

H<sub>1</sub> antagonists crossing BBB: diphenhydramine, chlorpheniramine  
(sedation) (drowsiness)

H<sub>1</sub> antagonists not entering CNS: Cetirizine, terfenadine.

Drugs used to treat ulcers:

H<sub>2</sub> antagonists:

Proton pump inhibitors: ↓ acid secretion by blocking the H<sup>+</sup>/K<sup>+</sup> ATPase of the parietal cell: Omeprazole.

Antacids: Neutralize gastric acid: Aluminium Hydroxide, Magnesium Bicarbonate.

Coating agent: Provide a protective to the G1 epithelium:  
Sucralfate.

Prostaglandins: stimulate gastric acid secretion, enhance bicarbonate secretion. Mucus production and blood flow. Misoprostol.

Anticholinergic agents: ↓ acid secretion by blocking mACH receptors on parietal cells.  
(↓ parasympathetic signalling)  
Dicyclomine.

## Eicosanoids:

PAF: Acyl-PAF acted on by PLA<sub>2</sub>, form lyso-PAF to be acetylated and yield PAF.

Aggregate platelets and also a vasoconstrictor, ↑ vascular permeability.  
Causes hyperalgesia and leukocyte accumulation.

Non-steroidal anti-inflammatory drug (NSAID)

Inhibits cyclooxygenase.

Lipocortin (e.g. Annexin I) inhibits phospholipase A<sub>2</sub>.

Actions upon stimulating prostanoid receptors shown in PPT.

Blood vessels and thrombosis:

PGE<sub>2</sub>: arteriolar vasodilator (acting on EP<sub>2</sub>). Produce little increase in venular permeability but promotes increases in permeability produced by other agent (e.g. histamine) by increasing flow into permeabilized vessel.

PGI<sub>2</sub> (prostacyclin): Powerful vasodilators and it inhibits platelet aggregation (via IP receptor). It is produced by vascular endothelial cells, not by platelets.

TXA<sub>2</sub> (Thromboxane A<sub>2</sub>) and cyclic endoperoxides (catalyzes PGG<sub>2</sub> → PGH<sub>2</sub>, see diagram in Note): both are vasoconstrictors, induce platelet aggregation (via TP). Promote the release of ADP from platelets and the outer layers of vessel walls.  
TXA<sub>2</sub> produced by platelets and the outer layers of vessel walls.

Anti- $\text{PGI}_2$  antibody prevent normal antiaggregatory activity of endothelium.

Lipid peroxides in atheroma prevent  $\text{PGI}_2$  synthesis.

Ways to reduce thrombus formation:

Aspirin: irreversible acetylation of cyclooxygenase: Platelets more sensitive than other tissue (no protein synthesis in platelets  $\rightarrow$  effect of aspirin disappears when megakaryocytes release new platelets). Endothelial cells can regenerate cyclooxygenase.

$\text{PGI}_2$  ↑ flow in blood vessels (initial flow partially obliterated by thrombi)

Diet of unsaturated fat is preferred. Saturated fat gives rise to lipid peroxidation: lipid peroxidases inhibit  $\text{PGI}_2$  synthesis. Diet of unsaturated fat reduce thrombus formation.

Feeding relative excess of eicosapentaenoic acid produces  $\text{PGG}_3$ ,  $\text{TXA}_3$ .

Not platelet aggregators, also  $\text{PGD}_2$ : anti-inflammatory.

(But longer bleeding time + less ischaemic heart disease.)

Uterus action:

$\text{PGE}_2$  ( $\text{EP}_3$ ) and  $\text{PGF}_{2\alpha}$  ( $\text{TP}$ ) cause contraction of pregnant uterus.

Non-pregnant uterus:  $\text{PGF}_{2\alpha}$  induces contraction and ↑ blood flow.

Branchial SM:

$\text{PGF}_{2\alpha}$  (FP) potent bronchoconstrictors

$\text{PGT}_{2}$  (EP<sub>1</sub>) constrictor    (EP<sub>2</sub>) dilator.

$\text{TXA}_2$ , leukotrienes  $\text{C}_4, \text{D}_4, \text{E}_4$ : potent bronchoconstrictors.

$\text{PGI}_2$ : bronchodilators.

also mediators of asthmatic airway obstruction

G.I. Tract:

$\text{PGE}_2$  (EP<sub>3</sub>) and  $\text{PGF}_{2\alpha}$  (FP) contract longitudinal

$\text{PGF}_{2\alpha}$  contracts circular muscle but  $\text{PGE}_2$  relaxes it.

$\text{PGI}_2 \longrightarrow$  relax

$\text{PGE}_1$  (EP<sub>3</sub>) &  $\text{PGI}_2$  reduces gastric secretion.  $\text{PGE}_2$  analogues (enprostil) used to treat duodenal ulcer.  $\text{PGE}_2$  (EP<sub>2</sub>) causes ↑ mucus and water secretion into gut

Fever:

$\text{PGE}$  produced by hypothalamus in response to endogenous pyrogen (interleukin-1) when bacteria interacts with leukocytes.  $\text{PGE}$  mediates rise in temperature in response to pyrogens in circulation.

## Anti-inflammatory drugs:

### Glucocorticoid:

The naturally occurring glucocorticoid is hydrocortisone.

It has roughly equal potency as an anti-inflammatory and a mineralocorticoid.

Synthetic compound of glucocorticoid: Prednisolone (moderate-potency)

betamethasone (high-potency): They offer (a) improved potency (b) greater selectivity for anti-inflammatory action over mineralocorticoid action.

Local administration (e.g. onto skin, into nose, into lung) avoids unwanted effects of glucocorticoids.

\*Mechanism in Note: (a) anti-inflammatory (b) immunosuppressive.

Suppress early events of inflammation: e.g. vasodilation, oedema.

Suppress later events of inflammation: e.g. cell proliferation, macrophage activity.

Suppress production of autacoids (mediators of inflammation).

e.g. PG's, LT's, TX's, PAF

Histamine release from basophils is inhibited.

They acts on DNA to translate lipocortin (inhibits PLA<sub>2</sub>) See Note.

### Unwanted effects:

Suppression of hypothalamic-pituitary-adrenal function (iatrogenic Addison's on withdrawal)

Iatrogenic Cushing's - carbohydrate, protein, fat metabolism etc. (in Note)

## Inhibition of cytokine effect using monoclonal antibody.

An example is infliximab: antibody against TNF<sub>d</sub>.  
(useful in the treatment of chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel diseases.)  
Prevent the actions of inflammatory cytokines without the side effects of the steroids.

## Non-steroidal anti-inflammatory drugs (NSAID)

Inhibitors of arachidonic acid cyclooxygenase.

Non selective COX inhibitors:

- Salicylates: — Salicylic acid
- acetyl salicylic acid (Aspirin): irreversibly acetylates the enzyme.
- methyl salicylate

Prazolone — oxyphenbutazone.

Para-aminophenols — Paracetamol: Good analgesic and antipyretic properties  
Poor anti-inflammatory.

Indoles — Indomethacin: a competitive inhibitor at low concentrations.  
Prescribed to treat rheumatoid arthritis.

Fenamates — meclofenamic acid.

Propionic acid — ibuprofen, naproxen

COX-2 selective inhibitor — celecoxib.  
(appear to have therapeutic advantages)

Actions of groups:

- (a) anti-inflammatory
- (b) analgesic
- (c) antipyretic.

### Anti-inflammation:

NSAIDs block the synthesis of PG<sub>E2</sub> and PG<sub>I2</sub> to reduce inflammation but not to block effects of other inflammatory mediators - histamine, HETE, HPETE, leukotrienes.

### Analgesia:

Aside from stopping PG synthesis NSAID have central effect to reduce perception of pain.

### Antipyretic:

Block the synthesis of PGE.

Side effects of NSAID: E.g. gastrointestinal bleeding [by inhibiting COX-1] NSAID reduce platelet stickiness → prolong bleeding time. PG<sub>E2</sub> inhibits acid production, without it → ulceration susceptible.

### New anti-inflammatory drugs:

Biologics: Humanized anti-TNF<sub>α</sub> infliximab

# Anti-asthma drugs:

Asthma features and Stimuli in Note

Pathogenesis in Note as well. (IgE: the antibody type responsible for allergic asthma)

Drugs used in the treatment of asthma:

Cromoglycate, nedocromil (Prophylactic inhaled)

Also called anti-allergic drugs.

Hypothesis for its action: 1. Inhibition of the release of mediators of inflammation from cells

(e.g. mast cells, eosinophils, neutrophils)

2. Inhibition of sensory nerve

activity involved in the reflexes

which promote bronchoconstriction and neurogenic inflammation of the airways.

Salbutamol:  $\beta_2$  adrenoceptor antagonists: Relax bronchial SM. Also prevent (inhaled or oral) the release of mediators derived from mast cells.

Ipratropium bromide: (given by inhalation; poorly absorbed into circulation)

Muscarinic antagonists: alleviates reflex bronchoconstriction.

(Most effective in this case)

Methylxanthines (including caffeine, theobromine, theophylline)

(oral or parenteral) (a) At high concentration: release  $[Ca^{2+}]$  from intracellular pools.

(b) Inhibition of cAMP and cGMP phosphodiesterases.  $\uparrow cAMP, cGMP$  levels.

(c) Competitive antagonism of adenosine at adenosine receptors.

## Pharmacological effects in Notes

Probably explained by its action on adenosine receptors.

Side effects: tachycardia with dysrhythmias, etc.

Anti-inflammatory glucocorticoids (inhaled or oral)

oral, potent steroids have to be used for severe asthma despite major unwanted side effects. Inhaled, potent steroids (e.g. beclomethasone)

Histamine H<sub>1</sub> antagonists (oral or parenteral) (e.g. clemizine)

of little value in asthma.