

Agents which decrease blood coagulation:

Injectable anticoagulants: Heparin

Found in mast cells & plasma.

A polysaccharide often found in mucus: Mucopolysaccharide

prevents blood coagulation both in vivo and in vitro.

↳ Inactivates thrombin (II_a) And factors IX_a, X_a, XI_a & XII_a.
↳ Achieved by combining with and accelerating the action of antithrombin III.

Prolonged use: deplete stores of antithrombin III → diminish the effects of heparin.

Can reduce the risk of deep venous thrombosis and pulmonary embolism.

Adverse effect: haemorrhage, prevented by protamine sulphate, a heparin antagonist.

- Other anticoagulants which don't involve antithrombin III:

Hirudin, lepirudin, bivalirudin: Inhibitors of thrombin.

Useful for patients who develop an immune response to heparin.

Plaxin: Inhibitor of Factor X.

Danaparoid: Inhibitor of Factor X_a.

NAPc2 (nemafied anticoagulant complex)

Drugs that enhance endogenous anticoagulant activity (protein C-activated protein C)

Anicrod acts on fibrinogen to produce unstable fibrin fibres leading to depletion of fibrinogen.

- Oral anticoagulants (e.g. Warfarin)

Interfere with the reduction of Vitamin K (a cofactor in the post-translational γ -carboxylation of glutamate residues at the N-terminus) → producing non-functional factors II, VII, IX and X

Main adverse effect: excessive bleeding, counteracted by increasing vitamin K intake

The drug effect only when the existing pool of active factors is depleted.

- Direct thrombin inhibitors (DTIs)

Dabigatran

- Drug interactions with oral anticoagulants:

Response to oral anticoagulants is decreased by:

{ Oral contraceptives

{ Prior administration of drugs which cause induction of liver microsomal (P_{450} enzymes) e.g. barbiturates, phenytoin

increased by:

Drugs displacing plasma protein binding of the anticoagulants e.g. aspirin, chloral hydrate etc. (in Note)

-(Acid Citrate Dextrose):

Precipitate Ca^{2+} as an insoluble chelate complex.
(Factor IV)

Fibrinolysis:

Plasminogen : b-globulin.

Fibrinolysis enzymatically breaks down fibrin as well as factors II, V and VII.

Drugs promoting fibrinolysis:

Streptokinase: forms complexes with plasminogen which activates the enzyme. (May act as an antigen) (Plasminogen \rightarrow Plasmin)

Urokinase: directly activates plasminogen through its enzymatic activity.

Adverse effects: Bleeding : reverse with tranexamic acid or fresh plasma.

Hypersensitivity reactions.

Histamine and other mediators of inflammation.

Local hormone (autacoid) include : histamine, 5-hydroxytryptamine (5-HT), kinins, platelet activating factors (PAFs), cytokines (eg interleukins, tumor necrosis factor, interferon).

Enzyme inhibitor α -methyl histidine blocks histidine decarboxylase
(\downarrow histamine formation)

Mediators involved in inflammation and released by cells are autacoids.

Histamine release can be inhibited by β_2 -agonists from basophils or mast cells by \uparrow intracellular cyclic AMP.

Antigen - antibody (IgE class) interaction triggers histamine release -

Complement fragments (5a C3a (anaphylatoxins) also release histamine from most cells. Peptides such as Substance P and vasoactive intestinal polypeptide release histamine. The polybasic molecule Compound 48/80 release histamine from mast cells in some tissue.

Drugs that release histamine: tubocurarine, morphine.

Inflammatory mediators other than histamine:

Kinins (eg. bradykinin, kallidin [lys-bradykinin])

Formed from plasma protein precursors called kininogens by plasma and tissue kallikreins : split the active kinins from the precursors (HMW kininogen)

Kinins are destroyed by carboxypeptidase N and ACE.
Kinins are also vasodilators: acting on A_2 (mostly) and B_1 .

Icatibant : experimental β_2 antagonist

PAF: Membrane precursor: acyl-PAF

PAF formed when released by phospholipase A₂ (PLA₂)

PLA₂ acts on acyl-PAF to produce lyso-PAF → acetylated to yield PAF

PAF: aggregates platelets, also vasoconstrictor ↑ vascular permeability.

Eicosanoids (see later)

Cytokines:

Comprise interleukins, tumor necrosis factor and interferons.

Interleukin-1 (IL-1): has many properties which make it a likely mediator of chronic inflammation. (involved in many mechanisms; see Note)

Antagonist of histamine & treatment of peptic ulcers.

Selective agonists for 3 histamine receptors:

2-methylhistamine → H₁ (G_q)

4-methylhistamine, dimaprit, imipramine → H₂ (G_s)

R-α-methylhistamine → H₃ (G_{i/b})

Selective antagonists at H₁ receptors:

Older compounds cross blood-brain barrier (BBB) have atropine-like action and are sedative.

Newer antihistamine (H₁) don't cross BBB into CNS: No sedative action: Astemizole, terfenadine, cetirizine.

Selective antagonists at H₂:

Cimetidine, Ranitidine (competitive antagonists) inhibit gastric acid secretion.

Selective antagonists at H₃:

Thioperamide Function of H₃ receptors uncertain.

Effects of different histamine receptors at different parts of the body are in Note.

Vasopressin release from posterior pituitary can be triggered by histamine neuron.

H₁ antagonists crossing BBB: diphenhydramine, chlorpheniramine
(sedation) (drowsiness)

H₁ antagonists not entering CNS: Cetirizine, terfenadine.

Drugs used to treat ulcers:

H₂ antagonists:

Proton pump inhibitors: ↓ acid secretion by blocking the H⁺/K⁺ 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 PLA₂, 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 A₂.

Actions upon stimulating prostanoid receptors shown in PPT.

Blood vessels and thrombosis:

PGE₂: arteriolar vasodilator (acting on EP₂). Produce little increase in venular permeability but promotes increases in permeability produced by other agent (e.g. histamine) by increasing flow into permeabilized vessel.

PGI₂ (prostacyclin): Powerful vasodilators and it inhibits platelet aggregation (via IP receptor). It is produced by vascular endothelial cells, not by platelets.

TXA₂ (Thromboxane A₂) and cyclic endoperoxides (catalyzes PGG₂ → PGH₂, 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.
TXA₂ produced by platelets and the outer layers of vessel walls.

Anti- PGI_2 antibody prevent normal antiaggregatory activity of endothelium.

Lipid peroxides in atheroma prevent 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.

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 PGI_2 synthesis. Diet of unsaturated fat reduce thrombus formation.

Feeding relative excess of eicosapentaenoic acid produces PGG_3 , TXA_3 .

Not platelet aggregators, also PGD_2 : anti-inflammatory.

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

Uterus action:

PGE_2 (EP_3) and $\text{PGF}_{2\alpha}$ (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

PGT_{2} (EP₁) constrictor (EP₂) dilator.

TXA_2 , leukotrienes $\text{C}_4, \text{D}_4, \text{E}_4$: potent bronchoconstrictors.

PGI_2 : bronchodilators.

also mediators of asthmatic airway obstruction

G.I. Tract:

PGE_2 (EP₃) and $\text{PGF}_{2\alpha}$ (FP) contract longitudinal

$\text{PGF}_{2\alpha}$ contracts circular muscle but PGE_2 relaxes it.

$\text{PGI}_2 \longrightarrow$ relax

PGE_1 (EP₃) & PGI_2 reduces gastric secretion. PGE_2 analogues (enprostil) used to treat duodenal ulcer. PGE_2 (EP₂) causes ↑ mucus and water secretion into gut

Fever:

PGE produced by hypothalamus in response to endogenous pyrogen (interleukin-1) when bacteria interacts with leukocytes. 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 PLA₂) 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_d.
(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_{E2} and PG_{I2} 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_{E2} inhibits acid production, without it → ulceration susceptible.

New anti-inflammatory drugs:

Biologics: Humanized anti-TNF_α 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: β_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 H₁ antagonists (oral or parenteral) (e.g. clemizine)

of little value in asthma.