Afferent and Efferent in the ANS
Parasympathetic

- Stimulates flow of saliva
- Slows heartbeat
- Constricts bronchi
- Stimulates peristalsis and secretion
- Stimulates release of bile
- Contracts bladder

Sympathetic

- Dilates pupil
- Inhibits flow of saliva
- Accelerates heartbeat
- Dilates bronchi
- Inhibits peristalsis and secretion
- Conversion of glycogen to glucose
- Secretion of adrenaline and noradrenaline
- Inhibits bladder contraction
Sympathetic nervous system

- Sympathetic outflow to smooth muscle of hair follicles, sweat glands, and peripheral blood vessels.

Parasympathetic nervous system

- Eye
- Ciliary ganglion
- Pterygopalatine ganglion
- Submandibular ganglion
- Lacrimal gland
- Salivary glands
- Otic ganglion
- Heart
- Bronchi and lungs
- Vagus nerve
- Liver
- Pancreas
- Stomach
- Spleen
- Intestines
- Bladder and external genitalia
- Distal colon
- Pelvic nerve

Diagram showing the sympathetic and parasympathetic nervous system pathways and ganglia distribution.
<table>
<thead>
<tr>
<th>Organ</th>
<th>PSymp</th>
<th>Symp</th>
<th>Importance</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atria</td>
<td>Bradycardia</td>
<td>Tachycardia</td>
<td>P=S</td>
<td></td>
</tr>
<tr>
<td>Ventricle</td>
<td>No effect</td>
<td>Positive force</td>
<td>S&gt;&gt;&gt;PS</td>
<td>Important</td>
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<tr>
<td>AV node</td>
<td>Slow</td>
<td>Increase</td>
<td>Equal</td>
<td></td>
</tr>
<tr>
<td>Blood vessel</td>
<td>Very little</td>
<td>Constrict</td>
<td>S&gt;&gt;&gt;PS</td>
<td>Raise blood pressure</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial muscle</td>
<td>Contract</td>
<td>Relax</td>
<td>PS&gt;&gt;S</td>
<td>Bronchial muscle tone</td>
</tr>
<tr>
<td>Bronchial glands</td>
<td>Secretions inc</td>
<td>Dry secretions</td>
<td>PS&gt;&gt;&gt;S</td>
<td>Dominant effect</td>
</tr>
<tr>
<td>Eye</td>
<td>Narrow iris</td>
<td>Dilate pupil</td>
<td>PS&gt;&gt;&gt;S</td>
<td>Accommodation</td>
</tr>
<tr>
<td></td>
<td>Contracts lens</td>
<td></td>
<td>PS</td>
<td></td>
</tr>
<tr>
<td>Nose</td>
<td>Reduces patency</td>
<td>Increases patency</td>
<td>S&gt;&gt;PS</td>
<td></td>
</tr>
<tr>
<td>Salivary glands</td>
<td>Watery secretions</td>
<td>Thick mucoid secretions</td>
<td>PS&gt;&gt;S</td>
<td>Dry mouth if PS blocked</td>
</tr>
<tr>
<td>Tear glands</td>
<td>Tears</td>
<td></td>
<td>PS</td>
<td>Dry eyes if PS blocked</td>
</tr>
<tr>
<td>Adrenal glands</td>
<td>Nicotinic ganglion</td>
<td></td>
<td>PS (celiac ganglion)</td>
<td>Release of adrenaline</td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>Stimulates gall bladder</td>
<td>Glycogenolysis</td>
<td>S liver</td>
<td>PS gall bladder</td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large intestine</td>
<td>Contracts</td>
<td>Contracts rectum</td>
<td>PS controls defecation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relaxes rectum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small intestine</td>
<td>Contracts</td>
<td>Relaxes</td>
<td>PS&gt;&gt;&gt;S</td>
<td>Enteric nerves important</td>
</tr>
<tr>
<td>Stomach</td>
<td>Acid release</td>
<td>Slows digestion</td>
<td>PS&gt;&gt;&gt;S</td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>Contracts</td>
<td></td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>Contracts</td>
<td>Relaxes</td>
<td>PS&gt;&gt;S</td>
<td>PS controls micturition</td>
</tr>
<tr>
<td>Genitalia</td>
<td>Male – tumescence</td>
<td>De-tumescence</td>
<td>PS for up, S for down</td>
<td>Involves NO</td>
</tr>
</tbody>
</table>
In general, drugs modify junctional/synaptic transmission by acting:-

- Pre-synaptically (pre-junctionally), to interfere with the
  - Synthesis
  - Storage
  - Release
    
    of the neurotransmitter

- Post-synaptically, to interfere with the
  - Receptors
  - Removal mechanism
    
    for the neurotransmitter
Langley (1905); after Claude Bernard had shown site of action of curare, investigated nicotine.

**Nicotine** - causes twitch only at a selective site (where nerve ending was on muscle)

**Curare** - blocks the action of nicotine at that same site at which it blocks nerve stimulation but has no effect on direct muscle stimulation
AGONISTS – are neurotransmitters, hormones, (natural or synthetic) molecules that, by binding, activate (i.e. agonize) receptors and thereby produce a functional response.

RECEPTORS - for drugs are generally proteins to which drugs bind, and subsequently do, or do not, produce a functional action.

ANTAGONIST – bind selectively to a receptor without activating it; thereby denying agonists access to their receptor binding site.

PARTIAL AGONIST – stimulate a receptor inefficiently: will produce a functional response when the receptor is not occupied by a full agonist, but will reduce the actions of a full agonist

INVERSE AGONISTS - reduce activity in receptors that are spontaneously active in the absence of agonist.

ALLOSTERIC MODULATORS – do not bind to agonist recognition site but their binding at an allosteric site modulates receptor activity.
Cholinoceptors (cholinergic) Receptors
Two main types

1. **Muscarinic receptors**

2. **Nicotinic receptors**

Based on selective drug actions (by *muscarine* and *nicotine*) and their selective antagonism by *atropine* and *curare* respectively.
Cholinoceptors (cholinergic receptors)  
Where are they?

1. Postganglionic parasympathetic effectors (muscarinic)
2. All autonomic ganglia (nicotinic)
3. At the neuromuscular endplate (nicotinic)
4. In the CNS (muscarinic and nicotinic)
5. At special post ganglionic sympathetic effectors (in skin – muscarinic)
Cholinoceptor agonism

By two (2) possible mechanisms

Directly-
  • occupy and activate receptors with alkaloids, ACh, and synthetic choline esters

Indirectly -
  • inhibit acetylcholinesterase thereby increase ACh concentrations at effector junctions
Muscarinic cholinoceptors

• on cells innervated by PNS
  – smooth muscle
  – heart
  – exocrine glands
• endothelial cells of the vascular beds
  (even though these are not innervated)
• brain
**Subtypes of Muscarinic Receptors**

- At least 5: M1 to M5
- Their mechanisms of transduction, binding and formation of second messengers vary
- All GPCRs (G protein coupled receptors) act by way of:
  - **M1,3 & 5** via Gq/11 family and **M2 & 4** through Gi and Go
  - *when receptor is agonized to:*
    - activate phospholipase C to form inositol triphosphate (IP3) and diacylglycerol (DAG) - intracellular second messengers
    - inhibit adenylate cyclase to reduce intracellular cAMP
    - inhibit opening of calcium channels
    - activate potassium channels to generate an inward potassium current (iKMACh)
Choline ester type muscarinics

• hydrophilic
• differ in breakdown by ACh-esterase and in their actions on muscarinic (M) and nicotinic (N) receptors
  – acetylcholine - very susceptible M=N
  – methacholine - 3X less susceptible M>>N
  – bethanechol - not susceptible M>>>N
• methacholine & bethanechol
  – longer duration of action than ACh
Alkaloid muscarinics (muscarine, pilocarpine and nicotine)

- Highly lipid soluble
  - well absorbed from GI tract
  - enters the brain
- Capable of either muscarinic or nicotinic receptor activation
Effects of Muscarinic Agonists

• Cardiovascular system
  – Heart
  – Blood vessels
• Gastrointestinal tract
• Eye
• Respiratory tract
Cardiac Actions via Muscarinic Activation

- Increased $K^+$ conductance – slows conduction and impulse formation in
  - SA node
  - AV node
- Decrease inward $Ca^{++}$ current to reduce force of contraction in atria
- Slows pacemaker rate but this can be opposed by reflex sympathetic activity
- Ventricles are less directly affected (virtually no parasympathetic innervation of ventricles)
Vascular Actions of cholinocceptor (cholinergic) muscarinic agonists

• **Reduce vascular resistance** –
  – activation of receptors on endothelium to generate nitric oxide (NO) production
  – NO causes vascular muscle relaxation

• **Effects on BP modified by reflexes since a fall in blood pressure will cause a reflex increase in sympathetic activity.**

**Note:** *Stimulation of nicotinic receptors on ganglia will raise blood pressure and heart rate via a dominating sympathetic stimulation.*
Integrated whole animal responses to drugs

Responses to drugs acting on receptor will produce tissue, organ and whole animal responses. Functional response can be countered by reflexes, e.g., an ACh injection will lower blood pressure and possibly slow heart rate. BUT the lowered blood pressure can initiate a reflex activation of sympathetic nerves to increase heart rate in an attempt to raise blood pressure.
GI and urinary bladder actions of cholinoceptor (cholinergic) muscarinic agonists

- Increased secretion
  - gastric glands
  - salivary glands

- Contract smooth muscle of most g.i. tract but relax sphincter muscle e.g. empty urinary bladder.

- Increased overall gastro-intestinal motility - diarrhea
Ocular Actions of cholinoceptor (cholinergic) muscarinic agonists

- iris sphincter muscle contraction –narrows pupil

- ciliary muscle contraction
  - opens drainage canals in anterior chamber
  - lowers intraocular pressure
  - thickens lens for near vision
Respiratory Actions of cholinoreceptor (cholinergic) muscarinic agonists

- bronchial smooth muscle contraction
- respiratory gland secretion

asthmatics can be very sensitive to muscarinic receptor agonists
CNS actions of cholinoceptor (cholinergic) muscarinic agonists

• Brain has muscarinic and nicotinic receptors
  – Ester M agonists don’t penetrate
  – Alkaloid M agonists penetrate well

• Brainstem and spinal cord contain nicotinic receptors
  – Mild alerting with tobacco smoking
  – Seizures in overdose
Muscarinic receptor sub–type actions and mechanisms

- **M1**: neuronal tissue, ANS ganglia, CNS, exocrine glands - involve Gq, IP3 and DAG to elevate Ca$$^{++}$$, produces "slow" excitation in ganglia.

- **M2**: cardiac tissue (cholinergic nerves in atria, atrioventricular and sinus nodes, *not ventricles*) - decrease heart rate, reduce atrial contraction via Gi (decrease in cAMP), as well as K channel activation. Inhibit synaptic transmission.

- **M3**: increase glandular secretions, relax blood vessels via NO

- **M4**: in CNS and acts as regulatory auto receptor – inhibits adenyl cyclase- regulates CNS dopamine transmission

- **M5** down regulates cAMP and protein kinase A
Therapeutic actions of muscarinic agonists

- Few selective muscarinic agonists are presently used in therapeutics.
- For cognitive brain dysfunction very limited success – anticholinesterases an alternative.
- Pilocarpine topically in glaucoma and xerostomia (dry mouth) and miscellaneous other uses.
Indirect Cholinoceptor Activation via Anticholinesterase elevation of ACh

• ACh accumulation in ganglia, PS neuro-effector, and neuromuscular junctions

• Magnifies effects of endogenously released ACh

• Used therapeutically but irreversible ones used as nerve gases and insecticides
Chemical Structure of Acetylcholinesterase Inhibitors

1. simple alcohols (e.g. edrophonium)

2. carbamic acid esters (e.g. neostigmine)

3. organophosphates (e.g. isofluorophosphonate)
Nature of Enzyme Inactivation

- Two possible recognition sites on enzyme for N+ and ester groups of ACh

- simple alcohols - bind to enzyme reversibly

- carbamates - long-lasting binding

- organophosphates - bind irreversibly; very long acting
Actions of cholinesterase inhibitors

• Two possible actions:

  o Primarily by virtue of accumulation of ACh at synapses and junctions where muscarinic and nicotinic cholinoreceptors are found

  o Also some have other actions
    ▪ Direct stimulation of receptors
    ▪ Actions on other enzymes
Actions of cholinesterase Inhibitors

• All those actions expected from heightened parasympathetic cholinergic activity in the heart, gastrointestinal tract, urinary, respiratory systems, skeletal muscle, brain that involve cholinoreceptors

• CNS - convulsions may occur with inhibitors which enter the brain (CNS)
Cardiovascular actions of cholinesterase Inhibitors

• Cardiovascular
  – both sympathetic & parasympathetic stimulation
  – parasympathetic actions may dominate the clinical symptoms
  – bradycardia, decreased CO, modest fall in BP
Skeletal muscle actions of cholinesterase inhibitors

• Skeletal muscle
  – therapeutic doses –
  • prolong presence of nerve-released ACh at neuromuscular junction
  • ACh elevating actions is the basis of their use to reverse paralysis due to neuromuscular blocking drugs (*nicotinic antagonists*)

  – toxic doses
  • fibrillation of muscle fibers
  • depolarizing neuromuscular junction blockade and skeletal muscle paralysis
Clinical uses of anticholinesterases versus cholinergic agonists

• Glaucoma – physostigmine occasionally used

• GI and urinary stimulation – bethanechol

• myasthenia gravis
  – edrophonium for diagnosis or testing
  – pyridostigmine for treatment

  \*Treatment also includes removal of thymus and various immunosuppressant drugs
Edrophonium

- A short acting (alcohol-type) anticholinesterase

- Uses
  - In diagnosis of myasthenia gravis (m.g.)
    - Muscle strength tested shortly after administration where a marked improvement is a positive test for m.g.
  - To test adequacy of maintained m.g. treatment with a longer acting anticholinesterase such as pyridostigmine.
    - Improvement means that dose of long acting agent is too low
    - No improvement or worsening indicates “depolarizing block” by long-acting agent. Lower dose indicated.
Organophosphates

• Phosphorylate ester recognition site on enzyme

• Form a co-valent irreversible bond with esteratic site of enzyme

• Initially there is some reversibility of their binding but with time a co-valent irreversible bond forms

• In the early stages enzyme may be reactivated with pralidoxime, before binding becomes irreversible
Some Insecticides

- **Organophosphates** (organic compound containing PO₄ group and sometimes N)
  - Chlorpyrifos (a trichloropyridin phosphorothioate)
  - Malathion
  - Diazinon: no longer on sale

- **Carbamate**
  - Carbaryl (1-naphthyl methylcarbamate powder)
SLUDGE: Acronym for toxicity symptoms due to irreversible anticholinesterases

All that expected from a massive over expression of cholinergic nerve activity (PNS, ganglia, neuromuscular junction and CNS)

- Salivation
- Lacrimation
- Urination
- Defaecation
- Gastric Emptying

Treatment: Move from source of poison, atropine (always, and enough), enzyme re-activators (PAM,DAM2-oximes) if given early after exposure, general medical support. Short acting reversible agents can be given pro-actively for prevention of irreversible binding.
Cholinoceptor Antagonists
(muscarinic then nicotinic)

Antagonists have higher affinity than agonists especially for muscarinic receptors. *Much more selective than agonists* in terms of M or N receptor type.
Cholinoceptor antagonists

- **Muscarnic receptor antagonists** - very useful in medicine
- **Ganglionic nicotinic receptor antagonists** – hardly ever used therapeutically
- **Neuromuscular nicotinic receptor antagonists** - used for skeletal muscle relaxation in surgery and skeletal muscle spasm conditions
Competitive Muscarinic Receptor Antagonists

- alkaloids – naturally occurring
  - atropine
  - scopolamine
- tertiary amines
  - dicyclomine
  - benztropine
- quaternary amines - ipratropium
Atropine & Scopolamine

- **plant origin**
  - atropine - *Atropa belladonna*
  - scopolamine - *Hyoscyamus niger*
- well absorbed from mucous membranes or skin
- reversibly compete with ACh for muscarinic receptors
- organs differ in sensitivity to these drugs
Competitive Muscarinic Antagonists “Atropinics”

- tertiary amines & alkaloids
  - lipid soluble
  - good absorption from mucous membranes and skin
  - penetration into brain
  - wide distribution to brain & periphery
  - highly selective for muscarinic receptor

- quaternary amines - opposite of above
‘Atropinic’ Drug Effects

• highly selective for muscarinic receptors
• most ‘sensitive’ tissues
  – salivary glands
  – bronchial glands
  – sweat glands
• intermediate sensitivity - heart tissues
• least sensitive - parietal cells in stomach
Atropinic effects - CNS

• sedation in therapeutic doses
• hallucinations in toxic doses
• bradycardia when given parenterally
• anti-motion sickness short term
• anti-parkinsonism actions
Atropinic Drug Effects - Eye

- relaxes pupillary constrictor muscle
  - unopposed sympathetic effects
  - mydriasis (pupil dilation)
- paralysis of the ciliary muscle – cycloplegia
- reduction in lacrymal secretion - dry eye
Atropinic Drug Effects: Heart & Cardiovascular System

• initial bradycardia - central effect (?)
• tachycardia due to blockade of vagal slowing
  – prevents ACh having actions on SAN depolarization
  – prevents ACh having actions on AVN conduction
• ventricles no affect
• overall - little affect on BP
Atropinic Drug Effects – Organs

• respiratory tract
  – some bronchodilation
  – reduction of respiratory secretions
  – a quaternary drug (ipatropium) given as an aerosol to asthmatics

• genitourinary tract - ureter and bladder relaxation

• sweat gland activity - suppressed by atropine
Atropinic Drug Effects - Gastrointestinal Tract

• dry mouth

• slight, if any, decrease in gastric secretion

• GI motility decreased
  – decreased gastric emptying
  – constipation
Symptoms of Atropine Poisoning

Occurs in children from ingestion of plants containing atropinic substances

- **dry** as a bone - no sweating, no saliva
- **blind** as a bat - paralysis of accommodation
- **mad** as a hatter – CNS effects
- **red** as a beet – vasodilation and hyperpyrexia
- dangerous in children
Atropinic: Contraindications

- Glaucoma (elevate pressure and endanger eye)

- Benign hypertrophic prostrate- further impeded urination
Therapeutic Uses

• antiparkinsonism effects
• motion sickness - scopolamine given via transdermal patch
• eye examinations - usually a short-acting is used rather than atropine
• asthma - ipatropium aerosol
• insecticide poisoning
Nicotinic receptors
(Stimulated by nicotine)

• autonomic ganglia - SNS & PNS
• neuromuscular junction (somatic nerves)
• brain – especially the spinal cord
Nicotine

• Complex effects on receptors
  – Agonist effects
    • brain nicotinic receptors
    • ganglionic nicotinic receptors – turns on both PNS and SNS
    • neuromuscular nicotinic receptors – only in overdose
  – Blockade - may produce a “depolarizing block” of nicotinic receptors in high doses
Nicotine

• Organ effects
  – Determined by predominate branch of the autonomic nervous system in that organ
  – CV effects - largely sympathetic
    • Increased HR, SV and CO
    • Vasoconstriction of vascular beds
  – GI & Urinary - largely parasympathetic

• Chronic toxicity is the most serious from a societal point of view
Nicotinic receptors are susceptible to depolarizing blockade

• depolarizes ganglion cell or neuromuscular endplate

• if present in high concentration, they produce a “depolarizing block”
  – neuron or endplate stays depolarized
  – skeletal muscle relaxation
  – ganglia of both PNS & SNS systems may be paralyzed
Nicotinic Ganglionic Blockers

block the action of ACh, and related agonists, at nicotinic receptors at both sympathetic and parasympathetic ganglia
Ganglionic Blockers

- lack of selectivity
- almost completely abandoned for clinical use
- used for short-term reduction of BP
- agents
  - mecamylamine – only one available in the US
  - trimethaphan
Ganglionic Blockers

• trimethaphan is devoid of CNS effects
• mecamylamine is not
  – sedation, tremor, choreiform movements
• eye
  – cycloplegia
  – pupil variously affected
• BP decreased - highly orthostatic
Neuromuscular Blockers

- block transmission at the neuromuscular junction
- used as principally as an adjunct to general anesthesia
- 2 classes:
  - non-depolarizing competitive antagonist – classified by tubocurarine
  - depolarizing - typified by succinylcholine
Neuromuscular transmission

Axon

Nerve terminal

ACh Nicotinic receptors

Acetylcholinesterase

End-plate

Skeletal muscle

Skeletal muscle
Curare - more correctly d-tubocurarine

• Found as an arrow poison in South American – extract is curare
• active principle d-tubocurarine
• structure includes N⁺ - therefore polar and water soluble and poor oral absorption
• competitive antagonist to ACh at its receptor therefore prevents ACh induced depolarization of end-plate
• relaxes skeletal muscles by blocking nerve control of muscle
Neuromuscular and general pharmacology of tubocurarine

• Order of effect on skeletal muscle:
  o jaw & eye paralyzed first
  o larger muscle (trunk & limbs) paralyzed before
  o the diaphragm

• more selective for skeletal muscle nicotinic receptor
  ganglionic nicotinic receptor

• releases histamine clinically in some

• can lower blood pressure (ganglion blockade)

• restricted distribution in body with a moderate duration of action
Other Non-depolarizing Agents

- Atracurium
- doxacurium
- mivacurium
- pancuronium
- vecuronium
- pipecuronium
- rocuronium
Depolarizing type:
Succinylcholine

• consists of 2 Ach molecules end-to-end
• produces a depolarizing block
  – phase I - depolarizes the end-plate & adjacent muscle
  – phase II - with continued presence, it desensitizes the end-plate to Ach
• metabolized by plasma pseudocholinesterases
Succinylcholine

- not metabolized at the neuromuscular junction (nmj)
- plasma cholinesterase determines
  - concentration that reaches the nmj
  - duration of action
- some people have atypical cholinesterase and can’t metabolize succinylcholine; they over-react to the drug
- block lasts only 10 to 15 minutes in normal patients
- blockade NOT overcome by ACh or acteylcholinesterase inhibitors
Depolarizing Blockers

*adverse effects*

- hyperkalemia - not well understood
- increased intraocular pressure
- increased intragastric pressure
- muscle pain - presumably because of the unsynchronized contractions just before paralysis