## B9 - Anticholinergic Drugs

### (a) To describe the pharmacology of Ach & the muscarinic & nicotinic receptors.

**Ach Receptor**

- two types based on their pharmacologic properties (muscarinic & nicotinic)

**Nicotinic Receptor**

- 3 types based on location - NMJ, ganglionic & CNS
- ligand gated ion channels

- pentameric structures
- 5 subunits that form receptor-channel complex
- alpha (9 types), beta (4), gamma (1), zeta (1) & E (1)
- binding sites for Ach on each alpha subunit -> induces a conformational change in channel -> increases conductance of Na+ and other cations -> depolarisation.

*Sub-types:*

(1) NMJ act in muscle (obviously)

- (alpha1)2, beta1, gamma, E
- increase in Na+ & K+ permeability

(2) Ganglionic (transmission at sympathetic & parasympathetic ganglia)

- (alpha3)2, (beta4)3
- increase in Na+ & K+ permeability

(3) CNS (widespread and a heterogeneous with respect to their molecular composition & location.)

- (alpha4)2(beta2)3 -> increase in pre & post excitation via increase in Na+ & K+ permeability
- (alpha7)5 -> pre & postsynaptic excitation via increased Ca2+ permeability.

See diagram - foetal nicotinic Ach receptor (zeta in foetus, E in adult -> decreases channel opeining time but increases conductance)

**Muscarinic Receptor**

- muscarine (alkaloid responsible for toxicity of toadstools) -> mimics action of Ach on smooth muscle & glands
- blocked by atropine
- 5 types of receptor
- all G protein coupled -> adenylyl cyclase -> K+ channels or phospholipase C

Subtypes

M1 - 'neural'

- brain, gastic parietal cells & peripheral neurons
- mediate excitation effects in sympathetic gangila * CNS via decreased K+ conductance -> depolarisation.
- vagal stimualtion -> increase in gastric acid secretion

M2 - 'cardiac'

- heart, presynaptic terminals  of peripheral & central neurons
- exert inhibitory effects by increasing K+ conductance & inhibiting Ca2+ channels.
- responsible for vagal inhibition of heart & presynaptic inhibition in the CNS & periphery.

M3 - 'glandular & smooth muscle'

- stimulation of glandular secretion (bronchial, salivary, sweat, pancreatic)
- contraction & relaxation of visceral smooth muscle
- increased IP3 stimulation & Ca2+ concentration

M4 -

- lung
- cortex, striatum
- see M2 for mechanism

M5

- substantia nigra, salivary glands, iris, ciliary muscle.
- see M2 for mechanism

**(b) To compare & contrast the pharmacodynamics & pharmacokinetics of atropine, hyoscine & glycopyrrolate.**

**Atropine**

Chemical

- alkaloid from Atropa belladona
- tertiary amine
- ester of tropic acid & tropine

Uses

(1) dry secretion

(2) bradycardia due to vagal stimulation
(3) counter muscarinic effects of anticholinergic agents
(4) CPR
(5) cycloplegic - paralysis of ciliary muscle & thus accommodation
(6) organophosphate poisoning
(7) tetanus

## Preparation

- clear, colourless solution
- 600 mcg/mL
- also available in tablets

## Physiochemical

- racemic mixture of D & L - hyoscyamine
- L isomer that is active at the muscarinic site
- no antimicrobial agents
- pH 3 with HCl

## Route - IV, IM or PO

## Doses

- IV: 0.2mg/kg
- PO: 0.2 to 0.6mg/kg

- 3mg for complete vagal block

## PK

*Absorption* - bioavail = 20%

*Distribution*

- 50% protein bound
- Vd = 3L/kg
- crosses BBB & placenta

*Metabolism* - hydrolysed in liver & tissues

*Elimination*

- 94% excreted in urine in 24hrs
- Cl 70L/hr
- t1/2 2.5hrs

PD

*Main action* - anticholinergic

*Mode of action*

- competitive antagonism of Ach @ muscharinic receptors.

*CVS*

- low dose -> bradycardia (Bezold-Jarich reflex)
- Q increased
- little effect on BP
- decreased AV conduction time -> arrhythmias
- dilation of facial capillaries

*RESP*

- bronchodilation
- increase in physiological dead space
- increase RR
- decrease in incidence of laryngospasm

*CNS*

- central excitation or depression may occur (central anticholinergic syndrome = somnolence, confusion, amnesia, agitation, hallucinations, dysarthria, ataxia or delirium)

*GI*

- reduces salivation
- reduces gastric secretions
- reduces tone & peristalsis throughout gut
- antispasmotic effect on bilary tree
- decrease in lower oesophageal spinchter tone

*GU*

- tone & peristalsis in urinary tract decreased.

*Metabolic effects*

- increase in metabolic rate
- suppresses ADH secretion

*Other adverse effects*

- cyclplegia
- mydriasis
- increased IOP
- sweating inhibited
- has LA properties

*Toxicity*

- painful on IM injection
- dry mouth
- sweating
- hyperpyrexia
- urinary retention
- glaucoma

'Red as a beat
Mad as a hatter
Blind as a bat
Dry as chip
Constipated as a brick'

**Hyocine**

Chemical

- alkaloid derivative of Scopolia carniolica
- ester of tropic acid & scopine

Uses

1. premed
2. prophylaxis for motion sickness
3. antispasmotic

Preparation

- hyoscine hydrobromide - clear solution, 0.4mg/mL
- hyosine  butylbromide - clear solution, 20mg/mL & tablet
- transdermal patch

Route - IV, IM, SC, transdermal & PO

Dose

- IM: 0.1mg/kg
- PO: 20mg Q 6hrly

PK

*Absorption* - 10% bioavailability

*Distribution*

- 10% protein bound
- Vd 2 L/kg

*Metabolism* - extensive liver & tissue metabolism

*Elimination*

- Cl 45L/hr
- t1/2 2.5hrs

PD

*Main action* - anticholinergic with marked sedative effects

*Mode of action* - competitive antagonism of Ach receptor @ muscarinic sites

*CVS*

- tach -> bradycardia

*RESP*

- decrease in bronchial secretions
- mild bronchodilation
- mild stimulation of respiration

*CNS*

- CNS depressant -> sleep & amnesia
- antianalgesic, antiemetic & antiparkinsonian
- may cause central anticholinergic syndrome

*GI*

- antiisialogogue
- antispasmotic throughout gut & billary tree

*GU*

- tone of bladder & uterus reduced following administration.

*Metabolic*

- more marked effect on sweat & eye than atropine.

**Glycopyrolate**

Chemical - a quaternary ammonium compound

Uses

1. Antisialogogue
2. Premed
3. Protection against the peripheral muscarinic effects anticholinesterases.
4. Bradycardia in the anaesthetised
5. Hyperhydrosis via topical administration

Preparation

- clear solution (IV) or powder (topical)
- also in fixed dose combination containing 0.5mg of glycopyrronium & 2.5mg of neostigmine

Route - IV, IM or topical

Dose

- bradycardia: 0.2mg Q5min (adults)
- 5 micrograms/kg (children)

Peak effect in 3 min post IV
Vagolytic effects last for 3 hours

PK

*Absorption* - bioavailability = 5%

*Distribution*

- redistribuition occurs rapidly
- 90% disappears in 5 min
- crosses placenta
- Vd 0.4L/kg

*Metabolism* - very little biotransformation

*Excretion*

- urine (85%)
- bile (20%)
- clearance 1L/min
- t1/2 1 hr

PD

*Main action* - anticholinergic with profound effect on secretions

*Mode of action* - competitive antagonism of Ach at peripheral muscarinic receptors.

*CVS*

- little effect on BP
- less dysrhythmias than atropine
- tachycardia
- protects against bradycardia associated with sux

*RESP*

- long lasting bronchodilation effect -> increase in physiological deadspace.

*CNS*

- unable to cross the BBB
- meant to be devoid of central effects however, headache, drowsiness are common.
- post anaesthetic recovery is more rapid with glycopyrronium than with atropine.
- no effect on pupil size or accommodation

*GI*

- powerful antisialogogue effect
- X 5 more powerful than atropine for anti-salivation
- reduces gastric volume by 90% for 4 hrs
- reduces lower oesophageal sphincter tone

*Metabolic effects*

- inhibits sweat gland activity
- little effect on tempreature
- weak LA action

*Special points for anaesthesia*

- when used with neostigmine to reverse NDNMB causes less tachycardias than atropine -> time of onset better matched
- incompatible with thio, methohexitone, diazepam
- X 5 more powerful than atropine for decreasing salivation
- 'unable to cross BBB'
- protective agains sux induced bradycardia
- less dysrhythmias than atropine

**(c) To describe the effects of overdosage of anti-cholinergic drugs and its management.**

**Clinically**

- dilated pupils
- difficulty swallowing
- hot dry skin
- increase in body temperature
- vasodilation
- urinary retension
- tachycardia
- hypertension
- anxiety
- delirium
- hallucinations
- hyperactivity
- convulsions
- muscle paralysis
- coma

Fitzgerald: 'Red as a beet, mad as a hatter, blind as a bat, constipated as a brick, dry as chip'

**Management**

- airway management
- fluid replacement
- lower temperature (cold packs)
- urinary catheter
- activated charcoal
- diazepam

- phytostigmine IV if life threatening - tertiary amine that crosses the BBB