B. 11 Pharmacology of the autonomic nervous system.

a. Describe the physiological roles of the sympathetic and parasympathetic nervous systems.

**sympathetic**
- thoracolumbar outflow T₁ to L₃
  - efferent: cell body in grey matter of cord, ventral root, white ramus to sympathetic chain or grey ramus to spinal nerves
  - afferent: sympathetic chain, white ramus, dorsal root (body in ganglion), dorsal horn
- preganglionic fibres are B type myelinated nicotinic
- synapse in chain and ganglia (cervical, coeliac, mesenteric and sacral) and adrenal medulla
- postganglionic
  - adrenergic secretory cells in adrenal medulla
  - noradrenergic postganglionic fibres
    - mydriasis, distant vision accommodation, vasoconstriction/dilation, bronchodilation, inotropy, chronotropy, ↓ gut motility, ↑ renin, detrusor relaxation, trigone contraction, ejaculation, ↑ glucagon, ↑ glucose & lipid mobilization. Lipolysis
  - muscarinic postganglionic fibres
    - sweating, piloerection, some vasodilation

**parasympathetic**
- craniosacral outflow (III, VII, IX, X, S₂ to S₄) 75% in vagus
  - efferent: cell body in CNS, peripheral ganglia (ciliary, sphenopalatine, otic, local synapses in organs)
- preganglionic fibres are nicotinic
- postganglionic fibres are muscarinic
  - III miosis, near vision accommodation
  - VII lacrimation, submandibular gland secretion
  - IX parotid gland secretion
  - X ↑ gut secretions, ↑ motility, palmar sweating, negative inotropy & chronotropy, bronchoconstriction
  - sacral detrusor contraction, trigone relaxation, erection, defaecation

**afferent**
- minor component
  - substance P, peptide neurotransmitters including glutamate

b. Describe the physiological actions of adrenergic, cholinergic and dopaminergic receptors including their subtypes, and their molecular effects.

α and β receptors differentiated by Alquist (1948)
β subtypes identified by Lands (1967)

cotransmitters found at probably all sites of autonomic transmission
- noradrenaline ± dopamine, NO, neuropeptide Y...
- ACh ± substance P, VIP...

**α₁A,B,C,D**
- G-protein linked, ↑ IP₃, DAG except possibly α₁A which ↑ Ca²⁺ conductance
- vasoconstriction, ↑ contractility, glycogenolysis, mydriasis, piloerection, apocrine sweating, salivation, uterine contraction, bladder neck contraction, ejaculation, detumescence

**α₂A,B,C**
- G-protein linked, ↓ cAMP
- central functions (sedation, descending inhibitory pathways, ↓ CO₂ response)
platelet activation, vasoconstriction, ↓ lipolysis, ↓ insulin
presynaptic inhibition at postganglionic sympathetic terminals
↓ renin, ADH, ↓ stress response

$$\beta_1$$
- G-protein linked, ↑ cAMP
- ↑ contractility, ↑ HR, ↑ conduction velocity, ↑ diastolic relaxation
- ↑ renin

$$\beta_2$$
- G-protein linked, ↑ cAMP
- bronchodilation, vasodilation, uterine relaxation, ↑ HR
- ↑ K⁺ uptake by skeletal muscle, ↑ glycogenolysis, ↑ insulin

$$\beta_3$$
- G-protein linked, ↑ cAMP
- ↑ lipolysis

$$D_1$$
- G-protein linked, ↑ cAMP
- vasodilation: renal, splanchnic, coronary, cerebral

$$D_2$$
- G-protein linked, ↓ cAMP, ↑ K⁺ conductance, ↑ Ca²⁺ conductance
- ? presynaptic inhibition

$$D_4$$
- G-protein linked, ↓ cAMP
- possible site of action of clozapine (with 5HT₃)

$$D_5$$
- G-protein linked, ↑ cAMP

$$M_1$$
- G-protein linked, ↑ IP₃, DAG, Ca²⁺
- CNS neurotransmission
- sympathetic postganglionic
- ↑ gut motility
- presynaptic

$$M_2$$
- G-protein linked, open K⁺ channels, ↓ cAMP
- myocardial and vascular innervation of vagus
- preganglionic function (site of action of pancuronium and gallamine)

$$M_3$$
- G-protein linked, ↑ IP₃, DAG, Ca²⁺
- exocrine glands, vasodilation via NO & cGMP, miosis
- bronchoconstriction
- ↑ gut motility, defaecation, urination

$$N_N$$
- gated ion channel, ↑ Na⁺, Ca²⁺ flux
- presynaptic potentiation at NMJ
- CNS

$$N_M$$
- gated ion channel, ↑ Na⁺, Ca²⁺ flux
- neuromuscular junction

c. Describe the synthesis, release and fate of adrenergic and cholinergic transmitters.

catecholamines
- synthesized from tyrosine (or phenylalanine if tyrosine is unavailable)
tyrosine hydroxylase (rate limiting step, requires biopterine) →

DOPA decarboxylase (inhibited by disulfiram, requires pyridoxal phosphate) →

vesicular dopamine β-hydroxylase (requires ascorbate) →

phenylethanolamine N-methyl transferase (requires 5-adenosyl methionine) →

adrenaline or noradrenaline are metabolized by MAO and COMT to

acetylcholine
active uptake of choline from interstitial fluid, reacted with acetyl-CoA:
CH₃CO-O-CoA + HO-CH₂-CH₂-N(CH₃)₃ → CH₃CO-O-CH₂-CH₂-N(CH₃)₃
breakdown is by hydrolysis due to acetylcholinesterase, with recycling of choline and return of acetate to the TCAC

d. Describe the structure-activity relationships of adrenergic and cholinergic drugs

adrenergic
ligands bind in their ionized form
receptor affinity
β-OH or 3-OH required for direct activity
4-OH or > methyl group on N: ↑ β affinity, potency
> isopropyl group on N or α or 3 sidechain: β₂ selective
imidazole group: α selectivity (α₂ > α₁)
distribution, metabolism
few OH, no N‘; enters CNS
> methyl on N: not a substrate for uptake 1 (no indirect action)
> methyl on N or α methyl: not a substrate for MAO
3,4 di-OH required for COMT
all bind to the receptor in the ionized form
cholinergic
similar to ACh, all have N‘ except pilocarpine
receptor affinity
side groups on chain: muscarinic selective
metabolism
no acetyl group (e.g. carbamoyl): not a substrate for AChE

e. Compare and contrast the mechanism of action and effects of sympathomimetic and cholinomimetic agents used clinically.

f. Describe α₁, α₂, β₁ and β₂ adrenergic agonists and their clinical applications.

Endogenous (direct acting catecholamines)
adrenaline
β > α , not α or β selective
↑ CO, HR, MAP, CNS activity, blood glucose
↓ RBF, airway resistance
arrhythmogenic
vasoconstrictor in local anaesthetics
used for anaphylaxis, asystole (100 µg-1 mg),
инотроп, небуллизирован for croup
noradrenaline
α > β, >> β₁, not a selective
↑ TPR, MAP
↓ RBF
used as an inotrope (5-15 µg/min)
dopamine
D₁ > β₁ > α₁ > β₂ > α₂
↑ CO, HR, TPR, MAP, RBF
suppresses hypoxic drive
used for renal "protection" (low dose), inotrope (high dose) 2-20 µg/kg/min

Exogenous catecholamines (direct acting)
isoprenaline (isopropyl noradrenaline)
non-selective β
↑ HR, CO, CNS activity
↓ TPR, airway resistance
arrhythmogenic
reduces pulmonary vascular resistance
used as an inotrope (1-5 µg/min),
bronchodilator (obsolete)
dobutamine
selective β₁ (not dopaminergic)
↑ CO, HR, MAP, RBF
used as an inotrope without
vasoconstrictor effects
salbutamol (and terbutaline, fenoterol and
orciprenaline)
selective β₂
↑ HR, CNS activity
↓ airway resistance, labour
used for bronchodilation (IV, oral or nebulized), chronotrope, tocolytic

dopexamine
selective D₂ (>ß) agonist

Direct acting non-catecholamines
phenylephrine (and methoxamine)
selective α₁,
↑ TPR, MAP (methoxamine is a more potent arteriolar constrictor)
↓ RBF
arrhythmogenic (methoxamine is mildly antidysrhythmic)
used for hypotension (20-50 µg/min IV)
topical mydriatic, nasal decongestant

clonidine
α₂ selective, imidazoline antagonist
↓ HR, CO, TPR, MAP, CNS activity
used for hypertension, reduces sympathetic outflow
sedative, reduced anaesthetic & opiate requirements
spinal/epidural analgesic (inhibits substance P release)
reduces opiate withdrawal symptoms

BRL37344
β₃ selective
↑ lipolysis
? fat-loss agent

Indirect acting non-catecholamines
ephedrine (ß-OH methamphetamine)
α > ß (non selective, has some direct activity)
↑ HR, CO, TPR, MAP, CNS activity
↓ RBF
used short-term for hypotension (5-25 mg IV/IM)
does not reduce uterine blood flow
abused as CNS stimulant, anorectic
amphetamine (and dexamphetamine, methamphetamine, methylphenidate)
alphamethylphenylethylamine
non selective, enter CNS rapidly, displaces noradrenaline
↑ CNS activity, HR, CO, TPR
used for ADHD (oral), widely abused orally and IV.

metaraminol
α >> ß (direct and indirect), weak false transmitter
↑ TPR, MAP (reflex ↓ HR)
↓ RBF
used for hypotension (0.5-5 mg IV 40-500 µg/min)

g. Describe the drugs used as inotropic and vasoactive agents including the phosphodiesterase inhibitors.

phosphodiesterase inhibitors

bipyridines include milrinone, amrinone, vesarinone etc.
flosequinan is a fluoroquinolone

milrinone

Autonomic 2.B.11.5 James Mitchell (December 24, 2003)
parenteral inotrope (oral preparation withdrawn due to toxicity)

**Pharmacokinetics**
- orally active
- \( t^{1/2} \beta \) 2-3 h
- 50% renal excretion

**Pharmacodynamics**
- selective inhibitor of phosphodiesterase III
- onset of action over 15 minutes
- ↑ intracellular cAMP in cardiac and smooth muscle
  - ↑ Ca\(^{2+}\) release in cardiac muscle
  - inotrope, ↑ HR, diastolic compliance & proportion of cycle
- ↑ phosphorylation of MLCK in smooth muscle (↓ activity)
  - ↓ MLC phosphate, ↓ contraction
  - systemic, coronary and pulmonary vasodilation
- net ↑ MAP

**Adverse Effects**
- amrinone
  - nausea, vomiting, hepatotoxicity, thrombocytopenia, arrhythmogenic
- milrinone
  - less adverse effects but same risk of arrhythmia

**Clinical Use**
- milrinone: 50 µg/kg load, 0.25-0.75 µg/kg/min infusion
- intensive monitoring required
- used for short term inotropy, especially where vasoconstriction is to be avoided

h. Outline the interactions with drugs used in the perioperative period.