B18 - Histamine & Serotonin

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

Histamine

= an amine present in mast cells, basophils, gastric mucosa & in the CNS.

Involved in:

(1) inflammatory response - cytokines, complement, leukotrienes & coagulation.
(2) gastric acid secretion
(3) ? neurotransmission

Synthesised from decarboxylation of L-histidine
Metabolised by deamination or methylation
Eliminated renally

Histamine Receptors

See diagram - Histamine & Histamine Receptors

H1

- post-synaptic G-protein coupled -> increase in phopholipase C -> hydrolysis of membrane phospholipid (PIP2) to inositol triphosphate (IP3) & diacylglycerol (DAG) -> activates protein kinase & Ca2+ dependent kinases ->

(1) contraction of smooth muscle - bronchoconstriction, GI tract & coronaries.
(2) vasodilation & increased permeability in vessels -> increased NO & prostacylcin secretion -> oedema, headache, tachycardia, hypotension, urticaria.

H2

- postpsynaptic Gs coupled -> increase in adenylate cyclase -> increase in cAMP ->

(1) increase in gastric parietal cell hydrogen ion & intrinsic factor secretion.
(2) increase myocardial contractility & HR
(3) bronchodilation
(4) coronary vasodilation
(5) mast cell degranulation (IgE mediated type I hypersensitibity rxns)
(6) some vasodilation (not as much as H1)

H3

- presynaptic Gi coupled -> decrease in adenylate cyclase -> decrease in cAMP -> inhibition of histamine release in CNS.

Serotonin

- 5-Hydroxytryptamine (5-HT)
- found throughout body but especially in:

(1) GI tract enterochromaffin cells (90%)
(2) smooth muscle
(3) platelets
(4) mast cells
(5) PNS
(6) CNS

Involved in:

(1) inflammatory mechanism - increases vascular permeability & platelet aggregation, vasodilatation/vasoconstriction at different vascular beds.
(2) bronchoconstriction
(3) increases GI motility
(4) increases GI water & electrolyte secretion
(5) arousal
(6) muscle tone
(7) parasympathetic regulatory mechanisms
(8) mood
(9) spinal modulation of pain sensation
(10) inhibitor neurotransmitter in brain stem, descending spinal pathways, hypothalamic, cortical, limbic & extrapyramidal systems.

Synthesis

- hydroxylation and decarboxylation of tryptophan
- stored in cytoplasmic vesicles.

Metabolised by MAO -> 5-hydroxyindoleacetic acid

Serotonin Receptors

- 7 (atleast)
- 6 are G protein coupled
- 1 acts on fast Na+/K+ channel (5-HT3)

5-HT1

- Gi protein coupled -> decrease in adenylate cyclase -> decrease in cAMP -> cerebral vasoconstriction

5-HT2

- Gp protein coupled -> increase in phopholipase C -> PIP2 -> IP3 & DAG -> activation of protein kinase -> wide spread vasoconstriction, bronchoconstriction & platelet aggregation.

5-HT3

- directly coupled to fast Na+/K+ ion channel -> visceral pain, anxiety, nausea & vomiting

5-HT4

- Gs protein coupled -> increase in adenylate cyclase -> increase in cAMP in myenteric neurons -> prokinetic, smooth muscle vasodilator (smooth muscle, sk muscle & cardiac)

5-HT 5, 6, 7

- Gs protein coupled -> increase in cAMP -> brain ? involved in anxiety.

(b) To outline the pharmacology of histamine antagonists

Promethazine - H1 antagonist
Cimetidine, Ranitidine - H2 antagonist

Promethazine

Chemical - phenothiazine

Uses

(1) PONV
(2) motion sickness
(3) allergic reactions
(4) pruritis
(5) sedation in children

Preparation - tablets, elixir & injection

Routes - PO, IM, IV

Doses

- PO: 25-50mg in divided doses
- IV: 25-50mg

- acts in 15min

- duration 10-20hrs

PK

Absorption - well absorbed orally

Distubution

- 93% protein bound
- Vd 2.5 L/kg

Metabolism

- hepatically by sulphoxidation & N-dealkylation

Elimination

- urinary
- 2% unchanged
- Cl = 1.5mL/min/kg
- t1/2 = 10hrs

PD

Main action - anti-histaminergic, sedative & antiemetic

Mechanism of action

(1) revesible, competitive antagonism at H1 receptors
(2) anti-cholinergic
(4) anti-serotinergic
(5) anti-dopaminergic

CVS - no effects @ normal dosage

RESP

- bronchodilation
- reduced secretions
- anti-tussive

CNS

- potent sedative & anxiolysis
- reduced motion sickness by suppression of vestibular end-organ receptors & by inhibition at chemoreceptor trigger zone.

GI - decreases tone of oesophageal sphincter

Other adverse effects

- extrapyramdial side effects
- jaundice
- photosensitivity
- excitatory phenonmena

H2 Antagonists

- ranitidine, cimetidine, famotidine & nizatidine
- produce selective & reversible inhibition of H2-receptor mediated secretion of acidic gastric fluid.

Mechanism

- histamine-H2 receptor complex -> increase intracellular cAMP -> activation of proton pump of gastric parietal cells -> secretion H+ against a large concentration gradient in exchange for K+ (H+/K+ ATPase)
- H2 antagonists competitively & selectively inhibit the binding of histamine to H2 receptor...

Uses

(1) DU
(2) antacid
(3) attenuation of allergic response

Onset - 1 to 3 hrs

Duration

- cimetidine - 6hrs
- ranitidine - 10hrs

PK

Absorption

- rapid via PO route
- bioavailability = 50% (except nizatidine = 100%)

Distribution

- Vd = 1-2 L/kg
- cross BBB, placenta & appear in breast milk

Elimination

- t1/2 = 2-4 hrs
- combination of hepatic metabolism, glomerular filtration & renal secretion.
- decrease dose in renal dysfunction

PD

CVS

- hypotension & arrhythmia (rare)

CNS

- headache
- fatigue
- confusion (rare)
- dizziness (rare)
- somnolence (rare)

GI

- diarrhoea
- increase LFTs (rare)

Metabolic

- gynacomastia (rare)
- galactorrhoea (rare)

Other adverse effects

- sk muscle pain
- thrombocytopenia (rare)
- drug fever (rare)

Drug interactions

- diazepam, lignocaine & propanolol -> increases plasma concentration
- ethanol -> increased absorption
- Mg2+ & NaOH -> decrease bioavailability

Ranitidine

Chemical - a furan derivative

Uses

(1) peptic ulder disease
(2) GORD
(3) Zollinger-Ellison syndrome
(4) preventionf of stress ulceration in ICU
(5) prior to GA in aspiration risk

Presentation

- injection: 25mg/mL
- tablets: 150, 300mg
- syrup: 15mg/mL

Routes - IV, PO, IM

Dose

- IV: 50mg QID
- PO: 150mg bd

PK

Absorption - bio = 50%
Distribution - protein bound = 15%, Vd = 1.5 L/kg
Metabolism - oxidation & methylation
Elimination - Cl = 10ml/min/kg, t1/2 = 2hrs, reduce dose in renal failure

PD

Main action - inhibtion of gastric acid secretion

Mechanism

- competitive blockade of H2 receptors -> decrease in secretion
- also decreases action of gastrin & Ach

CVS - none

RESP - none

GI

- gastric acid inhibtion
- increase in LES tone

Metabolic

- anti-adrongenic, antidopaminergic
- crosses placenta (no adverse effects on bubs)

Other adverse effects

- LFTs derangement
- rash
- anaphylactoid reaction
- confusion
- thrombocytopenia
- leukopenia

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

Serotonin agonists - sumatriptan, SSRI's (fluoxetine)

Serotonin receptor antagonists - ondansetron, tropisetron.

Sumatriptan

Chemical - sympathethic amine with similar structure to amphetamine.

Uses

(1) treatment of migrane
(2) treatment of postural puncture headache

PK - t1/2 = 2hrs

PD

Mechanism of action - 5-HT1 agonist -> cerebral vasoconstriction.

Side effects

- diarhoea
- polyuria
- dry moth
- insomnia
- somnolence

SSRI's

- block the reuptake of serotonin
- fluoxetine, paroxitine, sertraline, fluvoxamine, citalopram

- lack anti-cholinergic side effects of TCA's:

- postural hypotension
- delayed cardiac conduction
- doesn't effect seizure threshold

- common side-effects:

- insomnia
- agitation
- headache
- nausea
- diarrhoea
- sexual dysfunction (delayed ejaculation, anorgasmia, decreased libido).

Fluoxetine

Chemical - a propylamine derivative

Uses

(1) depression
(2) bulimia
(3) OCD

Presentation

- tablet: 20 to 60mg
- suspension: 4mg/mL

Route - PO

Dose - once a day 20-60mg

PK

Absorption - bioavailability 70%
Distribution - 95% protein bound, Vd 3 L/kg
Metabolism - hepatic -> desmethyl-metabolite (active)
Elimination - 60% administered in urine, Cl 43L/hr, t1/2 = 3 days

PD

Main action - antidepressant

Mechanism of action - selective inhibition of neuronal uptake of 5-HT by presynaptic serotonin re-uptake pump.

CVS - no effects
RESP - no effects
CNS - see above

GI

- decreased appetite
- dose related nausea, abdo pain, diarrhoea

Metabolic

- decreased serum Na+ (inappropriate ADH secretion)
- elevates corticosterone concentration

Other adverse side effects

- PK is altered by hepatic but not renal dysfunction

Drug interactions

- co-administration of pentazocine -> severe CNS excitatory responses.
- potent inhibitor of certain CYP450 enzymes -> decrease in hepatic metabolism -> increase in concentration of drugs...

- TCA's
- cardiac antidysrhythmics
- beta-adrenergic antagonists

- MAOI's -> serotonin syndrome (anxiety, restlessness, chills, ataxia & insomnia)
- fluoxetine + lithium + carbamazepine -> fatal syndrome

Serotonin antagonists (5-HT3 antagonists)

- act:
(1) peripherally by blockade of 5-HT3 receptor on intestinal afferents
(2) centrally by blockade of 5-HT3 in vomiting center & chemoreceptor trigger zone.

- agents: ondansetron, granisetron, dolasetron, tropesitron.

Ondansetron

Chemical - synthetic carbazole

Uses

(1) N & V induced by chemotherapy & radiation
(2) PONV

Preparation

- IV: clear, colourless solution in 2 or 4mg amp
- PO: tablets or waffers

Routes - PO, IV, IM

Dose

- PO: 8mg Q8hrly
- IV or IM: 4mg Q8hrs

PK

Absorption - bioavailability = 50%

Distribution

- 75% protein bound
- Vd 2 L/kg

Metabolism

- hepatic
- hydrolylation or N-demethylation of the indole nucleus -> conjugation with glucuronic acid or sulphate.

Elimination

- <5% excreted unchanged in urine
- Cl = 6mL/min/kg
- t1/2 = 3hrs

PD

Main action - antiemetic

Mechanism of action

- highly selective antagonist @ 5-HT3 receptors peripherally & centrally

- emetogenic stimuli -> release of 5-HT in small intestine & initiation of vomiting reflex via vagal afferents & 5-HT3 receptors.
- ondansetron blocks the initation of this reflex

CVS - no effects

RESP - no effects

CNS - headache (rarely)

GI - increases large bowel transit time, constipation

Metabolic - no effect

Other adverse effects

- anaphylaxis has been reported.
- no alteration needed in renal failure
- adjust for hepatic failure (8mg/day max)