PNS physiology (Ch. 13)

PNS review

- Spinal and cranial nerves = PNS
    - Plexus = bundle of nerves innervating dermatome/common region
- Anterior root = motor fibers
- Posterior spinal ganglion = sensory cell bodies
- Mixed nerves = motor and sensory

Learning About PNS Pharmacology

What to learn for each PNS drug:

1. Receptors onto which it binds
2. Normal physiologic function of those receptors
3. Drug effect on receptor activity (increase or decrease)

Unlike the CNS, where most of the drugs for CNS we lack knowledge. For the PNS, the functioning is much more clear. A lot of the drugs we will talk about focus on the Autonomic NS.

*** Get familiar with the receptors, what drugs bind to them and their activity ***

3 main ANS regulatory functions

1. Cardiac muscle: rate and strength of contractions
2. Secretory glands: sweat, saliva, GI fluids
3. Smooth muscle regulation: Bronchi, blood vessels, GIT

Parasympathetic

- Nickname: rest and digest
- Main goal: energy optimization (homeostasis)
- 7 pharmacologically relevant functions
    - Decreases HR
    - Near vision eye focus
    - Increase gastric secretions
    - Pupil constriction
    - Bowel emptying
    - Bladder emptying
    - Bronchial airway diameter regulation

Sympathetic

- Nickname: fight or flight
- Main goal: respond to stress/threats
- 3 pharmacologically relevant functions
    - Cardiovascular regulation:

        - Brain blood supply maintenance
        - Blood flow redistribution during exercise
        - Blood loss compensation
    - Temperature regulation
        - Skin blood flow regulation
        - Skin hair erection
        - Sweat gland secretion
    - Acute stress response
        - Increased HR and BP
        - Blood flow redistribution to muscles
        - Bronchi dilation
        - Pupil dilation
        - Increased energy catabolism

ANS Regulation

Parasympathetic vs. sympathetic regulation

1. Opposite effects (majority)
2. Complementary effects (ex. Male reproduction)
3. Only one system involved (ex. Blood vessels)

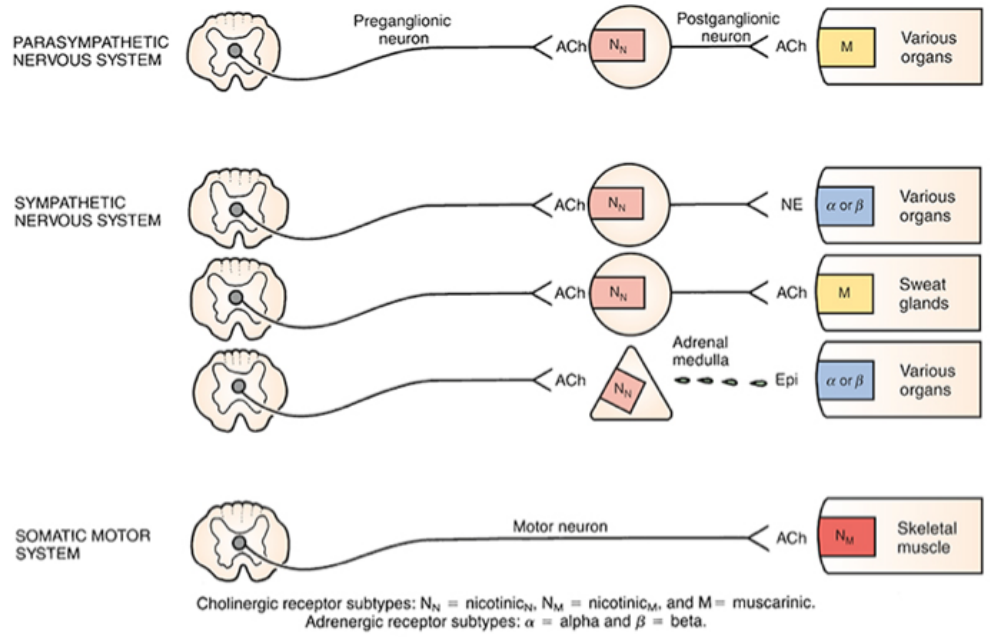
Important to keep in mind, its neither just the parasympathetic or just the sympathetic. They are in form of opposition with their function. It's not that when one is on, the other is off. It's more which one is more on/present.

You're often at rest, that's why we say the **parasympathetic system is the predominant autonomic tone**, the default state. Sympathetic is the emergency state, when you don't need it anymore, parasympathetic becomes dominant again.

At most organs, they act in opposite ways. There's some situations (rare) where they will be complimentary (ie. male reproductive system/reproduction – parasympathetic responsible for penile erection and sympathetic is responsible for ejaculation).

Feedback regulatory loop: the baroreceptor reflex regulates BP. Neurons are connected to the aorta and carotid artery. Receptors are triggered by the distention of your arteries, the signals are sent to the brain. For example, if your BP is too high (distension of the vessels), the brain will get these signals, and send them back to an effector to attempt to decrease the BP. The effectors are often smooth muscles at the blood vessels – dilate or constrict.

ANS Transmission Pathways



Cholinergic receptors are receptors onto which acetylcholine binds to.

- 3 subtypes of cholinergic receptors: nicotinic(n), nicotinic(m), and muscarinic

Adrenergic receptors (alpha/beta receptors) where epinephrine and norepinephrie bind to.

- 4 major subtypes of adrenergic receptors: alpha 1&2, beta 1&2.
- Dopamine receptor - responds only to DA NT, not NE.

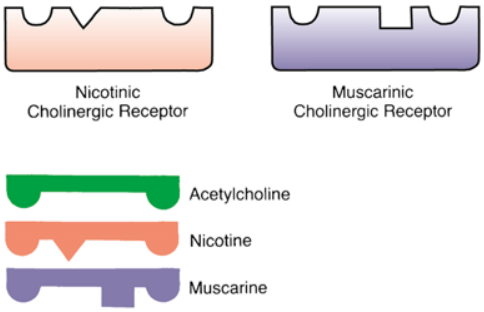
Yellow: muscarinic receptors – from the cholinergic system – received information from the parasympathetic system

- the transmission of information leave the medulla and spinal cord to a preganglionic neuron onto a second neuron, the postganglionic neuron which releases ach onto muscarinic receptors.

Blue: adrenergic receptors – sympathetic system

- the information leaves the spinal cord via the first preganglionic neuron onto a post-ganglionic neuron which releases E or NE onto adrenergic receptors.
- there's one exception for the sympathetic system, where ach is released onto muscarinic receptor. This happens at the sweat glands for temperature regulation.

Receptor Subtypes

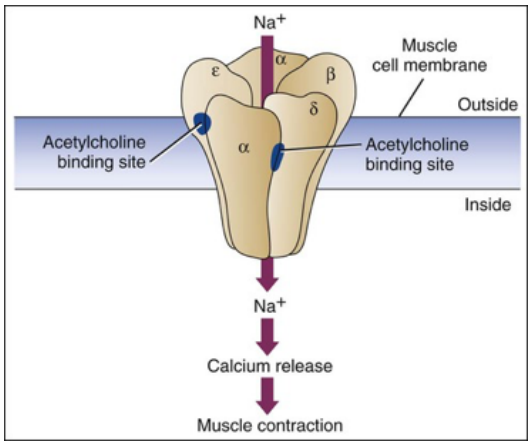


- Ach binds to both nicotinic and muscarinic receptors
- Nicotine binds only to the nicotinic receptor (each receptor has different shapes) and vice versa for muscarine
- Physiologically irrelevant: ach can bind to both receptors. The body cannot tell the difference. But from the perspective of different drugs, they are different (pharmacologically important)

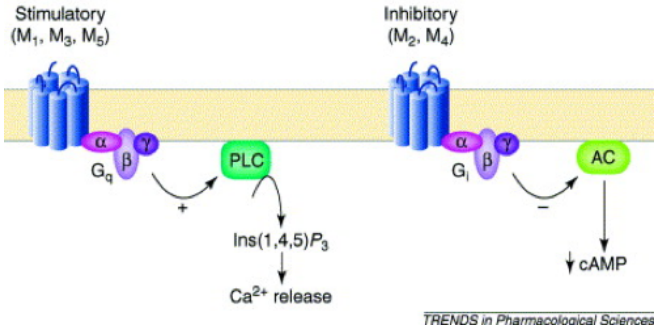
Receptor Specificity of Adrenergic Transmitters[a]

Transmitter	$Alpha_1$	$Alpha_2$	$Beta_1$	$Beta_2$	Dopamine
Epinephrine	←			→	
Norepinephrine	←		→		
Dopamine	↔		↔		↔

Nicotinic vs. Muscarinic Receptors



- Above is a ligand-gated sodium channel that 5 subunits to form a pore where sodium ions can float through.
- Subunit variations → receptor subtypes action potential transmission



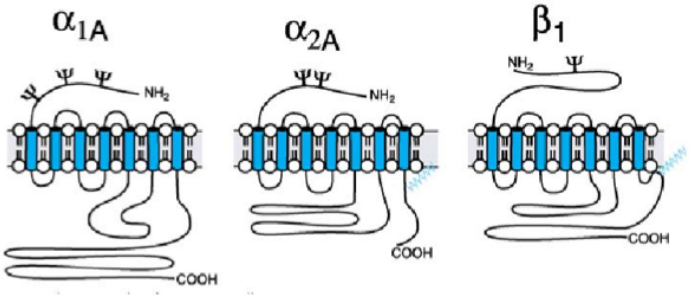
- Muscarinic receptor is from the G-protein coupled receptor type. It has 7 transmembrane domain that activates the G-protein.
- G-protein variations → receptor subtypes
- Smooth muscle contraction and relaxation regulation

Cholinergic Receptor Functions

Functions of Peripheral Cholinergic Receptor Subtypes

Receptor Subtype	Location	Response to Receptor Activation
Nicotinic$_N$	All autonomic nervous system ganglia and the adrenal medulla	Stimulation of parasympathetic and sympathetic postganglionic nerves and release of epinephrine from the adrenal medulla
Nicotinic$_M$	Neuromuscular junction	Contraction of skeletal muscle
Muscarinic	All parasympathetic target organs:	
	Eye	Contraction of the ciliary muscle focuses the lens for near vision Contraction of the iris sphincter muscle causes miosis (decreased pupil diameter)
	Heart	Decreased rate
	Lung	Constriction of bronchi Promotion of secretions
	Bladder	Contraction of detrusor increases bladder pressure Relaxation of trigone and sphincter allows urine to leave the bladder Coordinated contraction of detrusor and relaxation of trigone and sphincter causes voiding of the bladder
	GI tract	Salivation Increased gastric secretions Increased intestinal tone and motility Defecation
	Sweat glands[a]	Generalized sweating
	Sex organs	Erection
	Blood vessels[b]	Vasodilation

Adrenergic Receptors



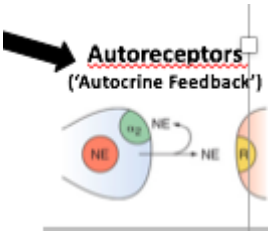
Alpha 1A	Alpha 2A	Beta1
Alpha 1B	Alpha 2B	Beta2
Alpha 1D	Alpha 2C	Beta3

*Know Alpha 1 & 2 / Beta 1 & 2

Adrenergic Receptor Functions

Functions of Peripheral Adrenergic Receptor Subtypes

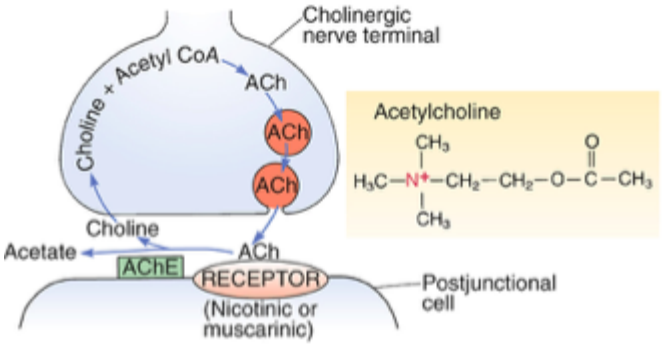
Receptor Subtype	Location	Response to Receptor Activation
Alpha$_1$	Eye	Contraction of the radial muscle of the iris causes mydriasis (increased pupil size)
	Arterioles Skin Viscera Mucous membranes	Constriction
	Veins	Constriction
	Sex organs, male	Ejaculation
	Prostatic capsule	Contraction
	Bladder	Contraction of trigone and sphincter
Alpha$_2$	Presynaptic nerve terminals	Inhibition of transmitter release
Beta$_1$	Heart	Increased rate
		Increased force of contraction
		Increased AV conduction velocity
	Kidney	Release of renin
Beta$_2$	Arterioles Heart Lung Skeletal muscle	Dilation
	Bronchi	Dilation
	Uterus	Relaxation
	Liver	Glycogenolysis
	Skeletal muscle	Enhanced contraction, glycogenolysis
Dopamine	Kidney	Dilation of kidney vasculature



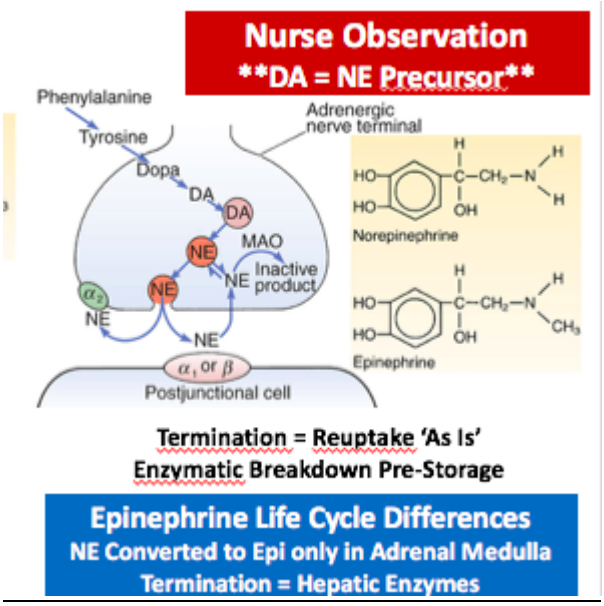
- All related to sympathetic system: bladder relaxation (retention), pupil dilation, increased HR, heart/lung/vessel dilation

- Autoreceptors: alpha 2 receptor's main role is to act as a feedback receptor, neuron releases NE onto another neuron. The neuron that released the NE has its own alpha 2 receptors, so that the NE can bind to and activate the same neuron that released it. It serves as a confirmation that the NE was in fact released. Acting to suppress further NE release when enough has already accumulated in the junction.
- Dopamine: dilation of kidney vasculature → enhance renal perfusion

Transmitter life cycles



Cholinergic life cycle – where neurons that release ach combine choline with acetylCoA forming ach. It then gets packaged into small vesicles and can then be released in the synaptic cleft, in response to action potential. Ach can then bind to the nicotinic or muscarinic receptor on the postsynaptic neuron. Ach can is then broken down by enzyme Ach-esterase into its two divided components: acetate and choline. Choline is then reabsorbed into the cholinergic nerve to be reused in the presynaptic nerve.
The termination of the cycle – enzymatic breakdown + partial reuptake & diffusion.



Adrenergic life cyle – where the NE is synthesized after a series of metabolic steps that begins with phenylalanine, which gets transformed to Dopamine. DA is a precursor of NE. DA is the NT that gets packaged into the vessel and within the vessel it gets transformed into NE. Then NE is released onto the postsynaptic cell (alpha1 or beta1 receptors) and on the autoreceptor (alpha 2 receptor). NE gets reabsorbed as is, and get either repackaged or it will be broken down in house by MAO enzyme. The breakdown happens pre-storage.

At the adrenal glands, epinephrine is released (it is more water soluble so it can be sent more as a hormone than a NT). For NE to be converted into E happens only in the adrenal glands.

Cholinergic Drugs (Ch. 14-15-16)

Intro to Cholinergic Agents

Cholinergic Drugs and Their Receptors

	Receptor Subtype		
	Muscarinic	**Nicotinic$_N$**	**Nicotinic$_M$**
Receptor Location	Sweat glands Blood vessels All organs regulated by the parasympathetic nervous system	All ganglia of the autonomic nervous system	Neuromuscular junctions (NMJs)
Effects of Receptor Activation	Many, including: ↓ Heart rate ↑ Gland secretion Smooth muscle contraction	Promotes ganglionic transmission	Skeletal muscle contraction
Receptor Agonists	Bethanechol	Nicotine	Nicotine*
Receptor Antagonists	Atropine	Mecamylamine	*d*-Tubocurarine, succinylcholine
Indirect-Acting Cholinomimetics	Cholinesterase inhibitors: Physostigmine, neostigmine, and other cholinesterase inhibitors can activate *all* cholinergic receptors (by causing accumulation of acetylcholine at cholinergic junctions)		

*The doses of nicotine needed to activate nicotinic$_M$ receptors of the NMJs are much higher than the doses needed to activate nicotinic$_N$ receptors in autonomic ganglia.

Categories of Cholinergic Drugs

Category	Representative Drugs
Muscarinic agonists	Bethanechol
Muscarinic antagonists	Atropine
Ganglionic stimulating agents	Nicotine
Ganglionic blocking agents	Mecamylamine
Neuromuscular blocking agents	*d*-Tubocurarine, succinylcholine
Cholinesterase inhibitors	Neostigmine, physostigmine

Muscarinic Antagonists: Atropine

- Atropine blocks the activation of Ach. Competitive antagonism of Muscarinic receptors
- Atropine Dose-response relationship: depending on the dosage, the affinity for muscarinic receptors will change. It doesn't bind to all muscarinic receptors equally. When you give atropine in lower dosage, it will have effects on the salivary glands and sweat glands first. As you keep increasing the dosage, it will act on the bronchial glands, heart and eyes, etc.
- The dosage to treat gastric ulcers and asthma is too high, can easily lead to toxicity, so we don't use them for these purposes.
- Therapeutic Uses:
    - Administration = topical or parenteral
    - Pre-anesthesia prophylaxis
    - Prevent decreased HR and increased airway mucus secretions
    - Decreased eye movements for ocular exams and surgery
    - Bradycardia & GI hypermotility therapy
    - Muscarinic agonist poisoning antidote
- Adverse effects/contraindications (similar to sympathetic stimulation):
    - Similar to excessive sympathetic stimulation
    - Ex: urinary retention, tachycardia, dry mouth
    - Photophobia and blurred vision (paralysis of the ciliary muscle and the sphincter of the iris)
    - Interactions with antihistamines & TCAs
    - **inappropriate for geriatric patients (because cardiac risk too high)**

Overactive Bladder (OAB) Treatment

- 1st line treatment = behavioral therapy - Scheduled voiding, Kegel exercises
    - Monitor fluids & avoiding caffeine
    - Initiate medication only if BT fails
- Drug therapy

- Table 14-5 → best strategy = target M3 subtype
- These drugs are the preferred drugs for OAB because they avoid CNS & heart adverse effects

- M3-selective muscarinic antagonists for OAB
  - Oxybutynin / darifenach /tolterodine→ block muscarinic receptors on the bladder detrusor and thereby inhibit bladder contractions and the urge to void
  - Not one is clearly superior
  - Only slightly better than placebo
  - If one fails, another could succeed → PK differences

<u>Reversible Cholinesterase Inhibitors</u>

- Anticholinesterase prototype: Neostigmine
  - Slows down break-down activity of cholinesterase (indirect way of increasing the amount of Ach in the synaptic cleft = boost in effect of Ach)
    - Neostigmine and cholinesterase become bound, remains this way for a really long time. Cholinesterase only becomes free when it has completely degraded neostigmine, meaning there is less enzyme available to breakdown Ach, therefore increasing amount of Ach available for cholinergic receptor activation.
  - No receptor selectivity
  - Similar profile to muscarinic agonists
  - It is a Quaternary Ammonium: when you have a nitrogen atom that is bound to 4 different things. It has a positive charge, not lipid-soluble. So it has poor BBB permeability and therefore only acts in the periphery.
  - **Muscarinic effects** = muscarinic agonists (ex: bradycardia, miosis, increased secretions, urinary urgency, bronchial constriction, increased tone and motility of GI)
  - **Neuromuscular effects**: therapeutic doses increase contraction force vs. toxic dose decrease force (nb. Ach is released at the neuromuscular junction. So at higher doses of neostigmine, it may start to have an effect here, where signals for muscle contractions may increase, keeping it in a state of constant depolarization).
  - **CNS effects**: depressive action → only at very high/toxic doses since difficulty crossing BBB.
  - Adverse effects/toxicity
    - Excessive muscarinic actions & respiratory muscle paralysis → reverse with atropine antidote
    - Drug interactions: increased effects of succinylcholine
  - Atropine may be used as an antidote because their actions are contradictory

<u>Irreversible Cholinesterase Inhibitors</u>

- Organophosphates Pharmacologic Effects & toxicity
  - Same as reversible but increased duration
  - Highly lipid-soluble → very toxic!!
  - Only medical application is glaucoma because of its high risk for toxicity

- Organophosphate poisoning risk: agriculture workers/warfare/suicides
- Cholinergic crisis: excessive muscarinic actions & neuromuscular blockade
- Sx mnemonics; DUMBBELS
  - Diarrhea
  - Urination
  - Miosis
  - Bradycardia
  - Bronchospasms
  - Emesis
  - Lacrimation
  - Salivation
- Treatment (antidote): atropine & pralidoxime (direct antagonist)

Myasthenia Gravis Treatment

- Autoimmune disorder where the immune system attacks nicotinic(m) receptors on skeletal muscle.
- Symptoms of disease: ptosis (drooping of eyelids), difficulty swallowing, and weakness of skeletal muscles. Difficulty breathing is caused by weakness of the respiratory muscles.
- Main therapeutic usage of anticholinesterase drugs
- Drugs of choice: neostigmine & pyridostigmine → symptomatic relief only (increasing muscle strength)
- Dosage management:
  - Administration → PO preferred if capable of swallowing
  - Individualized dosage via symptoms monitoring
- Side effects management
  - Atropine admin against unwanted muscarinic activation
  - But not routinely!!! → risks of masking early signs of cholinergic crisis (ex. Excessive salivation)
- Myasthenia crisis vs. Cholinergic crisis
  - Similar Sx → muscle weakness & respiratory muscle paralysis
  - Different Tx → neostigmine vs. atropine
  - Differential diagnosis → medication monitoring & muscarinic involvement (cholinergic crisis only)

Competitive Neuromuscular Blocker

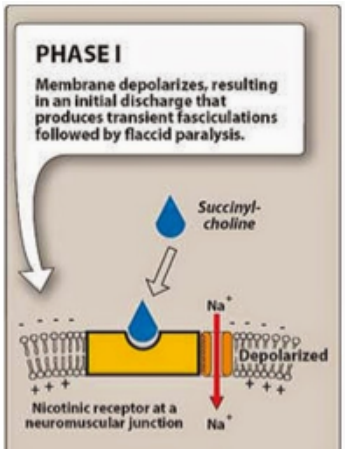
- Rocuronium
- Roc is a quaternary ammonium, so poor BBB crossing (water-soluble) and poor GI absorption. Has a similar shape as Ach so it can bind to the nicotinic receptor, preventing the binding of Ach which prevents voluntary muscle contraction.
- It is a derivative of Curare.
- Pharmacologic effects and toxicity

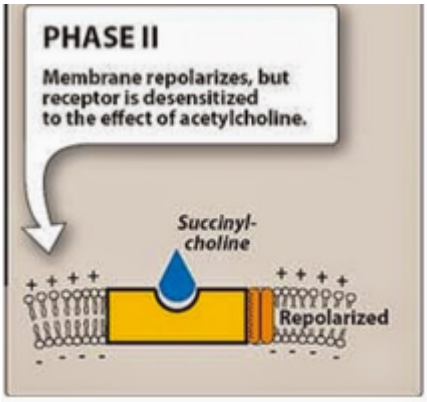
- Gradual muscle relaxation
- First effects are smaller muscles such as eyelid, mouth, then moves onto the limbs, and thankfully respiration is last.
- Can cause hypotension due to mast cell degranulation releasing histamine, promoting massive vasodilation
- No loss of pain or consciousness (cannot cross BBB)

- Contraindications
  - Myasthenia gravis & electrolyte imbalances
- Interactions
  - Increase response: antibiotics or inhalational anesthetics
  - Decrease response: anticholinesterase

<u>Depolarizing Neuromuscular Blocker</u>

- Succinylcholine
- Pharmacologic effects & toxicity
  - Same as competitive blockers EXCEPT: transient contractions, ultra short duration (4-10min)
  - Instead of just blocking the receptor, it binds to the receptor, but then remains there and maintaining it in a constant state of depolarization. So what you get is a transient contraction (small contractions), then paralysis.
  - No CNS action





- Eliminated by plasma cholinesterase: this enzyme lives in the plasma, so whenever Succ circulates in the bloodstream, it gets broken down as it travels through = short duration
- Specific toxicity
  - Post-op muscle pain
  - Malignant hyperthermia

- Contraindications
  - Low plasma cholinesterase activity → increased risk of prolonged apnea
  - Major burns/multiple trauma → increased risk of hyperkalemia
- Interactions
  - Increases response: antibiotics or anticholinesterases (competitive)

Neuromuscular Blockers: Therapeutic Uses

- General anesthesia adjunct
  - Benefits = facilitates surgeon's work & decreases anesthesia dosage
  - Remember → NO CNS action → imagine paralysis with PAIN & CONSCIOUSNESS
  - **Rocuronium** = long duration → **preferred agent**
- Mechanical ventilation adjunct
  - Benefits = decreased resistance to ventilation
  - Treat patient as if he/she is awake → pain & hearing functions are working!!!
  - Usage contraindicated in long-term mechanical ventilation (ex. ICU)
- Endotracheal intubation
  - Benefits = decreased gag reflex to ease intubation of trachea
  - **Succinylcholine** = short duration → **preferred agent**
- Electroconvulsive therapy → treatment of depression
  - Benefits = inhibit harmful muscular convulsions
  - **Succinylcholine** = short duration → **preferred agent**

Adrenergic Drugs (Ch. 17-18-19)

Adrenergic Agonists Overview

- Oral availability & duration
  - Depends on metabolism by MAO & COMT (these enzymes quickly destroy catecholamines, which is why they cannot be PO)
  - Catecholamine >> Non-catecholamine
- BBB crossing
  - Depends on metabolism by MAO & COMT
  - Catecholamine = very polar
  - Noncatecholamine = less polar

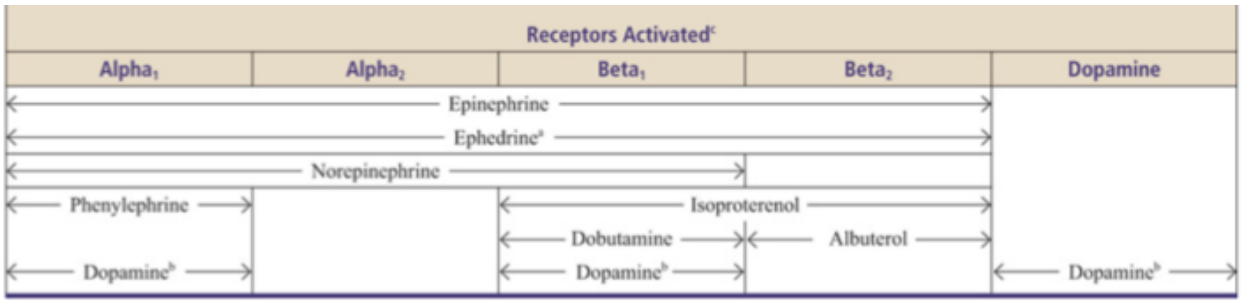
	Catecholamine	Noncatecholamine
Oral Availability	No	Yes
Duration of Action	Short	Long
BBB X-ing	Very Low	> Cathecholamine

Adrenergic Receptor Activation

Mechanisms of Adrenergic Receptor Activation

Mechanism of Stimulation	Examples
DIRECT MECHANISM	
Receptor activation through direct binding	Dopamine Epinephrine Isoproterenol Ephedrine[a]
INDIRECT MECHANISMS	
Promotion of NE release	Amphetamine Ephedrine[a]
Inhibition of NE reuptake	Cocaine Tricyclic antidepressants
Inhibition of MAO	MAO inhibitors

- Sympathomimetic drugs
  - Effects = sympathetic system stimulation
  - Ex: bronchodilation; increase CO, increased blood glucose

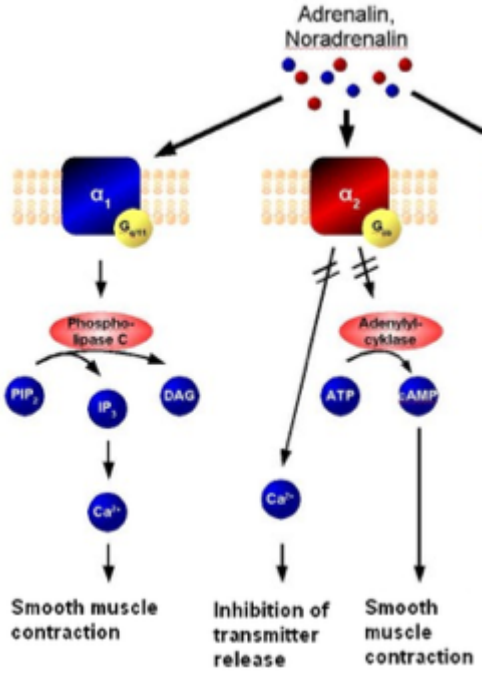


Alpha-Adrenergic Actions

Alpha-1

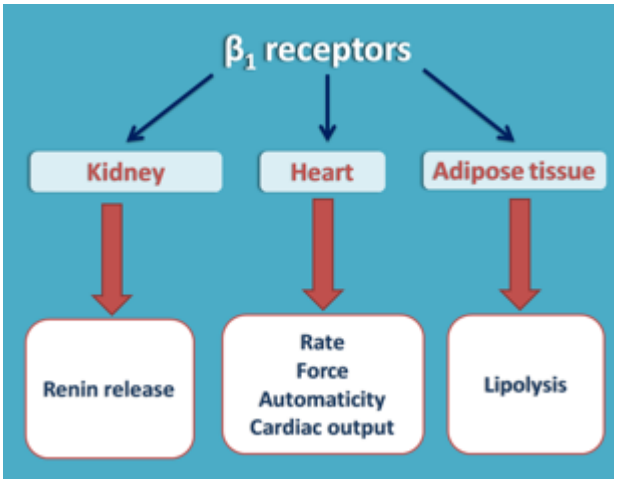
- Effects
  - Vasoconstriction
  - Mydriasis (pupil dilation)
- Therapeutic usage: uncommon
  - Hemostasis
  - Nasal decongestion
  - Adjunct to local anesthesia
  - Hypotension
  - Mydriasis for eye exam & surgery
- Adverse effects
  - Hypertension (IV administration increases risk)
  - Extravasation tissue necrosis (hypoxia)
  - Bradycardia (baroreceptor reflex trigger)

Alpha-2

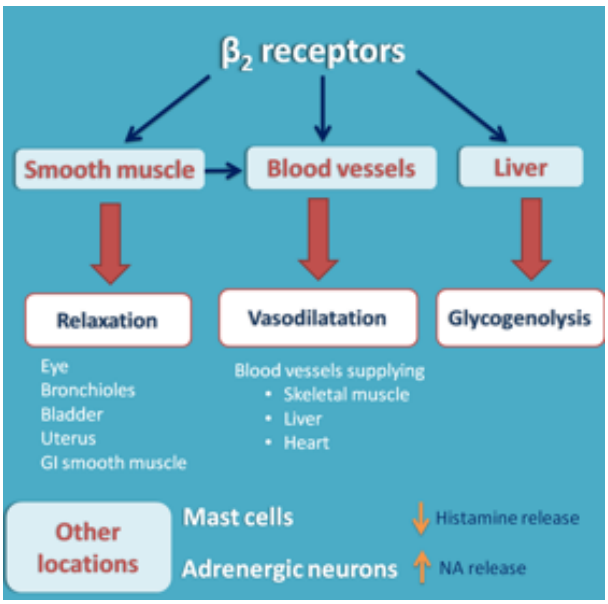


- Effects
  - Presynaptic autoreceptors (if there is activation of the autoreceptor, it inhibits further release of the NT)
  - Inhibit transmitter release
- Therapeutic usage
  - PNS alpha-2 = no therapeutic application
  - CNS alpha-2 → see indirect alpha blockers
    - Severe hypertension
    - Pain relief
- Adverse effects:
  - PNS = no significant ADR
  - CNS = rebound hypertension & CNS depression

<u>Beta-Adrenergic Actions</u>



- Therapeutic usage = mostly heart
  - Heart failure
  - Shock
  - Short-term AV block therapy
  - Cardiac arrest (last resort)
- Adverse effects:
  - Tachycardia → dysrhythmias
  - Angina pectoris (atherosclerotic patients)



- Therapeutic usage = lungs & uterus
  - Asthma (selective beta-2 agonists)
  - Delay preterm labor
- Adverse effects
  - Hyperglycemia (diabetic patients)
  - Transient muscle tremor

Dopamine receptors are only found on the kidney. Promotes renal vasodilation. Only used for shock treatment

Adrenergic Agonists Summary

Drug	Epinephrine	Dopamine
Chemistry Kinetics	Catecholamine → Topical/IM/IV Administration & Short $T_{1/2}$	
Receptor Affinity	α1 / α2 / β1 / β2	DA Moderate Dose → β1 Very High Dose → α1
Therapeutic Usage	Prolong Local Anaesthesia (α1) Topical Hemostasis (α1) ↑ BP (α1) AV Block Therapy & Cardiac Arrest/Shocks (β1) Anaphylactic Shock (α1 + β1+ β2)	Shock (DA & β1)
Adverse Effects	Hypertensive Crisis & Extravasation Necrosis (α1) Dysrhythmias & Angina Pectoris (β1) Diabetic Patients Hyperglycemia (β2)	β1-Related High Doses: α1-Related
Drug Interactions	MAO Inhibitors → ↑ $T_{1/2}$ Tricyclic Antidepressants → ↑ Effects Inhalational Anaesthetics → ↑ Dysrhythmias Adrenergic Blockers → ↓ Effects	Idem Epi Diuretics → ↑ Benefits

Drug	Isoproterenol	Albuterol
Chemistry Kinetics	Catecholamine Topical/IM/IV Administration & Short $T_{1/2}$	Noncatecholamine Inhalation & Longer $T_{1/2}$
Receptor Affinity	β1 / β2	β2-selective High Dose → β1
Therapeutic Usage	AV Block Therapy (β1) Cardiac Arrest/Shocks (β1)	Asthma (β2)
Adverse Effects	Idem Epinephrine Except no α1-Related	Minimal at Therapeutic Doses Tremor & Tachycardia at High Doses
Drug Interactions	Idem Epi	Adrenergic Blockers

<u>Anaphylactic Shock Treatment</u>

Life threatening emergency allergic reaction

- Common causes = food allergy, bee stings, penicillins

Pathophysiologic manifestations → severe decreased tissue perfusion

- Widespread vasodilation → hypotension
- Bronchoconstriction → airway obstruction
- Edema of glottis → airway obstruction

Treatment

- Epinephrine (Epipen) IM or IV
- Activation of beta1 → Increased CO → increased BP
- Activation of beta2 → bronchodilation → decreased airway obstruction
- Activation of alpha1 → vasoconstriction → increased BP + decreased glottis edema
- ***antihistamines = insufficient** many more mediators involved

Prevention

- At risk individuals should always carry Epipen with them
- Hospitalization recommended after Epipen administration

<u>Therapeutic Beta-Blockers (Ch.18)</u>

- Propranolol - 1st generation
- Metoprolol - 2nd generation
- Cardioselective > Nonselective
- 3rd Gen vasodilating → unclear benefits over 2nd Gen

Prototypes Beta-Blockers

Propranolol: nonselective beta 1 & 2 blocker

- Highly lipid-soluble → widespread distribution
- Hepatic metabolism + renal excretion
- Therapeutic usage & Adverse effects (see previously)
- Specific toxicity/contraindications:
    - Very rare CNS toxicity (ex. Insomnia; depression)
    - Placental barrier crossing → neonate toxicity
    - Inhibits Epipen → avoid in allergic patients
    - Calcium channels blockers interaction → increase effects
- Dosage considerations:
    - Therapeutic dose depends on sympathetic activity
    - MUST be individualized by patient via monitoring

Metoprolol: selective beta 1 blocker

- Highly lipid-soluble → widespread distribution
- Hepatic metabolism + renal excretion
- Therapeutic usage & adverse effects (see previously)
    - Safer for asthmatic & diabetic patients

Indirect Adrenergic Blockers

- Indirect decrease of peripheral adrenergic activation
    - Its indirect because its action is in the CNS but the effects are in the PNS
    - 1. Alpha-2 autoreceptor agonists → clonidine
    - 2. Decrease adrenergic transmitter release → reserpine
- Pharmacologic effects & toxicity
    - = adrenergic antagonists
    - Decreased CO + increased vasodilation = decreased BP
- Contraindications
    - Geriatric patients / pregnancy
- Specific toxicity
    - clonidine: CNS depression and rebound hypertension
- Therapeutic usage
    - Clonidine: severe hypertension / pain / ADHD
    - Methyldopa: severe HT during pregnancy