PharmacoLearn

MPL102T Advanced Pharmacology I, M.Pharm Semester 1

Unit 5: Autocoid Pharmacology

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5.1 Autocoids: local hormones

Autocoids are locally produced, locally acting signalling substances, made on demand rather than stored in endocrine glands, and destroyed near their site of release: histamine, serotonin, the kinins, prostaglandins and related eicosanoids, and, in the syllabus's grouping, the endogenous opioid peptides. They share a pharmacology of inflammation, allergy, pain and vascular control, and their receptors are among the most drugged targets in medicine. This unit takes each in turn: physiology and pathology first, then the drugs.

5.2 Histamine and antihistamines

Histamine is formed from histidine by histidine decarboxylase and stored in mast cells, basophils, gastric enterochromaffin like cells and histaminergic neurons. Release is triggered immunologically (IgE cross linking on mast cells, the mechanism of allergy and anaphylaxis) and by drugs and venoms (morphine, tubocurarine, vancomycin's red man syndrome). Its receptors divide its actions:

Receptor	Location and action	Drug consequence
H1 (Gq)	Vessels (vasodilation, increased permeability), bronchi and gut (contraction), skin (itch, wheal and flare), brain (wakefulness)	H1 antihistamines treat allergy; sedation follows brain H1 blockade
H2 (Gs)	Gastric parietal cells (acid secretion), heart, vessels	H2 blockers (cimetidine, ranitidine, famotidine) suppress acid; largely replaced by proton pump inhibitors
H3 (Gi, pr esynaptic)	Brain and peripheral nerves, limits histamine and other transmitter release	Pitolisant (H3 antagonist/inverse agonist) treats narcolepsy
H4 (Gi)	Immune cells, itch and inflammation	Research target in allergy and pruritus

Histamine's pathological roles are allergy in all its forms (rhinitis, urticaria, conjunctivitis, anaphylaxis, where adrenaline, not an antihistamine, is the life saving drug), gastric acid secretion, motion sickness and vertigo pathways, and wakefulness.

H1 antihistamines. First generation agents (chlorpheniramine, promethazine, diphenhydramine, hydroxyzine, meclizine) cross the blood brain barrier: sedation and anticholinergic effects are both their burden and, for promethazine and meclizine, part of their antiemetic and antivertigo use. Second generation agents (**cetirizine and its enantiomer levocetirizine, loratadine and desloratadine, fexofenadine, bilastine, rupatadine**) are kept out of the brain by P-glycoprotein and charge, giving allergy relief (allergic rhinitis, chronic urticaria, conjunctivitis) without meaningful sedation at licensed doses. Fexofenadine is the active metabolite of terfenadine, which was withdrawn for QT prolonging arrhythmias, the standing lesson that antihistamine safety is cardiac as well as sedative. Antihistamines do not treat asthma (the wrong mediators dominate there) and do not reverse anaphylaxis; intranasal and ocular preparations serve local disease, and in chronic spontaneous urticaria, licensed dose escalation of a second generation agent precedes omalizumab.

5.3 Serotonin: physiology and pathology

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Serotonin (5-hydroxytryptamine, 5-HT) is made from tryptophan (hydroxylation, then decarboxylation) in enterochromaffin cells of the gut (about 90 percent of the body's store), in serotonergic neurons of the raphe nuclei, and is carried, not made, by platelets, which take it up by SERT. It is destroyed by MAO to 5-HIAA, whose urinary measurement diagnoses **carcinoid syndrome**, the flushing, diarrhoea, wheezing and right sided valvular fibrosis of a serotonin secreting tumour. Its receptor family is the largest in this unit:

Receptor	Type	Key actions and drugs
5-HT1 (Gi)	Inhibitory; 1B/1D on cranial vessels and nerve terminals	**Triptans** (sumatriptan and successors) agonise 1B/1D to abort migraine; buspirone is a 1A partial agonist (Unit 3)
5-HT2 (Gq)	Vessels, platelets, CNS; 2A and 2C prominent	Cyproheptadine and ketanserin block; atypical antipsychotics block 2A (Unit 3); 2B activation caused the valvular fibrosis of fenfluramine
5-HT3	Ligand gated ion channel, gut and chemoreceptor trigger zone	**Ondansetron** and the setrons block it: the standard antiemetics of chemotherapy, radiotherapy and postoperative vomiting
5-HT4 (Gs)	Gut, prokinetic	Prucalopride treats chronic constipation; older cisapride was withdrawn for arrhythmias

Pathological roles span migraine (where CGRP now shares the stage: gepants and monoclonal antibodies are the newest antimigraine pharmacology), mood and anxiety (Unit 3's SSRIs raise synaptic serotonin by blocking the same SERT platelets use), gut motility disorders, emesis, carcinoid syndrome (managed with the synthesis inhibitor telotristat and somatostatin analogues) and the serotonin syndrome of excess described in Unit 3. The **5-HT antagonists** the syllabus names are therefore a working set: the setrons for emesis, cyproheptadine (also an appetite stimulant and a serotonin syndrome adjunct), methysergide (retired by retroperitoneal fibrosis), and the atypical antipsychotics and mirtazapine, whose 5-HT2 and 5-HT3 blockade is part of their design.

5.4 Kinins: bradykinin and its relatives

The **kinins** are peptides generated from plasma kininogens by the enzymes **kallikreins**, themselves activated when factor XII (Hageman factor) contacts damaged surfaces, tying the kinin system to coagulation (Unit 4). **Bradykinin** (9 amino acids) and **kallidin** (lysyl bradykinin, 10) act on **B2 receptors** (constitutive, Gq) to produce intense vasodilation through nitric oxide and prostacyclin, increased vascular permeability, pain (bradykinin is among the most potent algesic substances known, sensitising nociceptors), bronchoconstriction and gut contraction. **B1 receptors** are absent in health and induced by inflammation and tissue injury, where their ligands (the des-Arg metabolites) sustain inflammatory pain, a division that makes B1 blockade an analgesic research target. Kinins are destroyed within seconds by peptidases, principally **ACE, here in its second identity as kininase II**, which is why ACE inhibitors raise bradykinin and cause their dry cough and angioedema (section 4.3), and why those risks are worse where bradykinin breakdown is genetically slow.

The clinical pharmacology of the pathway: **icatibant**, a B2 receptor antagonist, treats acute attacks of hereditary angioedema, a disease of deficient C1 esterase inhibitor in which uncontrolled kallikrein generates bradykinin excess; the kallikrein inhibitors ecallantide and lanadelumab and C1 inhibitor concentrates complete that niche. Aprotinin, a kallikrein inhibitor once used to reduce surgical bleeding, was withdrawn and restricted over safety. The kinins otherwise teach a principle: a mediator can be central to angioedema and inflammatory pain and still be drugged at only a few points, because its physiology is too entangled with blood pressure control to block casually.

5.5 Prostaglandins and the eicosanoid family

Prostaglandins are twenty carbon lipids made on demand from **arachidonic acid**, liberated from membrane phospholipids by phospholipase A2 (the step corticosteroids suppress through lipocortin/annexin). **Cyclo-oxygenase** converts arachidonate to the endoperoxides PGG2 and PGH2, from which tissue specific synthases make the family: **PGE2** (fever, pain sensitisation, gastric protection, ductus patency), **PGI2 prostacyclin** (vasodilator and platelet inhibitor from endothelium), **TXA2 thromboxane** (vasoconstrictor and platelet activator from platelets, prostacyclin's opponent), **PGF2 alpha** (uterine contraction, luteolysis, aqueous outflow in the eye) and **PGD2** (sleep, allergy). The parallel 5-lipoxygenase branch makes the **leukotrienes** (section 3.11 and Unit 3 of MPC103T chemistry; here: LTB4 the neutrophil attractant, and LTC4, LTD4, LTE4, the slow reacting substance of anaphylaxis driving bronchospasm in asthma, blocked by zileuton at synthesis and by montelukast at the CysLT1 receptor).

Receptors (EP, IP, TP, FP, DP) are all G protein coupled, and the analogues are established drugs: **misoprostol** (PGE1 analogue: gastric protection against NSAID ulcers, and obstetric uses in induction and postpartum haemorrhage), **dinoprostone** (PGE2, cervical ripening), **carboprost** (PGF2 analogue, postpartum haemorrhage), **latanoprost** and relatives (FP agonists, first line eye drops in glaucoma, with iris darkening and lash growth as their signature), **epoprostenol and iloprost** (prostacyclin analogues, pulmonary arterial hypertension), and alprostadil (PGE1 keeping the ductus arteriosus open in duct dependent congenital heart disease, and in erectile dysfunction). The physiology explains the pathology list of section 3.11 in reverse: block synthesis with NSAIDs and fever, pain and inflammation improve while stomach, kidney, platelet and ductus pay; the whole of eicosanoid pharmacology is one pathway read from two directions.

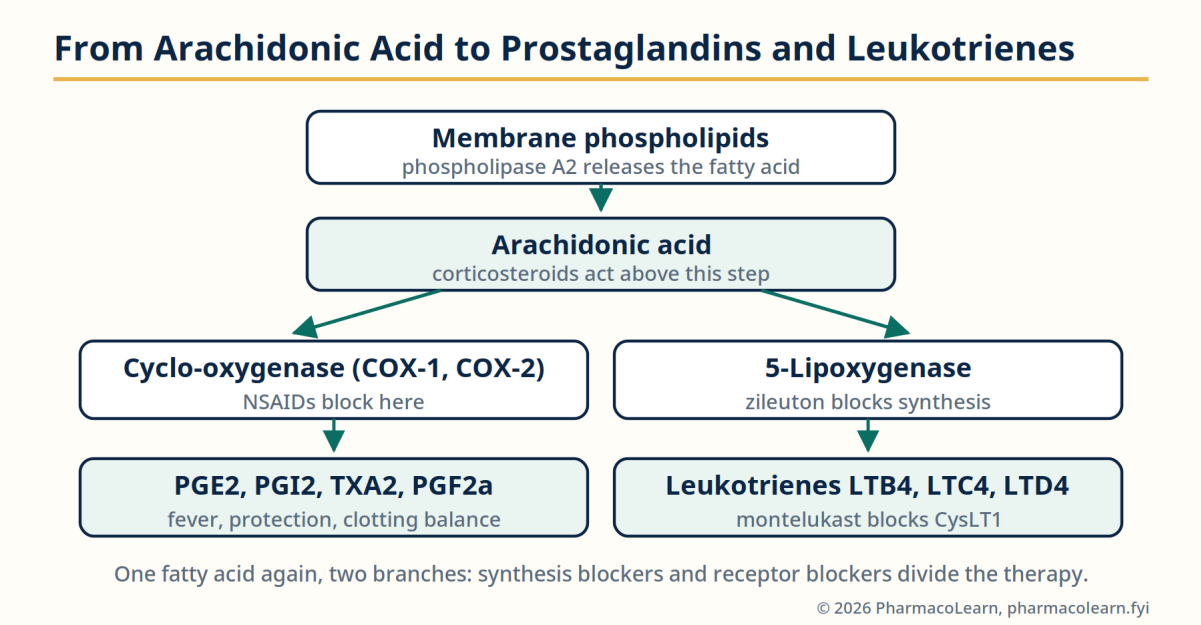

Figure: Arachidonic acid metabolism. The cyclo-oxygenase branch makes the prostaglandins and thromboxane, the lipoxygenase branch makes the leukotrienes.

5.6 Opioid autocoids: the endogenous opioid system

The body runs its own opioid pharmacology. Three precursor proteins are cleaved into peptide families: **pro-opiomelanocortin** gives beta endorphin (with ACTH and MSH as siblings), **proenkephalin** gives the met and leu enkephalins, and **prodynorphin** gives the dynorphins; a fourth pair, the endomorphins, is highly mu selective. The peptides map onto the receptors of section 3.10 with preferences: endorphins at mu, enkephalins at delta, dynorphins at kappa. They are released in stress, exercise, pain and parturition, degrade within minutes by peptidases (enkephalinases), and modulate pain transmission in the dorsal horn

and midbrain, reward and mood, gut motility, respiration and the stress hormone axis.

Their roles complete several stories told earlier in this subject. **Placebo analgesia is partly endogenous opioid release**, reversible by naloxone, one of the neatest demonstrations in all pharmacology. Stress induced analgesia, the analgesia of acupuncture in part, and the runner's high all recruit the system. The peptidase step is drugged: **racecadotril** inhibits enkephalinase to treat acute diarrhoea by protecting endogenous enkephalins in the gut, opioid effect without an opioid drug. And the antagonist side closes the loop of Unit 3: naloxone and naltrexone block receptors whose natural ligands are these peptides, which is why antagonist therapy in dependence must reckon with a system that also carries normal reward and pain control. With the autocoids, the subject ends where it began in Unit 1: every drug mechanism in these notes is a hand laid on a system the body already owned.

Frequently Asked Questions

Q: What is the difference between clearance and half life, and which one sets the maintenance dose? Clearance is the volume of plasma cleared of drug per unit time; half life is the time for the plasma concentration to halve, and it depends on both clearance and volume of distribution ($t_{1/2} = 0.693 \times V_d / CL$). The maintenance dose rate is set by clearance alone, because at steady state input must match elimination: dosing rate = CL x target steady state concentration. The loading dose, in contrast, is set by Vd.

Q: Why does phenytoin show non-linear kinetics, and why does it matter at the bedside? Phenytoin is eliminated by hepatic enzymes that saturate within the therapeutic range. Below saturation it behaves first order; once the enzymes approach their maximum rate, elimination becomes zero order, a constant amount per day, so a small dose increase produces a disproportionately large rise in plasma level and the apparent half life lengthens. Dose changes must therefore be small, levels must be measured, and steady state may take weeks rather than days.

Q: A patient on phenytoin develops hypoalbuminaemia. Why can the laboratory total level mislead? Only free phenytoin crosses membranes, acts and is cleared, but the routine assay measures total (bound plus free) drug. Phenytoin is about 90 percent albumin bound, so when albumin falls, the free fraction rises: the patient can be toxic at a total level that looks therapeutic or even low. The correct responses are to measure the free level or apply a correction, and to judge the patient clinically rather than by the total figure alone.

Q: How do competitive and non-competitive antagonists differ on a dose response curve? A competitive antagonist binds the agonist's site reversibly, so enough agonist outcompetes it: the agonist curve shifts right in parallel, potency (EC_{50}) falls, but the maximum response (E_{max}) is unchanged. A non-competitive antagonist acts at a separate site or irreversibly, so no amount of agonist restores the full response: E_{max} is depressed once the receptor reserve is used up, while the EC_{50} of the remaining response may be little changed.

Q: Why must beta blockers never be started before alpha blockade in phaeochromocytoma? The tumour secretes adrenaline and noradrenaline, stimulating both alpha (vasoconstrictor) and beta (including vasodilator beta2) receptors. If beta receptors are blocked first, the beta2 vasodilator escape is removed while alpha vasoconstriction continues unopposed, and blood pressure can rise to a crisis. The correct order is alpha blockade first (phenoxybenzamine or an alpha1 blocker, with volume repletion), and only then a beta blocker for the tachycardia.

Q: How does pralidoxime help in organophosphate poisoning, and why does timing matter? Organophosphates inhibit acetylcholinesterase by phosphorylating it. Pralidoxime is an oxime that pulls the phosphate group off the enzyme and reactivates it, restoring neuromuscular and autonomic function that

atropine cannot reach (atropine only blocks muscarinic receptors). With time the phosphorylated enzyme undergoes ageing, a chemical change that makes the bond permanent, after which oximes no longer work; hence pralidoxime is given as early as possible.

Q: Why is aspirin dosed once daily for antiplatelet effect when its plasma half life is only a few hours? Aspirin irreversibly acetylates platelet cyclo-oxygenase 1. Platelets have no nucleus and cannot synthesise replacement enzyme, so thromboxane A2 production is suppressed for the platelet's whole lifespan of about 7 to 10 days. Only the roughly 10 percent of platelets replaced each day restore activity, so a small daily dose keeps the whole population inhibited despite the drug itself disappearing from plasma within hours.

Q: ACE inhibitors cause cough and angioedema, but ARBs largely do not. Why? ACE is also kininase II, the enzyme that destroys bradykinin. ACE inhibitors therefore raise bradykinin levels in the airways and tissues, and bradykinin produces the dry cough and, in susceptible patients, angioedema. ARBs block the angiotensin AT1 receptor and leave ACE free to break down bradykinin, so bradykinin does not accumulate and cough is no more common than with placebo; angioedema is much rarer, though not impossible.

Q: Triptans and ondansetron both act on serotonin receptors. How are their actions opposite in spirit? Sumatriptan is an agonist at 5-HT1B/1D receptors: it constricts dilated cranial vessels and blocks neuropeptide release from trigeminal terminals, aborting a migraine attack. Ondansetron is an antagonist at 5-HT3 receptors, the ion channel receptors of the gut and the chemoreceptor trigger zone, and so prevents chemotherapy and postoperative vomiting. Same transmitter, different receptor subtypes, opposite pharmacological verbs, different diseases entirely.

Q: Why is clozapine reserved for treatment resistant schizophrenia despite being the most effective antipsychotic? Clozapine carries risks the other agents do not: agranulocytosis in about 1 percent of patients, which can be fatal and demands mandatory regular blood monitoring, plus myocarditis, dose dependent seizures, severe constipation that can progress to ileus, and the heaviest metabolic burden of the class. It is therefore reserved for schizophrenia that has failed at least two other antipsychotics, where its superior efficacy, including reduced suicidality, justifies the monitoring system built around it.

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