HISTAMINE AND SEROTONIN

(a) ***To describe the roles of histamine and serotonin receptor subtypes.***

(b) ***To outline the pharmacology of histamine antagonists.***

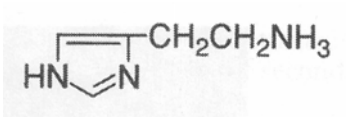
(c) ***To outline the pharmacology of drugs acting via effects on serotonin or serotonin receptors.***

Histamine and Histamine Antagonists:

(I) Histamine:

Overview of histamine:

- Histamine is an endogenous basic amine (autocoid) → found in all tissues, but especially:
  - (i) 1°ly in storage granules of circulating basophils and mast cells (in CT beneath epithelial surfaces of skin, lungs and GIT)
  - (ii) Also in histaminergic cells → ECL cells (stomach) and histaminergic neurons (posterior hypothalamus)
- It is hydrophilic → cannot cross BBB



Synthesis, storage and release of histamine:

- Histamine is produced by decarboxylation of histidine → then stored in vesicles (complexed to heparin and acidic protein)
- Degranulation of histamine-containing cell occurs in response to – (i) Immunological stimulus (IgE-Ag complex, C3a/C5a), (ii) Mechanical stimulus, or (iii) Drugs → causes ↑ IC Ca^{2+} → results in Ca^{2+}-induced exocytosis of histamine
- Post-degranulation → replenishment of histamine in mast cells/basophils take several days-weeks (cf. ECL/histaminergic neurons, which have rapid turnover)

Metabolism of histamine:

- Via two pathways:
  - (i) Methylation (main) via Histamine-N-methyltransferase → then [O] by MAO
  - (ii) Oxidative deamination via Diamine oxidase (aka. Histaminase)
- Both pathways produce inactive metabolites → excreted in urine

Histamine receptors:

Receptor	Mechanism	Location and effects	Inhibited by

H1	GPCR → via Gq	- (i) CVS
		  o ↓ HR 2° to ↓ AV nodal conduction
		  o Coronary vasoconstriction
		- (ii) Vascular
		  o Vasodilation 2° to vascular SM relaxation (due to NO release from vascular endothelium → ↑cGMP)
		  o ↑ capillary permeability 2° to PGI-2 release from vascular endothelium
		- (iii) Respiratory
		  o Bronchial SM contraction
		  o Pulmonary vasodilation
		- (iv) CNS – Postsynaptic excitatory effect → wakefulness, appetite suppression, vomiting
		- (v) PNS – Sensory nerve endings → pain, pruritis, sneezing
		- (vi) GI/GU – GI and uterine SM contraction
			H1R antagonists

H2	GPCR → via Gs	- (i) CVS
		  o ↑ contractility 2° to +ve intropy
		  o ↑ HR 2° to +ve chronotropy
		  o Coronary vasodilation
		- (ii) Vascular
		  o Vasodilation (due to vascular SM relaxation)
		  o ↑ capillary permeability
		- (iii) Respiratory
		  o Bronchial SM relaxation
		  o Pulmonary vasoconstriction
			H2R antagonists

		- (iv) CNS – Postsynaptic inhibitory effect - (v) GI – ↑ gastric acid secretion (parietal cell)	
H3	GPCR	- Located presynaptically to histamine-secreting cells - Exerts –ve feedback → inhibits synthesis/release of histamine	H2R antagonists

Note: H3R inhibition by H2RBs → there is an issue of ↑ histamine release in response to histamine-releasing drugs in patients pre-treated with H2RB → thus, (i) pretreat with H1RBs also, or (ii) avoid such drugs!

Physiological effects of histamine:

CVS	(i) ↓ BP (2° to ↓ SVR) and generalised flushing (esp face and upper body) → due to arteriolar and capillary dilation (H1 and H2) (ii) Oedema → due to ↑ capillary permeability (H1 and H2) Note – Either H1 or H2 cause maximal vasodilation/capillary permeability → BUT H1 is activated at ↓ [ ], and has rapid but transient effects. H2 is activated at ↑ [ ] , and has slower but sustained effects (iii) ↑ myocardial contractility → due to +ve inotropy (H2) (iv) ↑ HR and arrhythmias → due to +ve chronotropy (H2) (v) Slowed conduction through AVN → due to antidromic effect (H1) (vi) Coronary – Vasoconstriction (H1) or vasodilation (H2)
CNS	Wakefulness, appetite suppression, and vomiting (H1)
Respiratory	(i) Bronchoconstriction and pulmonary vasodilation (H1) (ii) Bronchodilation and pulmonary vasoconstriction (H2)
GIT	(i) Major stimulus for parietal cell secretion of HCl (H2) (ii) ↑ intestinal motility
Cutaneous	(i) Pruritis, pain, sneezing (H1) (ii) "Triple response" (H1 >> H2) – (a) Capillary dilation, (b) Wheal due to oedema (a/w ↑ capillary permeability), and (c) Flare due to arteriolar dilation (histamine stimulates axon reflex in sensory nerves to release dilator peptide)
Allergic reactions	Histamine is one of several chemical mediators in type I hypersensitivity reactions (Nb. thus antihistamines only limited effects on preventing hypotension, bronchoconstriction, oedema/pruritis)
Others	Uterine contractions (H1)

(II) <u>H1 Receptor Antagonists (H1RBs)</u>:

Overview of H1RBs:

- Mechanism – H1RBs competitively and reversibly inhibit histamine activity at H1R
- There are two types:
  - 1st generation H1RBs (promethazine, diphenhydramne; chlorphiramine) → highly selectively blockade of H1R, but also blocks mAChR, 5-HT, α- adrenoceptors → causes sedating effect, antiemetic and anticholinergic effects
  - 2nd generation H1RBs (loratidine, fexofenadine) → highly selective blockade of H1R only (cannot cross BBB and blocks mAChR, 5-HT, α-receptors) → thus, non-sedating and without antiemetic or anticholinergic effects

Clinical uses of H1RBs:

- (1) Treat symptoms of allergic rhinoconjunctivitis (sneezing, nasal/ocular itching, rhinorrhoea, tearing, conjunctival erythema)
- (2) Treat pruritis and chronic urticarial lesions
- (3) Treat vertigo and nausea/vomiting (esp motion sickness and Meniere's disease) → 1st generation agents only
- (4) Sedation → 1st generation agents only

- (5) Protection against bronchospasm induced by histamine, exercise, cold/dry air (Nb. cannot be used to prevent bronchial asthma due to presence of other mediators)
- (6) Treat anaphylactic reactions → block further histamine-mediated vascular effects (causing haemodynamic instability) and airway effects. Also used to treat prutitis, urticaria and angiooedema

> Note – H1RBs AND H2RBs should be combined to block all vascular effects of histamine (Ie. treat hypotension)!!!

- (7) Prophylaxis against drug-induced anaphylactoid reactions (Ie. to contrast)

Pharmacokinetics of H1RBs:

Absorption	PO: - Well-absorbed but ↓ bioavailability due to extensive 1st pass metabolism → time to peak [ ] (and onset of action) ~ 2 hrs - Diphenhydramine 50 mg, chlorpheniramine 2-4 mg, promethazine 25-50 mg, loratadine 10 mg IV → 1st generation H1RBs only (as H2RBs have ↓ H_2O solubility)
Distribution	- Protein binding 80-99%; - 1st generation H1RBs can cross BBB (but not 2nd generation H1RBs) - Duration of action – 1st generation (diphenhydramine 3-6 hrs; promethazine and chlorpheniramine 4-24 hrs), 2nd generation (loratidine 24 hrs)
Metabolism and elimination	- Hepatic metabolism (CYP450) - Variable elimination t ½ (10 hrs for loratidine and diphenhydramine; 30 hrs for chlopheniramine)

Issues with H1RBs:

- 1st generation H1RBs (cf. 2nd generation agents) have a ↑ incidence of:
  - CNS side-effects – Somnolence, diminished alertness, slowed reaction time, impaired cognitive function
  - Anticholinergic effects – Dry mouth, blurred vision, urinary retention, impotence
- CVS side-effects – Tachycardia, prolonged QTc, heart block, arrhythmias (esp if concurrent liver disease, prolonged QTc, ↓ K^+, ↓ Mg^{2+})
- ↑ respiratory depression when used concurrently with opioids (Ie. to treat PONV/pruritis), barbiturates or Bz's
- Antihistamine OD → seizures and cardiac arrhythmias

(III) <u>H2 Receptor Antagonists (H2RBs)</u>:

Types of H2RBs:

- Famotidine (most potent) > Ranitidine = Nizatidine > Cimetidine (least potent)

Mechanism of action of H2RBs:

- Competitive and reversible inhibition of histamine activity at H2R (acts via Gi – ↓ IC cAMP) → selectively inhibits H2R at parietal cell (despite H2R being distributed widely in body)

Clinical uses of H2RBs:

- H2RBs inhibit gastric acid secretion (both basal and stimulated secretions) → a/w ↓ gastric acidity AND gastric fluid volume (but it has no effect on LOS tone or gastric emptying) → it can be used to:
  - (1) Treat PUD (duodenal and gastric ulcers)
  - (2) Treat GORD
  - (3) Treat Zollinger-Ellison syndrome
  - (4) Prevent stress ulceration in critically ill patients

    - (5) Provide aspiration prophylaxis prior to GA
        - More reliable than PPI in ↓ gastric fluid volume and ↑ gastric fluid pH
        - H2RB given 1.5-2 hrs preoperative and night before
        - No immediate influence on current gastric pH (cf. antacids)
- Also provide protection against drug-induced allergic reactions (Ie. contrast) → when used prophylactically with H1RBs, it can ↓ hypotension (but NOT histamine release)

Pharmacokinetics of H2RBs:

Absorption	PO: - Well-absorbed but 50% bioavailability (due to extensive 1st pass metabolism) → EXCEPT nizatidine (100% bioavailability) - Cimetidine 300-800 mg, Ranitidine 150-300 mg, Nizatidine 150-500 mg, Famotidine 20-40 mg IV → Cimetidine 300 mg, Ranitidine 50 mg, Famotidine 20 mg
Distribution	- Protein binding 15-30%; V_D 1-1.5 L/kg - Can cross BBB and placenta - Time to peak [ ] (and onset of action) ~ 1-3 hrs after oral administration - Duration of single dose 6 hrs (cimetidine); 10 hrs for other H2RBs
Metabolism and elimination	- Hepatic metabolism (CYP450) into renal clearance (filtration and secretion): o Oral intake → mainly hepatic clearance (EXCEPT nizatidine) o IV intake → mainly renal clearance o Nb. Nizatidine is metabolised to an active metabolite (60% activity) - Elimination t ½ ~ 1.5-4 hrs - Dose reduction required with renal failure only (and NOT hepatic failure)

Issues with H2RBs:

- Side-effects are rare:
    - Mainly diarrhoea, dizziness, myalgia and rash
    - Cardiac effects occur 2° rapid IVI (esp in critically unwell or elderly patient) → hypotension, bradycardia, arrhythmia, cardiac arrest
    - Gastric achlorhydria → alter gastric flora due to change of pH → potential for systemic and/or pulmonary infections (esp in critically unwell patients)
    - Hypergastrinaemia and rebound hypersecretion of gastric acid → with cessation of chronic therapy
- Side-effects specific to cimetidine (>> ranitidine):
    - Inhibition of hepatic CYP450 → ↓ drug metabolism of warfarin, phenytoin, TCAs, propanolol, amide LAs, quinidine, Bz's, ketoconazole
    - Hepatotoxicity (elevated serum transaminase)
    - Cimetidine crosses BBB → cerebral effects (headaches, fatigue, confusion, hallucinations, seizures) → esp with renal failure
    - Interstitial nephritis
    - Granulocytopaenia and thrombocytopaenia
    - Impotency/↓ sperm count → due to binding of androgen receptors
    - Galactorrhoea (females) and gynaecomastia (males) → due to ↑ PRL

Note:
- Ranitidine weakly inhibits CYP450, while famotidine and nizatidine do NOT affect it
- Other H2RBs do not cross BBB readily nor affect androgen receptors

Serotonin and Serotonin-Mediated Drugs:

(I) Serotonin:

Overview of 5-HT:

- Serotonin (5-hydroxytryptamine (5-HT)) → endogenous vasoactive substance (autocoid)
- Widely distributed in body → mainly in 3 sites:
    - (1) GI tract (90% – main site)
        - (i) 1°ly in enterchromaffin cells → 5-HT is synthesised and stored
        - (ii) Neurons of ENS → 5-HT acts as excitatory NT
    - (2) Platelets → Actively take up 5-HT and store into dense core granules (as an inactive store of 5-HT)
    - (3) CNS → Excitatory/inhibitor NT in various parts of brain

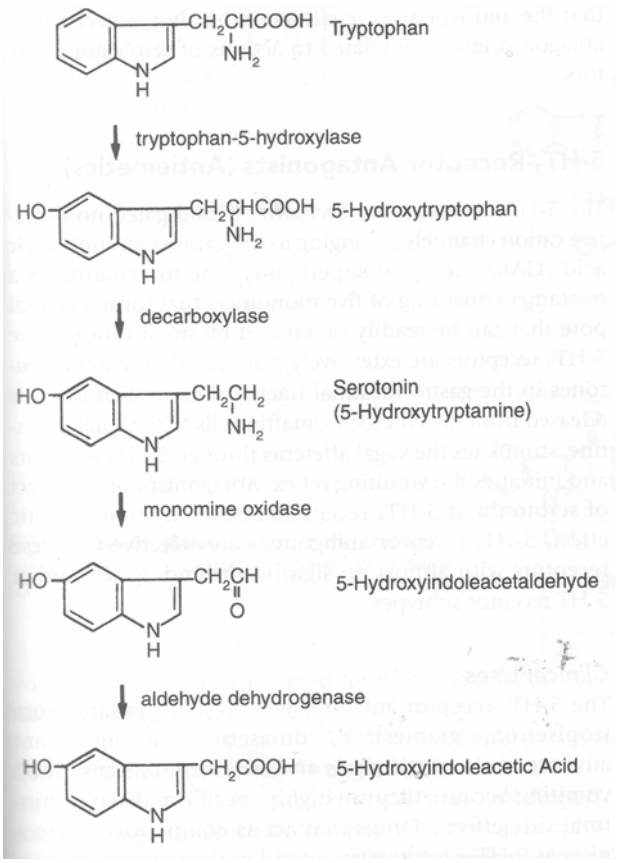
Synthesis, storage and release of 5-HT:

- 5-HT is derived from tryptophan → essential a.a. obtained only from diet
- Tryptophan is hydroxylated via Tryptophan hydroxylase (* rate-determining step *) → forms 5-OH-tryptophan → decarboxylated (via decarboxylase) → forms 5-HT → stored in vesicles
- Stored 5-HT is released from vesicles via exocytosis in response to appropriate stimulus

> 5-HT synthesis occurs within EC cells and some neurons only (and NOT platelets) → platelets and neurons that do not synthesis 5-HT actively take up 5-HT from plasma → stored in vesicles

Metabolism of 5-HT:

- 5-HT undergoes oxidative deamination (via MAO) → forms 5-HO-indoleacetaldehyde → then converted by aldehyde dehydrogenase into 5-HO-indoleacetic acid (5-HIAA) → 5-HIAA is then renally excreted
- Nb. Urinary measurement of 5-HIAA is used as a measure of 5-HT turnover (Ie. diagnose carcinoid syndrome)



5-HT receptors:

Receptor	Subtypes	MOA	Location	Effect
5-HT1	A, B, D, E, F	GPCR – Gi	(i) CNS (all subtypes)	Neuronal inhibition (presynaptic mechanism) and behaviour (sleep, feeding, thermoregulation, anxiety, Etc.)
			(ii) Vascular SM (1D)	Cerebral vasoconstriction
5-HT2	A, B, C	GPCR – Gq	(i) CNS	Neuronal excitation
			(ii) PNS (esp ANS)	Neuronal excitation
			(iii) SM (lungs, GI, vascular)	Coronary/pulmonary vasoconstriction, vascular SM relaxation (due to NO from endothelial cells), bronchoconstriction, gastric contraction,
			(iv) Platelets	Platelet aggregation
5-HT3		Excitatory ligand-gated channel (fast Na^+/K^+)	(i) Enteric neuron (ENS)	Emesis
			(ii) CNS	Emesis (area postrema; CTZ) and behaviour (anxiety)
			(iii) PNS	Pain (nociceptive afferent neurons), ANS excitation
5-HT4		GPCR – Gs	(i) Enteric neuron (ENS)	↑ GI motility
			(ii) CNS	Neuronal excitation
5-HT5		GPCR – Gi	Brain and GIT	Unknown
5-HT6		GPCR – Gs	Brain and GIT	Unknown
5-HT7		GPCR – Gi	Brain and GIT	Unknown

Physiological effects of 5-HT:

CNS	Appetite control, wake/sleep, mood, behaviour, anxiety, N/V → excitation/inhibition of CNS neurons
CVS	Vasoconstriction (cerebral, coronary, pulmonary, renal/splanchnic) Vasodilation → release if NO from vascular endothelium Nb. IV 5-HT causes ↑ MAP initially (vasoconstriction), then ↓ MAP later (vasodilation) Transient and modest +ve inotropy → causes reflex bradycardia
GIT	↑ GI motility → direct effect on GI SM and indirect effect via ENS) ↑ GI fluid secretion → via ENS stimulation N/V
Platelets	Platelet aggregation → release of 5-HT stores
PNS	Pain → stimulation of nociceptive nerve endings
Others	Bronchial and uterine SM contraction (minor)

(II) Serotonin-Mediated Drugs:

5-HT agonists:

Drug	Receptor	Clinical use	Issues
Sumitriptan	5-HT1D	Acute migraine treatment → causes cerebral vasoconstriction	Contraindicated in IHD (due to coronary vasoconstriction)
Buspirone	5-HT1A	Anxiolytic	
Metoclopramide	5-HT4	Prokinetic	Extrapyramidal symptoms
Cisapride	5-HT4	Prokinetic	Prolonged QTc

5-HT antagonist:

Drug	Receptor	Clinical use	Issues
Methysergide	5-HT2A/C	(i) Migraine prophylaxis → causes cerebral vasodilation (ii) Carcinoid syndrome (iii) Postgastrectomy dumping syndrome	Retroperitoneal, pleural, coronary, endocardial fibrosis

Cyproheptadine	5-HT2A	(i) Carcinoid syndrome (ii) Postgastrectomy dumping syndrome	H1RB and anticholinergic effects (sedation), weight gain
Ketanserin	5-HT2A	Carcinoid syndrome	Hypotension (α1 antagonism)
Pizotifen	5-HT2A	Migraine prophylaxis	Anticholinergic effects, weight gain
Ondansetron, tropisetron, Etc.	5-HT3	Antiemetics	
Mirtazapine	5-HT2/3	Antidepressant	

5-HT partial agonist/antagonist:

Drug	Receptor	Clinical use	Issues
Ergotamine and dihydroergotamine	5-HT1B agonist/5-HT1A and D antagonist	Acute migraine treatment	Emesis, HTN (avoid if IHD), uterine contractions (avoid if pregnant)
Ergometrine	5-HT1	Prevent PPH	HTN and tachycardia
LSD	5-HT2A/C		

5-HT-modulating agents:

- Increase release of 5-HT
  - Fenfluramine/dexfenfluramine → sympathomimetic amine given in combination for weight loss by appetite suppression
- Inhibit 5-HT reuptake
  - SSRI (Eg. fluoxetine, sertraline) → antidepressant → highly selective 5-HT reuptake inhibitors
  - TCA (Eg. imipramine) → antidepressant → weakly inhibits 5-HT reuptake
  - Venlafaxine → antidepressant agent → weak non-selective 5-HT (and NAd) reuptake inhibitor
- Inhibit 5-HT breakdown
  - MAOi (Eg. phenelzine, moclobemide) → antidepressant → inhibits MAO-A, thus preventing break down of 5-HT (and NAd)

Tramadol is a unique 5-HT modulating agent that acts by:
- (i) Indirectly inhibiting presynaptic 5-HT reuptake
- (ii) Causes 5-HT release by presynaptic mechanism
- (iii) Antagonises 5-HT2C receptor