (Fig. 18.2) to form T_3 and T_4.

Normally much more T_4 than T_3 is formed, but during I_2 deficiency relatively more MIT is available and a greater proportion of T_3 is formed. Thus, more active hormone is generated with lesser amount of I_2.

Coupling is an oxidative reaction and is catalysed by the same thyroid peroxidase. Thyroglobulin is the most efficient protein, compared to other similar proteins, in supporting coupling by providing favourable spatial configuration to facilitate the reaction. Oxidation of iodide and coupling are both stimulated by TSH.

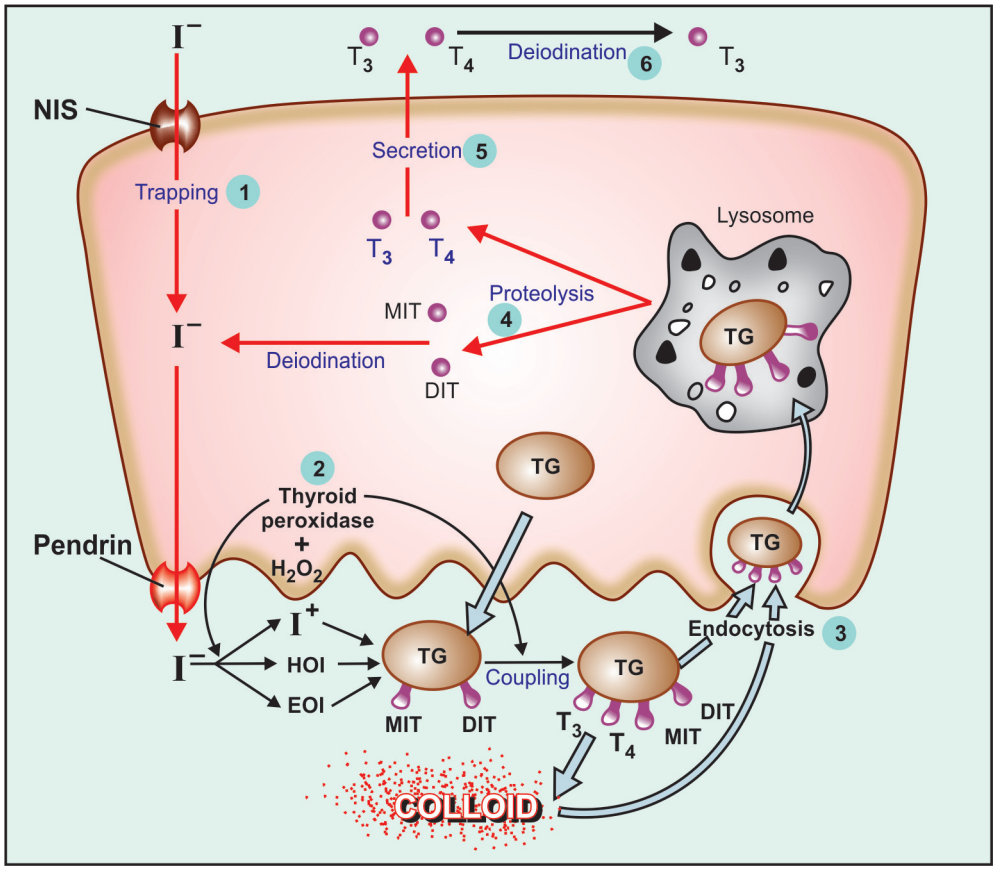


Fig. 18.1: Synthesis, storage and secretion of thyroid hormone
TG—Thyroglobulin; MIT—Monoiodotyrosine; DIT—Diiodotyrosine; T_3—Triiodothyronine; T_4—Thyroxine (Tetraiodothyronine); HOI—Hypoiodous acid; EOI—Enzyme linked hypoiodate; NIS—Na^+-iodide symporter; Thyroid-stimulating hormone (TSH) activates steps 1, 2, 3, 4, and 5; Ionic inhibitors block step 1; Excess iodide interferes with steps 1, 2, 3 and 5 with primary action on step 3 and 5; Propylthiouracil inhibits steps 2 and 6; Carbimazole inhibits step 2 only

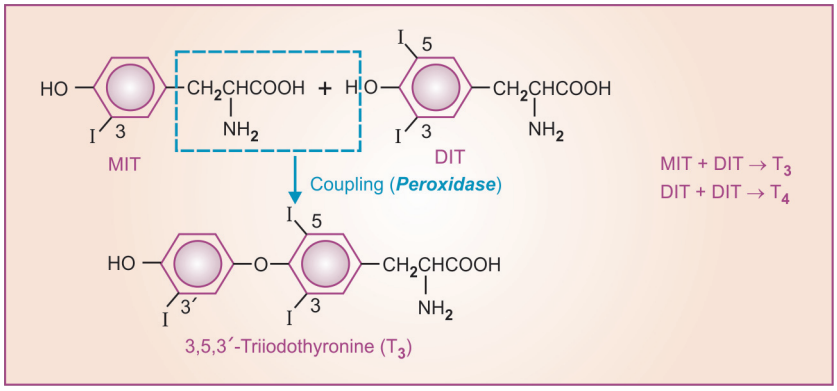


Fig. 18.2: Coupling of monoiodotyrosine (MIT) and diiodotyrosine (DIT) to produce triiodothyronine (T_3)

4. *Storage and release* Thyroglobulin containing iodinated tyrosil and thyronil residues is transported to the interior of the follicles and remains stored as thyroid colloid till it is taken back into the cells by endocytosis and broken down by lysosomal proteases. The T_4 and T_3 so released is secreted into circulation while MIT and DIT residues are deiodinated and the iodide released is reutilized. The uptake of colloid and proteolysis are stimulated by TSH: the quiscent gland has follicles distended with colloid and cells are flat or cubical, while the TSH stimulated gland has columnar cells and colloid virtually disappears. Normal human thyroid secretes 60–90 µg of T_4 and 10–30 µg of T_3 daily.

5. *Peripheral conversion of T_4 to T_3* Peripheral tissues, especially liver and kidney, convert T_4 to T_3. About 1/3 of T_4 secreted by thyroid undergoes this change and most of the T_3 in plasma is derived from liver. Target tissues take up T_3 from circulation for their metabolic need, except brain and pituitary which take up T_4 and convert it to T_3 within their own cells. Almost equal amounts of 3, 5, 3′ triiodothyronine (normal T_3 : active) and 3, 3′, 5′ triiodothyronine (reverse T_3 or rT_3: inactive) are produced in the periphery. The T_4 to T_3 conversion is carried out by the enzyme *iodothyronine deiodinase* which exists in 3 forms (D1, D2, D3). These forms differ in their organ and cellular localization as well as product formed. Whereas type 2 deiodinase (D2) generates T_3 and D3 generates rT_3, the D1 form generates both T_3 and rT_3. The antithyroid drug propylthiouracil (but not carbimazole) inhibits Type1 deiodinase and the antiarrhythmic amiodarone inhibits both D1 and D2 forms. Propranolol (high dose) and glucocorticoids also inhibit peripheral conversion of T_4 to T_3 (except in brain and in pituitary).

TRANSPORT, METABOLISM AND EXCRETION

Thyroid hormones are avidly bound to plasma proteins—only 0.03–0.08% of T_4 and 0.2–0.5% of T_3 are in the free form. Almost all protein bound iodine (PBI) in plasma is thyroid hormone, of which 90–95% is T_4 and the rest T_3. Binding occurs to 3 plasma proteins in the following decreasing order of affinity for T_4:

(i) Thyroxine binding globulin (TBG)
(ii) Thyroxine binding prealbumin (transthyretin)
(iii) Albumin

The normal concentration of PBI is 4–10 µg/dl; only 0.1–0.2 µg/dl of this is T_3, rest is T_4. During pregnancy thyroxine binding globulin is increased—PBI levels are elevated, but there is no effect on thyroid status because the concentration of free hormone remains unaltered.

Only the free hormone is available for action as well as for metabolism and excretion. Metabolic inactivation of T_4 and T_3 occurs by deiodination and glucuronide/sulfate conjugation of the hormones as well as that of their deiodinated products. Liver is the primary site (also salivary glands and kidneys). The conjugates are excreted in bile, of which a significant fraction is deconjugated in intestines and reabsorbed (enterohepatic circulation) to be finally excreted in urine.

Plasma t½ of T_4 is 6–7 days, while that of T_3 is 1–2 days. The half-lives are shortened in hyperthyroidism and prolonged in hypothyroidism due respectively to faster and slower metabolism.

REGULATION OF SECRETION

The secretion of hormones from the thyroid is controlled by anterior pituitary by the elaboration of thyrotropin, while TSH secretion itself is regulated by TRH produced in hypothalamus (*see* p. 243). Somatostatin elaborated by hypothalamus inhibits not only GH and prolactin, but also TSH secretion from pituitary. The relation between thyroid, anterior pituitary and hypothalamus is depicted in Fig. 18.3. The negative feedback by the thyroid hormones is exercised directly on the pituitary as well as through hypothalamus. The action of TRH on pituitary and that of TSH on thyroid cells is mediated by enhanced cAMP synthesis. High concentration of TSH also acts *via* IP_3/DAG–increased intracellular Ca^{2+} pathway in the thyroid cells.

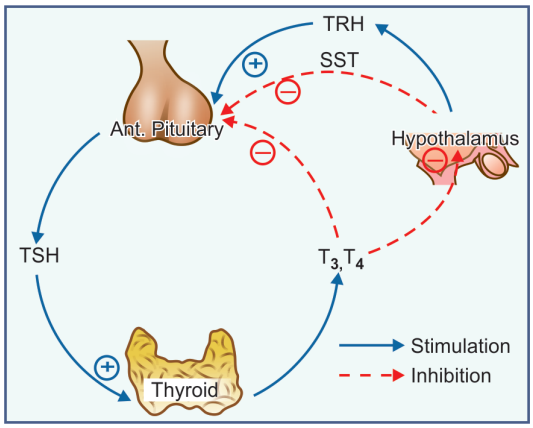


Fig. 18.3: Regulation of thyroid function
TSH—Thyroid stimulating hormone; TRH—Thyrotropin releasing hormone; T_3—Triiodothyronine; T_4—Thyroxine; SST—Somatostatin

ACTIONS

The actions of T_4 and T_3 are qualitatively similar and are nicely depicted in the features of hypo and hyperthyroidism. They affect the function of practically every body cell.

1. Growth and development T_4 and T_3 are essential for normal growth and development. The most remarkable action is metamorphosis of tadpole to frog: the tail is used-up to build lungs, limbs and other organs. The action cannot be broadly labelled as catabolic or anabolic. It is exerted through a critical control of protein synthesis in the translation of the genetic code. Congenital deficiency of T_4 and T_3 resulting in cretinism emphasizes their importance. The milestones of development are delayed and practically every organ and tissue of the body suffers. The greatest sufferer, however, is the nervous system. Retardation and nervous deficit is a consequence of paucity of axonal and dendritic ramification, synapse formation and impaired myelination. In adult hypothyroidism also, intelligence is impaired and movements are slow.

2. Intermediary metabolism Thyroid hormones have marked effect on lipid, carbohydrate and protein metabolism.

Lipid T_4 and T_3 indirectly enhance lipolysis by potentiating the action of catecholamines and other lipolytic hormones, probably by suppressing a phosphodiesterase → increased cAMP. As a result plasma free fatty acid levels are elevated. Lipogenesis is also stimulated. All phases of cholesterol metabolism are accelerated, but its conversion to bile acids dominates. Thus, hyperthyroidism is characterized by hypocholesterolemia. LDL levels in blood are reduced.

Carbohydrate Carbohydrate metabolism is also stimulated. Though utilization of sugar by tissues is increased (mainly secondary to increased BMR), glycogenolysis and gluconeogenesis in liver as well as faster absorption of glucose from intestines more than compensate it → hyperglycaemia and diabetic-like state with insulin resistance occur in hyperthyroidism.

Protein Synthesis of certain proteins is increased, but the overall effect of T_3 is catabolic—increased amounts of protein being used as energy source. Prolonged action results in negative nitrogen balance and tissue wasting. Weight loss is a feature of hyperthyroidism. T_3, T_4 in low concentrations inhibit mucoprotein synthesis which so characteristically accumulates in myxoedema.

3. Calorigenesis T_3 and T_4 increase BMR by stimulation of cellular metabolism and resetting of the energystat. This is important for maintaining body temperature. However, metabolic rate in brain, gonads, uterus, spleen and lymph nodes is not significantly affected. The mechanism of calorigenesis was believed to be uncoupling of oxidative phosphorylation: excess energy being released as heat. However, this occurs only at very high doses and is not involved in mediating the physiological actions of T_3, T_4. Dinitrophenol uncouples oxidative phosphorylation, but has no thyroid-like activity.

4. CVS T_3 and T_4 cause a hyperdynamic state of circulation which is partly secondary to increased peripheral demand and partly due to direct cardiac actions. Heart rate, contractility and

output are increased resulting in a fast, bounding pulse. T_3 and T_4 stimulate heart by direct action on contractile elements (increasing the myosin fraction having greater Ca^{2+} ATPase activity) and probably by up regulation of β adrenergic receptors. Atrial fibrillation and other irregularities are common in hyperthyroidism. Thyroid hormones can also precipitate CHF and angina. BP, specially systolic, is often raised. Myocardial O_2 consumption can be markedly reduced by induction of hypothyroidism.

5. Nervous system T_3, T_4 have profound functional effect on CNS. Mental retardation is the hallmark of cretinism; sluggishness and other behavioral features are seen in myxoedema. Hyperthyroid individuals are anxious, nervous, excitable, exhibit tremors and hyperreflexia.

6. Skeletal muscle Muscles are flabby and weak in myxoedema, while thyrotoxicosis produces increased muscle tone, tremor and weakness due to myopathy.

7. GIT Propulsive activity of gut is increased by T_3/T_4. Hypothyroid patients are often constipated, while diarrhoea is common in hyperthyroidism.

8. Kidney T_3 and T_4 do not cause diuresis in euthyroid individuals, but the rate of urine flow is often increased when myxoedematous patients are treated with it.

9. Haemopoiesis Hypothyroid patients suffer from some degree of anaemia which is restored only by T_4 treatment. Thus, T_4 appears to be facilitatory to erythropoiesis.

10. Reproduction Thyroid has an indirect effect on reproduction. Fertility is impaired in hypothyroidism and women suffer from oligomenorrhoea. Normal thyroid function is required for maintenance of pregnancy and lactation.

Mechanism of action

Both T_3 and T_4 penetrate cells by active transport and produce majority of their actions by combining with a nuclear thyroid hormone receptor (TR) which belongs to the steroid and retinoid superfamily of intracellular receptors.

Two TR isoform families (TRα and TRβ) have been identified. Both bind T_3 and function in similar manner, but their tissue distribution differs, which may account for quantitative differences in the sensitivity of different tissues to T_3.

In contrast to the steroid receptor, the TR resides in the nucleus even in the unliganded inactive state. It is bound to the *'thyroid hormone response element'* (TRE) in the enhancer region of the target genes along with corepressors (Fig. 18.4). This keeps gene transcription suppressed. When T_3 binds to the ligand-binding domain of TR, it heterodimerizes with retinoid X receptor (RXR) and undergoes a conformation change releasing the corepressor and binding the coactivator. This induces gene transcription → production of specific mRNA and a specific pattern of protein synthesis → various metabolic and anatomic effects. The expression of certain genes is repressed by T_3. In their case, the unliganded TR allows gene transcription, while binding of T_3 to TR halts the process.

Many of the effects, e.g. tachycardia, arrhythmias, raised BP, tremor, hyperglycaemia are mediated, at least partly, by sensitization of adrenergic receptors to catecholamines. Induction of adenylyl cyclase, proliferation of β adrenoceptors and a better coupling between these two has been demonstrated.

Apart from the nuclear T_3 receptor, other sites of thyroid hormone action have been described. It acts on cell membrane to enhance amino acid and glucose entry and on mitochondria to increase oxygen consumption. At these sites T_4 appears to be equipotent to T_3, while at the nuclear receptor T_4 has much lower affinity, and even when bound to the TR, T_4 does not promote gene transcription.

Relation between T_4 and T_3

- Thyroid secretes more T_4 than T_3, but in iodine deficient state this difference is reduced.
- T_4 is the major circulating hormone because it is 15 times more tightly bound to plasma proteins.
- T_3 is 5 times more potent than T_4 and acts faster. Peak effect of T_3 comes in 1–2 days while that of T_4 takes 6–8 days.

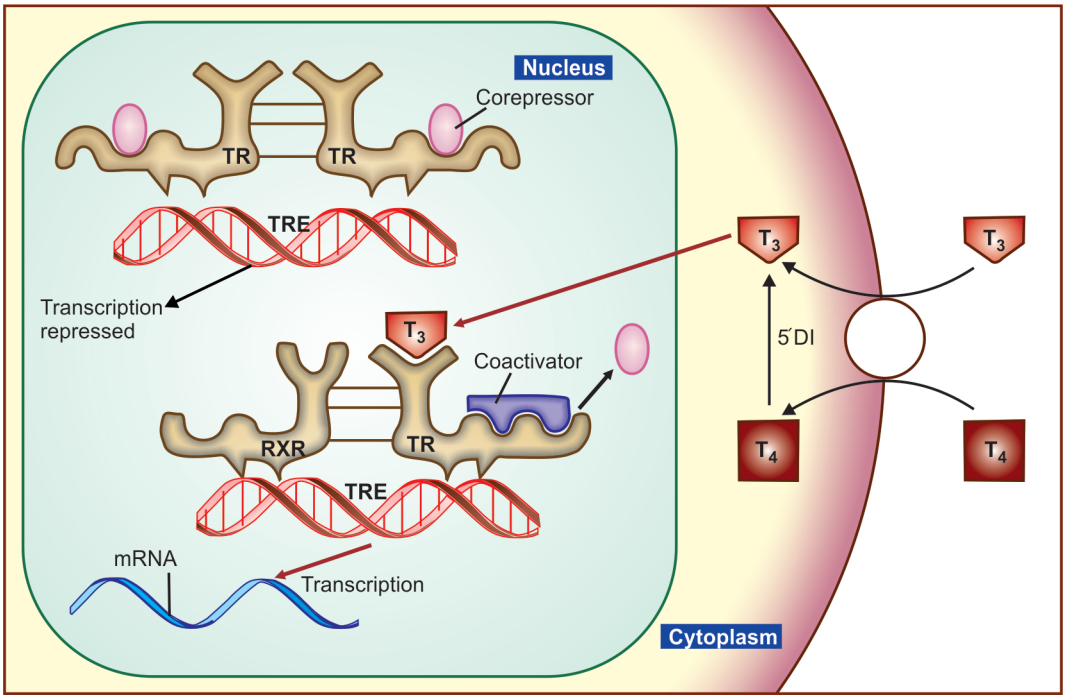


Fig. 18.4: Mechanism of action of thyroid hormone on nuclear thyroid hormone receptor (TR). T_3—Triiodothyronine; T_4—Thyroxine; TRE—Thyroid hormone response element; RXR—Retinoid X receptor; mRNA—Messenger ribonucleic acid; 5'DI—5'Deiodinase (*See* text for explanation)

- T_3 is more avidly bound to the nuclear receptor than T_4 and the T_4-receptor complex is unable to activate/derepress gene transcription.
- About 1/3 of T_4 is converted to T_3 in the thyroid cells, liver and kidney by type 1 deiodinase (D1) and released into circulation. In addition, T_3 is generated within the target cells (skeletal muscle, heart, brain, pituitary) by another type (D2) of deiodinase.

Thus, it may be cocluded that T_3 is the active hormone, while T_4 is mainly a transport form; functions as a prohormone of T_3. However, it may directly produce some nongenomic actions.

Preparations

l-thyroxine sod.: ELTROXIN 25 µg, 50 µg, 100 µg tabs, ROXIN 100 µg tab, THYRONORM 12.5 µg, 25 µg, 50 µg, 62.5 µg, 75 µg, 88 µg, 100 µg, 112 µg, 125 µg, 137 µg, 150 µg tabs, THYROX 25 µg, 50 µg, 75 µg, 100 µg tabs. An injectable preparation for i.v. use is available elsewhere.

Triiodothyronine (Liothyronine) is not freely available in India. It is occasionally used i.v. along with l-thyroxine in myxoedema coma.

Clinically, l-thyroxine is preferred for all indications over liothyronine because of more sustained and uniform action as well as lower risk of cardiac arrhythmias.

Pharmacokinetics and interactions

Oral bioavailability of l-thyroxine is ~ 75%, but severe hypothyroidism can reduce oral absorption. It should be administered in empty stomach to avoid interference by food. Sucralfate, iron, calcium and proton pump inhibitors also reduce l-thyroxine absorption. CYP3A4 inducers like rifampin, phenytoin and carbamazepine accelerate metabolism of T_4; dose of l-thyroxine may need enhancement.

USES

The most important use of thyroid hormone is for *replacement therapy* in deficiency states:

1. Cretinism It is due to failure of thyroid development or a defect in hormone synthesis (sporadic cretinism) or due to extreme iodine deficiency (endemic cretinism). It is usually detected during infancy or childhood; but screening of neonates is the best preventive strategy. Treatment with thyroxine (8–12 µg/kg) daily should be started as early as possible, because mental retardation that has already ensued is only partially reversible. Response is dramatic: physical growth and development are restored and further mental retardation is prevented.

2. Adult hypothyroidism (Myxoedema) This is one of the commonest endocrine disorders which develops as a consequence of autoimmune thyroiditis or thyroidectomy; It may accompany simple goiter if iodine deficiency is severe. Antibodies against thyroid peroxidase or thyroglobulin are responsible for majority of cases of adult hypothyroidism. Important drugs that can cause hypothyroidism are ^{131}I, iodides, lithium and amiodarone. Treatment with T_4 is most gratifying. It is often wise to start with a low dose—50 µg of l-thyroxine daily and increase every 2–3 weeks to an optimum of 100–200 µg/day (adjusted by clinical response and serum TSH levels). Further dose adjustments are made at 4–6 week intervals needed for reaching steady-state. Individualization of proper dose is critical, aiming at normalization of serum TSH levels. Increase in dose is mostly needed during pregnancy.

Subclinical hypothyroidism characterized by euthyroid status and normal free serum thyroxine (FT_4) level (≥ 9 pmol/L) but raised TSH level (>10 mU/L) should be treated with T_4. For TSH level between 6–10 mU/L, replacement therapy is optional. It is preferable if patient has other cardiovascular risk factors.

3. Myxoedema coma It is an emergency; characterized by progressive mental deterioration due to acute hypothyroidism: carries significant mortality. Rapid thyroid replacement is crucial. Though liothyronine (T_3) acts faster, its use is attended by higher risk of cardiac arrhythmias, angina, etc. Drug of choice is l-thyroxine (T_4) 200–500 µg i.v. followed by 100 µg i.v. OD till oral therapy can be instituted. Some authorities recommend adding low dose i.v. T_3 10 µg 8 hourly in younger patients with no arrhythmia or ischaemia. Alternatively oral T_4 500 µg loading dose followed by 100–300 µg daily may be used, but in severe hypothyroidism, oral absorption is delayed and inconsistent.

Other essential measures needed are—warming the patient, i.v. corticosteroids to cover attendant adrenal insufficiency, ventilatory and cardiovascular support, correction of hyponatraemia and hypoglycaemia.

4. Nontoxic goiter It may be endemic or sporadic. Endemic is due to iodine deficiency which may be accentuated by factors present in water (excess calcium), food or milk (goitrin, thiocyanates). A defect in hormone synthesis may be responsible for sporadic cases. In both types, deficient production of thyroid hormone leads to excess TSH → thyroid enlarges, more efficient trapping of iodide occurs and probably greater proportion of T_3 is synthesized → enough hormone to meet peripheral demands is produced so that the patient is clinically euthyroid. Thus, treatment with T_4 is in fact replacement therapy in this condition as well, despite no overt hypothyroidism. Full maintenance doses must be given. Most cases of recent diffuse enlargement of thyroid regress. Long-standing goiter with degenerative and fibrotic changes and nodular goiter regress little or not at all. Thyroxine therapy may be withdrawn after a year or so in some cases if adequate iodine intake is ensured. Others need life-long therapy.

Endemic goiter and cretinism due to iodine deficiency in pregnant mother is preventable by ensuring daily ingestion of 150–200 µg of iodine. This is best achieved by iodizing edible salt by adding iodate (preferred over iodide). In India iodization of table salt (100 µg iodine/g salt) is required under the National Programme, but recently mandatory iodization rule has been withdrawn.

5. Thyroid nodule Certain benign functioning nodules regress when TSH is suppressed by

T_4 therapy. Nonfunctional nodules and those nonresponsive to TSH (that are associated with low TSH levels) do not respond and should not be treated with levothyroxine. T_4 therapy should be stopped if the nodule does not decrease in size within 6 months, and when it stops regressing after the initial response.

6. Papillary carcinoma of thyroid This type of cancer is often responsive to TSH. In nonresectable cases, full doses of T_4 suppress endogenous TSH production and may induce temporary regression.

7. Empirical uses T_4 has been sometimes used in the following conditions without any rationale; response is unpredictable.

Refractory anaemias.
Mental depression
Menstrual disorders, infertility not corrected by usual treatment.
Chronic/non-healing ulcers.
Obstinate constipation.

Thyroxine is not to be used for obesity and as a hypocholesterolemic agent.

THYROID INHIBITORS

These are drugs used to lower the functional capacity of the hyperactive thyroid gland.

Thyrotoxicosis is due to excessive secretion of thyroid hormones. The two main causes are *Graves' disease* and *toxic nodular goiter*. Graves' disease is an autoimmune disorder: IgG class of antibodies to the TSH receptor are detected in blood. They bind to and stimulate thyroid cells, and produce other TSH like effects. Due to feedback inhibition, TSH levels are low. The accompanying exophthalmos is due to autoimmune inflammation of periorbital tissues.

Toxic nodular goiter, which produces thyroid hormone independent of TSH, mostly supervenes on old nontoxic goiters. It is more common in the elderly; ocular changes are generally absent.

CLASSIFICATION

1. *Inhibit hormone synthesis (Antithyroid drugs)*
   Propylthiouracil, Methimazole, Carbimazole.
2. *Inhibit iodide trapping (Ionic inhibitors)*
   Thiocyanates (–SCN), Perchlorates ($–ClO_4$), Nitrates ($–NO_3$).
3. *Inhibit hormone release*
   Iodine, Iodides of Na and K, Organic iodide.
4. *Destroy thyroid tissue*
   Radioactive iodine (^{131}I, ^{125}I, ^{123}I).

Compounds in groups 1 and 2 may be collectively called *goitrogens* because, if given in excess, they cause enlargement of thyroid by feedback release of TSH.

In addition, certain drugs used in high doses for prolonged periods cause hypothyroidism/goiter as a side effect:

- Lithium: inhibits thyroid hormone release.
- Amiodarone: inhibits peripheral conversion of T_4 to T_3; also interferes with thyroid hormone action.
- Sulfonamides, paraaminosalicylic acid: inhibit thyroglobulin iodination and coupling reaction.
- Phenobarbitone, phenytoin, carbamazepine, rifampin: induce metabolic degradation of T_4/T_3.

Goitrin—found in plants (cabbage, turnip, mustard, etc.), is the cause of goiter in cattle who feed on these plants. May contribute to endemic goiter in certain iodine deficient regions.

ANTITHYROID DRUGS (Thioamides)

By convention, only the hormone synthesis inhibitors are called antithyroid drugs, though this term has also been applied to all thyroid inhibitors.

Thiourea derivatives were found to produce goiter and hypothyroidism in rats in the 1940s. Open chain compounds were found to be toxic. Subsequently, methyl and propyl thiouracil and thioimidazole derivatives methimazole and carbimazole were found to be safe and effective.

Antithyroid drugs bind to the thyroid peroxidase and prevent oxidation of iodide/iodotyrosyl residues, thereby;

(i) Inhibit iodination of tyrosine residues in thyroglobulin
(ii) Inhibit coupling of iodotyrosine residues to form T_3 and T_4.

Action (ii) has been observed at lower concentration of antithyroid drugs than action (i). Thyroid colloid is depleted over time and blood levels of T_3/T_4 are progressively lowered.

TABLE 18.1 Differences between propylthiouracil and carbimazole

	Propylthiouracil	*Carbimazole*
1.	Dose to dose less potent	About 5 × more potent
2.	Highly plasma protein bound	Less bound
3.	Less transferred across placenta and in milk	Larger amounts cross to foetus and in milk
4.	Plasma t½ 1–2 hours	6–10 hours
5.	Single dose acts for 4–8 hours	12–24 hours
6.	No active metabolite	Produces active metabolite—methimazole
7.	Multiple (2–3) daily doses needed	Mostly single daily dose
8.	Inhibits peripheral conversion of T_4 to T_3	Does not inhibit T_4 to T_3 conversion

Thioamides do not interfere with trapping of iodide and do not modify the action of T_3 and T_4 on peripheral tissues or on pituitary. Goiter is not the result of potentiation of TSH action on thyroid, but is due to increased TSH release as a consequence of reduction in feedback inhibition. No goiter occurs if antithyroid drugs are given to hypophysectomised animals or if T_4 is given along with them. Antithyroid drugs do not affect release of T_3 and T_4—their effects are not apparent till thyroid is depleted of its hormone content.

Propylthiouracil also inhibits peripheral conversion of T_4 to T_3 by D1 type of 5'DI, but not by D2 type. This may partly contribute to its antithyroid effects. Methimazole and carbimazole do not have this action (Table 18.1) and may even antagonize that of propylthiouracil.

Pharmacokinetics All antithyroid drugs are quickly absorbed orally, widely distributed in the body, enter milk and cross placenta; are metabolized in liver and excreted in urine primarily as metabolites. All are concentrated in thyroid: intrathyroid t½ is longer: effect of a single dose lasts longer than would be expected from the plasma t½. Carbimazole acts largely by getting converted to methimazole in the body and is longer acting than propythiouracil.

Adverse effects Hypothyroidism and goiter can occur due to overtreatment, but is reversible on stopping the drug. It is indicated by enlargement of thyroid, and is due to excess TSH production. Goiter does not develop with appropriate doses which restore T_4 concentration to normal so that feedback TSH inhibition is maintained.

Important side effects are: g.i. intolerance, skin rashes and joint pain.

Loss or graying of hair, loss of taste, fever and liver damage are infrequent.

A rare but serious adverse effect is agranulocytosis (1 in 500 to 1000 cases); It is mostly reversible.

There is partial cross reactivity between propylthiouracil and carbimazole.

Preparations and dose

Propylthiouracil: 50–150 mg TDS followed by 25–50 mg BD–TDS for maintenance. PTU 50 mg tab.

Methimazole: 5–10 mg TDS initially, maintenance dose 5–15 mg daily in 1–2 divided doses.

Carbimazole: 5–15 mg TDS initially, maintenance dose 2.5–10 mg daily in 1–2 divided doses, NEO MERCAZOLE, THYROZOLE, ANTITHYROX 5 mg tab.

Carbimazole is more commonly used in India. Propylthiouracil (600–900 mg/day) may be preferred in thyroid storm for its inhibitory action on peripheral conversion of T_4 to more active T_3. It is also used in patients developing adverse effects with carbimazole.

Use Antithyroid drugs control thyrotoxicosis in both Graves' disease and toxic nodular goiter. Clinical improvement starts after 1–2 weeks or more (depending on hormone content of thyroid gland). Iodide loaded patients (who have received

iodide containing contrast media/cough mixtures, amiodarone) are less responsive. Maintenance doses are titrated on the basis of clinical status of the patient. The following strategies are adopted.

(i) *As definitive therapy* (a) Remission may occur in upto half of the patients of Graves' disease after 1–2 years of treatment: the drug can then be withdrawn. If symptoms recur—treatment is reinstituted. This is preferred in young patients with a short history of Graves' disease and a small goiter. (b) Remissions are rare in toxic nodular goiter: surgery (or ^{131}I) is preferred. However, in frail elderly patient with multinodular goiter who may be less responsive to ^{131}I, permanent maintenance therapy with antithyroid drugs can be employed.

(ii) *Preoperatively* Surgery in thyrotoxic patients is risky. Young patients with florid hyperthyroidism and substantial goiter are rendered euthyroid with carbimazole before performing subtotal thyroidectomy.

(iii) *Along with ^{131}I* Initial control with antithyroid drug—1 to 2 weeks gap—radioiodine dosing—resume antithyroid drug after 5–7 days and gradually withdraw over 3 months as the response to ^{131}I develops. This approach is preferred in older patients who are to be treated with ^{131}I, but require prompt control of severe hyperthyroidism. This will also prevent initial hyperthyroidism following ^{131}I due to release of stored T_4.

Advantages of antithyroid drugs over surgery/^{131}I are:

(a) No surgical risk, scar or chances of injury to parathyroid glands or recurrent laryngeal nerve.
(b) Hypothyroidism, if induced, is reversible.
(c) Can be used even in children and young adults.

Disadvantages are:

(a) Prolonged (often life-long) treatment is needed because relapse rate is high.
(b) Not practicable in uncooperative/unintelligent patient.
(c) Drug toxicity.

Thyroidectomy and ^{131}I are contraindicated during pregnancy. With antithyroid drugs risk of foetal hypothyroidism and goiter is there. However, low doses of propylthiouracil are preferred: its greater protein binding allows less transfer to the foetus. For the same reason it is to be preferred in the nursing mother. However, methimazole has also now been found to be safe during pregnancy.

Propylthiouracil is used in thyroid storm as well (*see* p. 256).

IONIC INHIBITORS

Certain monovalent anions inhibit iodide trapping by NIS into the thyroid probably because of similar hydrated ionic size—T_4/T_3 cannot be synthesized. Perchlorate is 10 times more potent than thiocyanate in blocking NIS, while nitrate is very weak.

They are toxic and not clinically used now.

Thiocyanates: can cause liver, kidney, bone marrow and brain toxicity.

Perchlorates: produce rashes, fever, aplastic anaemia, agranulocytosis.

IODINE AND IODIDES

Though iodine is a constituent of thyroid hormones, it is the fastest acting thyroid inhibitor. In Grave's disease the gland, if enlarged, shrinks, becomes firm and less vascular. The thyroid status starts returning to normal at a rate commensurate with complete stoppage of hormone release from the gland. The thyroid gland involutes and colloid is restored. The response to iodine and iodides is identical, because elemental iodine is reduced to iodide in the intestines. With daily administration, peak effects are seen in 10–15 days, after which 'thyroid escape' occurs and thyrotoxicosis may return with greater vengeance. Worsening of hyperthyroidism especially occurs in multinodular goiter.

All facets of thyroid function seem to be affected, but the most important action is inhibition of hormone release—'thyroid constipation'. Endocytosis of colloid and proteolysis of thyroglobulin comes to a halt. The mechanism of action is not clear. Excess iodide inhibits its own transport into thyroid cells by interfering with expression of NIS on the cell membrane. In addition, it

attenuates TSH and cAMP induced thyroid stimulation. Excess iodide rapidly and briefly interferes with iodination of tyrosil and thyronil residues of thyroglobulin (probably by altering redox potential of thyroid cells) resulting in reduced T_3/T_4 synthesis (Wolff-Chaikoff effect). However, within a few days, the gland 'escapes' from this effect and hormone synthesis resumes.

Preparations and dose Lugol's solution (5% iodine in 10% Pot. iodide solution): LUGOL'S SOLUTION, COLLOID IODINE 10%: 5–10 drops/day. COLLOSOL 8 mg iodine/5 ml liq.
Iodide (Sod./Pot.) 100–300 mg/day (therapeutic), 5–10 mg/day (prophylactic) for endemic goiter.

Uses

1. *Preoperative preparation* for thyroidectomy in Graves' disease: Iodine is generally given for 10 days just preceding surgery. The aim is to make the gland firm, less vascular and easier to operate on. Though iodide itself will lower the thyroid status, it cannot be relied upon to attain euthyroidism which is done by use of carbimazole before starting iodide. Propranolol may be given additionally for rapid control of symptoms.

2. *Thyroid storm* Lugol's iodine (6–10 drops) or iodine containing radiocontrast media (iopanoic acid/ipodate) orally are used to stop any further release of T_3/T_4 from the thyroid and to decrease T_4 to T_3 conversion.

3. *Prophylaxis of endemic goiter* It is generally used as "iodized salt"(*see* p. 251).

4. *Antiseptic* As tincture iodine, povidone iodine, etc. *see* Ch. 65.

Adverse effects

1. *Acute reaction* It occurs only in individuals sensitive to iodine, and can be triggered even by a minute quantity. Manifestations are swelling of lips, eyelids, angioedema of larynx (may be dangerous), fever, joint pain, petechial haemorrhages, thrombocytopenia, lymphadenopathy. Further exposure to iodine should be stopped immediately.

2. *Chronic overdose (iodism)* Inflammation of mucous membranes, salivation, rhinorrhoea, sneezing, lacrimation, swelling of eyelids, burning sensation in mouth, headache, rashes, g.i. symptoms, etc. The symptoms regress on stopping iodide ingestion.
Long-term use of high doses can cause hypothyroidism and goiter.

Iodide may cause flaring of acne in adolescents. Given to pregnant or nursing mothers, it may be responsible for foetal/infantile goiter and hypothyroidism. Thyrotoxicosis may be aggravated in multinodular goiter.

RADIOACTIVE IODINE

The stable isotope of iodine is ^{127}I. Its radioactive isotope of medicinal importance is:

^{131}I: physical half-life 8 days.

The chemical behaviour of ^{131}I is similar to the stable isotope.

^{131}I emits X-rays as well as β particles. The former are useful in tracer studies, because they traverse the tissues and can be monitored by a counter, while the latter are utilized for their destructive effect on thyroid cells. ^{131}I is concentrated by thyroid, incorporated in colloid—emits radiation from within the follicles. The β particles penetrate only 0.5–2 mm of tissue. The thyroid follicular cells are affected from within, undergo pyknosis and necrosis followed by fibrosis when a sufficiently large dose has been administered, without damage to neighbouring tissues. With carefully selected doses, it is possible to achieve partial ablation of thyroid.

Radioactive iodine is administered as sodium salt of ^{131}I dissolved in water and taken orally.
Diagnostic 25–100 μ curie is given; counting or scanning is done at intervals. No damage to thyroid cells occurs at this dose.

Therapeutic The most common indication is *hyperthyroidism* due to Graves' disease or toxic nodular goiter. The average therapeutic dose is 3–6 m curie—calculated on the basis of previous tracer studies and thyroid size. Higher doses are generally required for toxic multinodular goiter

than for Graves' disease. The response is slow—starts after 2 weeks and gradually increases, reaching peak at 3 months or so. Thyroid status is evaluated after 3 months, and a repeat dose, if needed, is given. About 20–40% patients require one or more repeat doses.

Advantages

1. Treatment with ^{131}I is simple, conveniently given on outpatient basis and inexpensive.
2. No surgical risk, scar or injury to parathyroid glands/recurrent laryngeal nerves.
3. Once hyperthyroidism is controlled, cure is permanent.

Disadvantages

1. Hypothyroidism: About 5–10% patients of Graves' disease treated with ^{131}I become hypothyroid every year (upto 50% or more patients may ultimately require supplemental thyroxine treatment). This probably reflects the natural history of Graves' disease, because only few patients of toxic nodular goiter treated with ^{131}I develop hypothyroidism. Moreover, eventual hypothyroidism is a complication of subtotal thyroidectomy/prolonged carbimazole therapy as well.
2. Long latent period of response.
3. Contraindicated during pregnancy—foetal thyroid will also be destroyed resulting in cretinism, other abnormalities if given during first trimester.
4. Not suitable for young patients: they are more likely to develop hypothyroidism later and would then require life-long T_4 treatment. Genetic damage/cancer is also feared, though there is no evidence for it.

^{131}I is the treatment of choice after 25 years of age and if CHF, angina or any other contraindication to surgery is present.

Metastatic carcinoma of thyroid (especially papillary or those cases of follicular carcinoma which concentrate iodine), ^{131}I may be used as palliative therapy after thyroidectomy. Much higher doses are required and prior stimulation with TSH is recommended.

β ADRENERGIC BLOCKERS

Propranolol (and other nonselective β blockers) have emerged as an important form of therapy to rapidly alleviate manifestations of thyrotoxicosis that are due to sympathetic overactivity, *viz.* palpitation, tremor, nervousness, severe myopathy, sweating. They have little effect on thyroid function and the hypermetabolic state. They are used in hyperthyroidism in the following situations.

(i) While awaiting response to propylthiouracil/carbimazole or ^{131}I.

(ii) Along with iodide for preoperative preparation before subtotal thyroidectomy.

(iii) *Thyroid storm (thyrotoxic crisis):* This is an emergency due to decompensated hyperthyroidism. Vigorous treatment with the following is indicated:

- Nonselective β blockers (e.g. propranolol) are the most valuable measure. They afford dramatic symptomatic relief. In addition, they reduce peripheral conversion of T_4 to T_3. Propranolol 1–2 mg slow i.v. may be followed by 40–80 mg oral every 6 hours .
- Propylthiouracil 200–300 mg oral 6 hourly: reduces hormone synthesis as well as peripheral T_4 to T_3 conversion.
- Iopanoic acid (0.5–1 g OD oral) or ipodate are iodine containing radiocontrast media. They are potent inhibitors of thyroid hormone release from thyroid, as well as of peripheral T_4 to T_3 conversion.
- Corticosteroids (hydrocortisone 100 mg i.v. 8 hourly followed by oral prednisolone): help to tide over crisis, cover any adrenal insufficiency and inhibit conversion of T_4 to T_3 in periphery.
- Diltiazem 60–120 mg BD oral may be added if tachycardia is not controlled by propranolol alone, or when it is contraindicated.
- Rehydration, anxiolytics, external cooling and appropriate antibiotics are the other measures.

☞ PROBLEM DIRECTED STUDY

18.1 A 20-year girl was diagnosed as a case of recent onset Graves' disease with mild diffuse pulsatile thyroid enlargement. She was treated with tab. Carbimazole 5 mg 2 tab 3 times a day. Her symptoms started subsiding after 2 weeks and were fully controlled after 3 months. The thyroid swelling also subsided and she was maintained on a dose of carbimazole 5 mg twice daily. After one year she noticed that the neck swelling was reappearing and her body weight increased by 2 kg in the last one month, but without recurrence of her earlier symptoms. She rather felt dull, sleepy and depressed. The serum TSH was 12 µU/ml and free thyroxine (FT_4) was 9 pmol/L.

(a) Why was the initial response to carbimazole delayed? Could any additional medicine be given to her initially to afford more rapid symptomatic relief?

(b) What was the cause of reappearance of the neck swelling and her condition after 1 year? What measures need to be taken at this stage?

(see Appendix-1 for solution)

Chapter 19 Insulin, Oral Hypoglycaemic Drugs and Glucagon

Diabetes mellitus (DM) It is a metabolic disorder characterized by hyperglycaemia, glycosuria, hyperlipidaemia, negative nitrogen balance and sometimes ketonaemia. A widespread pathological change is thickening of capillary basement membrane, increase in vessel wall matrix and cellular proliferation resulting in vascular complications like lumen narrowing, early atherosclerosis, sclerosis of glomerular capillaries, retinopathy, neuropathy and peripheral vascular insufficiency.

Enhanced nonenzymatic glycosylation of tissue proteins due to persistent exposure to high glucose concentrations and the accumulation of larger quantities of sorbitol (a reduced product of glucose) in tissues are believed to be causative in the pathological changes of diabetes. The concentration of glycosylated haemoglobin (HbA_{1c}) is taken as an index of protein glycosylation: it reflects the state of glycaemia over the preceding 2–3 months.

Two major types of diabetes mellitus are:

Type I Insulin-dependent diabetes mellitus (IDDM)/juvenile onset diabetes mellitus:
There is β cell destruction in pancreatic islets; majority of cases are autoimmune (type 1A) antibodies that destroy β cells are detectable in blood, but some are idiopathic (type 1B)—no β cell antibody is found. In all type 1 cases circulating insulin levels are low or very low, and patients are more prone to ketosis. This type is less common and has a low degree of genetic predisposition.

Type II Noninsulin-dependent diabetes mellitus (NIDDM)/maturity onset diabetes mellitus:
There is no loss or moderate reduction in β cell mass; insulin in circulation is low, normal or even high, no anti-β-cell antibody is demonstrable; has a high degree of genetic predisposition; generally has a late onset (past middle age). Over 90% cases of diabetes are type 2 DM. Causes may be:

- Abnormality in gluco-receptor of β cells so that they respond at higher glucose concentration or relative β cell deficiency. In either way, insulin secretion is impaired; may progress to β cell failure.
- Reduced sensitivity of peripheral tissues to insulin: reduction in number of insulin receptors, 'down regulation' of insulin receptors. Many hypertensives are hyperinsulinaemic, but normoglycaemic; and have associated dyslipidaemia, hyperuricaemia, abdominal obesity (metabolic syndrome). Thus, there is relative insulin resistance, particularly at the level of

Approaches to drug therapy in type 2 DM

Improve insulin availability	*Overcome insulin resistance*
Exogenous insulin	Biguanides
Sulfonylureas	Thiazolidinediones
Meglitinide/phenylalanine analogues	α glucosidase inhibitors
Dipeptidyl peptidase-4 inhibitors (DPP-4Is)	
Major limitations (except for DPP-4Is)	*Major limitations*
Hypoglycaemic episodes	Inability to achieve normoglycaemia by themselves in many patients, especially moderate-to-severe cases
Weight gain	
Concern about premature atherosclerosis due to hyperinsulinaemia	

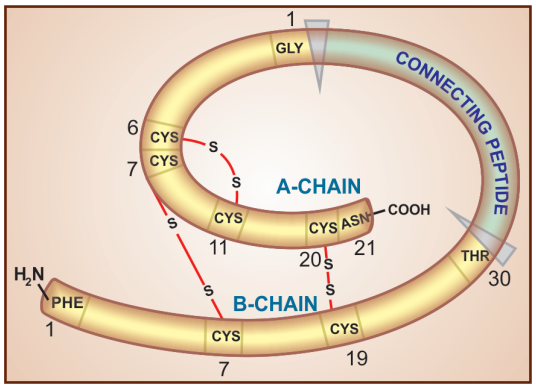


Fig. 19.1: Human proinsulin; simplified structure depicting the main features. The connecting peptide, having 35 amino acids, is split off leaving insulin molecule with two chains joined by two disulfide bridges

liver, muscle and fat. Hyperinsulinaemia *per se* has been implicated in causing angiopathy.

- Excess of hyperglycaemic hormones (glucagon, etc.)/obesity: cause relative insulin deficiency—the β cells lag behind.

Other rare forms of DM are those due to specific genetic defects (type-3) like 'maturity onset diabetes of young' (MODY), other endocrine disorders, pancreatectomy and 'gestational diabetes mellitus' (GDM, type-4).

INSULIN

Insulin was discovered in 1921 by Banting and Best who demonstrated the hypoglycaemic action of an extract of pancreas prepared after degeneration of the exocrine part due to ligation of pancreatic duct. It was first obtained in pure crystalline form in 1926 and the chemical structure was fully worked out in 1956 by Sanger.

Insulin is a two chain polypeptide having 51 amino acids and MW about 6000. The A-chain has 21 while B-chain has 30 amino acids. There are minor differences between human, pork and beef insulins:

Species	*A-chain*		*B-chain*
	8th AA	*10th AA*	*30th AA*
Human	THR	ILEU	THR
Pork	THR	ILEU	ALA
Beef	ALA	VAL	ALA

Thus, pork insulin is more homologous to human insulin than is beef insulin. The A and B chains are held together by two disulfide bonds.

Insulin is synthesized in the β cells of pancreatic islets as a single chain peptide *Preproinsulin* (110 AA) from which 24 AAs are first removed to produce *Proinsulin* (Fig. 19.1). The connecting or 'C' peptide (35 AA) is split off by proteolysis in Golgi apparatus; both insulin and C peptide are stored in granules within the cell. The C peptide is secreted in the blood along with insulin.

Assay Insulin is bioassayed by measuring blood sugar depression in rabbits (1 U reduces blood glucose of a fasting rabbit to 45 mg/dl) or by its potency to induce hypoglycaemic convulsions in mice. 1 mg of the International Standard of insulin = 28 units. With the availability of pure preparations, it can now be assayed chemically and quantity expressed by weight. Plasma insulin can be measured by radioimmunoassay or enzyme immunoassay.

Regulation of insulin secretion

Under basal condition ~1U insulin is secreted per hour by human pancreas. Much larger quantity is secreted after every meal. Secretion of insulin from β cells is regulated by chemical, hormonal and neural mechanisms.

Chemical The β cells have a glucose sensing mechanism dependent on entry of glucose into β cells (through the aegis of a glucose transporter GLUT1) and its phosphorylation by *glucokinase*. Glucose entry and metabolism leads to activation of the glucosensor which indirectly inhibits the ATP-sensitive K^+ channel (K^+_{ATP}) resulting in partial depolarization of the β cells (*see* Fig. 19.6). This increases intracellular Ca^{2+} availability (due to increased influx, decreased efflux and release from intracellular stores) → exocytotic release of insulin storing granules. Other nutrients that can evoke insulin release are—amino acids, fatty acids and ketone bodies, but glucose is the principal regulator and it stimulates synthesis of insulin as well. Glucose induces a brief pulse of insulin output within 2 min (*first phase*) followed by a delayed but more sustained *second phase* of insulin release.

Glucose and other nutrients are more effective in invoking insulin release when given orally than i.v. They generate chemical signals *'incretins'* from the gut which act on β cells in the pancreas to cause anticipatory release of insulin. The incretins involved are glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), vasoactive intestinal peptide (VIP), pancreozymin-cholecystokinin, etc.; but different incretin may mediate signal from different nutrient. Glucagon and some of these peptides enhance insulin release by increasing cAMP formation in the β cells.

Hormonal A number of hormones, e.g. growth hormone, corticosteroids, thyroxine modify insulin release in response to glucose. PGE has been shown to inhibit insulin release. More important are the intra-islet paracrine interactions between the hormones produced by different types of islet cells. The β cells constitute the core of the islets and are the most abundant cell type. The α cells, comprising 25% of the islet cell mass, surround the core and secrete glucagon. The δ cells (5–10%) elaborating somatostatin are interspersed between the α cells. There are some PP (pancreatic polypeptide containing) cells as well.

- Somatostatin inhibits release of both insulin and glucagon.
- Glucagon evokes release of insulin as well as somatostatin.
- Insulin inhibits glucagon secretion. Amylin, another β cell polypeptide released with insulin, inhibits glucagon secretion through a central site of action in the brain.

The three hormones released from closely situated cells influence each other's secretion and appear to provide fine tuning of their output in response to metabolic needs (Fig. 19.2).

Neural The islets are richly supplied by sympathetic and vagal nerves.

- Adrenergic α_2 receptor activation decreases insulin release (predominant) by inhibiting β cell adenylyl cyclase.
- Adrenergic β_2 stimulation increases insulin release (less prominent) by stimulating β cell adenylyl cyclase.
- Cholinergic—muscarinic activation by ACh or vagal stimulation causes insulin secretion through IP_3/DAG-increased intracellular Ca^{2+} in the β cells.

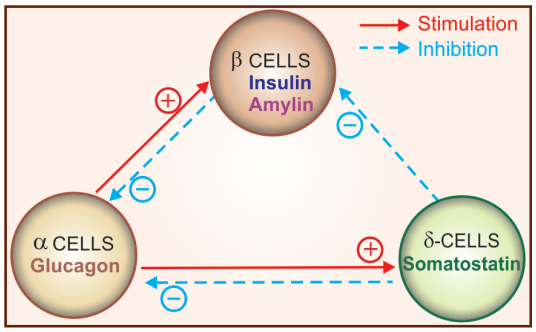


Fig. 19.2: Paracrine modulation of hormone secretion within the pancreatic islets of Langerhans

These neural influences appear to govern both basal as well as evoked insulin secretion, because the respective blocking agents have effects opposite to that mentioned above. The primary central site of regulation of insulin secretion is in the hypothalamus: stimulation of ventrolateral nuclei evokes insulin release, whereas stimulation of ventromedial nuclei has the opposite effect.

ACTIONS OF INSULIN

The overall effects of insulin are to dispose meal derived glucose, amino acids, fatty acids and favour storage of fuel. It is a major anabolic hormone: promotes synthesis of gylcogen, lipids and protein. The actions of insulin and the results of its deficiency can be summarized as:

1. Insulin facilitates glucose transport across cell membrane; skeletal muscle and fat are highly sensitive. The availability of glucose intracellularly is the limiting factor for its utilization in these and some other tissues. However, glucose entry in liver, brain, RBC, WBC and renal medullary cells is largely independent of insulin. Ketoacidosis interferes with glucose utilization by brain and contributes to diabetic coma. Muscular activity induces glucose entry in muscle cells without the need for insulin. As such, exercise has insulin sparing effect.

The intracellular pool of vesicles containing glucose transporter glycoproteins GLUT4 (insulin activated) and GLUT1 is in dynamic equilibrium

with the GLUT vesicles inserted into the membrane. This equilibrium is regulated by insulin to favour translocation to the membrane. Moreover, on a long-term basis, synthesis of GLUT4 is upregulated by insulin.

2. The first step in intracellular utilization of glucose is its phosphorylation to form glucose-6-phosphate. This is enhanced by insulin through increased production of glucokinase. Insulin facilitates glycogen synthesis from glucose in liver, muscle and fat by stimulating the enzyme glycogen synthase. It also inhibits glycogen degrading enzyme phosphorylase → decreased glycogenolysis in liver.

3. Insulin inhibits gluconeogenesis (from protein, FFA and glycerol) in liver by gene mediated decreased synthesis of phosphoenol pyruvate carboxykinase. In insulin deficiency, proteins and amino acids are funneled from peripheral tissues to liver where these substances are converted to carbohydrate and urea. Thus, in diabetes there is underutilization and over production of glucose → hyperglycaemia → glycosuria.

4. Insulin inhibits lipolysis in adipose tissue and favours triglyceride synthesis. In diabetes increased amount of fat is broken down due to unchecked action of lipolytic hormones (glucagon, Adr, thyroxine, etc.) → increased FFA and glycerol in blood → taken up by liver to produce acetyl-CoA. Normally acetyl-CoA is resynthesized to fatty acids and triglycerides, but this process is reduced in diabetics and acetyl CoA is diverted to produce ketone bodies (acetone, acetoacetate, β-hydroxy-butyrate). The ketone bodies are released in blood—partly used up by muscle and heart as energy source, but when their capacity is exceeded, ketonaemia and ketonuria result.

5. Insulin enhances transcription of vascular endothelial lipoprotein lipase and thus increases clearance of VLDL and chylomicrons.

6. Insulin facilitates AA entry and their synthesis into proteins, as well as inhibits protein breakdown in muscle and most other cells. Insulin deficiency leads to protein breakdown → AAs are released in blood → taken up by liver and converted to pyruvate, glucose and urea. The excess urea produced is excreted in urine resulting in negative nitrogen balance. Thus, catabolism takes the upper hand over anabolism in the diabetic state.

Most of the above metabolic actions of insulin are exerted within seconds or minutes and are called the *rapid actions*. Others involving DNA mediated synthesis of glucose transporter and some enzymes of amino acid metabolism have a latency of few hours—the *intermediate* actions. In addition insulin exerts major *long-term* effects on multiplication and differentiation of many types of cells.

Mechanism of action Insulin acts on specific receptors located on the cell membrane of practically every cell, but their density depends on the cell type: liver and fat cells are very rich. The insulin receptor is a receptor tyrosine kinase (RTK) which is heterotetrameric glycoprotein consisting of 2 extracellular α and 2 transmembrane β subunits linked together by disulfide bonds. It is oriented across the cell membrane as a heterodimer (Fig. 19.3). The α subunits carry insulin binding sites, while the β subunits have tyrosine protein kinase activity.

Binding of insulin to α subunits induces aggregation and internalization of the receptor along with the bound insulin molecules. This activates tyrosine kinase activity of the β subunits → pairs of β subunits phosphorylate tyrosine residues

Actions of insulin producing hypoglycaemia

Liver	Muscle	Adipose tissue
▲ Increases glucose uptake and glycogen synthesis ▲ Inhibits glycogenolysis and glucose output ▲ Inhibits gluconeogenesis from protein, pyruvate, FFA and glycerol	▲ Increases glucose uptake and utilization ▲ Inhibits proteolysis and release of amino acids, pyruvate, lactate into blood which form the substrate for gluconeogenesis in liver	▲ Increases glucose uptake and storage as fat and glycogen ▲ Inhibits lipolysis and release of FFA + glycerol which form substrate for gluconeogenesis in liver

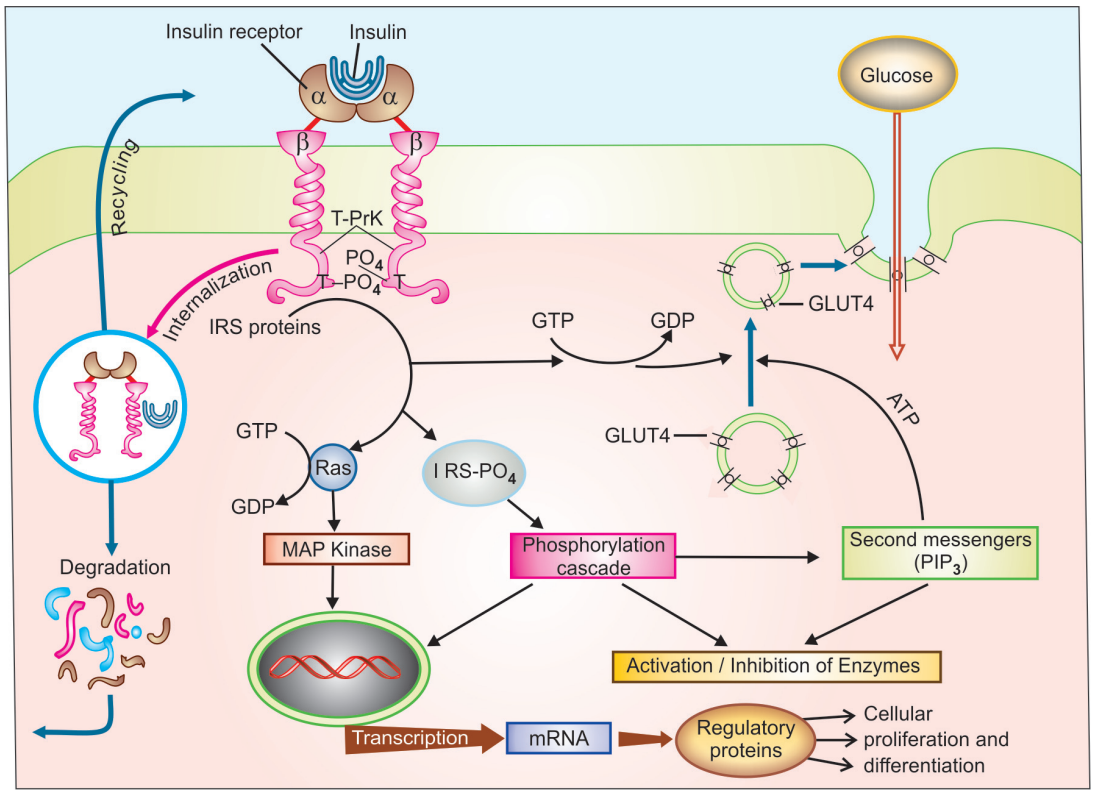


Fig. 19.3: A model of insulin receptor and mediation of its metabolic and cellular actions.
T—Tyrosine residue; GLUT4—Insulin dependent glucose transporter; IRS—Insulin receptor substrate proteins; PIP_3—Phosphatidyl inositol trisphosphate; MAP kinase—Mitogen-activated protein kinase; T-PrK—Tyrosine protein kinase; Ras—Regulator of cell division and differentiation (protooncogene product).

on each other → expose the catalytic site to phosphorylate tyrosine residues of Insulin Receptor Substrate proteins (IRS1, IRS2, etc). In turn, a cascade of phosphorylation and dephosphorylation reactions is set into motion which amplifies the signal and results in stimulation or inhibition of enzymes involved in the rapid metabolic actions of insulin.

Certain second messengers like phosphatidyl inositol trisphosphate (PIP_3) which are generated through activation of a specific PI_3-kinase also mediate the action of insulin on metabolic enzymes.

Insulin stimulates glucose transport across cell membrane by ATP dependent translocation of glucose transporter GLUT4 to the plasma membrane. The second messenger PIP_3 and certain tyrosine phosphorylated guanine nucleotide exchange proteins play crucial roles in the insulin sensitive translocation of GLUT4 from cytosol to the plasma membrane, especially in skeletal muscle and adipose tissue. Over a period of time insulin also promotes expression of the genes directing synthesis of GLUT4. Genes for a large number of enzymes and carriers are regulated by insulin through Ras/Raf and MAP-Kinase as well as through the phosphorylation cascade. Long-term effects of insulin are exerted by generation of transcription factors promoting proliferation and differentiation of specific cells.

The internalized receptor-insulin complex is either degraded intracellularly or returned back to the surface from where the insulin is released extracellularly. The relative preponderance of these two processes differs among different tissues: maximum degradation occurs in liver, least in vascular endothelium.

Fate of insulin Insulin is distributed only extracellularly. It is a peptide; gets degraded in the g.i.t. if given orally. Injected insulin or that released from pancreas is metabolized primarily in liver and to a smaller extent in kidney and muscles. Nearly half of the insulin entering portal vein from pancreas is inactivated in the first passage through liver. Thus, normally liver is exposed to a much higher concentration (4–8 fold) of insulin than are other tissues. As noted above, degradation

TABLE 19.1 Types of insulin preparations and insulin analogues

Type	*Appearance*	*Onset (hr)*	*Peak (hr)*	*Duration (hr)*	*Can be mixed with*
Rapid acting					
Insulin lispro	Clear	0.2–0.3	1–1.5	3–5	Regular, NPH
Insulin aspart	Clear	0.2–0.3	1–1.5	3–5	Regular, NPH
Insulin glulisine	Clear	0.2–0.4	1–2	3–5	Regular, NPH
Short acting					
Regular (soluble) insulin	Clear	0.5–1	2–3	6–8	All preparations (except insulin glargine/detemir)
Intermediate acting					
Insulin zinc suspension or Lente*	Cloudy	1–2	8–10	20–24	Regular
Neutral protamine hagedorn (NPH) or isophane insulin	Cloudy	1–2	8–10	20–24	Regular
Long acting					
Insulin glargine	Clear	2–4	—	24	None
Insulin detemir	Clear	1–4	—	20–24	None

* Lente insulin is a 7:3 mixture of ultralente (crystalline) and semilente (amorphous) insulin zinc suspension. Ultralente (long-acting) and semilente (short-acting) are not separately marketed. The older protamine zinc insulin is also not marketed.

of insulin after receptor mediated internalization occurs to variable extents in most target cells. During biotransformation the disulfide bonds are reduced—A and B chains are separated. These are further broken down to the constituent amino acids. The plasma t½ is 5–9 min.

Preparations of insulin

The older commercial preparations were produced from beef and pork pancreas. They contained ~1% (10,000 ppm) of other proteins (proinsulin, other polypeptides, pancreatic proteins, insulin derivatives, etc.) which were potentially antigenic. They are no longer produced and have been totally replaced by highly purified pork/beef insulins/recombinant human insulins/insulin analogues.

Highly purified insulin preparations

In the 1970s improved purification techniques like gel filtration and ion-exchange chromatography were applied to produce 'single peak' and 'monocomponent (MC)' insulins which contain <10 ppm proinsulin. The MC insulins are more stable and cause less insulin resistance or injection site lipodystrophy. The immunogenicity of pork MC insulin is similar to that of recombinant human insulin.

Types of insulin preparations

Regular (soluble) insulin It is a buffered neutral pH solution of unmodified insulin stabilized by a small amount of zinc. At the concentration of the injectable solution, the insulin molecules self aggregate to form hexamers around zinc ions. After s.c. injection, insulin monomers are released gradually by dilution, so that absorption occurs slowly. Peak action is produced only after 2–3 hours and action continues upto 6–8 hours. The absorption pattern is also affected by dose; higher doses act longer. When injected s.c. just before a meal, this pattern often creates a mismatch between need and availability of insulin to result in early postprandial hyperglycaemia and late postprandial hypoglycaemia. It is generally injected ½-1 hour before a meal. Regular insulin injected s.c. is also not suitable for providing a low constant basal level of action in the interdigestive period. The slow onset of action is not applicable to i.v. injection, because insulin hexamer dissociates rapidly to produce prompt action.

To overcome the above problems, some long-acting 'modified' or 'retard' preparations of insulin were soon developed. Recently, both rapidly acting as well as peakless and long-acting insulin analogues have become available.

For obtaining retard preparations, insulin is rendered insoluble either by complexing it with protamine (a small molecular basic protein) or by precipitating it with excess zinc and increasing the particle size.

Lente insulin (Insulin-zinc suspension): Two types of insulin-zinc suspensions have been produced. The one with large particles is crystalline and practically insoluble in water (ultralente). It is long-acting. The other has smaller particles and is amorphous (semilente), is short-acting. Their 7:3 ratio mixture is called 'Lente insulin' and is intermediate-acting.

Isophane (Neutral Protamine Hagedorn or NPH) insulin: Protamine is added in a quantity just sufficient to complex all insulin molecules; neither of the two is present in free form and pH is neutral. On s.c. injection, the complex dissociates slowly to yield an intermediate duration of action. It is mostly combined with regular insulin (70:30 or 50:50) and injected s.c. twice daily before breakfast and before dinner (split-mixed regimen).

1. Highly purified (monocomponent) pork regular insulin: ACTRAPID MC, RAPIDICA 40 U/ml inj.
2. Highly purified (MC) pork lente insulin: LENTARD, MONOTARD MC, LENTINSULIN-HPI, ZINULIN 40 U/ml
3. Highly purified (MC) pork isophane (NPH) insulin: INSULATARD 40 U/ml inj.
4. Mixture of highly purified pork regular insulin (30%) and isophane insulin (70%): RAPIMIX, MIXTARD 40 U/ml inj.

Human insulins In the 1980s, the human insulins (having the same amino acid sequence as human insulin) were produced by recombinant DNA technology in *Escherichia coli*—'proinsulin recombinant bacterial' (prb) and in yeast—'precursor yeast recombinant' (pyr), or by 'enzymatic modification of porcine insulin' (emp).

1. HUMAN ACTRAPID: Human *regular* insulin; 40 U/ml, 100 U/ml, ACTRAPID HM PENFIL 100 U/ml pen inj., WOSULIN-R 40 U/ml inj vial and 100 U/ml pen injector cartridge.
2. HUMAN MONOTRAD, HUMINSULIN-L: Human *lente* insulin; 40 U/ml, 100 U/ml.
3. HUMAN INSULATARD, HUMINSULIN-N: Human *isophane* insulin 40 U/ml. WOSULIN-N 40 U/ml inj. vial and 100 U/ml pen injector cartridge.
4. HUMAN ACTRAPHANE, HUMINSULIN 30/70, HUMAN MIXTARD: Human *soluble* insulin (30%) and *isophane* insulin (70%), 40 U/ml. and 100 U/ml vials. WOSULIN 30/70: 40 U/ml vial and 100 U/ml cartridge.
5. ACTRAPHANE HM PENFIL: Human *soluble* insulin 30% + isophane insulin 70% 100 U/ml pen injector.
6. INSUMAN 50/50: Human *soluble* insulin 50% + *isophane* insulin 50% 40 U/ml inj; HUMINSULIN 50:50, HUMAN MIXTARD 50; WOSULIN 50/50 40 U/ml vial, 100 U/ml cartridge.

In the USA pork and beef insulins are no longer manufactured, but they are still available in U.K., India and some European countries. In Britain now > 90% diabetics who use insulin are taking human insulins or insulin analogues. In India also human insulins and analogues are commonly used, except for considerations of cost. Human insulin is more water soluble as well as hydrophobic than porcine or bovine insulin. It has a slightly more rapid s.c. absorption, earlier and more defined peak and slightly shorter duration of action. Human insulin is also modified similarly to produce isophane (NPH) and lente preparations. Lente human insulin is no longer prepared in the USA.

The allegation that human insulin produces more *hypoglycaemic unawareness* has not been substantiated. However, after prolonged treatment, irrespective of the type of insulin, many diabetics develop relative hypoglycaemic unawareness/change in hypoglycaemic symptoms, because of autonomic neuropathy, changes in perception/attitude and other factors.

Clinical superiority of human insulin over pork MC insulin has not been demonstrated. Though new patients may be started on human insulins, the only indication for transfer from purified pork to human insulin is allergy to pork insulin. It is unwise to transfer stabilized patients from one to another species insulin without good reason.

Insulin analogues

Using recombinant DNA technology, analogues of insulin have been produced with modified pharmacokinetics on s.c. injection, but similar pharmacodynamic effects. Greater stability and consistency are the other advantages.

Insulin lispro: Produced by reversing proline and lysine at the carboxy terminus B 28 and B 29 positions, it forms very weak hexamers that dissociate rapidly after s.c. injection resulting in a quick and more defined peak as well as shorter duration of action. Unlike regular insulin, it needs to be injected immediately before or even after the meal, so that dose can be altered according to the quantity of food consumed. A better control of meal-time glycaemia and a lower incidence of late post-prandial hypoglycaemia have been obtained. Using a regimen of 2–3 daily meal-time insulin lispro injections, a slightly greater reduction in HbA_{1c} compared to regular insulin has been reported. Fewer hypoglycaemic episodes occurred.

HUMALOG 100 U/ml, 3 ml cartridge, 10 ml vial.

Insulin aspart: The proline at B 28 of human insulin is replaced by aspartic acid. This change reduces the tendency for self-aggregation, and a time-action profile similar to insulin lispro is obtained. It more closely mimics the physiological insulin release pattern after a meal, with the same advantages as above.

NOVOLOG, NOVORAPID 100 U/ml inj; Biphasic insulin aspart - NOVO MIX 30 FEXPEN injector.

Insulin glulisine: Another rapidly acting insulin analogue with lysine replacing asparagine at B 23 and glutamic acid replacing lysine at B 29. Properties and advantages are similar to insulin lispro. It has been particularly used for continuous subcutaneous insulin infusion (CSII) by a pump.

Insulin glargine: This long-acting biosynthetic insulin has 2 additional arginine residues at the carboxy terminus of B chain and glycine replaces asparagine at A 21. It remains soluble at pH4 of the formulation, but precipitates at neutral pH encountered on s.c. injection. A depot is created from which monomeric insulin dissociates slowly to enter the circulation. Onset of action is delayed, but relatively low blood levels of insulin are maintained for upto 24 hours. A smooth 'peakless' effect is obtained. Thus, it is suitable for once daily injection to provide background insulin action. Fasting and interdigestive blood glucose levels are effectively lowered irrespective of time of the day when injected or the site of s.c. injection. It is mostly injected at bed time. Lower incidence of night-time hypoglycaemic episodes compared to isophane insulin has been reported. However, it does not control meal-time glycaemia, for which a rapid acting insulin or an oral hypoglycaemic is used concurrently. Because of acidic pH, it cannot be mixed with any other insulin preparation; must be injected separately.

LANTUS OPTISET 100 U/ml in 5 ml vial and 3 ml prefilled pen injector.

Insulin detemir Myristoyl (a fatty acid) radical is attached to the amino group of lysine at B29 of insulin chain. As a result, it binds to albumin after s.c. injection from which the free form becomes available slowly. A pattern of insulin action almost similar to that of insulin glargine is obtained, but twice daily dosing may be needed.

REACTIONS TO INSULIN

1. Hypoglycaemia This is the most frequent and potentially the most serious reaction. It is commonly seen in patients of 'labile' diabetes in whom insulin requirement fluctuates unpredictably. Hypoglycaemia can occur in any diabetic following inadvertent injection of large dose, by missing a meal after injection or by performing vigorous exercise. The symptoms can be divided into those due to counter-regulatory sympathetic stimulation—sweating, anxiety, palpitation, tremor; and those due to deprivation of the brain of its essential nutrient glucose (neuroglucopenic symptoms)—dizziness, headache, behavioural changes, visual disturbances, hunger, fatigue, weakness, muscular incoordination and sometimes fall in BP. Generally, the reflex sympathetic symptoms occur before the neuroglucopenic, but the warning symptoms of hypoglycaemia differ from patient to patient and also depend on the rate of fall in blood glucose level. After long-term treatment about 30% patients lose adrenergic symptoms. Diabetic neuropathy can abolish the autonomic symptoms. Hypoglycaemic unawareness tends to develop in patients who experience frequent episodes of hypoglycaemia.

Finally, when blood glucose falls further (to < 40 mg/dl) mental confusion, abnormal behaviour, seizures and coma occur. Irreversible

neurological deficits are the sequelae of prolonged hypoglycaemia.

Treatment Glucose must be given orally or i.v. (for severe cases)—reverses the symptoms rapidly. Glucagon 0.5–1 mg i.v. or Adr 0.2 mg s.c. (less desirable) may be given as an expedient measure in patients who are not able to take sugar orally and injectable glucose is not available.

2. Local reactions Swelling, erythema and stinging sometimes occur at the injected site, especially in the beginning. *Lipodystrophy* of the subcutaneous fat around the injection site may occur if the same site is injected repeatedly. This is rare with the newer preparations.

3. Allergy This is due to contaminating proteins, and is very rare with human/highly purified insulins. Urticaria, angioedema and anaphylaxis are the manifestations.

4. Edema Some patients develop short-lived dependent edema (due to Na^+ retention) when insulin therapy is started.

Drug interactions

1. β adrenergic blockers prolong hypoglycaemia by inhibiting compensatory mechanisms operating through β_2 receptors (β_1 selective blockers are less liable). Warning signs of hypoglycaemia like palpitation, tremor and anxiety are masked. Rise in BP can occur due to unopposed α action of released Adr.
2. Thiazides, furosemide, corticosteroids, oral contraceptives, salbutamol, nifedipine tend to raise blood sugar and reduce effectiveness of insulin.
3. Acute ingestion of alcohol can precipitate hypoglycaemia by depleting hepatic glycogen.
4. Lithium, high dose aspirin and theophylline may also accentuate hypoglycaemia by enhancing insulin secretion and peripheral glucose utilization.

USES OF INSULIN

Diabetes mellitus The purpose of therapy in diabetes mellitus is to restore metabolism to normal, avoid symptoms due to hyperglycaemia and glucosuria, prevent short-term complications (infection, ketoacidosis, etc.) and long-term sequelae (cardiovascular, retinal, neurological, renal, etc.)

Insulin is effective in all forms of diabetes mellitus and is a must for type 1 cases, as well as for post pancreatectomy diabetes and gestational diabetes. Many type 2 cases can be controlled by diet, reduction in body weight and appropriate exercise supplemented, if required, by oral hypoglycaemics. Insulin is needed by such patients when:

- Not controlled by diet and exercise or when these are not practicable.
- Primary or secondary failure of oral hypoglycaemics or when these drugs are not tolerated.
- Under weight patients.
- Temporarily to tide over infections, trauma, surgery, pregnancy. In the perioperative period and during labour, monitored i.v. insulin infusion is preferable.
- Any complication of diabetes, e.g. ketoacidosis, nonketotic hyperosmolar coma, gangrene of extremities.

When instituted, insulin therapy has to be tailored according to the requirement and convenience of each patient. A tentative regimen is instituted and the insulin requirement is assessed by testing urine or blood glucose levels (glucose oxidase based spot tests and glucometers are available). Most type 1 patients require 0.4–0.8 U/kg/day. In type 2 patients, insulin dose varies (0.2–1.6 U/kg/day) with the severity of diabetes and body weight: obese patients require proportionately higher doses due to relative insulin resistance.

Any satisfactory insulin regimen should provide basal control by inhibiting hepatic glucose output, lipolysis and protein breakdown, as well as supply extra amount to meet postprandial needs for disposal of absorbed glucose and amino acids. A single daily injection of any long/intermediate/short-acting insulin or a mixture of these cannot fulfil both these requirements. Either multiple (2-4) injections daily of long and short acting insulins or a single injection daily of long-acting insulin supplemented by oral hypoglycaemics for meal time glycaemia is used. A frequently selected regimen utilizes mixture of regular with lente/

isophane insulin. The total daily dose of a 30:70 or 50:50 mixture of regular and NPH insulin is usually split into two (*split-mixed regimen*) and injected s.c. before breakfast and before dinner. Several variables, *viz.* site and depth of s.c. injection, posture, regional muscular activity, injected volume and type of insulin can alter the rate of absorption of s.c. injected insulin, so that the anticipated time-course of insulin action may not be obtained each time. The advantage is that only two daily injections are required, but the post-lunch glycaemia may not be adequately covered (*see* Fig. 19.4 A), and late postprandial hypoglycaemia may occur.

A more intensive regimen termed the '*basal-bolus regimen*' that is now advised needs 3–4 daily injections (*see* Fig. 19.4B). A long-acting insulin (glargine) is injected once daily either before breakfast or before bed-time for basal coverage along with 2–3 meal-time injections of a rapid acting preparation (insulin lispro or aspart). Such intensive regimens more completely meet the objective of achieving round-the-clock euglycaemia, but are more demanding and expensive. The large multicentric Diabetes Control and Complications Trial (DCCT) among type 1 patients has established that intensive insulin therapy markedly reduces the occurrence of primary diabetic retinopathy, neuropathy, nephropathy and slows progression of these complications in those who already have them, in comparison to conventional regimens which attain only intermittent euglycaemia. Thus, the risk of microvascular disease appears to be related to the glycaemia control. The 'UK prospective diabetes study' (UK PDS, 1998) has extended these observations to type 2 DM patients as well. Since the basis of pathological changes in both type 1 and type 2 DM is accumulation of glycosylated proteins and sorbitol in tissues as a result of exposure to high glucose concentrations, tight glycaemia control can delay end-organ damage in all diabetic subjects.

However, regimens attempting near normoglycaemia are associated with higher incidence

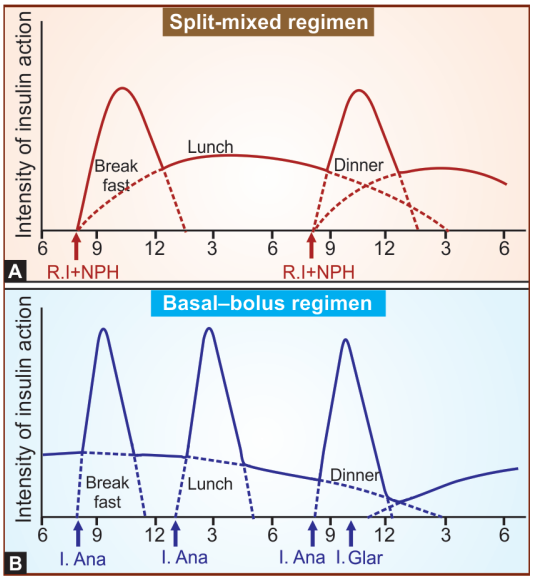


Fig. 19.4: Diagrammatic depiction of pattern of insulin action obtained with two commonly employed insulin regimens.
Arrow indicates subcutaneous insulin injection.
I. Ana—Insulin analogue (rapid acting); I. Glar—Insulin glargine; R.I—Regular insulin; NPH—Neutral protamine Hagedorn (isophane) insulin

of severe hypoglycaemic episodes. Moreover, injected insulin fails to reproduce the normal pattern of increased insulin secretion in response to each meal, and liver is exposed to the same concentration of insulin as other tissues, while normally it receives much higher concentration through portal circulation. As such, the overall desirability and practicability of intensive insulin therapy has to be determined in individual patients. Intensive insulin therapy is best avoided in young children (risk of hypoglycaemic brain damage) and in the elderly (more prone to hypoglycaemia and its serious consequences).

Diabetic ketoacidosis (Diabetic coma)

Ketoacidosis of different grades generally occurs in insulin dependent diabetics. It is infrequent in type 2 DM. The most common precipitating cause is infection; others are trauma, stroke, pancreatitis, stressful conditions and inadequate doses of insulin.

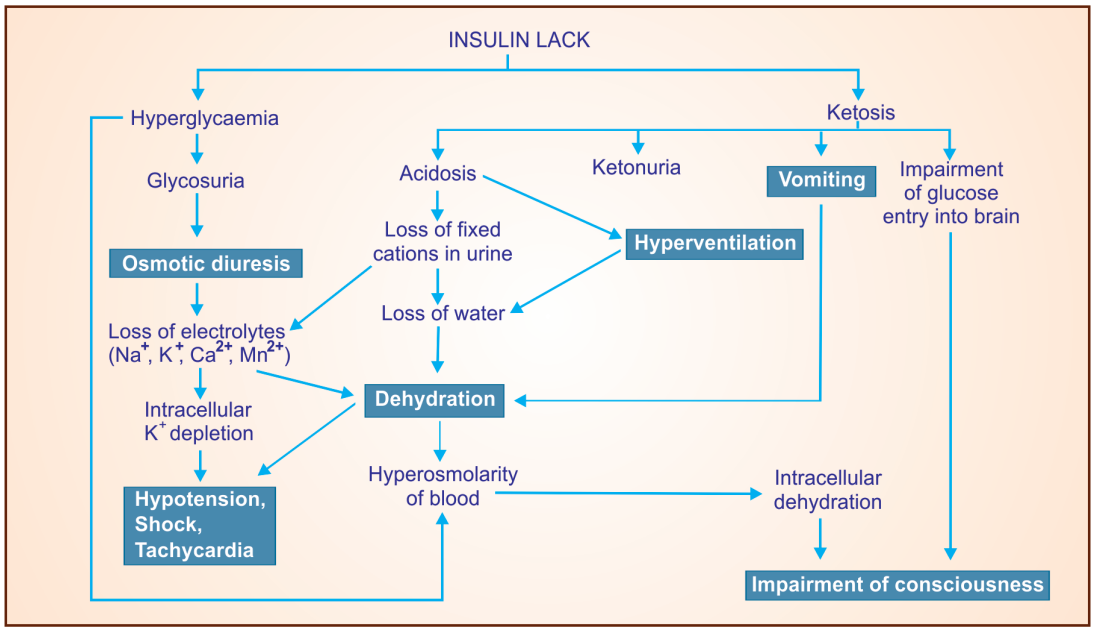


Fig. 19.5: Schematic depiction of the development of diabetic ketoacidosis due to insulin lack. Symptoms produced are shown within boxes

The development of cardinal features of diabetic ketoacidosis is outlined in Fig. 19.5. Patients may present with varying severity. Typically they are dehydrated, hyperventilating and have impaired consciousness. The principles of treatment remain the same, irrespective of severity, only the vigour with which therapy is instituted is varied.

1. *Insulin* Regular insulin is used to rapidly correct the metabolic abnormalities. A bolus dose of 0.1–0.2 U/kg i.v. is followed by 0.1 U/kg/hr infusion; the rate is doubled if no significant fall in blood glucose occurs in 2 hr. Fall in blood glucose level by 10% per hour can be considered adequate response.

Usually, within 4–6 hours blood glucose reaches 300 mg/dl. Then the rate of infusion is reduced to 2–3 U/hr. This is maintained till the patient becomes fully conscious and routine therapy with s.c. insulin is instituted.

2. *Intravenous fluids* It is vital to correct dehydration. Normal saline is infused i.v., initially at the rate of 1 L/hr, reducing progressively to 0.5 L/4 hours depending on the volume status. Once BP and heart rate have stabilized and adequate renal perfusion is assured change over to ½N saline. After the blood sugar has reached 300 mg/dl, 5% glucose in ½N saline is the most appropriate fluid because blood glucose falls before ketones are fully cleared from the circulation. Also glucose is needed to restore the depleted hepatic glycogen.

3. *KCl* Though upto 400 mEq of K^+ may be lost in urine during ketoacidosis, serum K^+ is usually normal due to exchange with intracellular stores. When insulin therapy is instituted ketosis subsides and K^+ is driven back intracellularly—dangerous hypokalemia can occur. After 4 hours it is appropriate to add 10–20 mEq/hr KCl to the i.v. fluid. Further rate of infusion is guided by serum K^+ measurements and ECG.

4. *Sodium bicarbonate* It is not routinely needed. Acidosis subsides as ketosis is controlled. However, if arterial blood pH is < 7.1, acidosis is not corrected spontaneously or hyperventilation

is exhausting, 50 mEq of sod. bicarbonate is added to the i.v. fluid. Bicarbonate infusion is continued slowly till blood pH rises above 7.2.

5. *Phosphate* When serum PO_4 is in the low-normal range, 5–10 m mol/hr of sod./pot. phosphate infusion is advocated. However, routine use of PO_4 in all cases is still controversial.

6. *Antibiotics* and other supportive measures and treatment of precipitating cause must be instituted simultaneously.

Hyperosmolar (nonketotic hyperglycaemic) coma This usually occurs in elderly type 2 patients. Its cause is obscure, but appears to be precipitated by the same factors as ketoacidosis, especially those resulting in dehydration. Uncontrolled glycosuria of DM produces diuresis resulting in dehydration and haemoconcentration over several days → urine output is finally reduced and glucose accumulates in blood rapidly to > 800 mg/dl, plasma osmolarity is > 350 mOsm/L → coma, and death can occur if not vigorously treated.

The general principles of treatment are the same as for ketoacidotic coma, except that faster fluid replacement is to be instituted and alkali is usually not required. These patients are prone to thrombosis (due to hyperviscosity and sluggish circulation), prophylactic heparin therapy is recommended.

Despite intensive therapy, mortality in hyperosmolar coma remains high. Treatment of precipitating factor and associated illness is vital.

Insulin resistance

Insulin resistance refers to suboptimal response of body tissues, especially liver, skeletal muscle and fat to physiological amounts of insulin. As already stated, relative insulin resistance is integral to type 2 DM. Advanced age, obesity and sedentary life-style promote insulin resistance.

Insulin sensitivity has been found to decline with age. Glucose entry into muscle and liver in response to insulin is deficient in individuals with large stores of body fat. Bigger adipocytes have fewer insulin receptors. However, in most type 2 diabetics the transducer mechanism linking insulin receptor to the response appears to be faulty, rather than the receptor itself. Exercise increases insulin sensitivity and lack of it contributes to insulin resistance.

Pregnancy and oral contraceptives often induce relatively low grade and reversible insulin resistance. Other rare causes are—acromegaly, Cushing's syndrome, pheochromocytoma, lipoatrophic diabetes mellitus. Hypertension is often accompanied with relative insulin resistance as part of metabolic syndrome.

Acute insulin resistance This form of insulin resistance develops rapidly and is usually a short term problem. Causes are—

(a) Infection, trauma, surgery, emotional stress induce release of corticosteroids and other hyperglycaemic hormones which oppose insulin action.

(b) Ketoacidosis—ketone bodies and FFA inhibit glucose uptake by brain and muscle. Also insulin binding may increase resulting in insulin resistance.

Treatment is to overcome the precipitating cause and to give high doses of regular insulin. The insulin requirement comes back to normal once the condition has been controlled.

Treatment is to overcome the precipitating cause and to give high doses of regular insulin. The insulin requirement comes back to normal once the condition has been controlled.

Newer insulin delivery devices A number of innovations have been made to improve ease and accuracy of insulin administration as well as to achieve tight glycaemia control. These are:

1. *Insulin syringes* Prefilled disposible syringes contain specific types or mixtures of regular and modified insulins.

2. *Pen devices* Fountain pen like: use insulin cartridges for s.c. injection through a needle. Preset amounts (in 2 U increments) are propelled by pushing a plunger; convenient in carrying and injecting.

3. *Inhaled insulin* An inhaled human insulin preparation was marketed in Europe and the USA, but withdrawn due to risk of pulmonary fibrosis and other complications. The

fine powder delivered through a nebulizer controlled mealtime glycaemia, but was not suitable for round-the-clock basal effect. Attempts are being made to overcome the shortcomings.

4. *Insulin pumps* Portable infusion devices connected to a subcutaneously placed cannula—provide 'continuous subcutaneous insulin infusion' (CSII). Only regular insulin or a fast acting insulin analogue is used. The pump can be programmed to deliver insulin at a low basal rate (approx. 1 U/hr) and premeal boluses (4–15 times the basal rate) to control post-prandial glycaemia. Though, theoretically more appealing, no definite advantage of CSII over multidose s.c. injection has been demonstrated. Moreover, cost, strict adherence to diet, exercise, care of the device and cannula, risk of pump failure, site infection, are too demanding on the patient. The CSII may be appropriate for selected type 2 DM cases only.

5. *Implantable pumps* Consist of an electromechanical mechanism which regulates insulin delivery from a percutaneously refillable reservoir. Mechanical pumps, propellant driven and osmotic pumps have been utilized.

6. *Other routes of insulin delivery* Intraperitoneal, oral (by complexing insulin into liposomes or coating it with impermeable polymer) and rectal routes are being tried. These have the advantage of providing higher concentrations in the portal circulation, which is more physiological.

ORAL HYPOGLYCAEMIC DRUGS

These drugs lower blood glucose levels and are effective orally. The chief draw back of insulin is—it must be given by injection. Orally active drugs have always been saught.

The early sulfonamides tested in 1940s produced hypoglycaemia as side effect. Taking this lead, the first clinically acceptable sulfonylurea *tolbutamide* was introduced in 1957. Others followed soon after. In the 1970s many so called 'second generation' sulfonylureas were developed which are 20–100 times more potent. Clinically useful biguanide *phenformin* was produced parallel to sulfonylureas in 1957. Newer approaches have constantly been explored and have lately yielded *thiazolidinediones*, *meglitinide analogues*, *α-glucosidase inhibitors* and the latest are *dipeptidyl peptidase-4 (DPP-4) inhibitors*.

CLASSIFICATION

A. *Enhance Insulin secretion*

1. *Sulfonylureas (K_{ATP} Channel blockers)*
   First generation: Tolbutamide
   Second generation: Glibenclamide (Glyburide), Glipizide, Gliclazide, Glimepiride
2. *Meglitinide/phenylalanine analogues*
   Repaglinide, Nateglinide
3. *Glucagon-like peptide-1 (GLP-1) receptor agonists* (Injectable drugs)
   Exenatide, Liraglutide
4. *Dipeptidyl peptidase-4 (DPP-4) inhibitors*
   Sitagliptin, Vildagliptin, Saxagliptin, Alogliptin, Linagliptin

B. *Overcome Insulin resistance*

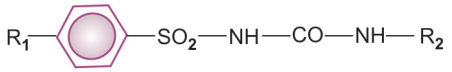
1. *Biguanide (AMP_K activator)*
   Metformin
2. *Thiazolidinediones (PPARγ activator)*
   Pioglitazone

C. *Miscellaneous antidiabetic drugs*

1. *α-Glucosidase inhibitors*
   Acarbose, Miglitol, Voglibose
2. *Amylin analogue*
   Pramlintide
3. *Dopamine-D2 receptor agonist*
   Bromocriptin
4. *Sodium-glucose cotransport-2 (SGLT-2) inhibitor*
   Dapagliflozin

Sulfonylureas (K_{ATP} Channel blockers)

The generic formula of sulfonylureas (SUs) is—



SULFONYLUREA

All SUs have similar pharmacological profile, their sole significant action being lowering of blood glucose level in normal subjects and in type 2 diabetics, but not in type 1 diabetics. Being more potent and clinically superior, only the second generation SUs are employed now. All first generation compounds have been discontinued except tolbutamide which is infrequently used.

Mechanism of action Sulfonylureas provoke a brisk release of insulin from pancreas, the mechanism of which is detailed in Fig. 19.6. The rate of insulin secretion at any glucose concentration is increased, i.e. insulin release is provoked even at low-glucose concentration risking production of severe and unpredictable hypoglycaemia. In type 2 DM the kinetics of insulin release in response to glucose or meals is delayed

and subdued. The SUs primarily augment the 2nd phase insulin secretion with little effect on the 1st phase. That they do not cause hypoglycaemia in pancreatectomised animals and in type 1 diabetics (presence of at least 30% functional β cells is essential for their action), confirms their indirect action through pancreas.

A minor action reducing glucagon secretion, probably by increasing insulin and somatostatin release has been demonstrated. Hepatic degradation of insulin is also slowed.

Extrapancreatic action After few months of administration, the insulinaemic action of SUs declines, probably due to down regulation of sulfonylurea receptors (SUR1) on β cells, but improvement in glucose tolerance is maintained. In this phase, they sensitize the target tissues (especially liver) to the action of insulin. This is due to increase in number of insulin receptors and/or a postreceptor action—improving translation of receptor activation. It is hypothesized that long-term improvement in carbohydrate tolerance leads to overall lowering of circulating insulin concentration which reverses the down regulation of insulin receptors. An apparent increase in their number occurs. A direct extrapancreatic action of SUs to increase insulin receptors on target cells and to inhibit gluconeogenesis in liver has been proposed, but appears to have little clinical relevance.

Pharmacokinetics All SUs are well absorbed orally, and are 90% or more bound to plasma proteins: have low volumes of distribution (0.2–0.4 L/kg). They are primarily metabolized—may produce active metabolite. The metabolites (active/inactive) are excreted in urine. As such, they should be used cautiously in patients with liver or kidney dysfunction.

The distinctive features of different SUs are given in Table 19.2.

Interactions

Drugs that enhance SU action (may precipitate hypoglycaemia) are—

(a) *Displace from protein binding:* Phenylbutazone, sulfinpyrazone, salicylates, sulfonamides.

(b) *Inhibit metabolism/excretion:* Cimetidine ketoconazole, sulfonamides, warfarin, chloramphenicol, acute alcohol intake (also synergises by causing hypoglycaemia).

(c) *Synergise with or prolong pharmacodynamic action:* Salicylates, propranolol (cardioselective β_1 blockers are less liable), sympatholytic antihypertensives, lithium, theophylline, alcohol (by inhibiting gluconeogenesis).

Drugs that decrease SU action (vitiate diabetes control) are—

(a) *Induce metabolism:* Phenobarbitone, phenytoin, rifampicin, chronic alcoholism.

(b) *Opposite action/suppress insulin release:* Corticosteroids, thiazides, furosemide, oral contraceptives.

Adverse effects Incidence of adverse effects is quite low (3–7%).

1. *Hypoglycaemia* It is the commonest problem, may occasionally be severe and rarely fatal. It is more common in elderly, liver and kidney disease patients and when potentiating drugs are added. Tolbutamide carries lowest risk due to its low potency and short duration of action.
Treatment of hypoglycaemic episode is to give glucose, may be for a few days because hypoglycaemia may recur.

2. *Nonspecific side effects* Majority of diabetics started on SUs tend to gain 1–3 kg weight. This may be a consequence of their insulinaemic action. Nausea, vomiting, flatulence, diarrhoea or constipation, headache and paresthesias are generally mild and infrequent.

3. *Hypersensitivity* Rashes, photosensitivity, purpura, transient leukopenia, rarely agranulocytosis.

Flushing and a disulfiram-like reaction after alcohol is reported to occur in some individuals taking SUs.

Tolbutamide reduces iodide uptake by thyroid but hypothyroidism does not occur.

Safety of SUs during pregnancy is not established. Change over to insulin is advised.

TABLE 19.2 **Important features of oral hypoglycaemics**

Drug	Preparations	Plasma t½ (hr)	Duration of action (hr)	Clearance route*	Daily dose	No. of doses per day	Remarks
SULFONYLUREAS							
1. Tolbutamide	RASTINON, 0.5 g tab.	6	6–8	L	0.5–3 g	2–3	Weaker, shorter acting, flexible dosage, safer in elderly and in those prone to hypoglycaemia.
2. Glibenclamide (Glyburide)	DAONIL, EUGLUCON, BETANASE 2.5, 5 mg tab.	2–4	24	L	2.5–15 mg	1–2	Potent but slow acting, higher incidence of hypoglycaemia, single daily dose despite short t½ due to active metabolite and sequestration in β cells.
3. Glipizide	GLYNASE, GLIDE MINIDIAB 5 mg tab	3–5	12	L	5–20 mg	1–2	Fast and shorter acting, higher daily dose to be devided, hypoglycaemia and weight gain less likely, preferable in elderly.
4. Gliclazide	DIAMICRON 80 mg tab. DIAZIDE 20, 80 mg tab GLIZID 30, 40, 80 mg tab	8–20	12–24	L	40–240 mg	1–2	Has antiplatelet action, generates only inactive metabolite, daily dose > 80mg to be divided.
5. Glimepiride	AMARYL, GLYPRIDE GLIMER 1, 2 mg tab	5–7	24	L	1–6 mg	1–2	Long acting, only inactive metabolite. Stronger extra-pancreatic action. Lower incidence of hypoglycaemia.
MEGLITINIDE / PHENYLALANINE ANALOGUES							
1. Repaglinide	EUREPA, RAPLIN REGAN 0.5, 1, 2 mg tab	≤ 1	3–5	L	1–8 mg	3–4	Given ½ hr before each meal for limiting p.p. hyperglycaemia.
2. Nateglinide	GLINATE, NATELIDE 60,120 mg tab	1.5	2–4	L	180–480 mg	3–4	Stimulates 1st phase insulin secretion, less likely to cause delayed hypoglycaemia.
DPP-4 INHIBITORS							
1. Sitagliptin	JANUVIA 100 mg tab.	~12	24	K	100 mg	1	Non-covalent binding to DPP-4; excreted unchanged in urine. Low risk of hypoglycaemia. Body weight neutral.
2. Vildagliptin	GALVUS, JALRA, ZOMELIS 50 mg cap	2–4	12–24	L,K	50–100 mg	1–2	Covalent binding to DPP-4; Metabolized in liver. Hepatotoxicity reported.
BIGUANIDE							
1. Metformin	GLYCIPHAGE, GLYCOMET 0.5, 0.85 g tab, 0.5 g and 1.0 g SR tabs	1.5–3	6–8	K	0.5–2.5 g	1–2	No hypoglycaemia. Not metabolized. Lactic acidosis rare, only in kidney disease.
THIAZOLIDINEDIONE							
1. Pioglitazone	PIONORM, PIOREST, PIOZONE 15, 30 mg tab	3–5	24	L	15–45 mg	1	May improve lipid profile. Reverses insulin resistance. No hypoglycaemia, C/I in liver and heart disease.

*L—Metabolized in liver; K—Excreted unchanged by kidney; p.p.—postprandial

Sulfonylureas are secreted in milk: should not be given to nursing mothers.

Chlorpropamide is one of the first SUs which has been discontinued because of long duration of action (≥ 2 days) and frequent hypoglycaemia. It was also prone to cause dilutional hyponatraemia (by sensitizing kidney to ADH action), cholestatic jaundice and alcohol flush.

Meglitinide / D-phenylalanine analogues (K_{ATP} Channel blockers)

These are K_{ATP} channel blockers with a quick and short lasting insulinemic action.

Repaglinide This meglitinide analogue oral hypoglycaemic is designed to normalise meal-time glucose excursions. Though not a sulfonylurea, it acts in an analogous manner by binding to SUR → closure of ATP dependent K^+ channels → depolarisation → insulin release (*see* Fig. 19.6).

Repaglinide is quickly absorbed and rapidly metabolized. It induces fast onset short-lasting insulin release. Because of this characteristic its pattern of use is different from that of SUs. It is administered before each major meal to control postprandial hyperglycaemia; the dose should be omitted if a meal is missed. Because of short lasting action it may have a lower risk of serious hypoglycaemia. Side effects are mild headache, dyspepsia, arthralgia and weight gain.

Repaglinide is indicated only in selected type 2 diabetics who suffer pronounced post prandial hyperglycaemia, or to supplement metformin/long-acting insulin. It should be avoided in liver disease.

Nateglinide It is a D-phenylalanine derivative which principally stimulates the 1st phase insulin secretion by closing β cell K_{ATP} channels resulting in faster onset and shorter lasting hypoglycaemia than repaglinide. Ingested 10 min before meal, it limits postprandial hyperglycaemia in type 2 diabetics without producing late phase hypoglycaemia. There is little effect on fasting blood glucose level. Episodes of hypoglycaemia are less frequent than with SUs. Side effects are dizziness, nausea, flu like symptoms and joint pain. It is used in type 2 DM along with other antidiabetics, to control postprandial rise in blood glucose.

Glucagon-like peptide-1 (GLP-1) receptor agonists

GLP-1 is an important incretin released from the gut in response to ingested glucose. It induces insulin release from pancreatic β cells, inhibits glucagon release from α cells, slows gastric emptying and suppresses appetite by activating specific GLP-1 receptors, which are cell surface GPCRs (*see* Fig. 19.6) expressed on β and α cells, central and peripheral neurones, gastrointestinal mucosa, etc. Characteristically GLP-1 induces insulin release only at high glucose concentration. The incretin system appears to promote β cell health as well. Failure of incretins has been implicated in the pathogenesis of β cell dysfunction of type 2 DM, particularly progression of the disease. GLP-1 based therapy appears to be the most effective measure for preserving β cell function in type 2 DM.

GLP-1 itself is not suitable for clinical use because of rapid degradation by the enzyme *dipeptidyl peptidase-4 (DPP-4)* which is expressed on the luminal membrane of capillary endothelial cells, kidney, liver gut mucosa and immune cells. Another incretin *glucose-dependent insulinotropic peptide* (GIP) also induces insulin release, but in human beings GLP-1 is the more important incretin and GIP has poor action in type 2 diabetics. The GIP receptor is distinct from GLP-1 receptor, but mediates mostly similar responses. Some more stable analogues of GLP-1 have been produced for clinical use in type-2 DM.

Exenatide It is a synthetic DPP-4 resistant analogue which activates GLP-1 receptors (Fig. 19.6) and produces the same responses. Being a peptide, it is inactive orally. After s.c. injection its plasma t½ is ~ 3 hours and duration of action 6–10 hours. It is marketed in USA, UK, Europe for use mainly as add-on drug to metformin/SU or a combination of these or pioglitazone in poorly controlled type 2 diabetics. Benefits noted are lowering of postprandial as well as fasting blood glucose, HbA_{1c} and body weight. The most important side effect is nausea and vomiting occurring in ~ 50% recipients, but tolerance develops later.

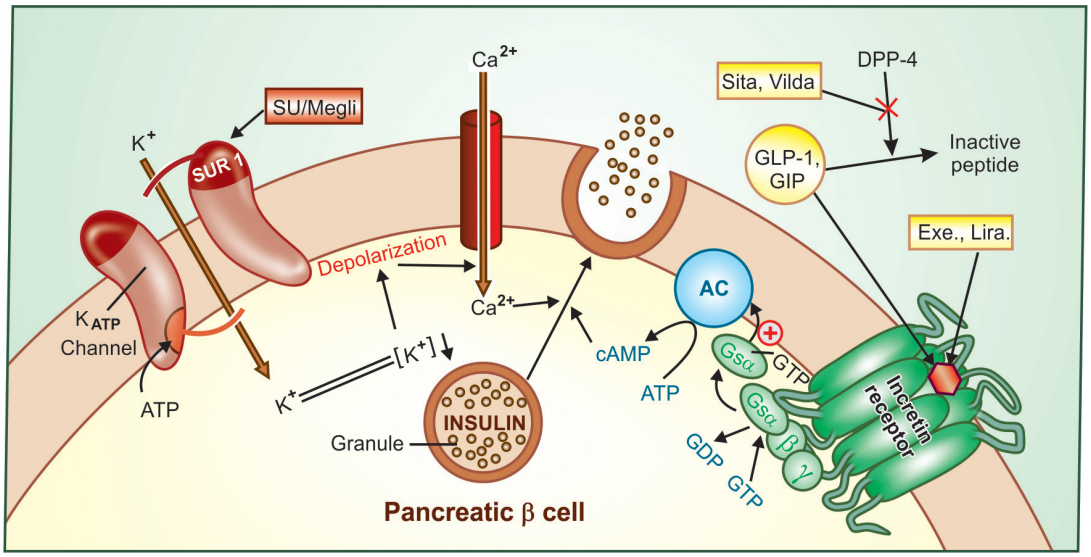


Fig. 19.6: Mechanism of action of insulin secretagogues

The sulfonylureas (SU) and meglitinide analogues (Megli) block the sulfonylurea receptor (SUR1) which constitutes a subunit of the inwardly rectifying ATP-sensitive K^+ channel (K_{ATP}) in the membrane of pancreatic β cells. The inward flow of K^+ ions is thereby restricted, intracellular K^+ concentration falls and the membrane is partially depolarized augmenting Ca^{2+} channel opening as well as release of Ca^{2+} from intracellular stores. The Ca^{2+} ions promote fusion of insulin containing intracellular granules with the plasma membrane and exocytotic release of insulin.

Incretins such as glucagon-like peptide 1 (GLP1) and glucose-dependent insulinotropic polypeptide (GIP) act upon their own G-protein coupled receptors on the β cell membrane to activate adenylyl cyclase and generate cAMP, which also promotes exocytosis of insulin. Exenatide (Exe) and liraglutide (Lira) are GLP1 receptor agonists—produce the same response as GLP1. The incretins GLP1 and GIP are rapidly inactivated by the capillary endothelial enzyme dipeptidyl peptidase-4 (DPP-4). Their action is enhanced by DPP-4 inhibitors sitagliptin (sita) and vildagliptin (vilda). The DPP-4 inhibitors thus markedly accentuate the insulin response to ingested glucose/meal and attenuate post-prandial glycaemia.

Liraglutide This recently developed long-acting GLP-1 agonist is closely related to the native peptide but its tight binding to plasma proteins extends t½ to > 12 hours and duration of action to > 24 hours. Injected s.c. once daily, alone or added to oral metformin ± SU or pioglitazone, it has achieved improved glycaemic control in type 2 diabetics. Nausea and diarrhoea are the frequent side effects, but decrease in incidence over time. Use of liraglutide is attended by weight loss, and it is being evaluated as an antiobesity drug even for nondiabetics.

Hypoglycaemia is rare with exenatide/liraglutide monotherapy, but can occur when combined with SUs/metformin.

Dipeptidyl peptidase-4 (DPP-4) inhibitors

Realizing the key role of the enzyme DPP-4 in rapid degradation of endogenous GLP-1, orally active inhibitors of this enzyme have been developed as indirectly acting insulin secretagogues. In the past few years, DPP-4 inhibitors have emerged as important adjunctive drugs in type 2 DM.

Sitagliptin This is the first DPP-4 inhibitor introduced in USA in 2006 and now available world wide. It is a competitive and selective DPP-4 inhibitor which potentiates the action of GLP-1 (Fig. 19.6) and GIP, boosts post prandial insulin release, decreases glucagon secretion and lowers meal-time as well as fasting blood glucose in type 2 diabetics. No effect on gastric emptying and appetite have been noted. It is body weight neutral and carries low risk of hypoglycaemia unless combined with SUs or insulin. The HbA_{1c} lowering caused by sitagliptin is equivalent to that with metformin. Further lowering of HbA_{1c} occurs when it is added to pioglitazone/SUs/insulin

with or without metformin. However, sitagliptin monotherapy is recommended only when metformin cannot be used. Most professional guidelines recommend DPP-4 inhibitors primarily as adjuvant drugs in type 2 diabetics not well controlled by metformin/SUs/pioglitazone or insulin. Though clinical efficacy of all DPP-4 inhibitors is comparable, one metaanalysis has found sitagliptin to cause greater reduction of fasting blood glucose than vildagliptin.

Sitagliptin is well absorbed orally, is little metabolized and is largely excreted unchanged in urine with a t½ averaging 12 hours. Dose reduction is needed in renal impairment, but not in liver disease. Sitagliptin is well tolerated, side effects are nausea, loose stools, headache, rashes, allergic reactions and edema. Nasopharyngitis and cough occurs in some patients, which has been ascribed to prevention of substance P degradation. Pancreatitis is rare.

Vildagliptin This is the second DPP-4 inhibitor available in Europe and India which binds to the enzyme covalently. The complex dissociates very slowly resulting in persistent DPP-4 inhibition even after the free drug has been cleared from circulation. This explains the longer duration of action (12–24 hours) despite short plasma t½ (2–4 hours). The major route of elemination is by hepatic metabolism; only 20–25% is excreted unchanged in urine. Dose reduction is needed in moderately severe liver and kidney disease. No significant drug interactions have been reported. Vildagliptin is less selective than sitagliptin for DPP-4; causes some inhibition of DPP-8, DPP-9 as well, but the clinical significance of this feature is not known. The tolerability of vildagliptin is similar to that of sitagliptin, but hepatotoxicity has been reported. Vildagliptin may require twice daily dosing; though single daily dose suffices in most cases when combined with another hypoglycaemic.

Saxagliptin It has been available in USA since 2009, and is recently marketed in India. Like vildagliptin, it binds covalently with DPP-4 and acts for 24 hours despite a plasma t½ of 2–4 hours. It is metabolized by CYP3A4 and generates an active metabolite that has a t½ of 3–7 hours. Drug interactions with CYP3A4 inhibitors are possible.

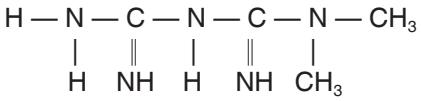
Dose: 5 mg OD; reduce by half in moderately severe renal failure, but not in liver disease.

ONGLYZA 2.5, 5 mg tabs

Alogliptin is marketed in Japan and *Linagliptin* has been recently approved in USA.

Biguanide (AMPK activator)

Two biguanide antidiabetics, *phenformin* and *metformin* were introduced in the 1950s. Because of higher risk of lactic acidosis, phenformin was withdrawn and has been banned in India since 2003.



METFORMIN

Metformin It differs markedly from SUs: causes little or no hypoglycaemia in nondiabetic subjects, and even in diabetics, episodes of hypoglycaemia are rare. It does not stimulate pancreatic β cells. Metformin is reported to improve lipid profile as well in type 2 diabetics.

Mechanism of action Biguanides do not cause insulin release, but presence of insulin is essential for their action. Metformin is not effective in pancreatectomized animals and in type 1 diabetics. Though the details are not clear, recent studies have recognized activation of AMP-dependent protein kinase (AMPK) to play a crucial role in mediating the actions of metformin, the key features of which are:

1. Suppresses hepatic gluconeogenesis and glucose output from liver. This is the major action responsible for lowering of blood glucose in diabetics.
2. Enhances insulin-mediated glucose uptake and disposal in skeletal muscle and fat. Insulin resistance exhibited by type-2 diabetics is thus overcome. This translates into—
   - glycogen storage in skeletal muscle

- reduced lipogenesis in adipose tissue and enhanced fatty acid oxidation.

3. Interferes with mitochondrial respiratory chain and promotes peripheral glucose utilization through anaerobic glycolysis.

AMPK activation by metformin appears to be an indirect consequence of interference with cellular respiration and lowering of intracellular ATP and other energy sources.

Metformin also retards intestinal absorption of glucose, other hexoses, amino acids and Vit B_{12}.

Pharmacokinetics The important features of metformin pharmacokinetics are given in Table 19.2. Clearance of metformin approximates g.f.r. It accumulates in renal failure and increases the risk of lactic acidosis.

Adverse effects Side effects with metformin are frequent, but generally not serious. Abdominal pain, anorexia, bloating, nausea, metallic taste, mild diarrhoea and tiredness are the usual complaints, which tend to subside with time. Metformin does not cause hypoglycaemia except in overdose.

Lactic acidosis Small increase in blood lactate occurs with metformin, but lactic acidosis is rare (<1 per 10,000 patient years) because it is poorly concentrated in hepatic cells. Alcohol ingestion can precipitate lactic acidosis.

Vit B_{12} deficiency due to interference with its absorption can occur with high dose of metformin.

In addition to general restrictions for use of oral hypoglycaemics (*see* below), metformin is contraindicated in hypotensive states, heart failure, severe respiratory, hepatic and renal disease, as well as in alcoholics because of increased risk of lactic acidosis.

Drugs like cimetidine, furosemide may compete with metformin excretion and enhance its toxicity.

Uses Metformin is now established as a first choice drug for all type 2 DM patients, except when not tolerated or contraindicated.

Advantages of metformin are:

- nonhypoglycaemic
- weight loss promoting
- has potential to prevent macrovascular as well as microvascular complications of diabetes
- no acceleration of β cell exhaustion/ failure in type 2 DM.
- antihyperglycaemic efficacy (HbA_{1c} reduction by 0.8–1.2%) equivalent to other oral drugs.
- can be combined with any other oral or injectable antidiabetic, if one drug is not adequate.

The limiting feature is g.i. intolerance, especially at higher doses, but lack of serious toxicity is well established by decades of use.

Infertility: Metformin has been found to improve ovulation and fertility in some infertile women with polycystic ovary. This benefit is observed irrespective of the glycaemic status of the woman. It may be due to mitigation of insulin resistance and lowering of circulating insulin levels.

Thiazolidinedione (PPARγ agonist)

Pioglitazone Only one thiazolidinedione *Pioglitazone* is currently available. *Rosiglitazone,* the other member, is banned in India since 2010 and has been withdrawn in Europe due to unacceptable increase in risk of myocardial infarction, CHF, stroke and death. This class of oral antidiabetic drugs are selective agonists for the nuclear *peroxisome proliferator-activated receptor* γ (PPARγ) which is expressed mainly in fat cells, but also in muscle and some other cells. It enhances the transcription of several insulin responsive genes. Glitazones tend to reverse insulin resistance by enhancing GLUT4 expression and translocation. Entry of glucose into muscle and fat is improved. Hepatic gluconeogenesis is also suppressed. Activation of genes regulating fatty acid metabolism and lipogenesis in adipose tissue contributes to the insulin sensitizing action. Lipolysis and plasma fatty acid levels are reduced. Adipocyte turnover and differentiation is accelerated by glitazones. Thus, fatty tissue is a major site of their action. The magnitude of blood glucose reduction is somewhat less than SUs and metformin. Improved glycaemic control results in lowering of circulating HbA_{1C} and insulin levels in type 2 DM patients.

Pioglitazone, in addition, lowers serum triglyceride level and raises HDL level without much change in LDL level, probably because it acts on PPARα as well to induce expression of reverse cholesterol transporter and some apoproteins.

Pioglitazone is well tolerated; adverse effects are plasma volume expansion, edema, weight gain, headache, myalgia and mild anaemia. Monotherapy with glitazones is not associated with hypoglycaemic episodes. Few cases of hepatic dysfunction have been reported; CHF may be precipitated or worsened. Monitoring of liver function is advised. It is contraindicated in liver disease and in CHF. Glitazones increase the risk of fractures, especially in elderly women.

Pioglitazone is metabolized by both CYP2C8 and CYP3A4. Failure of oral contraception may occur during pioglitazone therapy. Ketoconazole inhibits and rifampin induces metabolism of pioglitazone.

Pioglitazone is indicated in type 2 DM, but not in type 1 DM. It reduces blood glucose and HbA_{1c} (by 0.5–1.2%) without increasing circulating insulin. About 25% patients may not respond (nonresponders), probably due to low baseline insulin levels. It should be stopped if HbA_{1c} reduction is < 0.5% at 6 months. Pioglitazone is primarily used to supplement SUs/metformin and in case of insulin resistance. However, it is not likely to be effective when β cell failure has set in, which may be the cause of loss of efficacy to a combination of SUs + metformin. It may also be used as monotherapy (along with diet and exercise) in mild cases.

Several reports describe greater fluid retention, weight gain and precipitation of CHF after combined use of glitazones with insulin. Experts advise avoiding such combination. Pioglitazone should not be used during pregnancy. The Diabetes Prevention Programme (2005) has shown that glitazones have the potential to delay progression of prediabetics to overt type 2 DM. They may help to conserve β cell function in diabetics.

α Glucosidase inhibitors

Acarbose It is a complex oligosaccharide which reversibly inhibits α-glucosidases, the final enzymes for the digestion of carbohydrates in the brush border of small intestine mucosa. It slows down and decreases digestion and absorption of polysaccharides (starch, etc.) and sucrose. In addition, GLP-1 release is promoted which may contribute to the effect. Postprandial glycaemia is reduced without significant increase in insulin levels. Regular use lowers HbA_{1c} modestly (by 0.4–0.8%), but change in body weight and lipid levels is minimal. The stop-NIDDM trial (2002) has shown that long-term acarbose treatment in prediabetics reduces occurrence of type 2 DM as well as hypertension and cardiac disease. In diabetics, it reduces cardiovascular events.

Acarbose is a mild antihyperglycaemic and not a hypoglycaemic; may be used as an adjuvant to diet (with or without metformin/SU) in obese diabetics. Dose 50–100 mg TDS is taken at the beginning of each major meal. Only a small fraction of the dose is absorbed. Flatulence, abdominal discomfort and loose stool are produced in about 50% patients due to fermentation of unabsorbed carbohydrates. Patient acceptability of α-glucosidase inhibitors is poor due to uncomfortable g.i. symptoms. Hepatic transaminases may rise, but liver damage is rare.
GLUCOBAY 50, 100 mg tabs, ASUCROSE, GLUCAR 50 mg tabs.

Miglitol It has a smaller molecule than acarbose, and it is a stronger inhibitor of sucrase. Potency for other α-glucosidases is equivalent to acarbose. Absorption of miglitol is substantial, but variable. The absorbed drug is excreted by the kidney. No systemic toxicity is known.
Dose: 25–100 mg TDS at beginning of each meal.
MIGTOR, DIAMIG, ELITOX 25, 50 mg tabs.

Voglibose Has properties, use and side effects similar to that of acarbose.
Dose: 200–300 mg TDS just before meals.
VOGLITOR, VOLIX, VOLIBO 0.2, 0.3 g tabs.

Amylin analogue

Amylin, also called 'islet amyloid polypeptide' (IAP), is produced by pancreatic β cells and acts in the brain to reduce glucagon secretion from α cells, delay gastric emptying, retard glucose absorption and promote satiety.

Pramlintide It is a synthetic amylin analogue which on s.c. injection before meal attenuates postprandial glycaemia and exerts a centrally mediated anorectic action. The duration of action is 2–3 hours. It has been used as an adjuvant to meal time insulin injection to suppress the glycaemic peak in both type 1 and type 2 diabetics. Reduction in body weight is an additional benefit.

Dopamine D2 agonist

Bromocriptine Recently (2009) a quick release oral formulation of bromocriptine has been approved by US-FDA for adjunctive treatment of type 2 DM. Taken early in the morning it is thought to act on the hypothalamic dopaminergic control of the circadian rhythm of hormone (GH, prolactin, ACTH, etc.) release and reset it to reduce insulin resistance. Bromocriptin can be taken alone to supplement diet+exercise or added to metformin or SU or both. Started at 0.8 mg OD and increased upto 4.8 mg OD (as needed) it has been shown to marginally improve glycaemic control and lower HbA_{1c} by upto 0.5%.

Sodium-glucose co-transport-2 (SGLT-2) inhibitor

Practically all the glucose filtered at the glomerulus is reabsorbed in the proximal tubules. The major transporter which accomplishes this is *SGLT-2*, whose inhibition induces glucosuria and lowers blood glucose in type 2 DM, as well as causes weight loss.

Dapagliflozin This SGLT-2 inhibitor has been recently tested in type 2 DM patients. After single daily dose it produces round-the-clock glucosuria and lowers blood glucose levels. The concerns which appear inbuilt due to its mechanism of action are—glycosuria which can predispose to urinary and genital infections, electrolyte imbalance and increased urinary frequency. Tolerability and safety of this drug is yet to be established.

Status of oral hypoglycaemics in diabetes mellitus

After 8 years of prospective study involving large number of patients, the University Group Diabetes Programme (UGDP) of USA (1970) presented findings that cardiovascular mortality was higher in patients treated with biguanides and SUs than in those treated with diet and exercise alone or with insulin. A decline in their use followed. Subsequent studies both refuted and supported these conclusions.

The controversy has been settled by the UK PDS trial which found that both SUs and metformin did not increase cardiovascular mortality over > 10 years observation period. Related to degree of glycaemia control, both insulin and SUs reduced microvascular complications (retinopathy, neuropathy, nephropathy) in type 2 DM, but did not have significant effect on macrovascular complications (coronary artery disease, stroke, etc). Metformin, however, could reduce macrovascular complications as well; it decreased risk of death and other diabetes related endpoints in overweight patients. This may be related to the fact that both SUs and exogenous insulin improve glycaemic control by increasing insulin supply rather than by reducing insulin resistance, while metformin can lower insulin resistance which is a pathogenic factor in type 2 DM. All oral hypoglycaemics do however control symptoms that are due to hyperglycaemia and glycosuria, and are much more convenient than insulin.

Oral hypoglycaemics are indicated only in type 2 diabetes, in addition to diet and exercise. They are most effective in patients with—

1. Age above 40 years at onset of disease.
2. Obesity at the time of presentation.
3. Duration of disease < 5 years when starting treatment.
4. Fasting blood sugar < 200 mg/dl.
5. Insulin requirement < 40 U/day.
6. No ketoacidosis or a history of it, or any other complication.

The Diabetes Prevention Programme (2002) has established that in middle aged, obese prediabetics metformin prevented progression to type 2 DM, but not in older nonobese prediabetics. Glitazones also appear to have prophylactic potential. Long-term acarbose therapy as well can delay type 2 DM.

Oral hypoglycaemics should be used to supplement dietary management and not to replace it. In view of the prophylactic and outcome benefits, current recommendation is to institute metformin therapy right at the diagnosis of type 2 DM, along with dietary and other lifestyle measures, without waiting to see if the latter alone are sufficient. Metformin may delay progression of diabetic severity by favourably affecting β cell

health and retarding β cell failure. It is especially valuable for obese patients; may also aid weight reduction. Further, it has the potential to reduce the risk of myocardial infarction and stroke. Thus, unless contraindicated/not tolerated, metformin is prescribed to all type 2 diabetics, despite its inferior patient acceptability due to g.i. side effects.

Many type 2 DM patients do not attain desired level of glycaemia control and HbA_{1c} reduction (to < 7%) with metformin alone, and a second drug is needed. SUs are the most commonly selected 2nd drug. They have good patient acceptability, convenient dosing and high efficacy, but can cause weight gain and hypoglycaemia. There is some evidence that SUs given over long-term (2–10 years) expedite β cell apoptosis and failure. Receptor desensitization may also be a cause, and SUs tend to lose efficacy in few years (5–10% per year failure rate). There is no difference in the clinical efficacy of different 2nd generation SUs. However, this does not indicate that choice among them is irrelevant. Differences among them are mainly in dose, onset and duration of action which govern flexibility of regimens. Some specific features of various SUs are given in Table 19.2. If a particular SU proves inadequate in a given patient, another one may still work.

Patients with near normal fasting blood glucose but prominent post-prandial hyperglycaemia, or those experiencing late postmeal hypoglycaemia may do better with a premeal meglitinide/phenyl alanine analogue.

Pioglitazone is usually the 3rd choice drug; may be added to metformin or a combination of metformin + SU. Though it reduces insulin resistance, tends to preserve β cell function and does not cause hypoglycaemia, it is infrequently selected for monotherapy. Its major limitations are—tendency to fluid retention, weight gain, increased risk of heart failure and fractures, need to monitor liver function and inefficacy in a significant number of patients.

Acarbose-like drugs are mild antihyperglycaemics, mostly used as supplementary drugs to a combination hypoglycaemic regimen. They are disliked by many patients because of bloating, indigestion and other abdominal symptoms.

The latest hypoglycaemics gaining popularity are the DPP-4 inhibitors. Their favourable features are:

- Insulin release is glucose dependent; therefore not likely to induce hypoglycaemia.
- Suppress glucagon release, thus lowering fasting blood glucose as well.
- Improve β cell health and retard progression of β cell failure.
- Body weight neutral.
- Mostly single daily dose, well tolerated with few side effects, no serious toxicity, no drug interactions, except with saxagliptin.

However, they are new drugs and have not withstood the test of time yet. Their impact on cardiovascular mortality and other outcomes is yet to be measured. As such, most professional guidelines place them as second line/add on antidiabetic drugs. They are especially valuable for patients having body weight problem and those experiencing frequent episodes of hypoglycaemia.

Upto 50% patients of type 2 DM initially treated with oral hypoglycaemics ultimately need insulin. Moreover, when a diabetic on oral hypoglycaemics presents with infection, severe trauma or stress, pregnancy, ketoacidosis or any other complication, or has to be operated upon—switchover to insulin (*see* Flow chart in Fig. 19.7). Metformin and/or SUs or DPP-4 inhibitors can also be combined with insulin, particularly when a single daily injection of long-acting (e.g. glargine) insulin is used to provide basal control. The oral drug given before meals serves to check postprandial glycaemia.

Epalrestat Sorbitol is a minor metabolite of glucose generated by the enzyme *aldose reductase*. In diabetics, excess sorbitol is produced and gets deposited in nerves and other tissues. This is involved in the pathogenesis of diabetic neuropathy and other complications. *Epalrestat* is an aldose reductase inhibitor developed in Japan which has been found to delay sorbitol accumulation in sciatic nerve/other tissues of diabetics imparting potential to delay progression of diabetic neuropathy. In trials it has caused modest improvement in nerve conduction, neuropathic pain and other symptoms. However, magnitude of benefit and safety are yet to be defined. Nausea, vomiting and elevation of liver enzymes are the adverse effects.
Dose: 50 mg TDS before meals; ALRISTA 50 mg tab.

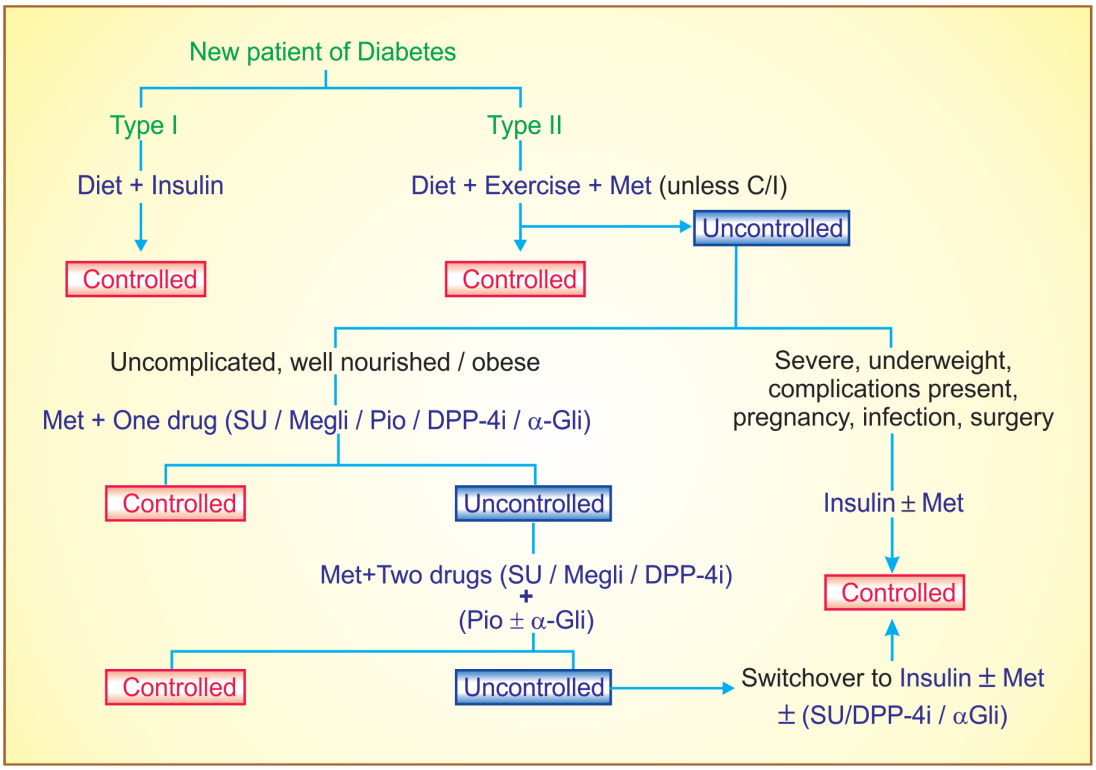


Fig. 19.7: Simplified flow chart of management approaches in diabetes mellitus.
Met—Metformin; SU—Sulfonylurea; Megli—Meglitinide/d-phenylalanine analogue; DPP-4i—Dipeptidyl peptidase-4 inhibitor; α Gli—α Glucosidase inhibitor; Pio—Pioglitazone
Note: A meglitinide drug is indicated only in patients with predominant postprandial hyperglycaemia.
An α glucosidase inhibitor can be additional add on drug.

GLUCAGON

A hyperglycaemic principle was demonstrated to be present in the pancreatic islets just two years after the discovery of insulin in 1921. It was named 'glucagon'. Glucagon is a single chain polypeptide containing 29 amino acids, MW 3500. It is secreted by the α cells of the islets of Langerhans and commercially produced now by recombinant DNA technology.

Regulation of Secretion Like insulin, glucagon is also derived by cleavage of a larger peptide prohormone. Its secretion is regulated by glucose levels, other nutrients, paracrine hormones and nervous system. Glucose has opposite effects on insulin and glucagon release, i.e. high glucose level inhibits glucagon secretion. The incretin GLP-1, FFA and ketone bodies also inhibit glucagon release. Amino acids, however, induce both insulin and glucagon secretion. Insulin, amylin and somatostatin, elaborated by the neighbouring β and δ cells, inhibit glucagon secretion. Sympathetic stimulation consistently and parasympathetic stimulation under certain conditions evokes glucagon release.

Actions Glucagon is hyperglycaemic; most of its actions are opposite to that of insulin. Glucagon causes hyperglycaemia primarily by enhancing glycogenolysis and gluconeogenesis in liver; suppression of glucose utilization in muscle and fat contributes modestly. Glucagon is considered to be the hormone of fuel mobilization. Its secretion is increased during fasting, and is largely responsible for the high fasting blood glucose levels in type 2 diabetics. It plays an essential role in the development of diabetic ketoacidosis. Increased secretion of glucagon has been shown to attend all forms of severe tissue injury.

Glucagon increases the force and rate of cardiac contraction and this is not antagonized by β blockers. It has a relaxant action on the gut and inhibits gastric acid production.

Mechanism of action Glucagon, through its own receptor and coupling Gs protein activates adenylyl cyclase and increases cAMP in liver, fat cells, heart and other tissues; most of its actions are mediated through this cyclic nucleotide.

Glucagon is inactive orally; that released from pancreas is broken down in liver, kidney, plasma and other tissues. Its t½ is 3–6 min.

Uses

1. *Hypoglycaemia* due to insulin or oral hypoglycaemics; use of glucagon is; only an expedient measure for the emergency, and must be followed by oral glucose/sugar given repeatedly till the blood glucose level stabilizes. It may not work if hepatic glycogen is already depleted.
Dose: 0.5–1.0 mg i.v. or i.m.
GLUCAGON 1 mg inj.

2. *Cardiogenic shock* to stimulate the heart in β adrenergic blocker treated patients. However, action is not very marked.

3. To facilitate radiographic examination of upper/lower g.i. tract by relaxing stomach and intestines.

Other hyperglycaemics

Diazoxide Chemically related to thiazides, it inhibits insulin release from β cells and causes hyperglycaemia lasting 4–8 hours. Its action on ATP sensitive K^+ channels of β cells is opposite to that of SUs. Other actions which may contribute to hyperglycaemia are decreased peripheral utilization of glucose and release of catecholamines. It has been used to prevent hypoglycaemia in insulinomas. Other actions are vasodilatation, fall in BP and antidiuresis.

Somatostatin It causes hyperglycaemia primarily by inhibiting insulin release.

Streptozocin It is obtained from *Streptomyces achromogenes*. Causes selective damage to insulin secreting β cells. It has been used to produce experimental diabetes in animals and to treat insulin secreting tumours of pancreas.

☞ PROBLEM DIRECTED STUDY

19.1 During routine medical checkup a 50-year male office executive with sedentary lifestyle was diagnosed to have developed type 2 diabetes mellitus. His fasting and post-meal blood glucose was 130 mg/dl and 190 mg/dl respectively, HbA_{1C} was 7.8%, BP was 130/82 mm Hg and body mass index was 27 kg/m^2. He was asymptomatic and investigations revealed no end organ damage. He was advised suitable diet, exercise and other lifestyle modifications.

(a) Should he be prescribed an antidiabetic medication as well? If so, which drug/combination of drugs should be selected, and why?

(see Appendix-1 for solution)

Chapter 20 Corticosteroids

The adrenal cortex secretes steroidal hormones which have glucocorticoid, mineralocorticoid and weakly androgenic activities. Conventionally, the term 'corticosteroid' or 'corticoid' includes natural gluco- and mineralo-corticoids and their synthetic analogues.

By the middle of 19th century it was demonstrated that adrenal glands were essential for life. Later it was appreciated that the cortex was more important than the medulla. A number of steroidal active principles were isolated and their structures were elucidated by Kendall and his coworkers in the 1930s. However, the gate to their great therapeutic potential was opened by Hench (1949) who obtained striking improvement in rheumatoid arthritis by using cortisone. The Nobel Prize was awarded the very next year to Kendall, Reichstein and Hench.

BIOSYNTHESIS

The corticoids (both gluco and mineralo) are 21 carbon compounds having a cyclopentanoperhydro-phenanthrene (steroid) nucleus. They are synthesized in the adrenal cortical cells from cholesterol. A simplified version of the biosynthetic pathways is presented in Fig. 20.1. Adrenal steroidogenesis takes place under the influence of ACTH which makes more cholesterol available for conversion to pregnenolone and induces steroidogenic enzymes. Since adrenal cortical cells store only minute quantities of the hormones, rate of release is governed by the rate of biosynthesis. The circulating corticosteroids inhibit ACTH release from pituitary as well as CRH production from hypothalamus (*see* Ch. 17) and thus provide negative feed back regulation of the hypothalamo-pituitary-adrenal (HPA) axis.

The normal rate of secretion of the two principal corticoids in man is—

Hydrocortisone— 10–20 mg daily (nearly half of this in the few morning hours).
Aldosterone — 0.125 mg daily.

ACTIONS

The corticoids have widespread actions. They maintain fluid-electrolyte, cardiovascular and

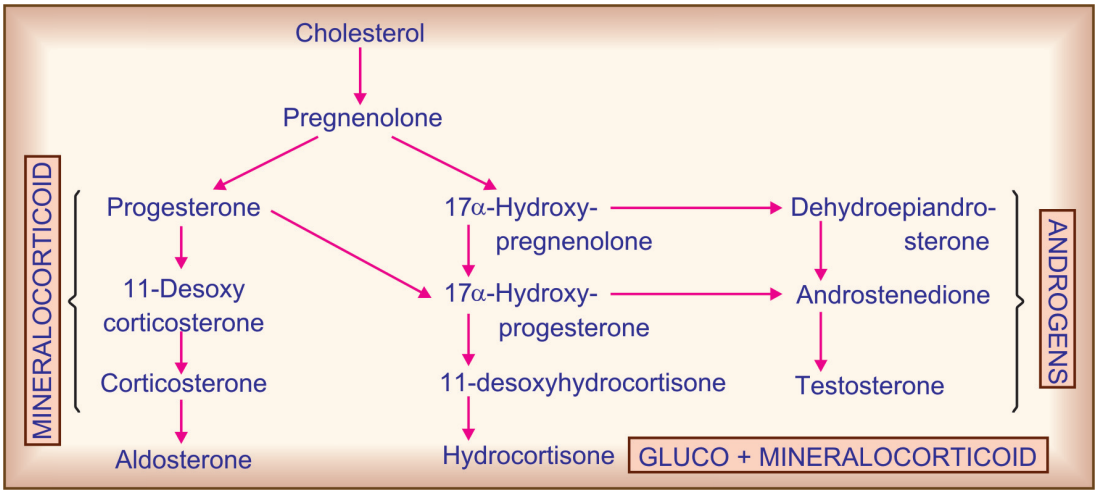


Fig. 20.1: Simplified depiction of the pathways of adrenal steroid hormone biosynthesis

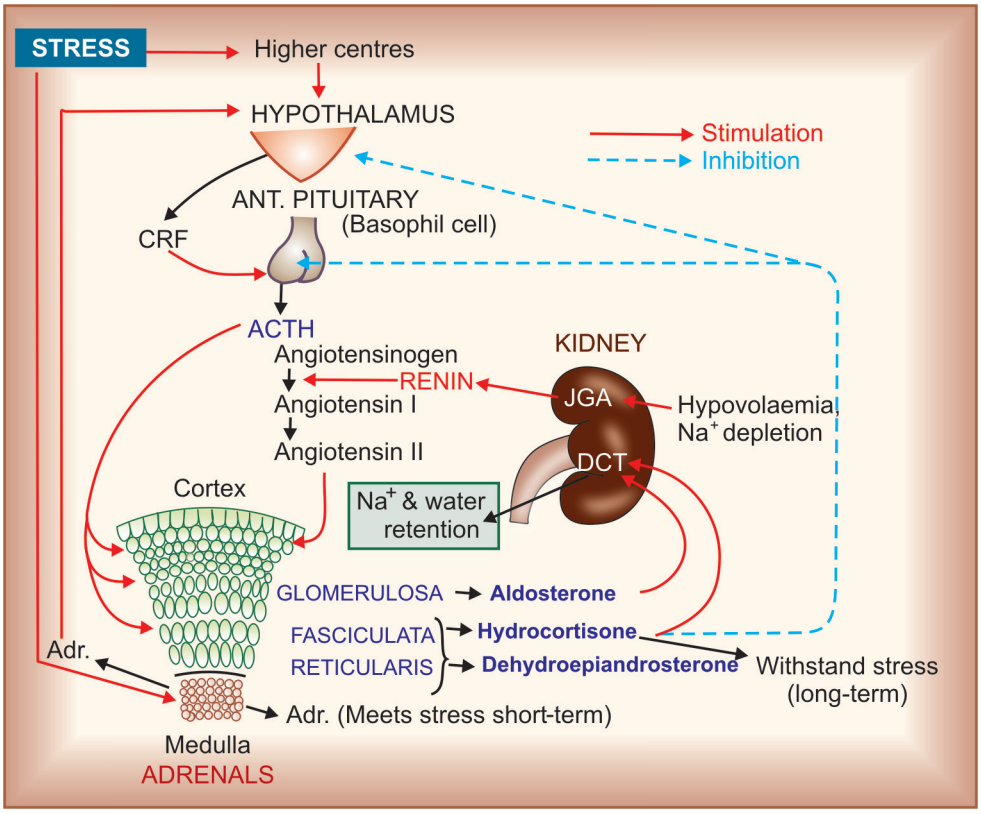


Fig. 20.2: Hypothalamo-pituitary-adrenal (HPA) axis; regulation of corticosteroid production and response to stress which overrides the negative feedback regulation of ACTH release

energy substrate homeostasis and functional status of skeletal muscles and nervous system. They prepare the body to withstand effects of all kinds of noxious stimuli and stress. The involvement of hypothalamo-pituitary-adrenal axis in stress response is depicted in Fig. 20.2.

Corticoids have some *direct* and some *permissive* actions. By permissive action is meant that while they do not themselves produce an effect, their presence facilitates other hormones to exert that action, e.g. they do not have any effect on BP but the pressor action of Adr is markedly blunted in their absence. Actions of corticoids are divided into:

Glucocorticoid Effects on carbohydrate, protein and fat metabolism, and other actions that are inseparably linked to these.

Mineralocorticoid Effects on Na^+, K^+ and fluid balance.

Marked dissociation between these two types of actions is seen among natural as well as synthetic corticoids. Accordingly, compounds are labelled as 'glucocorticoid' or 'mineralocorticoid'.

Mineralocorticoid actions

The principal mineralocorticoid action is enhancement of Na^+ reabsorption in the distal convoluted tubule in kidney. There is an associated increase in K^+ and H^+ excretion. Its deficiency results in decreased maximal tubular reabsorptive capacity for Na^+; kidney is not able to retain Na^+ even in the Na^+ deficient state → Na^+ is progressively lost: kidneys absorb water without the attendant Na^+ (to maintain e.c.f. volume which

nevertheless decreases) → dilutional hyponatraemia → excess water enters cells → cellular hydration: decreased blood volume and raised haematocrit. Hyperkalaemia and acidosis accompany. These distortions of fluid and electrolyte balance progress and contribute to the circulatory collapse. As such, these actions make adrenal cortex essential for survival.

Similar action on cation transport is exerted in other tissues as well. The action of aldosterone is exerted by gene mediated increased transcription of m-RNA in renal tubular cells which directs synthesis of proteins (aldosterone-induced proteins—AIP). The Na^+K^+ ATPase of tubular basolateral membrane responsible for generating gradients for movement of cations in these cells is the major AIP (*see* Fig. 41.3). Synthesis of β subunit of amiloride sensitive Na^+ channel is also induced. Because of the time taken to induce protein synthesis, aldosterone action has a latency of 1–2 hours. In addition, aldosterone rapidly induces phosphorylation and activation of amiloride sensitive Na^+ channel.

The main adverse effect of excessive mineralocorticoid action is fluid retention and hypertension. The natural and some of the synthetic glucocorticoids have significant mineralocorticoid activity responsible for side effects like edema, progressive rise in BP, hypokalemia and alkalosis. The diuretic induced hypokalemia is aggravated by mineralocorticoid excess.

Aldosterone has been shown to promote CHF associated myocardial fibrosis and progression of the disease (*see* Ch. 37).

SECTION 5

Glucocorticoid actions

1. Carbohydrate and protein metabolism Glucocorticoids promote glycogen deposition in liver (they are assayed on the basis of this action) by inducing hepatic glycogen synthase and promoting gluconeogenesis. They inhibit glucose utilization by peripheral tissues. This along with increased glucose release from liver results in hyperglycaemia, resistance to insulin and a diabetes-like state. They also cause protein breakdown and amino acid mobilization from peripheral tissues. This is responsible for side effects like muscle wasting, lympholysis, loss of osteoid from bone and thinning of skin. The amino acids so mobilized funnel into liver → used up in gluconeogenesis, excess urea is produced → negative nitrogen balance. Glucocorticoids are thus catabolic. Their function appears to be aimed at maintaining blood glucose levels during starvation—so that brain continues to get its nutrient. When food is withheld from an adrenalectomized animal—liver glycogen is rapidly depleted and hypoglycaemia occurs. Glucocorticoids also increase uric acid excretion.

2. Fat metabolism The action of glucocorticoids on fat metabolism is primarily permissive in nature. They promote lipolysis due to glucagon, growth hormone, Adr and thyroxine. cAMP induced breakdown of triglycerides is enhanced. Fat depots in different areas of the body respond differently—redistribution of body fat occurs. Subcutaneous tissue over extremities loses fat which is deposited over face, neck and shoulder producing 'moon face', 'fish mouth' and 'buffalo hump'. Explanation offered is—because peripheral adipocytes are less sensitive to insulin and more sensitive to corticosteroid-facilitated lipolytic action of GH and Adr, break down of fat predominates, whereas truncal adipocytes respond mainly to raised insulin levels caused by glucocorticoid induced hyperglycaemia.

Difference in the sensitivity of adipocytes at different locations to glucocorticoids is believed to arise from different levels of expression of the isoenzyme 11β-hydroxysteroid dehydrogenase type 1 (11β HSD1) which generates active hydrocortisone from inactive cortisone in the target tissues. Greater expression of 11βHSD1 in peripheral adipocytes than in truncal adipocytes would direct glucocorticoid-facilitated lipolysis to the subcutaneous fat in the limbs.

$$\text{Cortisone} \underset{\text{11}\beta\text{HSD2}}{\overset{\text{11}\beta\text{HSD1}}{\rightleftharpoons}} \text{Hydrocortisone}$$

On the other hand, high expression of the type 2 isoenzyme (11βHSD2) in the kidney tubule (also colon and salivary gland) which express mineralocorticoid receptor (MR) is believed to account for only weak mineralocorticoid activity of hydrocortisone whose inherent potency on MR is similar to that of aldosterone. As shown above, 11βHSD2 catalyses the reverse reaction inactivating hydrocortisone.

3. Calcium metabolism Glucocorticoids inhibit intestinal absorption and enhance renal excretion of Ca^{2+}. Loss of osteoid (decreased formation and increased resorption) indirectly results in loss of Ca^{2+} from bone, producing negative calcium balance. Spongy bones (vertebrae, ribs, pelvis, etc.) are more sensitive.

4. Water excretion The effect on water excretion is independent of action on Na^+ transport; hydrocortisone and other glucocorticoids, but not aldosterone, maintain normal g.f.r. In adrenal insufficiency, the capacity to excrete a water load is markedly reduced—such patients are prone to water intoxication from i.v. infusions.

Glucocorticoids also enhance secretory activity of renal tubules.

5. CVS Glucocorticoids restrict capillary permeability, maintain tone of arterioles and myocardial contractility. Applied topically, they cause cutaneous vasoconstriction. They have a permissive role for the pressor action of Adr and angiotensin. They also play a permissive role in development of hypertension—should be used cautiously in hypertensives.

Adrenal insufficiency is attended by low cardiac output, arteriolar dilatation, poor vasoconstrictor response to Adr (repeated doses of Adr cause destructive changes in blood vessels) and increased permeability of capillaries. These changes along with hypovolemia (due to lack of mineralocorticoid) are responsible for cardiovascular collapse.

6. Skeletal muscles Optimum level of corticosteroids is needed for normal muscular activity. Weakness occurs in both hypo- and hypercorticism, but the causes are different.

Hypocorticism: diminished work capacity and weakness are primarily due to hypodynamic circulation.

Hypercorticism: excess mineralocorticoid action → hypokalaemia → weakness;

Excess glucocorticoid action → muscle wasting and myopathy → weakness.

7. CNS Mild euphoria is quite common with pharmacological doses of glucocorticoids. This is a direct effect on brain, independent of relief of disease symptoms, and sometimes progresses to cause increased motor activity, insomnia, hypomania or depression. On the other hand, patients of Addison's disease suffer from apathy, depression and occasionally psychosis.

Glucocorticoids also maintain the level of sensory perception and normal level of excitability of neurones. High doses lower seizure threshold. Use in epileptics requires caution. This action is independent of electrolyte changes in the brain and is not shared by aldosterone.

8. Stomach Secretion of gastric acid and pepsin is increased—may aggravate peptic ulcer.

9. Lymphoid tissue and blood cells Glucocorticoids enhance the rate of destruction of lymphoid cells (T cells are more sensitive than B cells); but in man the effect on normal lymphoid tissue is modest. However, a marked lytic response is shown by malignant lymphatic cells. This is the basis of their use in lymphomas.

Glucocorticoids increase the number of RBCs, platelets and neutrophils in circulation. They decrease lymphocytes, eosinophils and basophils. This is not due to destruction of the concerned cells, but due to their sequestration in tissues. Blood counts come back to normal after 24 hours.

10. Inflammatory responses Irrespective of the type of injury or insult, the attending inflammatory response is suppressed by glucocorticoids. This is the basis of most of their clinical uses. The action is nonspecific and covers all components and stages of inflammation. This includes attenuation of—increased capillary permeability, local exudation, cellular infiltration, phagocytic activity and late responses like capillary proliferation, collagen deposition, fibroblastic activity and ultimately scar formation. This action is direct and can be restricted to a site by local administration. The cardinal signs of inflammation—redness, heat, swelling and pain are suppressed.

Glucocorticoids interfere at several steps in the inflammatory response (*see* cellular

mechanism below), but the most important overall mechanism appears to be limitation of recruitment of inflammatory cells at the local site and production of proinflammatory mediators like PGs, LTs, PAF through indirect inhibition of phospholipase A_2.

Corticoids are only palliative; do not remove the cause of inflammation; the underlying disease continues to progress while manifestations are dampened. They favour spread of infections because capacity of defensive cells to kill microorganisms is impaired. They also interfere with healing and scar formation: peptic ulcer may perforate asymptomatically. Indiscriminate use of corticoids is hazardous.

11. Immunological and allergic responses

Glucocorticoids impair immunological competence. They suppress all types of hypersensitization and allergic phenomena. At high concentrations and *in vitro* they have been shown to interfere with practically every step of the immunological response, but at therapeutic doses *in vivo* there is no impairment of antibody production or complement function. The clinical effect appears to be due to suppression of recruitment of leukocytes at the site of contact with antigen and of inflammatory response to the immunological injury.

Glucocorticoids cause greater suppression of CMI in which T cells are primarily involved, e.g. delayed hypersensitivity and graft rejection. This is the basis of their use in autoimmune diseases and organ transplantation (*see* Ch. 63). Factors involved may be inhibition of IL-1 release from macrophages; inhibition of IL-2 formation and action → T cell proliferation is not stimulated; suppression of natural killer cells, etc.

The broad action seems to be interruption of communication between cells involved in the immune process by interfering with production of or action of lymphokines.

Gene mediated cellular actions of glucocorticoids

Mechanism	Action
• Translocation of glucose transporters from plasma membrane to deeper sites.	• ↓ glucose uptake and utilization in peripheral tissues.
• Induction of hepatic gluconeogenetic enzymes.	• ↑ production of glucose from amino acids.
• Induction of hepatic glycogen synthase.	• Deposition of glycogen in hepatocytes.
• Site specific changes in sensitivity of adipocytes to GH, Adr, insulin.	• Altered distribution of body fat.
• ↑ expression of vascular adrenergic and AT_1 receptor.	• Enhanced reactivity to vasopressor substances.
• ↓ expression of POMC gene in pituitary corticotropes	• ↓ production of ACTH.
Antiinflammatory and Immunosuppressant actions	
• Induction of annexins in macrophages, endothelium and fibroblasts.	• Annexins inhibit phospholipase A_2 → decreased production of PGs, LTs & PAF.
• Negative regulation of COX-2	• ↓ inducible PG production.
• Negative regulation of genes for cytokines in macrophages, endothelial cells and lymphocytes.	• ↓ production of IL-1, IL-2, IL-3, IL-6, TNFα, GM-CSF, γ interferon → fibroblast proliferation and T-lymphocyte function are suppressed, chemotaxis interfered.
• ↓ production of acute phase reactants from macrophages and endothelial cells	• Complement function is interfered.
• ↓ production of ELAM-1 and ICAM-1 in endothelial cells.	• Adhesion and localization of leukocytes is interfered.
• ↓ expression of transcription factors AP-1, NF-κB	• ↓ histone acetylation • ↓ MAP kinase
• ↓ production of collagenase and stromolysin	• Prevention of tissue destruction

POMC—Proopiomelanocortin; IL—Interleukin; TNFα—Tumour necrosis factor α; GM-CSF—Granulocyte macrophage colony stimulating factor; ELAM-1—Endothelial leukocyte adhesion molecule-1; ICAM-1—Intracellular adhesion molecule-1; AP-1–Activator protein-1; NF-κB–Nuclear factor κB; MAP kinase–Mitogen activated protein kinase.

Mechanism of action at cellular level

Corticosteroids penetrate cells and bind to a high affinity cytoplasmic receptor protein → a structural change occurs in the steroid receptor complex that allows its migration into the nucleus and binding to glucocorticoid response elements (GRE) on the chromatin → transcription of specific m-RNA → regulation of protein synthesis (*see* Fig. 4.10). This process takes at least 30–60 min : effects of corticosteroid are not immediate, and once the appropriate proteins are synthesized—effects persist much longer than the steroid itself. In many tissues, the overall effect is catabolic, i.e. inhibition of protein synthesis. This may be a consequence of steroid directed synthesis of an inhibitory protein.

The glucocorticoid receptor (GR) is very widely distributed (in practically all cells). It has been cloned and its structure determined. It is made up of ~ 800 amino acids.

Several *coactivators* and *corepressors* modulate the interaction of liganded GR with the GREs, altering the intensity of response.

Because the GR largely maintains uniformity throughout the body, tissue specificity is not exhibited by different glucocorticoids, and all members produce the same constellation of effects.

The functional scheme of GR is presented in Fig. 4.10. Direct evidence of gene expression mediated action has been obtained for actions listed in the box (*see* p. 286).

Some actions of corticoids are exerted more rapidly (like inhibition of ACTH release from pituitary). These may be mediated by a cell membrane receptor or a different mechanism not involving protein synthesis.

PHARMACOKINETICS

All natural and synthetic corticoids, except DOCA are absorbed and are effective by the oral route. Absorption into systemic circulation occurs from topical sites of application as well, but the extent varies depending on the compound, site, area of application and use of occlusive dressing. Water soluble esters, e.g. hydrocortisone hemisuccinate, dexamethasone sod. phosphate can be given i.v. or i.m., act rapidly and achieve high concentrations in tissue fluids. Insoluble esters, e.g. hydrocortisone acetate, triamcinolone acetonide cannot be injected i.v., but are slowly absorbed from i.m. site and produce more prolonged effects.

Hydrocortisone undergoes high first pass metabolism, has low oral: parenteral activity ratio. Oral bioavailability of synthetic corticoids is high.

Hydrocortisone is 90% bound to plasma protein, mostly to a specific cortisol-binding globulin (CBG; transcortin) as well as to albumin. Transcortin concentration is increased during pregnancy and by oral contraceptives—corticoid levels in blood are increased but hypercorticism does not occur, because free cortisol levels are normal.

The corticosteroids are metabolized primarily by hepatic microsomal enzymes. Pathways are—

(i) Reduction of 4, 5 double bond and hydroxylation of 3-keto group.
(ii) Reduction of 20-keto to 20-hydroxy form.
(iii) Oxidative cleavage of 20C side chain (only in case of compounds having a 17-hydroxyl group) to yield 17-ketosteroids.

These metabolites are further conjugated with glucuronic acid or sulfate and are excreted in urine.

The plasma t½ of hydrocortisone is 1.5 hours. However, the biological t½ is longer because of action through intracellular receptors and regulation of protein synthesis—effects that persist long after the steroid is removed from plasma.

The synthetic derivatives are more resistant to metabolism and are longer acting.

Phenobarbitone and phenytoin induce metabolism of hydrocortisone, prednisolone and dexamethasone, etc. to decrease their therapeutic effect.

CHEMISTRY AND RELATIVE ACTIVITY OF CORTICOIDS

Fig. 20.3 depicts the chemical structure of desoxycorticosterone in blue line. It is a selective mineralocorticoid. Chemical modifications that result in clinically useful compounds are also indicated. Fluorination at position 9 or 6 has resulted in

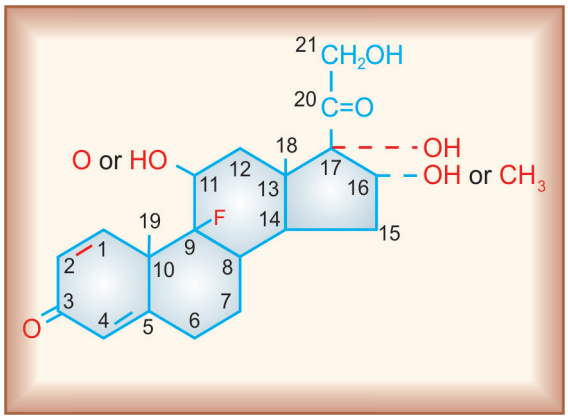


Fig. 20.3: Chemical structure of corticosteroids. The structure in blue is desoxycorticosterone. Important substitutions which yield other useful compounds are shown in red

+ OH at 11	— Corticosterone
+ OH at 11 + OH at 17	— Hydrocortisone
(if O at 11) + OH at 17	— Cortisone
+ OH at 11 + OH at 17 + Δ 1, 2	— Prednisolone
+ OH at 11 + OH at 17 + Δ 1, 2 + F at 9 + OH at 16	— Triamcinolone
+ OH at 11 + OH at 17 + Δ 1, 2 + F at 9 + CH_3 α at 16	— Dexamethasone
+ OH at 11 + OH at 17 + Δ 1, 2 + F at 9 + CH_3 β at 16	— Betamethasone
Hydrocortisone + F at 9	— Fludrocortisone
Corticosterone + CHO at 18	— Aldosterone

highly potent compounds. Synthetic steroids have largely replaced the natural compounds in therapeutic use, because they are potent, longer acting, more selective for either glucocorticoid or mineralocorticoid action and have high oral activity.

DISTINCTIVE FEATURES

The relative potency and activity of different natural and synthetic corticosteroids employed systemically is compared in Table 20.1.

1. Hydrocortisone (cortisol) Acts rapidly but has short duration of action. In addition to primary glucocorticoid, it has significant mineralocorticoid activity as well. Used for:

Replacement therapy—20 mg morning + 10 mg afternoon orally.

Shock, status asthmaticus, acute adrenal insufficiency—100 mg i.v. bolus + 100 mg 8 hourly i.v. infusion.

Topically (*see* Ch. 64) and as suspension for enema in ulcerative colitis (*see* Ch. 48).

LYCORTIN-S, EFCORLIN SOLUBLE 100 mg/2 ml inj. (as hemisuccinate for i.v. inj.) WYCORT, EFCORLIN 25 mg/ml inj (as acetate for i.m./intraarticular inj.). PRIMACORT 100, 200, 400 mg/vial inj.

2. Prednisolone It is 4 times more potent than hydrocortisone, also more selective glucocorticoid, but fluid retention does occur with high doses. Has intermediate duration of action: causes less pituitary-adrenal suppression when a single morning dose or alternate day treatment is given. Used for allergic, inflammatory, autoimmune diseases and in malignancies: 5–60 mg/day oral, 10–40 mg i.m., intraarticular; also topically.

DELTACORTRIL, HOSTACORTIN-H, 5, 10 mg tab, 20 mg/ml (as acetate) for i.m., intraarticular inj., WYSOLONE, NUCORT, 5, 10, 20, 30, 40 mg tabs.

3. Methylprednisolone Slightly more potent and more selective than prednisolone: 4–32 mg/day oral. Methylprednisolone acetate has been used as a retention enema in ulcerative colitis.

Pulse therapy with high dose methylprednisolone (1 g infused i.v. every 6–8 weeks) has been tried in nonresponsive active rheumatoid

TABLE 20.1 Relative activity of systemic corticosteroids

		Compound	Gluco	Mineralo	Equiv. dose (antiinflammatory)
GLUCOCORTICOIDS	Short acting (Biological t½ < 12 hr)	1. Hydrocortisone (cortisol)	1	1	20 mg
	Intermediate acting (Biological t½ 12–36 hr)	2. Prednisolone	4	0.8	5 mg
		3. Methyl-prednisolone	5	0.5	4 mg
		4. Triamcinolone	5	0	4 mg
		5. Deflazacort	3–4	0	6 mg
	Long acting (Biological t½ > 36 hr)	6. Dexamethasone	25	0	0.75 mg
		7. Betamethasone	25	0	0.75 mg
MINERALO-CORTICOIDS					Equiv. salt retaining dose
		8. Desoxycortico-sterone acetate (DOCA)	0	100	2.5 mg (sublingual)
		9. Fludrocortisone	10	150	0.2 mg
		10. Aldosterone	0.3	3000	not used clinically

arthritis, renal transplant, pemphigus, etc. with good results and minimal suppression of pituitary-adrenal axis.

SOLU-MEDROL Methylprednisolone (as sod. succinate) 4 mg tab; 40 mg, 125 mg, 0.5 g (8 ml) and 1.0 g (16 ml) inj, for i.m. or slow i.v. inj, DEESOLONE 4, 16 mg tabs, 0.5 g and 1.0 g. inj.

The initial effect of methylprednisolone pulse therapy (MPPT) is probably due to its antiinflammatory action, while long term benefit may be due to temporary switching off of the immunodamaging processes as a consequence of lymphopenia and decreased Ig synthesis.

4. Triamcinolone Slightly more potent than prednisolone but highly selective glucocorticoid: 4–32 mg/day oral, 5–40 mg i.m., intraarticular injection. Also used topically.

KENACORT, TRICORT 1, 4, 8 mg tab., 10 mg/ml, 40 mg/ml (as acetonide) for i.m., intraarticular inj., LEDERCORT 4 mg tab.

5. Dexamethasone Very potent and highly selective glucocorticoid. It is also long-acting, causes marked pituitary-adrenal suppression, but fluid retention and hypertension are not a problem.

It is used for inflammatory and allergic conditions 0.5–5 mg/day oral. For shock, cerebral edema, etc. 4–20 mg/day i.v. infusion or i.m. injection is preferred. It can also be used topically.

DECADRON, DEXONA 0.5 mg tab, 4 mg/ml (as sod. phosphate) for i.v., i.m. inj., 0.5 mg/ml oral drops; WYMESONE, DECDAN 0.5 mg tab, 4 mg/ml inj.

6. Betamethasone Similar to dexamethasone, 0.5–5 mg/ day oral, 4–20 mg i.m., i.v. injection or infusion, also topical.

BETNESOL, BETACORTRIL, CELESTONE 0.5 mg, 1 mg tab, 4 mg/ml (as sod. phosphate) for i.v., i.m. inj., 0.5 mg/ml oral drops. BETNELAN 0.5 mg, 1 mg tabs.

Dexamethasone or betamethasone are preferred in cerebral edema and other states in which fluid retention must be avoided.

7. Deflazacort The glucocorticoid potency of this newer steroid is somewhat less than of prednisolone, but it lacks mineralocorticoid activity. It is claimed to produce fewer adverse effects, but that may be due to its lower potency. In some trials it caused lesser growth retardation in children; has been particularly recommended for pediatric patients. It is used mainly for inflammatory and immunological disorders.

Dose: 60–120 mg/day initially, 6–18 mg/day for maintenance; children 0.25–1.5 mg/kg daily or on alternate days.

DEFGLU 6, 30 mg tabs, DEFLAR, DEFZA, DFZ 1, 6, 30 mg tabs.

8. Desoxycorticosterone acetate (DOCA) It has only mineralocorticoid activity. Used occasionally for replacement therapy in Addison's disease: 2–5 mg sublingual, 10–20 mg i.m. once or twice weekly.
In DOCABOLIN 10 mg/ml inj (along with nandrolone).

9. Fludrocortisone A potent mineralocorticoid having some glucocorticoid activity as well, orally active, used for:
Replacement therapy in Addison's disease 50–200 µg daily.
Congenital adrenal hyperplasia in patients with salt wasting 50–200 µg/day.
Idiopathic postural hypotension 100–200 µg/day.
FLORICORT 100 µg tab.

10. Aldosterone It is the most potent mineralocorticoid. Not used clinically because of low oral bioavailability and difficulties in regulating doses.

In addition a number of *topically* active glucocorticoids have been developed.

Beclomethasone dipropionate budesonide, fluticasone, etc. are used by inhalation in asthma, as spray in nasal allergy, as well as for skin and mucous membrane lesions (*see* Ch. 16).

Fluocinolone acetonide, fluocortolone, clobetasol propionate and esters of betamethasone, dexamethasone, triamcinolone are described in Ch. 64.

USES

A. Replacement therapy

1. *Acute adrenal insufficiency* It is an emergency. Hydrocortisone or dexamethasone are given i.v., first as a bolus injection and then as infusion, along with isotonic saline and glucose solution. The amount of fluid infused i.v. is guided by monitoring central venous pressure, because these patients have reduced capacity to excrete water load. Short-term i.v. infusion of a vasopressor (dopamine) may be needed. The cause of adrenal insufficiency should be treated.

2. *Chronic adrenal insufficiency (Addison's disease)* Hydrocortisone given orally is the most commonly used drug along with adequate salt and water allowance. Some patients who continue to excrete excess Na^+ need additional mineralocorticoid: fludrocortisone is added.

3. *Congenital adrenal hyperplasia (Adrenogenital syndrome)* It is a familial disorder due to genetic deficiency of steroidogenic enzymes, mostly 21-hydroxylase. As a result the synthesis of hydrocortisone and aldosterone suffers. There is compensatory increase in ACTH secretion—adrenals hypertrophy; enzyme deficiency being only partial in most cases, normal amounts of gluco- and mineralocorticoids are produced along with excessive amounts of weak androgens → virilization and/or precocious sexual development. If the deficiency is severe, salt wasting also occurs.

Treatment is to give hydrocortisone 0.6 mg/kg daily in divided doses round the clock to maintain feed back suppression of pituitary. If salt wasting persists—fludrocortisone 50–200 µg/day may be added.

B. Pharmacotherapy (for nonendocrine diseases)

Systemic as well as topical corticosteroids have one of the widest spectrum of medicinal uses for their antiinflammatory and immunosuppressive properties. Corticosteroids are powerful drugs. They have the potential to cause dramatic improvement in many severe diseases as well as produce equally dramatic adverse effects if not properly used. The use in nonendocrine diseases is empirical and palliative, but may be life saving. The following *general principles* must be observed.

(a) A single dose (even excessive) is not harmful: can be used to tide over mortal crisis, even when benefit is not certain.

(b) Short courses (even high dose) are not likely to be harmful in the absence of contraindications; starting doses can be high in severe illness.

(c) Long-term use is potentially hazardous: keep the duration of treatment and dose to minimum, which is found by trial and error; even partial relief may have to be tolerated.

(d) Initial dose depends on severity of the disease; start with a high dose in severe illness—reduce gradually after symptoms subside, while in mild cases start with the lowest dose and titrate upwards

to find the correct dose. The dose should be reassessed from time-to-time.
(e) No abrupt withdrawal after a corticoid has been given for > 2 to 3 weeks: may precipitate adrenal insufficiency.
(f) Infection, severe trauma, surgery or any stress during corticoid therapy—increase the dose.
(g) Use local therapy (cutaneous, inhaled, intranasal, etc) wherever possible.

1. *Arthritides*
(i) *Rheumatoid arthritis*: Corticosteroids are indicated only in severe cases as adjuvants to NSAIDs when distress and disability persists despite other measures, or to suppress exacerbations, or when there are systemic manifestations (*see* Ch. 15).
(ii) *Osteoarthritis*: It is treated with analgesics and NSAIDs; systemic use of corticoids is rare. Intraarticular injection of a steroid may be used to control an acute exacerbation. Injections may be repeated 2–3 times a year, but have the potential to cause joint destruction.
(iii) *Rheumatic fever:* Corticoids are used only in severe cases with carditis and CHF with the aim of rapid suppression of symptoms, because they act faster than aspirin, or in patients not responding to aspirin. Aspirin is given in addition and is continued after corticoids have been withdrawn.
(iv) *Gout:* Corticoids (short course) should only be used in *acute gouty arthritis* when NSAIDs have failed to afford relief and colchicine is not tolerated. Intraarticular injection of a soluble glucocorticoid is preferable to systemic therapy (*see* p. 214).

Though they are uricosuric—use in chronic gout is not recommended.

2. *Collagen diseases* Most cases of systemic lupus erythematosus, polyarteritis nodosa, dermatomyositis, nephrotic syndrome, glomerulonephritis and related diseases need corticosteroid therapy. They may be life saving in these diseases. Therapy is generally started with high doses which are tapered to maintenance dose when remission occurs. Later other immunosuppressants may be added or substituted.

3. *Severe allergic reactions* Corticoids may be used for short periods in anaphylaxis, angioneurotic edema, urticaria and serum sickness. However, even i.v. injection of a glucocorticoid takes 1–2 hours to act and is not a substitute for Adr (which acts immediately) in anaphylactic shock and angioedema of larynx. Topical use is made in allergic conjunctivitis and rhinitis.

4. *Autoimmune diseases* Autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, active chronic hepatitis respond to corticoids. Prednisolone 1–2 mg/kg/day is given till remission, followed by gradual withdrawal or low-dose maintenance depending on the response. Remission may also be induced in severe cases of myasthenia gravis, in which their use is adjunctive to neostigmine. Patients requiring long term maintenance therapy are better shifted to other immunosuppressants.

5. *Bronchial asthma* Early institution of inhaled glucocorticoid therapy is now recommended in most cases needing inhaled β_2 agonists almost daily (*see* Ch. 16). Systemic corticosteroids are used only for:
- Status asthmaticus: give i.v. glucocorticoid; withdraw when emergency is over.
- Actue asthma exacerbation: short-course of high dose oral corticoid, followed by gradual withdrawal.
- Severe chronic asthma not controlled by inhaled steroids and bronchodilators: add low dose prednisolone daily or on alternate days.

6. *Other lung diseases* Corticosteroids benefit aspiration pneumonia and pulmonary edema from drowning. Given during late pregnancy, corticoids accelerate lung maturation and surfactant production in the foetal lung and prevent respiratory distress syndrome at birth. Two doses of betamethasone 12 mg i.m. at 24 hour interval may be administered to the mother if premature delivery is contemplated.

7. *Infective diseases* Administered under effective chemotherapeutic cover, corticosteroids are indicated only in serious infective diseases

to tideover crisis or to prevent complications. They are indicated in conditions like severe forms of tuberculosis (miliary, meningeal, renal, etc.), severe lepra reaction, certain forms of bacterial meningitis and *Pneumocystis carinii* pneumonia with hypoxia in AIDS patients.

8. *Eye diseases* Corticoids are used in a large number of inflammatory ocular diseases—may prevent blindness. Topical instillation as eye drops or ointment is effective in diseases of the anterior chamber—allergic conjunctivitis, iritis, iridocyclitis, keratitis, etc. Ordinarily, steroids should not be used in infective conditions. But if inflammation is severe, they may be applied in conjunction with an effective antibiotic. Steroids are contraindicated in herpes simplex keratitis and in ocular injuries. Posterior segment afflictions like retinitis, optic neuritis, uveitis require systemic steroid therapy. Retrobulbar injection is occasionally given to avoid systemic side effects.

9. *Skin diseases* (*see* Ch. 64) Topical corticosteroids are widely employed and are highly effective in many eczematous skin diseases. Systemic therapy is needed (may be life-saving) in pemphigus vulgaris, exfoliative dermatitis, Stevens-Johnson syndrome and other severe afflictions.

10. *Intestinal diseases* Ulcerative colitis, Crohn's disease, coeliac disease are inflammatory bowel diseases with exacerbations and remissions. Corticoids are indicated during acute phases—may be used orally or as retention enema (for colonic involvement). They are particularly valuable for patients with systemic manifestions, and are given in addition to sulfasalazine/mesalazine ± other measures (*see* Ch. 48). Some specialists advocate small maintenance doses to prevent relapses.

11. *Cerebral edema* due to tumours, tubercular meningitis, etc., responds to corticoids. Dexa-or betamethasone are preferred because they donot have Na^+ retaining activity. Their value in traumatic and poststroke cerebral edema is questionable. Large doses given i.v. soon after spinal injury may reduce the resulting neurological sequelae.

A short course (2–4 weeks) of oral prednisolone can hasten recovery from Bell's palsy and acute exacerbation of multiple sclerosis. In the latter, methyl prednisolone 1 g i.v. daily for 2–3 days may be given in the beginning.

Neurocysticercosis: When albendazole/praziquantel is used to kill cysticerci lodged in the brain, prednisolone 40 mg/day or equivalent is given for 2–4 weeks to suppress the reaction to the dying larvae.

12. *Malignancies* Corticoids are an essential component of combined chemotherapy of acute lymphatic leukaemia, Hodgkin's and other lymphomas, because of their marked lympholytic action in these conditions. They have a secondary place in hormone responsive breast carcinoma—act probably by causing HPA suppression so as to reduce production of adrenal androgens which are converted to estrogens in the body (*see* Ch. 62).

Corticoids also afford symptomatic relief in other advanced malignancies by improving appetite and controlling secondary hypercalcaemia. For hypercalcaemia, however, bisphosphonates are more effective and have superseded corticosteroids.

13. *Organ transplantation and skin allograft* High dose corticoids are given along with other immunosuppressants to prevent the rejection reaction. Low maintenance doses are generally continued over long term ± maintenance doses of companion drugs. (*see* Ch. 63).

14. *Septic shock* High-dose corticosteroid therapy for septic shock has been abandoned, because it worsens the outcome. However, many such patients have relative adrenal insufficiency. Recent studies have documented beneficial effects of low-dose (hydrocortisone 100 mg 8 hourly i.v. infusion for 5–7 days) therapy in patients who are adrenal deficient and do not respond adequately to fluid replacement and vasopressors.

15. *Thyroid storm* Many patients in thyroid storm have concomitant adrenal insufficiency. Moreover, corticosteroids reduce peripheral T_4 to T_3 conversion. Hydrocortisone 100 mg i.v. 8 hourly may improve outcome.

16. *To test pituitary-adrenal axis function* Dexamethasone suppresses pituitary-adrenal axis at doses which do not contribute to steroid metabolites in urine. Responsiveness of the axis can be tested by measuring daily urinary steroid metabolite excretion after dosing with dexamethasone.

ADVERSE EFFECTS

These are extension of the pharmacological action which become prominent with prolonged therapy, and are a great limitation to the use of corticoids in chronic diseases.

A. Mineralocorticoid Sodium and water retention, edema, hypokalaemic alkalosis and a progressive rise in BP. These are now rare due to availability of highly selective glucocorticoids.

Gradual rise in BP occurs due to excess glucocorticoid action as well.

B. Glucocorticoid

1. Cushing's habitus: characteristic appearance with rounded face, narrow mouth, supraclavicular hump, obesity of trunk with relatively thin limbs.
2. Fragile skin, purple striae—typically on thighs and lower abdomen, easy bruising, telangiectasis, hirsutism. Cutaneous atrophy localized to the site occurs with topical application as well.
3. Hyperglycaemia, may be glycosuria, precipitation of diabetes.
4. Muscular weakness: proximal (shoulder, arm, pelvis, thigh) muscles are primarily affected. Myopathy occurs occasionally, warrants withdrawal of the corticoids.
5. Susceptibility to infection: this is nonspecific for all types of pathogenic organisms. Latent tuberculosis may flare; opportunistic infections with low grade pathogens (*Candida,* etc.) set in.
6. Delayed healing: of wounds and surgical incisions.
7. Peptic ulceration: risk is doubled; bleeding and silent perforation of ulcers may occur. Dyspeptic symptoms are frequent with high dose therapy.
8. Osteoporosis: especially involving vertebrae and other flat spongy bones. Compression fractures of vertebrae and spontaneous fracture of long bones can occur, especially in the elderly. Radiological evidence of osteoporosis is an indication for withdrawal of corticoid therapy. Corticosteroid induced osteoporosis can be prevented/arrested by calcium supplements + vit D, and by estrogen/raloxifene or androgen replacement therapy in females and males respectively. However, bisphosphonates are the most effective drugs in this regard.

   Avascular necrosis of head of femur, humerous, or knee joint is an occasional abrupt onset complication of high dose corticosteroid therapy.
9. Posterior subcapsular cataract may develop after several years of use, especially in children.
10. Glaucoma: may develop in susceptible individuals after prolonged topical therapy.
11. Growth retardation: in children occurs even with small doses if given for long periods. Large doses do inhibit GH secretion, but growth retardation may, in addition, be a direct cellular effect of corticoids. Recombinant GH given concurrently can prevent growth retardation, but risk/benefit of such use is not known.
12. Foetal abnormalities: Cleft palate and other defects are produced in animals, but have not been encountered on clinical use in pregnant women. The risk of abortion, stillbirth or neonatal death is not increased, but intrauterine growth retardation can occur after prolonged therapy, and neurological/behavioral disturbances in the offspring are feared. Prednisolone appears safer than dexa/beta methasone, because it is metabolized by placenta, reducing foetal exposure. There

is no evidence of foetal growth retardation occurring after short term use in the mother.

Prolonged corticosteroid therapy during pregnancy increases the risk of gestational diabetes, pregnancy induced hypertension and preeclampsia.

13. Psychiatric disturbances: mild euphoria frequently accompanies high dose steroid treatment. This may rarely progress to manic psychosis. Nervousness, decreased sleep and mood changes occur in some patients. Rarely a depressive illness may be induced after long-term use.
14. Suppression of hypothalamo-pituitary-adrenal (HPA) axis: occurs depending both on dose and duration of therapy. In time, adrenal cortex atrophies and stoppage of exogenous steroid precipitates withdrawal syndrome consisting of malaise, fever, anorexia, nausea, postural hypotension, electrolyte imbalance, weakness, pain in muscles and joints and reactivation of the disease for which they were used. Subjected to stress, these patients may go into acute adrenal insufficiency leading to cardiovascular collapse.

Any patient who has received > 20–25 mg/day hydrocortisone, or ≥ 5 mg prednisolone/day or equivalent for longer than 2–3 weeks should be put on a scheme of gradual withdrawal: 20 mg hydrocortisone/ day reduction every week and then still smaller fractions once this level has been achieved. Such patients may need protection with a corticosteroid (oral or i.v.) if a stressful situation develops up to one year after withdrawal. Administration of ACTH during withdrawal does not hasten recovery because it has been found that adrenals recover earlier than pituitary and hypothalamus.

If a patient on steroid therapy develops an infection—the *steroid should not be discontinued* despite its propensity to weaken host defence and delay healing. Rather, the dose may have to be increased to meet the stress of infection. Surgery is such a patient should be covered by intra-operative and postoperative i.v. hydrocortisone till the condition stabilizes, followed by oral prednisolone.

Measures that minimise HPA axis suppression are:

(a) Use shorter acting steroids (hydrocortisone, prednisolone) at the lowest possible dose.
(b) Use steroids for the shortest period of time possible.
(c) Give the entire daily dose at one time in the morning.
(d) Switch to alternate-day therapy if possible.

It has been found that moderate dose of a short acting steroid (e.g. prednisolone) given at 48 hr interval did not cause HPA suppression, whereas the same total amount given in 4 divided 12 hourly doses produced marked HPA suppression. Alternate-day therapy also resulted in less immunological suppression—lower risk of infection. The longer acting steroids (dexamethasone, etc.) are not suitable for alternate-day therapy. Only problem with alternate-day therapy is that many steroid dependent patients are incapacitated on the 'off day'.

(e) If appropriate, use local (dermal, inhaled, ocular, nasal, rectal, intrasynovial) preparations of a steroid with poor systemic availability (beclomethasone, triamcinolone acetonide, fluticasone, etc.)

CONTRAINDICATIONS

The following diseases are aggravated by corticosteroids. Since corticosteroids may have to be used as a life-saving measure, all of these are relative contraindications in the presence of which these drugs are to be employed only under compelling circumstances and with due precautions.

1. Peptic ulcer
2. Diabetes mellitus
3. Hypertension
4. Viral and fungal infections
5. Tuberculosis and other infections
6. Osteoporosis
7. Herpes simplex keratitis
8. Psychosis
9. Epilepsy
10. CHF
11. Renal failure

Combination of any other drug with corticosteroids in fixed dose formulation for internal use is banned.

Metyrapone Inhibits 11-β hydroxylase in adrenal cortex and prevents synthesis of hydrocortisone so that its blood level falls → increased ACTH release → increased synthesis, release and excretion of 11-desoxycortisol in urine. Thus, it is used to test the responsiveness of pituitary and its ACTH producing capacity.

Aminoglutethimide, trilostane and high doses of the antifungal drug *Ketoconazole* also inhibit steroidogenic enzymes—can be used to treat Cushing's disease when surgery or other measures are not an option. Ketoconazole reduces gonadal steroid synthesis as well.

Glucocorticoid antagonist The antiprogestin *mifepristone* (*see* p. 319–20) acts as a glucocorticoid receptor antagonist as well. In Cushing's syndrome, it can suppress the manifestations of corticosteroid excess, but blockade of feedback ACTH inhibition leads to oversecretion of ACTH → more hydrocortisone is produced, which tends to annul the GR blocking action of mifepristone. It is indicated only for inoperable cases of adrenal carcinoma and in patients with ectopic ACTH secretion.

☞ PROBLEM DIRECTED STUDY

20.1 A 35-year female patient of inflammatory bowel disease was treated with prednisolone 40 mg/day and mesalazine 800 mg TDS. After 4 weeks, the symptoms subsided and prednisolone dose was tapered at the rate of 10 mg every 2 weeks. When she was taking 10 mg prednisolone/day, she met with a road-side accident and suffered compound fracture of both bones of the right leg. Internal fixation of the fracture and suturing of wounds under general anaesthesia is planned.

(a) Whether any additional measure needs to be taken during surgery in view of her corticosteroid therapy?

(b) Does the prednisolone therapy need discontinuation or any alteration in the postoperative period? Give reasons.

(see Appendix-1 for solution)