B10 - Pharmacology of the autonomic nervous system

(a) To describe the physiological roles of the sympathetic & parasympathetic nervous system.

Function = involuntary defense to challenges against homeostasis

See diagram - Autonomic nervous system

Sympathetic

- originate from T1 to L3 neurons in intermediolateral column of spinal grey matter
- nerve fibers exit to 3 types of ganglia

(1) paired sympathetic ganglia
(2) unpaired distal plexuses (coelica, superior & inferior mesenteric, aorticorenal)
(3) terminal ganglia near target organ (adrenal medulla)

- all pregangilonic sympathetic neurons release Ach
- most postganglionic sympathetic neurons release noradrenaline (except: skin hair follicles, muscle blood vessels & sweat glands)

Sympathetic response

- increase in HR
- increase in BP
- increase in Q
- bronchodilation
- increased sk muscle blood flow
- decreased skin blood flow
- decreased GI tract blood flow
- increase BSL
- pupillary dilation
- viscous saliva
- sweating
- adrenaline release from adrenal medulla
- ejaculation

Parasympathetic

- orginates from mid-brain & medulla (CN III, VII, IX, X) & S2 to 4.
- Ach is the neurotransmitter through nervous system

Parasympathetic response

- decrease in HR
- decrease BP
- decrease Q
- increase GI tract blood flow
- protect retina from excess light (contricts)
- empty bladder & rectum
- watery saliva
- bronchoconstriction
- increase bronchial secretions
- increase GI motility
- erection

- there is no parasympathetic nervous system innervation in arm, leg or cardiac ventricles.

(b) To describe the physiological actions of adrenergic, cholinergic & dopaminergic receptors including their subtypes & cellular effects.

See table in notes

Adrenergic receptors

- alpha & beta
- neurotransmitter = Adr & norad
- alpha -> vasoconstriction
- beta -> vasodilation, lipolysis & glycogenolysis
- alpha & beta -> +ve ionotropy & chronotropy
- G protein coupled

Cholinergic receptors

- types = nicotinic & muscarinic
- Ach = neurotransmitter
- can be inhibitory or can stimulate
- stimulation occurs via Gp proteins -> increase in inositol phosphates (IP3) -> IP3 receptor on endoplasmic reticulum -> controls release of intracellular Ca2+ from stores
- inhibition occurs via Gi proteins -> decrease in cAMP -> decrease in protein phosphorylation -> decrease in intracellular Ca2+ availability

Dopaminergic receptors

- D1 to D5
- D1 = blood vessel innervation (dilation, naturiesis, diuresis)

- D2 to 4 = CNS neurotransmission
- act via G proteins -> increase or decrease cAMP
- Gi -> decrease cAMP
- Gs -> increase cAMP

(c) To describe the synthesis, release & fate of adrenergic & cholinergic transmitters.

Catecholamines

Synthesis

See diagram - catecholamine synthesis

- tyrosine hydroxylase = main control step because of limited cellular distribution, rate limiting (slowest), enzyme is highly substrate specific
- activity is subject to negative feedback of norad.

Release

- sympathetic post ganglionic nerve stimulation -> Ca2+ & microfilament stimulation -> exocytotic release of noradrenaline

Inactivation

- 2/3 of uptake via amine uptake mechanism for reincorporation into vesciles.
- 1/3 of uptake is non-neuronal (mainly in lungs)

Metabolism

See diagram - catecholamine metabolism

- rapidly inactivated by Catechol-O-methyl transferase (COMT) & Monoamine oxidase (MAO)

<u>MAO</u>

- flavin containing enzyme
- found in outer mitochondrial membranes
- replaces the CH2 & NH2 on noradrenaline with CHO

<u>COMT</u>

- from lots of tissues (esp kidneys & liver)
- NOT found in nerve endings (thus noradrenaline broken down in the synaptic cleft)
- transfers a methyl group to position 3 on benzene ring

Ach

Synthesis

- synthesised within nerve terminals
- choline + acetyl Co A
- enzyme = choline-O-acetyltransferase
- incorporated into synaptic vesicles

Release

- with stimulation from action potential -> Ca2+ influx -> exocytosis

Inactivation

- by AchE
- hydrolyses Ach -> choline and acetic acid

Metabolism

- taken up by nerve endings to be recycled as Ach.

(d) To describe the structure-activity relationships of adrenergic & cholinergic transmitters.

Adrenergic

- hydroxyl groups at 3 & 4 carbon on bezene ring -> maximal alpha & beta stimulation (adrenaline)

- removal of 4 hydroxyl group -> increases alpha 1 selectivity (phenylephrine, metaraminol)
- hydroxyl groups at 3 & 4 -> beta 2 agonist activity on compounds with long chain substituents. (adrenaline, dobutamine)

- natural catecholamines have limited lipid solubility -> do not cross BBB in amounts sufficient to cause excitability

- addition of isopropyl group rather than methyl group to the terminal amine of noradrenaline -> isoprenaline (see diagram)

Cholinergic

- nicotinic & muscarnic receptors
- muscarnic have 5 types
- M1, 3 & 5 are Gp protein coupled -> activation of phospholiapse C -> increase in DAG & PIP2 production -> increase production of IP3
- M2 & M4 receptors are Gi protein coupled -> decrease in adenyl cyclase -> decrease in cAMP -> K+ efflux + decreased Ca2+ influx.

(e) To compare & contrast the mechanism of action & effects of sympathomimetics & cholinomimetic agents used clinically.

See diagram - Mechanism of action of Sympathomimetics & Cholinomimetics

(f) To describe the pharmacology of the alpha 1, alpha 2, beta 1 & beta 2 adrenergic agonists and their clinical applications.

Alpha 1 agonists

- ie. noradrenaline, high dose adrenaline & dopamine
- vasconstriction of smooth muscle

- Gs protein activation -> increase in phospholipase C -> hydrolysis of phospholipid PIP2 -> inositol 1, 4, 5 triphosphate (IP3) & diacylglycerol (DAG) -> increases Ca2+ & phosphatidyl serine -> activation of protein kinase -> phosphorylation of intracellular proteins -> opening of L-type Ca2+ channels -> increase in cytosolic Ca2+

Alpha 2 agonists

- ie. clonidine & dexmedetomidiene
- acts on central, post-synaptic alpha 2 receptors -> sedation, anxiolysis, reduction in secretions, perioperative haemodynamic stability, analgesia.

- activation of Gi protein which inhibits adenyl cyclase -> decreased cAMP -> decreased Ca2+ entry into nerve channels -> decrease phophatidyl inositol metabolism

Beta 1 agonists

- ie. dobutamine
- +ve ionotropy, chronotropy, glycogenolysis, lipolysis
- located in heart & smooth muscle of intestine

- Gs protein stimulation -> increase in adenyl cyclase -> increase in cAMP -> increase in Ca2+ availability -> increase in excitation-contraction coupling

Beta 2 agonists

- ie. adrenaline, salbutamol
- +ve ionotropy, chronotrophy, vascular & bronchial dilatation, glyconeolysis & lipolysis

- Gs protein stimulation -> increase in adenyl cyclase -> increase in cAMP -> ....?

(g) To describe the clinically important drug interactions with the autonomic nervous system.

Metaminol

- potentiated with MAOI's
- caution with digitalis

Ephedrine

- potentiated with MAOI's
- with halothane -> increase dysrrhythmias

Alpha agonists

- ? maintain O2 supply/demand ratio in patients at risk of ischaemia
- ? may increase th ceiling to haemodynamic stabilising effects of opioids
- decreased sympathetic tone during emergence
- good for anxiolysis & antisialogue effect

Clonidine

- hypotension can persist into postop period
- sedation
- dry mouth
- rebound hypertension
- anxiety

Methyldopa

- additive effects with volatile agents
- nasal congestion

Noradrenaline

- halothane -> increase risk of VF
- incompatible with alkalalis & oxidising agents (barbiturates, phenytoin, NaHCO3)

Beta agonists

Adrenaline

- halothane sensitises myocardium to catcholamines -> increase in PVC's

Drugs

Natural Catecholamines

Adrenaline
Noradrenaline
Dopamine

Synthetic Catecholamines

Isoprenaline
Dobutamine
Dopexamine
Xamoterol

Synthetic Non-catecholamines

Direct & indirect acting

Metaraminol
Ephedrine

Direct acting

Phenylephrine
Methoxamine

Alpha agonits

Dexmedetomidine
Alpha-methyl dopa
Clonidine

Phosphodiesterase III inhibitors

Milrinone
Amrinone
Enoximone

Ephedrine

Chemical - naturally occuring sympathomimetic amine

Uses

(1) hypotension in GA or RA
(2) nocturnal enuresis

(3) narcolepsy
(4) diabetic autonomic
(5) hiccups
(6) nasal decongestant

Structure

Physiochemical

Presentation

- tablets
- elixir
- nasal drops
- solution (clear & colourless)

Route

- PO
- IV
- PN

Dose

- PO: 30mg Q8hrly (acts in 60min, lasts 4 hrs)
- PN: 1-2 drops Q4hrly
- IV: 3-30mg titrated to response (acts rapidly, lasts 1hr)

PK

Absorption

- rapid absorption all routes
- bioavailability 100% all routes

Distribution

- crosses placental barrier

Metabolism

- hepatic
- oxidative metabolism, demethylation & aromatic hydroxylation, then conjugation

Excretion

- 99% excreted unchanged.
- t1\2 = 6.3hrs

PD

Main action - sympathomimetic

Mode of action

- direct: alpha & beta adrenoreceptors
- indirect: causing release of norad from sympathetic nerve terminals

CVS

- increase in SVR
- increase in HR
- increase in Q
- coronary blood flow increased
- decrease in splanchnic & renal blood flow.
- increased sk muscle blood flow
- Beta1-receptor -> contractility

RESP

- bronchodilation
- respiratory stimulant

CNS

- CBF increases
- Mydriasis

GI

- relaxes GI smooth muscle
- splanchnic vasoconstriction

GU

- decreased RBF -> GFR
- contracts bladder sphincter, relaxes detruser -> retention.

Metabolic

- increases hepatic glycogenolysis
- increases basal metabolic rate -> O2 consumption.

Other adverse affects

- isomnia
- anxiety
- tremor
- headache
- dysrythmia
- N & V
- Chest pain

- exhibits tachyphylaxis

Phenylepherine

Chemical

- synthetic non-catecholamine
- 3-hyrdoxypenylethylamine (similar to adrenaline but is lacking the 4-hydroxyl group on benzene ring.)

Uses

(1) hypotension post GA or RA
(2) coronary artery disease & AS
(3) nasal decongestant
(4) mydriasis
(5) prolong duration of spinal

Presentation

- clear, colourless
- ampuole
- 10mg/mL

Route - IV, nasal

Doses

- bolus: 50-200mcg
- infusion: 20-50mcg/min

PK

Absorption
Distribution

Metabolism

Elimination

PD

Main action - vasoconstrictor

Mechanism

- stimulates alpha 1 & 2 adrenergic receptors directly -> venocontriction > arterial
- also evokes the release of noradrenaline (indirect)

- clinically mimics effects of norepinephrine but is less potent & longer lasting.

CVS

- increases coronary artery flow without chronotropic effect
- increase in SVR -> decrease in HR
- renal, splanchnic & cutaneous blood flow decreased
- pulmonary pressure increased
- palpatations

GI

- vomiting

Noradrenaline

Chemical - catecholamine

Uses - treatement of refractory hypotension

Presentation

- clear, colourless solution
- 2mg/mL
- norepinephrine bitartrate

Route - IV via central vein

Doses

- 2 to 20 mcg/min
- increased according to response

Duration = 30min

PK

Absorption - significant first-pass metabolism

Distribution - Vd =0.2L/kg

Metabolism

(1) oxidative deamination by MAO -> aldehyde
(2) methylation by COMT -> normetanephrine

Elimination

- 5% unchanged
- Cl = 75mL/min/kg
- t1/2 = 2min

PD

Main action - increased SVR

Mechanism

- direct & indirect sympathomimetic
- alpha > beta effects

CVS

- increase SVR
- Q unchanged
- reflex bradycardia
- coronary vasodilation
- may acause nodal rhythm, AV dissociation & ventricular dysrhythmias

RESP

- bronchodiation
- increase in MV

CNS

- increased cerebral blood flow
- mydriasis

GI

- decreased hepatic & splanchnic flow

GU

- decreases renal blood flow
- GFR well maintained
- bladder neck tone increased
- increased contractility of uterus

Metabolic

- decrease insulin secretion -> hyperglycaemia, increased plasma FFA
- plasma renin activity increased

Toxicity

- anxiety
- headache
- photophobia
- pallor
- sweating
- gangrene

Drug interactions

- halothane -> dysrrhythmias
- MAOI & TCA's -> hypertension

Dobutamine

Chemical - synthetic isoprenaline derivatvie

Uses - for low Q states from:

(1) MI
(2) cardiac surgery
(3) cardiomyopathy
(4) PEEP
(5) Septic shock
(6) cardiac stress testing

Presentation

- vials which hold solution
- 12.5 or 50mg/mL
- dobutamine HCl

Route - IV

Dose

- 0.5 to 40mcg/kg/min
- acts within 2 min

PK

Distribution

- t1/2 = 2min
- steady state reached in 10min
- Vd = 0.2 L/kg

Metabolism

- methylation by catechol-O-methyl transferase to 3-O-methyldobutamine

Elimination

- urine (80%), faeces (20%)
- Cl = 244 L/hr
- t1/2 = 2min

PD

Main action - +ve iontrope

Mechanism of action

- acts directly on catecholamine receptors -> activates adenyl cyclase -> converts ATP -> cAMP -> increased in Ca2+ permeability -> increase depolarisation & contractility

CVS

- increased contractility from beta 1 receptor agonism
- SA node automaticity increased
- increased HR
- increased AV node conduction velocity
- moderate activity at alpha & beta 2 adrenoceptors -> decrease in SVR

- dysrrhythmias
- excessive tachycardia
- hypertension

CNS

- stimulation at high doses
- fatigue
- nervousness
- headache

GU

- increased u/o c/o increased Q

Metabolic

- enhances natural killer cell activity
- increased BSL
- increase plasma FFA

Dopamine

Chemical - naturally occuring catecholamine

Uses

(1) low Q states
(2) septic shock
(3) impending renal failure to promote diuresis
(4) prevention of hepato-renal failure

Presentation

- clear, colourless solution
- 40, 160mg/mL
- dopamine HCl

Route - IV

Doses

- 1-20mcg/kg/min

Onset: 5min
Duration: 10min

PK

Absorption - ineffective when administered orally

Metabolism

- MAO & COMT -> homovanillic acid & 3, 4 dihyrdroxypenylactic acid
- 25% converted -> noradrenaline inside nerve terminals

Elimination

- urinary
- Cl = 250 L/hr
- t1/2 = 2min

PD

Main action - sympathomimetic & increased renal blood flow

Mechanism

- 1-5mcg/kg/min - D 1 & 2 receptors
- 5-10mcg/kg/min - direct & indirect effects on beta receptors
- >10mcg/kg/min - alpha effects

CVS

< 5mcg/kg/min

- +ve iontropy
- increased automaticity
- increased Q
- increased coronary blood flow

>15mcg/kg/min

- peripheral vasoconstriciton -> increased VR & SVR

RESP

- activate carotid bodies
- decrease ventilatory response to hypoxia

CNS

- exogenous dopamine does not cross BBB
- increased IOP

GI

- nausea
- splanchnic vasodilation
- decreased GI motility

GU

- increased renal blood flow by decrease in renal vascular resistance ? untrue

Metabolic

- reduces the release of prolactin & ALD
- depressed GH secretion
- aggrevates the sick euthyroid syndrome

Other adverse effects

- tachycardia
- dysrrhythmias
- angina
- hypertension
- nausea & vomiting

Drug interactions

- MAOI's -> hypertension
- halogenated volatiles -> dysrrhythmias
- phenothiazines -> antagonise

Adrenaline/Epinephrine

Chemical - a catecholamine

Uses

1. Analphylactic/oid shock
2. Asystole
3. Low cardiac output states
4. Glaucoma

5. Local vasoconstictor
6. Added to LA to increase duration of action

Preparation

- injection: clear, colourless, 0.1 & 1mg/mL
- eye: topical opthalmic solution (1%)
- aerosol: 280mcg metered doses

Route

- IV, SC, INH
- if given peripherally -> follow with a flush of 20mL of saline

Dose

- IV: 0.1 - 1mg boluses, or 0.01-1mcg/kg/min infusion.
- SC: 0.1-0.5mg
- INH: max 10-20 metered doses/day

PK

Absorption

- inactivated when administered orally
- slower absorption SC & I'M
- well absorbed from tracheal muscoa (need to double dose)

Distribution

Metabolism

- catecho-O-methyl transferase in liver -> metadrenaline & normetadrenaline
- some metabolised by MAO within adrenergic neurons

Elimination

- inactive products appear in urine

PD

Main action - sympathomimetic

Mechanism of action

- direct acting sympatheomimetic -> alpha & beta agonist
- low doses -> beta-effects
- higher doses -> alpha-effects
- maintains coronary & cerebral blood flow

CVS

- +ve inotrope
- +ve chronotrope
- increased Q
- increased O2 consumption
- increased coronary blood flow (increased diastolic blood pressure)
- increased in systolic BP from increased SVR
- increased HR
- plasma volume decreases (loss of protein free fluid into ECF)

RESP

- mild respirator sitmulant
- increased TV & RR
- potent bronchodilator
- increased viscosity of bronchial secretions

CNS

- penetrates CNS but doesn't have excitatory effects.
- increases cutaneous pain threshold
- enhances neurmuscular transmission
- increases CBF
- weak mydriatic effects when applied topically to eye

GI

- decreases intestinal tone & secretions
- splanchnic blood flow increases

GU

- decreases RBF by 40%
- although GFR is unaltered
- bladder tone decreased
- sphincteric tone increased -> difficulty micturating
- inhibits contractions in pregnant woman

Haemotalogical

- increased platelet adhesiveness & blood coagulability from increased factor V

Metabolic

- decreased insulin secretion
- increased glucagon secretion -> glyconeolysis -> increased BSL
- increased renin activity
- increased free fatty acids from activation of triglyceride lipase
- K+ rises -> then decreases (release from liver)
- increases basal metabolic rate by 30%
- pyrexia may result

Vasopressin

Chemical

- ADH
- neuropeptide synthesised in the supraoptic & paraventricular nuclei -> transported down axons to the posterior lobe of the pituitary

Uses

1. Diabetes insipidus (central)
2. Control of bleeding in oesophageal varicies
3. Haemophillia
4. von Willebrands disease
5. Cardiac arrest
6. Haemodynamic stabilization in prescence of haemorrhage & septic shock.

Presentation

- other names:

(1) arginine vasopressin
(2) AVP
(3) ADH

Route - IV, PN, IM

Dose

- cardiac arrest: 40IU once
- oesophageal varicies: 20IU over 5min

PK

Elimination

- t1/2 = 10-20min (longer than adrenaline)

PD

Main actions - potent endogenous vasoconstrictor

Mechanism of action

- intense vasoconstriction in skin & muscle beds
- vasodilation of cerebral beds

CVS

- reverse systemic hypotension associated with sepsis, anaphylaxis & multiple organ dysfunction

- increased systemic BP
- facial pallor
- coronary vasoconstiction -> ischaemia -> infarction

RESP

- increased pulmonary artery pressure

GI

- reduces hepatic blood flow & portal hypertension (marked splanchnic vasoconstriction)
- increased peristalsis -> abdo pain, nausea & vomiting

GU

- stimulation of uterine smooth muscle

Metabolic

- decrease in platelet count

Other adverse effects

- urticaria & anaphylaxis described

Clonidine

Chemical - aniline derivative

Uses

(1) hypertension
(2) migraine
(3) menopausal flushing
(4) chronic pain
(5) opiate & alcohol withdrawal
(6) regional analgesia

Presentation

- tablets: 0.1 to 0.3mg
- injection: clear, colourless 0.15mg/mL

Route - PO, IV, Epidural

Doses

- PO: 50-600mcg Q8hrs
- IV: 0.15-0.3mg Q8hrs
- epidural: 0.15mg

Onset: 10min
Duration: 3-7hrs

PK

Absorption - 100% bioavailability

Distribution

- very lipid solublw -> penetrates CNS
- 20% protein bound
- Vd = 2L/kg

Metabolism

- less than half hepatically

Elimination

- 60% unchanged in urine
- 20% in faeces
- Cl = 3mL/min/kg

- t1/2 = 20hrs

PD

Main action - antihypertensive, analgesic, sedative & anxiolytic

Mechanism

- alpha 2 agonist -> decrease noradrenaline release -> decrease in sympathetic tone

CVS

- transient rise in BP -> sustained decreased
- HR decreased
- VR decreased
- coronary vascular resistance decreased
- SVR decreased

RESP

CNS

- decreased cerebral blood flow
- decreased IOP

GI

- decreases gastric & small bowel motility
- antisialogogue

GU

- reduces renovascular resistance
- little alteration in GFR

Metabolic

- decrease in plasma catecholarmine concentration & renin activity
- BSL increases

Toxicity

- drowiness
- druy mouth
- fluid retension

- impotence
- constipation

Interactions

- decreases MAC
- decreased post-op shivering & N & V
- decreases amount of propofol for LMA insertion
- decreases postop agitation
- prolongs duration of LA

Other adverse effects

Isoprenaline

Chemical

Uses

(1) compete heart block (while awaiting pacing)
(2) asthma
(3) torsades de pointes
(4) inotropic support

Presentation

- tablets: 30mg
- injection: clear, colourless, 1mg/mL
- inh: 80 & 400mcg

Route - PO, IV, INH

Doses

- IV: 0.5 to 8mcg/min according to response

PK

Distribution - 65% protein bound
Metabolism - COMT in liver
Elimination - 70% unchanged, t1/2 = 5min

PD

Main actions

(1) positive inotropism
(2) positive chronotropism
(3) bronchodilation

Mechanism - beta agonist -> increase in adenylate cyclase -> increase in cAMP

CVS

- +ve inotrope & chronotrope -> increase in Q
- decreases SVR
- increased automaticity
- enhanced AV nodal conduction
- increased coronary blood flow

RESP

- potent bronchodilation
- increase in V/Q mismatch & dead space

CNS

- stimulant

GI

- decreases GI tone
- mesenteric blood supply increased

GU

- increases renal blood flow in shock
- reduces uterine tone

Metabolic

- increased plasma FFA
- increased BSL

Phosphodiesterase inhibitors

Chemicals - milirirone & amilrinone (bipyridines)

Uses

(1) after MI
(2) cardiosurgery
(3) cardiac failure

Dose

- amirinone: 2-10mcg/kg/min
- milrinone: 0.5mcg/kg/min

PK

Absorption - oral or IV
Elimination - renal

PD

Main actions

- increase ionotropy
- increase vascular & bronchial muscle relaxation

Mechanism of action

- non receptor mediated inhibitors of peak cAMP phosphodiesterase III isoenzyme -> decrease the hydrolysis of cAMP
- increase cAMP -> is like activating a Gs protein -> increase in adenyl cyclase -> increase protein kinases -> increased phosphorylation of proteins -> net influx of Ca2+ into muscle.

- located in cardiac, vascular muscle & platelets.

CVS

- hypotension
- thrombocytopenia

GI

- hepatic dysfunction