PHARMACOLOGY OF INFLAMMATION AND IMMUNOSUPPRESSION

Histamine

Mepyramine	H_1 antagonist	Used for allergy. Able to cross BBB, but CNS receptor antagonism leads to sedation
Terfanadine	H_1 antagonist	Used for allergy. Unable to cross BBB. But can be problems with cytochrome P_{450} in some patients due to mutation or other drugs metabolised by same enzyme. Result is block of K^+ channels in the heart leading to long Q/T syndrome.
Loratidine	H_1 antagonist	Used for allergy. Unable to cross BBB and no Long Q/T syndrome side effects. Taken as prophylaxis 1 day^{-1}
Cimetidine	H_2 antagonist	Used for gastric ulceration. (gastrin – histamine – H_2 receptors – parietal cells) Thought to be due to increased acid secretion. Drug acts to reduce acid secretion.
Dimenhydrinate	H_1 antagonist	Used for motion sickness as H_1 receptors thought to have a role in the CNS producing the motion sickness effect.

Prostanoids

Aspirin	COX non selective inhibitor	Analgesic, antipyretic and anti inflammatory actions. (note effect on PGE_2 absence resulting in gastric erosion due to $\uparrow H^+$ $\downarrow$mucin. PGI_2 regulates renal blood flow loss can lead to renal failure. Also AA may therefore be diverted to other prostanoids. E.g. 5-lioxygenase – 5-HPETE – leukotrienes [thought to have a role in genesis of asthma]) Acts to irreversibly acetylate serine 530 thus sterically blocking a catalytic site. Given low dose prophylaxis as anticoagulant. Antagonism between TXA_2 (TP – g_q – conformation change of platelets and vasoconstriction) PGI_2 (IP – g_s – opposite) Aspirin is irreversible – platelet no nuclei no capacity for regenerating COX, Endothelia can thus $PGI_2 > TXA_2$ hence anticoagulant.
Misoprostol	Prostaglandin agonist	Acts to compensate for gastric effects et al. by providing a source of PG stimulation. Co-administered with aspirin …
Ibuprofen	COX non selective inhibitor	Analgesic, antipyretic and anti inflammatory actions. (note effects as above) Acts reversibly bind to arginine 120 to thus sterically blocking a catalytic site.
Paracetamol	? COX-3	Analgesic, antipyretic but little anti-

	specific	inflammatory action. Suggested specificity can explain its effect as an antipyretic
Celecoxib	COX – 2 specific inhibitor	Aims to prevent occurrence of unwanted side effects due to specificity. Analgesic, antipyretic and anti inflammatory actions. Specificity is due to width differences of entry into COX. COX – 1 site is too narrow for drug entry.

Serotinin

Migrane

Sumatriptan	5-HT_{1D} agonist	Effects on both vasculature and neurones. Receptor coupled to g_i. On nociceptors, inhibits activation thus also of axonal reflex. VSM, via unusual βγ mechanism increases Ca^{2+} therefore causing contraction (to oppose the dilatation)
Ergotamine Dihydroergotamine	Ergot alkaloids	In periphery potent vasoconstrictors (can even cause gangrene) Effect here unknown. Putative partial agonist at 5-HT_{1D} and 5-HT_{1A}
Verapamil Propranolol		Sometimes used as prophylaxis
Valproic acid		Valproate – used as prophylaxis at concentrations lower than those effective as anti convulsants.

Emesis

Ondansetron Granisetron	5-HT_3 antagonist	LGIC. Such receptors found on primary afferents in gut that project to the CTZ. Drugs block channels and thus response. Administered with chemotherapeutic agents.

Irritable bowel syndrome

Alosetron	5-HT_3 antagonist	Theory IBS due to Δ bowel activity. 5-HT known to be involved in initiation of peristaltic waves. 5-HT_3 receptors identified in ENS. Thought possibly 5-HT transporter activity decreased causing raised 5-HT. Hence use of antagonist. BUT was withdrawn because it was found to decrease mobility to such an extent to prevent food passage! However found to only be in men. Now used only for women.

Chronic inflammatory processes – transplantation and autoimmunity

Calcineurin (calcium dependent serine/threonine protein phosphatase, bound to FKBP-12, able to activate NF-AT which then induces expression of IL-2 and is permissive to T-cell proliferation. Activation is via TK coupled receptors – fyn and zap-70 via PLCγ)

Ciclosporin	Calcineurin	Drug binds to CYCLOPHILIN which as a

	inhibitor	complex inhibits calcineurin activity thus inhibiting dephosphorylation of NF-AT thus T-cell proliferation.
Tacrolimus (FK-506)	Calcineurin inhibitor	Drug binds to FKBP-12 normally bound to calcineurin. Complex is thus inhibited from activation. Also inhibiting dephosphorylation of NF-AT and thus T-cell proliferation.

Glucocorticoid (acts as anti-inflammatory. Upregulates expression of lipocortin [PLA_2 inhibitor - ↓ inflammatory mediators] Downregulates expression of i) IL-2 by GCr binding to and inhibiting AP-1 responsible for IL-2 expression, and ii) COX-2. NF-κB normally responsible for COX-2 expression (also IL-2, TNFα) GCr* induces transcription IF- κBα which inhibits NF-κB)*

Cortisone Prednisone Dexamethasone	Taken topically (e.g. prednisone for colitis) or systemically – but has effects on negative feedback system at pituitary – inhibiting ACTH release. System takes time to recover so should gradually be weaned off drug to allow system recovery. May have side effects – reduced innate immunity, disturbance of mineralocorticoid system and may be effects after long term use.

Transplantation

Ciclosporin , Tacrolimus	Calcineurin inhibitors
Cortisol, Dexamethasone	Glucocorticoids
Azothioprine, Mycophenolate mofetil	T-cell proliferation inhibitors

Myasthenia Gravis (blocking autoantibodies nAChR nmj)

Edrophonium	Short acting AChE inhibitor to diagnose
Neostigmine	Medium acting inhibitor to treat by increasing ACh
Cortisol, Dexamethasone	Glucocorticoids
Ciclosporin, Tacrolimus	Calcineurin inhibitors

Rheumatoid arthritis (joint inflammation, unknown aetiology. Stiffness, arthritis >3 joints, often digits, often symmetrical; 70% RF+ (IgG); periods of remission; often inflammation leads to degenerative changes of joint)

NSAID	COXi – analgesic also so double effect. Only required during inflammatory stages – relieved during periods of remission
Cortisol, Dexamethasone	Glucocorticoids
Ciclosporin, Tacrolimus	Calcineurin inhibitors
Gold	Given systemically or injected into joints. Thought to have a role in inhibiting neutrophil migration
Sulphasalazine	Given as long term prophylaxis. Thought to modify lymphocyte

	behaviour, inhibiting migration to the joints
Methotrexate	Inhibits DHFR selective action on dividing cells – thus aiming to reduce lymphocyte proliferation.

Asthma

(*disease of lungs, reversible obstruction, chest tightness, wheezing. Triggered by allergens, irritants, cold air, NSAID, exercise Early and late (~10hr) phases)*

Short term – during an attack. Topical –aerosol/puffer (↓ systemic effects)

Salbutamol	β_2- adrenoreceptor agonist. ^cAMP – bronchodilatation
Ipratropium	Muscarinic antagonist – interferes with vagal innervation
Budesonide	Corticosteroid – short or long term.

Long term – prophylaxis

Salmeterol	Longer acting β_2- adrenoreceptor agonist. ^cAMP – bronchodilatation
Budesonide	Corticosteroid – short or long term.
Xanthines	Phosphodiesterase inhibitor. . ^cAMP – bronchodilatation. BUT wide acting so several effects if given orally
Cromolyn	Mast cell stabiliser – thought to decrease Ca^{2+} in cell thus degranulation. Evidence dodgy!
Zileuton	Leukotriene inhibitor – 5-lypoxygenase inhibitor
Motelukast	Leukotriene inhibitor – $CysLT_1$ receptor antagonist

(Leukotrienes – 5-lipoxygenase [and Five Lipoxygenase Activating Factor] convert AA – 5HPETE – LTA_4 – LTC_4. This is then exported from cell and converted to the bioactive cysteinyl LT – LTD_4 + LTE_4. These act on the cysteinyl LT receptors: $CysLT_1$ and $CysLT_2$ = GPCR - ^ Ca^{2+} causing bronchoconstriction and other pro-inflammatory effects)