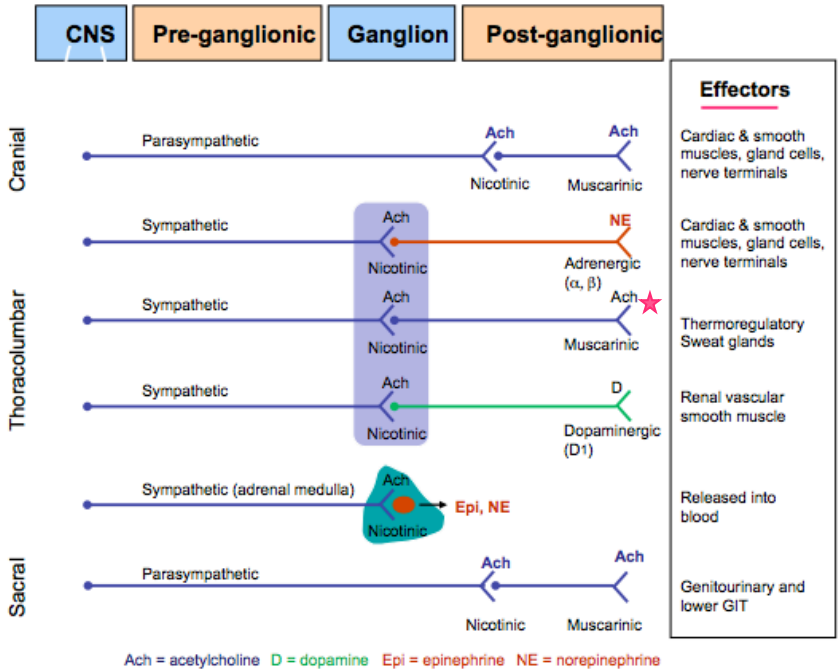
AUTONOMIC NERVOUS SYSTEM – Sympathetic & Parasympathetic



Major NT of Sympathetic NS: EPINEPHRINE, NOREPINEPHRINE

- **↑Vasoconstriction (α1) → ↑BP**
  - **Vasodilation (β2) → ↓BP** **not innervated; EPI*
- **↑HR & force of contraction (β1)**
- ↑Sweat secretion (sympathetic cholinergic)
- ↓Peristalsis
- **↑Mydriasis (dilation of pupil) (α1)**
- ↑Bronchodilation (β2)
- ↑Renin secretion (β1)
- Promotes ***ejaculation*** (α1)

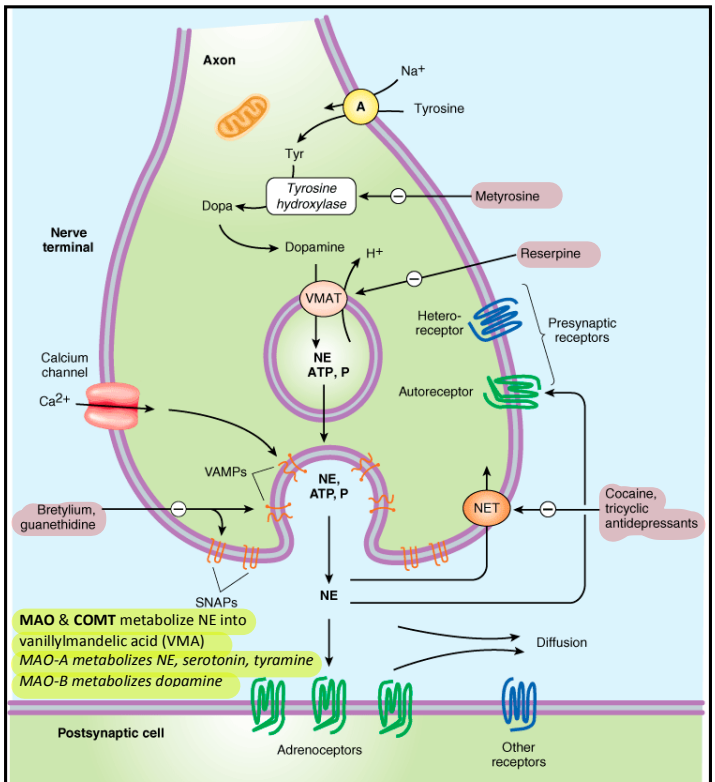
Major NT of Parasympathetic NS: ACETYLCHOLINE

- Does NOT *innervate* vasculature, but there are muscarinic receptors in the vasculature
- **Ach ↓BP** via binding to mAchR & ↑synthesis of nitric oxide (AKA endothelial-derived relaxation factor – EDRF)
- **↓HR (M2)**
- ↑Salivation, Lacrimation, Sweating
- ↑GI secretion & motility
- **↑Miosis (constriction of pupil via contraction of sphincter)**
- ↑Bladder detrusor muscle tone (↑urination)
- ↓Bronchodilation
- **↑Ciliary muscle contraction (↑accommodation)**

SITE	PREDOMINANT TONE
Arterioles	Sympathetic (adrenergic)
Veins	Sympathetic (adrenergic)
Heart	Parasympathetic (cholinergic)
Iris	Parasympathetic (cholinergic)
Ciliary muscle	Parasympathetic (cholinergic)
Gastrointestinal tract	Parasympathetic (cholinergic)
Urinary bladder	Parasympathetic (cholinergic)
Salivary glands	Parasympathetic (cholinergic)
Sweat glands	Sympathetic (cholinergic)
Genital tract	Sympathetic and parasympathetic

Green = Kaplan, Deja Review, Tulane Question

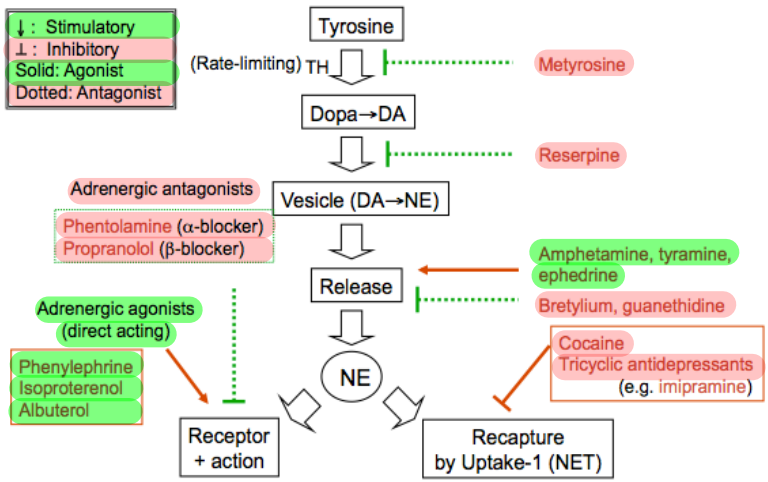
SYMPATHETIC NERVOUS SYSTEM – Adrenergic Neuroeffector Junction



SYNTHESIS OF EPINEPHRINE

1. Tyrosine → DOPA via tyrosine hydroxylase (*rate limiting*)
2. DOPA → dopamine via DOPA decarboxylase
3. Dopamine → NE via dopamine beta-hydroxylase
4. NE → epinephrine via methylation in the adrenal medulla

Tyramine (found in wine & cheese), **Ephedrine** (found in OTC cold meds), & **Amphetamines** should NOT be mixed with **MAO-A inhibitors**. These drugs ('releasers') stimulate release of NE from NE mobile pool → ***hypertensive crisis & death***



METYROSINE – inhibits catecholamine synthesis via inhibiting tyrosine hydroxylase

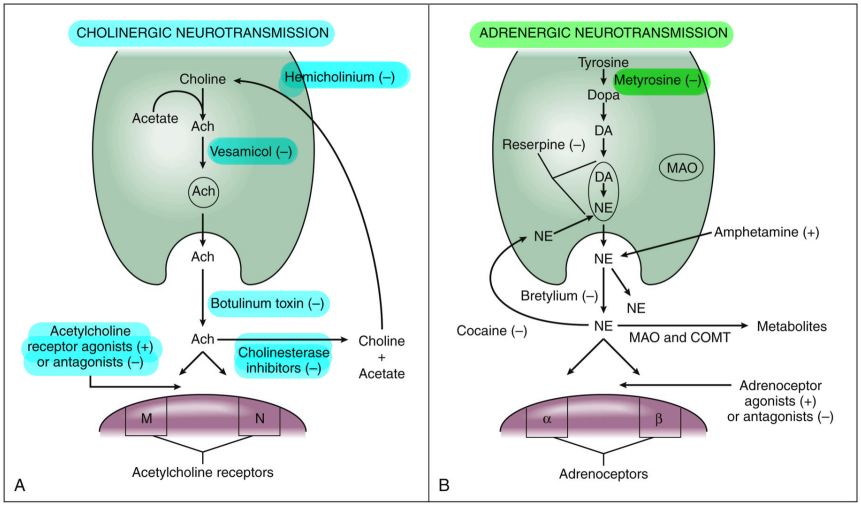
RESERPINE – inhibits the transport of NE from the neuronal cytoplasm into the synaptic vesicles & NE is broken down by MAO; *can cause depression & sedation*

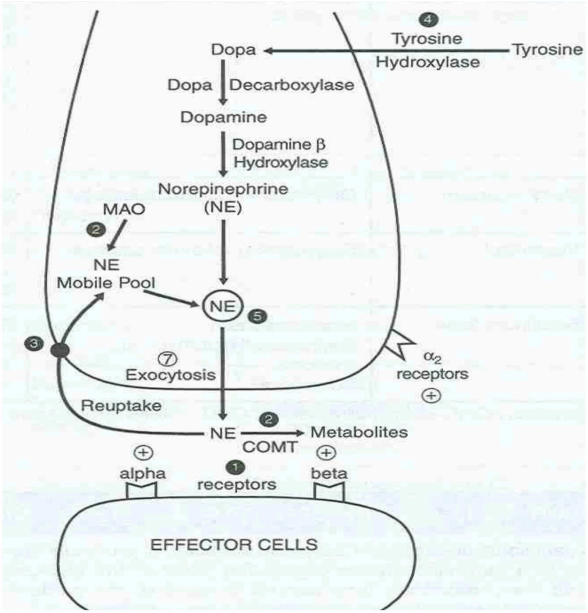
EPHEDRINE, TYRAMINE, AMPHETAMINE – increase NE levels by acting as indirect sympathomimetics & displacing NE from the mobile storage pool; *drug enters pre-synaptic nerve terminal via NET & displaces stored NE*

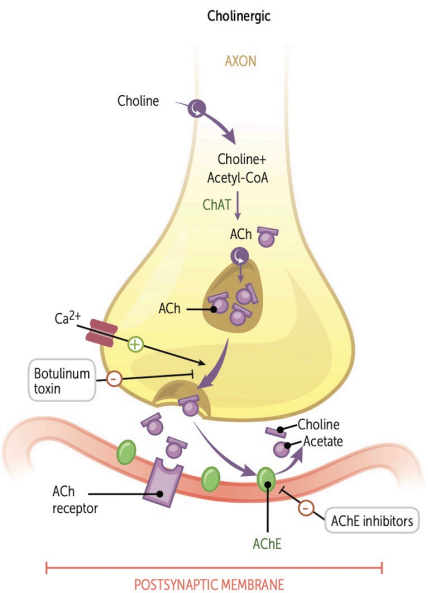
BRETYLIUM, GUANETHIDINE – inhibits the release of NE into the synapse

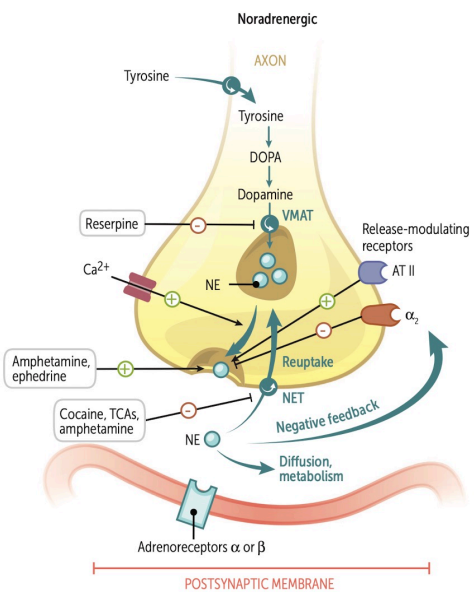
COCAINE – inhibits reuptake of NE back into the presynaptic neuron via inhibiting of NET & thus, increases NE levels in the synaptic cleft. *This prevents tyramine from getting into the nerve terminal to exert its effect to "kick out" NE & also increases & prolongs the response to NE.*

Green = Kaplan, Deja Review, Tulane Question


CHOLINERGIC NEUROTRANSMISSION
Choline
Hemicholinium (–)
Acetate
Ach
Vesamicol (–)
Ach
Ach
Botulinum toxin (–)
Acetylcholine receptor agonists (+) or antagonists (–)
Ach
Cholinesterase inhibitors (–)
Choline + Acetate
M
N
Acetylcholine receptors
A
ADRENERGIC NEUROTRANSMISSION
Tyrosine
Metyrosine (–)
Dopa
DA
Reserpine (–)
MAO
DA
NE
NE
Amphetamine (+)
NE
Bretylium (–)
NE
Cocaine (–)
NE
MAO and COMT
Metabolites
Adrenoceptor agonists (+) or antagonists (–)
α
β
Adrenoceptors
B


4
Tyrosine
Hydroxylase
Tyrosine
Dopa
Dopa Decarboxylase
Dopamine
Dopamine β Hydroxylase
Norepinephrine (NE)
MAO
2
NE Mobile Pool
NE
5
3
7 Exocytosis
α2 receptors
+
Reuptake
NE
2
COMT
Metabolites
+
+
alpha
1 receptors
beta
EFFECTOR CELLS


Cholinergic
AXON
Choline
Choline+ Acetyl-CoA
ChAT
ACh
ACh
Ca2+
Botulinum toxin
Choline
Acetate
ACh receptor
AChE inhibitors
AChE
POSTSYNAPTIC MEMBRANE


Noradrenergic
AXON
Tyrosine
Tyrosine
DOPA
Dopamine
VMAT
Reserpine
Release-modulating receptors
Ca2+
NE
AT II
α2
Amphetamine, ephedrine
Reuptake
NET
Cocaine, TCAs, amphetamine
Negative feedback
NE
Diffusion, metabolism
Adrenoreceptors α or β
POSTSYNAPTIC MEMBRANE

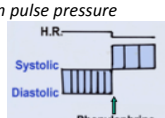
SYMPATHETIC NERVOUS SYSTEM – Adrenergic Receptors

RECEPTOR	α1 Adrenergic	α2 Pre-synaptic	β1 Heart <3	β2 Adrenergic
MECHANISM	G_q (PLC: ↑IP_3, DAG, Ca^{2+})	G_i (↓cAMP)	G_s (PKA: ↑cAMP)	G_s (PKA: ↑cAMP)
ACTIONS	*Smooth muscle contraction* *Vasoconstriction (↑diastolic P)*	***Inhibition of transmitter release*** *Smooth muscle contraction*	*Heart muscle contraction* *Tachycardia* ***+Inotropic (↑PP)*** *↑AV conduction*	*Vasodilation* *Bronchodilation*
	Eye – radial muscle – **mydriasis** **BVs** – ↑TPR; **vasoconstriction** **Bladder trigone/sphincter** – urinary retention **Vas deferens** – ejaculation	**Presynaptic** – inhibits release of NE **Pancreas** – ↓ insulin release **Platelets** – aggregation **Note: side effects of α_2 agonists can cause thrombus formation & diabetes*	**HEART** **SA Node** – **tachycardia**, *+ chronotropy* **AV Node** – ↑cond. vel, *+ dromotropy* **Atrial & Ventricle muscle** – *+ionotropy* **Kidney** – ↑renin release	**BLOOD VESSELS** – vasodilation *^skeletal muscle* **Uterus** – relaxation **BRONCHIOLES** – bronchodilation **Skeletal muscle** – tremors **Liver** – ↑ glycogenolysis **Pancreas** – ↑ insulin secretion
SELECTIVE AGONISTS	**Phenylephrine**	α-Methyldopa **Clonidine** Guanfacine	**Dobutamine**	**Albuterol**, Salmeterol, Terbutaline, Ritodrine
NON-SELECTIVE AGONISTS	**NE**: *Vasoconstriction* **EPI**: *Vasoconstriction*		**Isoproterenol**: *Heart stimulation + vasodilation + bronchodilation* **EPI**: *Heart stimulation + vasodilation + bronchodilation*	
			NE: *Heart stimulation*	*β2 is not innervated, so mostly EPI*
ANTAGONISTS	**↓BP, POSTURAL HYPOTENSION** Labetalol, Carvedilol		Labetalol, Carvedilol	
SELECTIVE ANTAGONISTS	Prazosin, *Tamulosin*: ***α1A*** **(BPH)**	Yohimbine	Atenolol	
NON-SELECTIVE ANTAGONISTS	**Phenoxybenzamine**: *irreversible (non-competitive)* **Phentolamine**: *reversible*		**Propanolol**	

B3 Selective Agonist = Mirabegron -> Detrusor muscle relaxation and increased bladder capacity. Use for overactive bladder. (M3 antagonist can also be used).

Green = Kaplan, Deja Review, Tulane Question

SYMPATHETIC NERVOUS SYSTEM – Sympathomimetic: NE, Epi, α Agonists

DRUG	RECEPTOR	LOCATION	ACTION	INDICATIONS	NOTES
NOREPINEPHRINE	**α1 agonist** β1 agonist	Blood vessels SA Node Ventricle	Vasoconstriction, ↑**DBP**, ↑TPR ↑HR +Inotropy, ↑**PP** *Overall ↓HR after NE injection due to opposing forces,: ACh > NE* *ACh (**Vagal Reflex Bradycardia**)* *NE (β1 agonist)*	**HYPOTENSION**	*Also binds α2 receptors – **negative feedback on NE release; PRESYNAPTIC RECEPTORS*** ***NE has NO β2 activity so it can NEVER ↓BP because it cannot vasodilate.*** ***Note**: Reflex Bradycardia is NEVER due to the drug, but rather to parasympathetic NS response to ↑BP*
LOW/MODERATE DOSE EPINEPHRINE **resembles Doputamine* **HIGH DOSE EPI** **resembles NE, phenylephrine*	**β1** agonist **β2 agonist** α1 agonist	SA Node Ventricle Skeletal muscle arterioles	↑**HR**, ↑**PP**, *no change in MAP* **Vasodilation > vasoconsriction** ↓TPR, ↓**DBP** **Vagal Reflex Tachycardia** **Vasoconstriction** > vasodilation ↑TPR, ↑**BP** Vagal Reflex Bradycardia	**ANAPHYLACTIC SHOCK**: ↑BP *(Type I HSR reaction)* **Bronchial asthma**: bronchodilation *Administered by **inhalation*** **Anaphylaxis**: bronchodilation **Anaphylaxis**: ↑BP	*Also binds α2 receptors* ***Adverse effects:** palpitation, restlessness, tremors, ↑BP, arrhythmia* ***Contraindicated in angina pectoris***
PHENYLEPHRINE α1>α2	**α1 agonist**	Blood vessels Radial muscle	**Vasoconstriction** (↑TPR, ↑BP) ↑PNS Vagal activity → ↓**HR** **(Vagal Reflexive Bradycardia)** Dilation of iris – **mydriasis**	**Nasal decongestant** Hypotensive states Mydriatic	*Has no β1 agonist action so it has no effect on pulse pressure* 
CLONIDINE	α2 agonist	Brain (CNS)	Inhibition of SNS Suppresses NE release of presynaptic α2 receptor	*Mild to moderate* **HTN**, ADHD *Severe pain, heroin withdrawal, ethanol dependence*	*Excellent oral bioavailability* *Transdermal preparation available* ***Adverse effects**: sedation, bradycardia, **Rebound HTN** if you suddenly stop dosing*
α-METHYLDOPA	α2 agonist	Brainstem (CNS)	Inhibit SNS output + ↓BP Blocks Dopa Decarboxylase inhibiting NE & DA synthesis	**HTN** in pregnancy	*Converted to α-methylnorepinephrine by dopamine β-hydroxylase (indirect)*

***Remember:** β-receptors are more sensitive than α-receptors, and thus non-selective adrenergic agonists will generally activate β first.

★*See Hexamethonium under Nicotinic Antagonists – Looking at the graphs, always look at Hexamethonium 1st. It will knock out the entire autonomic nervous system (PNS, SNS), so there will NOT be any reflexes (reflex bradycardia or reflex tachycardia)!*

Green = Kaplan, Deja Review, Tulane Question

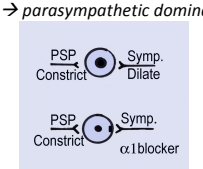
SYMPATHETIC NERVOUS SYSTEM – Sympathomimetic: β Agonists, Mixed Agonists, + Dopamine

DRUG	RECEPTOR	LOCATION	ACTION	INDICATIONS	NOTES
ISOPROTERENOL β1=β2	β1 agonist β2 agonist	SA Node Ventricle Skeletal muscle arterioles	↑SV +Inotropy (**↑PP**) **↑HR: Reflex Tachycardia** Vasodilation: ↓TPR, **↓DBP**	AV heart block (β1) Asthma: bronchodilator (β2)	***Adverse effects:*** *flushing, angina, arrhythmias*
DOBUTAMINE β1>β2	β1 agonist	Heart	↑ Contraction (↑CO) *Can have Reflex vasodilation* *Weakly ↑HR*	**Acute heart failure** – *↑CO in **CHF** without affected RBF* Cardiogenic **shock**	*Does not act on dopamine receptors*
ALBUTEROL FORMOTEROL SALMETEROL TERBUTALINE	β2 selective agonist	Skeletal muscle Bronchioles	Arteriolar vasodilation Bronchodilation *Greater affinity for β2 receptors in the lung than β1 receptors in the heart.*	Asthma	*Albuterol – fast acting* ***Salmeterol** – slow acting* ***Adverse effect:** stimulation of **<3**; acts like EPI, so may have tachycardia;*
RITODRINE	β2 selective agonist		Relaxation of uterus	Uterine relaxant; prevent premature labor	
EPHEDRINE	Mixed α & β agonist	CNS	Acts directly on receptors + Indirectly releases NE	Bronchial asthma Hypotension after spinal anesthesia Urinary incontinence Tachyphylaxis ***Cannot be mixed with MAO-A inhibitors → hypertensive crisis***	*Effective orally – resistant to MAO* ***Crosses the BBB – CNS stimulation***
AMPHETAMINE	Indirect adrenergic agonist, reuptake inhibitor, *'releaser'*	CNS	Activates RAS – *wakefulness* Competitively inhibits DA transport + Interferes with VMAT → **↑NE levels**	ADHD, Narcolepsy Alertness, ↑concentration, ↑work capacity ***Cannot be mixed with MAO-A inhibitors → hypertensive crisis***	*Orally active* *CNS action more prominent* ***MODAFANIL** has weak amphetamine-like effects; also elevates hypothalamic histamine levels*

LOW DOSE DA **MOD. DOSE DA** **LARGE DOSE DA** D>β>α	D1 β1 α1	Renal blood vessels Heart	↑cAMP: vasodilation +Inotropic & + chronotropic action Vasoconstriction	Renal failure with shock	*Receptor specific is dose-dependent*
FENOLDOPAM	Dopamine-1 (D1) agonist			HTN crisis	

Green = Kaplan, Deja Review, Tulane Question

SYMPATHETIC NERVOUS SYSTEM – α Blockers/Antagonists

	DRUG	RECEPTOR	ACTION	INDICATIONS	NOTES
α BLOCKERS	**PHENOXY-BENZAMINE (PBZ)**	Irreversible (non-competitive) **non-selective** α blocker	↓TPR, ↓**BP** **Potential Reflex Tachycardia** Postural Reflex interference – **postural hypotension*** Promotes urinary outflow Failure of ejaculation *In patients in shock, **infuse α1 blocker with NE** to prevent vasoconstriction & Reflex Bradycardia which leads to **tissue necrosis** & more damage*	**Pheochromocytoma**: *↑NE & hypertensive crisis; PBZ is the DOC because it's irreversible!*	*In the presence of PBZ, EPI will show a reversal in blood pressure from high to low.*
	PHENTOLAMINE	Reversible (**competitive**) **non-selective** α blocker		Pheochromocytoma Acute HTN – **i.e. WINE & CHEESE EFFECT OF TYRAMINE WHEN ON MAO INHIBITORS**	
	PRAZOSIN TERAZOSIN DOXAZOSIN	Reversible selective **α1** blocker		HTN **Benign Prostatic Hyperplasia:** *α1 blockers relax sphincters to help with urinating in BPH pts*	***Adverse effects of α1 blockers:*** ***Miosis**: inhibit sympathetic tone to pupil → parasympathetic dominant*  ***Nasal congestion**: dilate blood vessels in nose + ↑mucus gland secretion* ***Sexual dysfunction**: no ejaculation* **UPRIGHT POSITION: high sympathetic tone, marked fall in BP*
	TAMSULOSIN **SILODOSIN**	Reversible selective **α1A** blocker		BPH Tamsulosin facilitates bladder emptying by removing inhibitory action of the sympathetics *Tamsulosin has less cardiovascular side effects than traditional α1 antagonists*	
	YOHIMBINE	Selective **α2** blocker (CNS prejuctional)	↑NE release/exocytosis	Postural HTN Impotence	
	MIRTAZAPINE	Selective **α2** blocker (PRE-SYNAPTIC)		Depression, Anorexia	***Adverse effects:** weight gain*

**Selective α1 antagonists have less reflex tachycardia than non-selective α antagonists*

****Non-selective α-blockers produce "Epi reversal" & turn it into an "Isoproterenol-mimic" (β1 & β2 agonist).**

Green = Kaplan, Deja Review, Tulane Question

SYMPATHETIC NERVOUS SYSTEM – β Blockers (OLOL)

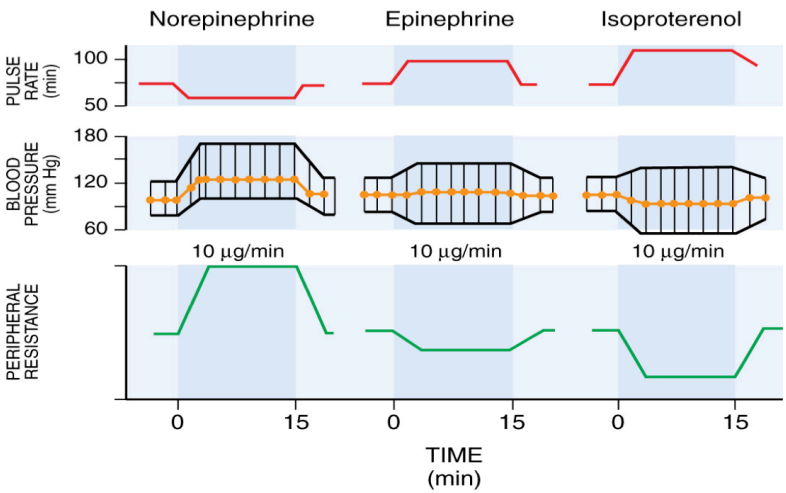
β BLOCKERS *Cornerstone of **CAD** therapy – except prinzmetal's angina (β blockers or high doses of ASA can cause vasospasm)* ***Standard therapy for unstable/stable angina & HTN + MI*** ***Major anti-arrhythmic group of drugs***	**LABETALOL** CARVEDILOL	**MIXED** non-selective **β + α1** blocker **Blocks same receptors as Epi (α1, β1, β2)*	↓Renin release → ↓angiotensin II → ↓TPR → ↓aldosterone → ↓edema	Most popular drug in **CHF** – *low dose & in mild/moderate cases* Mild HTN	***Adverse effects:** *bronchospasm in asthmatic, AV block + bradycardia, cold extremities, **dyslipidemia** (long-term use of METOPROLOL/ATENOLOL), sexual dysfunction or impotence* **BE CAUTIOUS IN DM!** *β blockers block warning signals due to counter-regulatory effects of catecholamines during hypoglycemia; delays recovery form hypoglycemia* *****β1 blocker benefits > risks in diabetes & MI***
	PROPANOLOL *Extensive 1st pass metabolism & oral bioavailability is low.* *TIMOLOL	**Non-selective** β blocker *(N→Z non-selective)*	**Heart: neg. inotropy/chronotropy**, ↓AV conduction **β Blockers have little effect on normal resting heart, but have profound effects when SNS control is dominant during stress/exercise* ***Eye:** ↓intraocular tension via ↓aqueous humor production **CNS**: sedation, lethargy, depression, sleep disturbances **Skeletal muscle:** antagonizes EPI & induces tremors (β2) **Respiratory Tract:** bronchoconstriction*	Hyperthryoidism: *Propanolol is the only β-blocker that inhibits deiodinase (inhibits T_4 → T_3)* Migraine prophylaxis ***Chronic Simple Glaucoma:** *↓secretion of aqueous humor* ***Contraindicated in diabetics, patients with PVD, & asthmatics.***	
	ATENOLOL ESMOLOL **METAPROLOL**	Cardio-selective **β1** blocker *(β1>β2)*	Negative ionotropic action Inhibit Reflex Tachycardia	**Preferred use in CAD & DM** Bronchial asthma *Atenolol is non-sedative β-blocker because does not cross BBB*	

Use of **glucagon through G_s coupled receptor is the best treatment for β-blockage overdose*

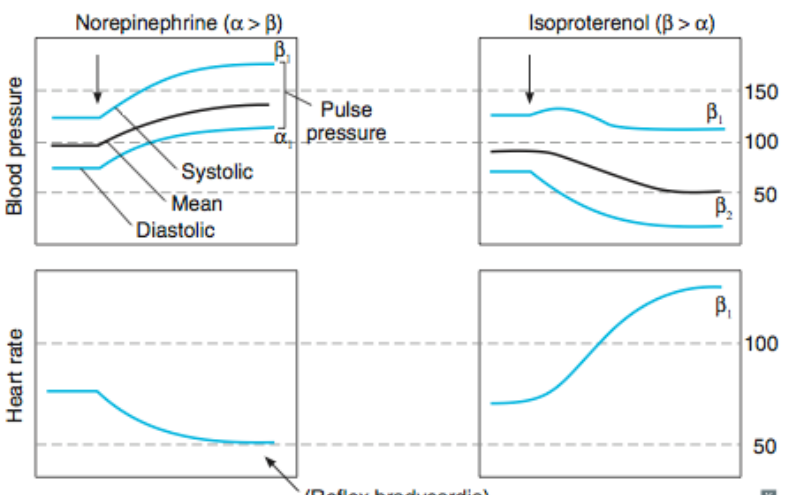
β-blockers that start with the letter A-M are **β1 selective.

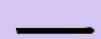
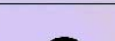
Green = Kaplan, Deja Review, Tulane Question

BLOOD PRESSURE CURVES



Drug	Agonist Action (Control)	Agonists Blocked	Agonist Action After Propranolol (β1 = β2)
Epinephrine	α1, β1,β2	~~α1, β1, β2~~	α1
Norepi	α1, β1	α1, ~~β1~~	α1
Isoproterenol	β1, β2	~~β1, β2~~	0
Phenylephrine	α1	α1	α1



Adrenergic Agonist	Control	α1 Blocker	β1 & β2 Blocker
Iso-proterenol β2			
Epi Hig Dose α1>β2			
NE α1			

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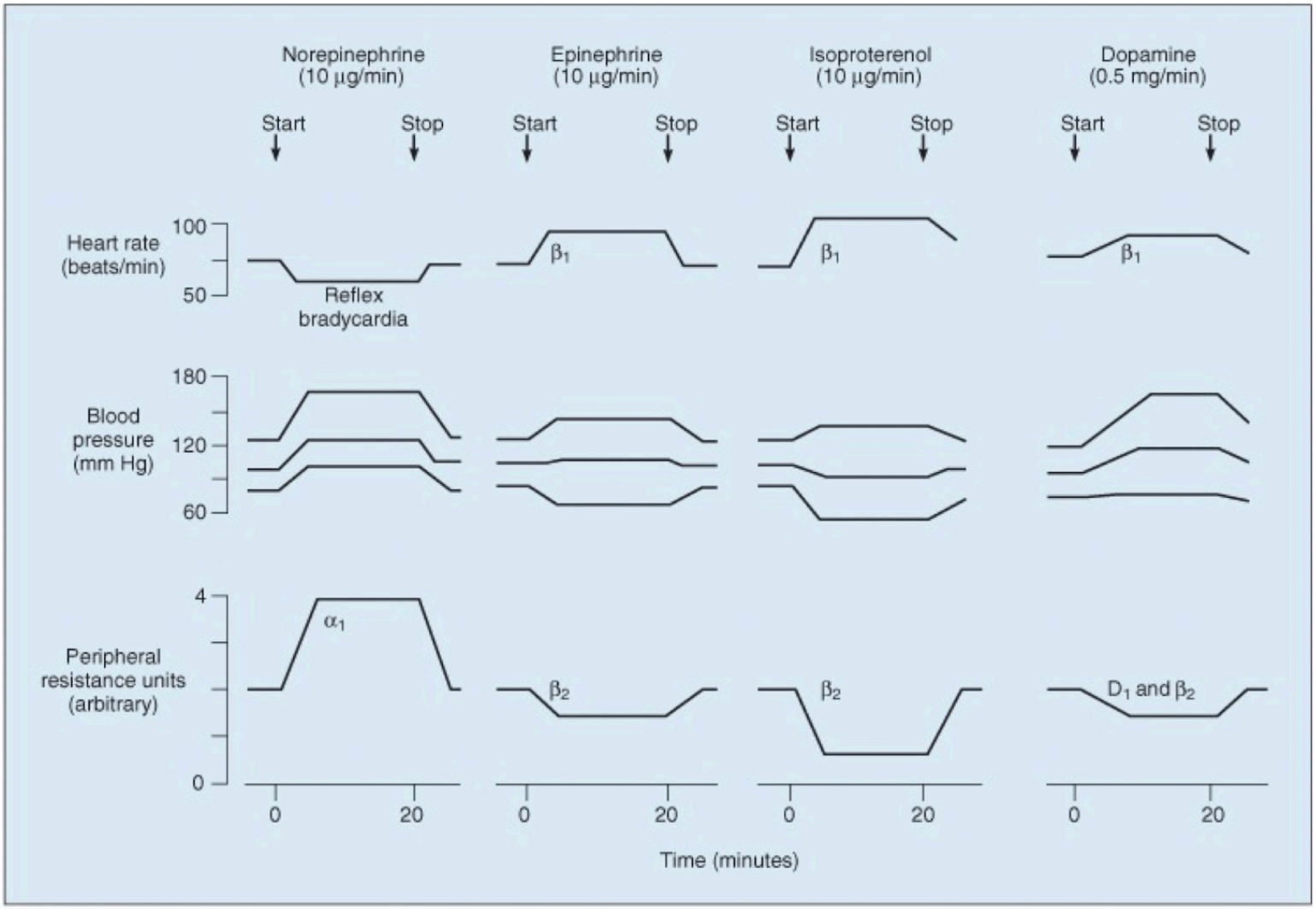
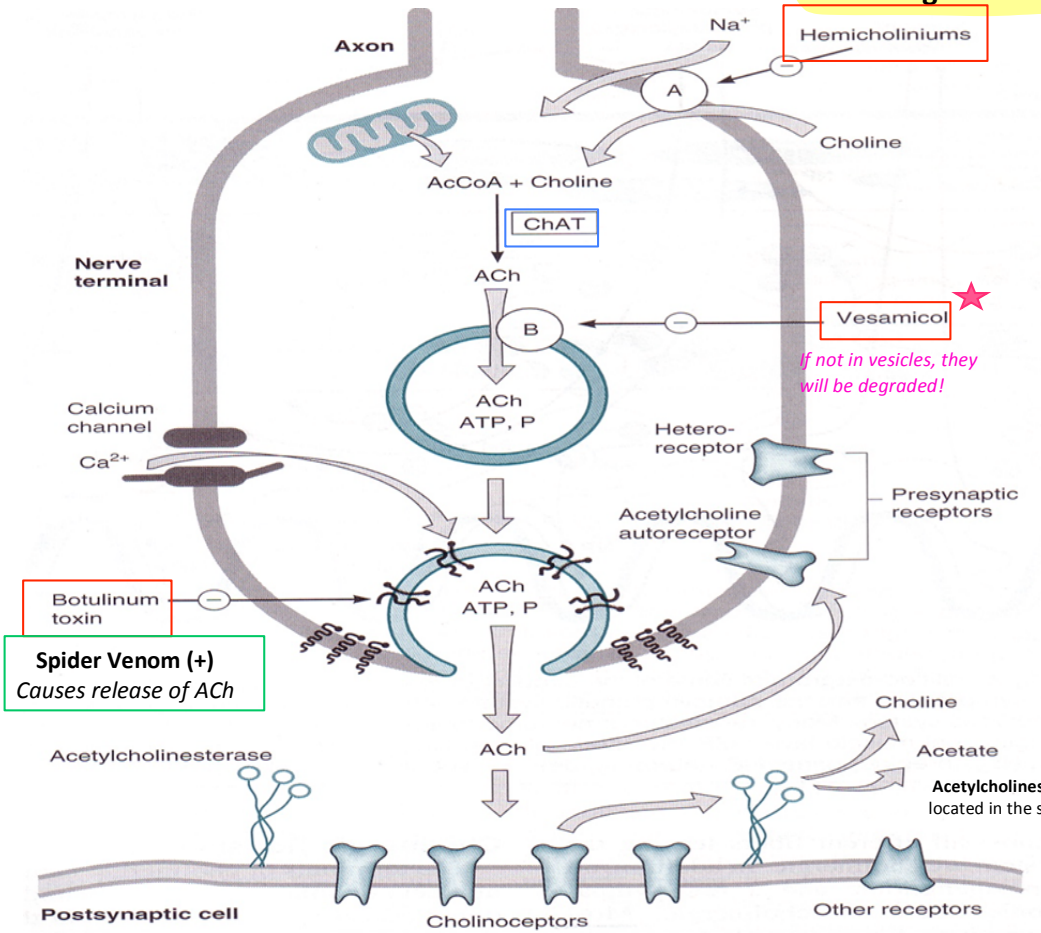
Comparison of the CV effects



PARASYMPATHETIC NERVOUS SYSTEM – Cholinergic Neuroeffector Junction



If not in vesicles, they will be degraded!

HEMICHOLINIUM – inhibits transport of choline from the ECF into the cytoplasm of a cholinergic neuron

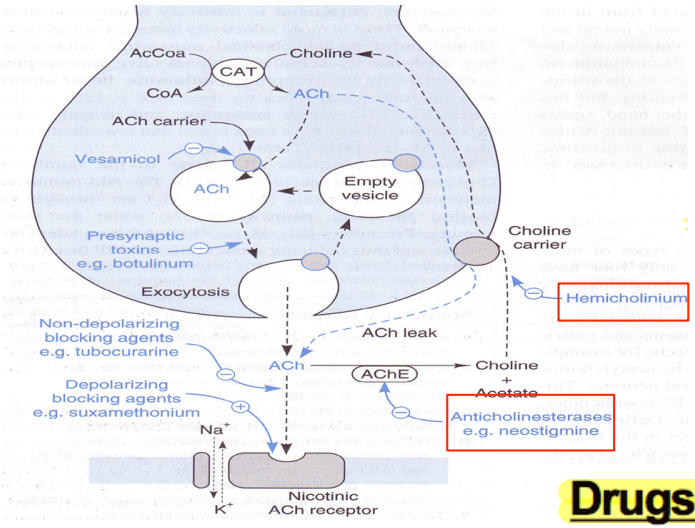
VESAMICOL – inhibits transport of Ach into synaptic vesicles

BOTILINIUM TOXIN – inhibits the neuronal release of Ach into the synapse

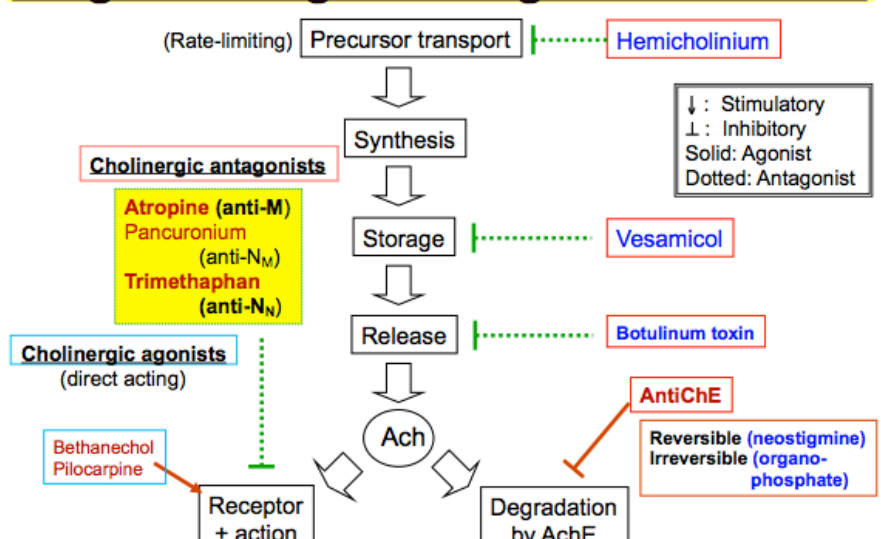
SPIIDER (Black Widow) VENOM – INCREASES the release of stored Ach into the synapse

Acetylcholinesterase (AChE) degrades Ach & is located in the synaptic cleft.

Green = Kaplan, Deja Review, Tulane Question



Drugs Affecting Cholinergic Transmission



Green = Kaplan, Deja Review, Tulane Question

PARASYMPATHETIC NERVOUS SYSTEM – Cholinergic Receptors

RECEPTOR	M1	M2 <3	M3	M4, M5
MECHANISM	G_q (↑IP_3/DAG/Ca^{2+}, phosphorylation) *Stimulated by muscarine* *Blocked by atropine*	G_i (↓cAMP, dephosphorylation) *Stimulated by muscarine* *Blocked by atropine*	G_q (↑IP_3, DAG, Ca^{2+}) *Stimulated by muscarine* *Blocked by atropine*	
LOCATION	**CNS** neurons, gastric parietal cells	**Heart** (myocardium, SA Node) Smooth muscles	Smooth muscles Bladder Exocrine glands (**sweat glands – thermoregulatory**) GIT (gastric parietal cells – *also M1*) Eye	CNS
ACTIONS of ACh		**↓HR** (neg. chronotropy) ↓Cond. vel. (neg. dromotropy)	**BV endothelium**: dilation via NO **No innervation, but **ACh-induced Nitric Oxide Mediated Vasodilation** from DIRECT administration of ACh* **GIT:** ↑ tone & peristalsis, ↑ secretions **Causes intestinal contractions → diarrhea & involuntary defecation* **LUNGS**: **Bronchospasm**, ↑secretions **EYE**: **miosis, accommodation for near vision**, & ↑outflow of aqueous humor & reduction in intraocular tension **– *this is why anti-cholinergics are contraindicated in glaucoma*** **URINARY BLADDER:** contraction of detrusor & relaxation of trigone/sphincter **Causes voiding & urinary incontinence* **GLANDS:** ↑ secretion of sweat, saliva, & lacrimation	Complex CNS responses: memory, arousal, attention, analgesia

**Odd numbers are G_q coupled:* M1, M3, M5
**Even numbers are G_i coupled:* M2, M4

****For dilation of pupils, use α1 agonists instead of M3 antagonists because M3 antagonist will cause blurry vision!***

RECEPTOR	Nicotinic Nerve (N_N)	Nicotinic Muscle (N_M)
MECHANISM	Open Na^+/K^+ Channels – ***No second messengers!***	
LOCATION	Postsynaptic neurons in ganglia of PNS & SNS, Adrenal Medulla, CNS	Neuromuscular Junction
ACTIONS	N_N of Ganglia: Stimulation of PNS & SNS *(net effect depends on dominance)* N_N of Adrenal Medulla: Secretion of EPI & NE **Important for BP/HR Reflexes**	Contraction of skeletal muscle (twitch/hyperactivity)
ANTAGONIST ★	Hexamethonium, Trimethaphan, Mecamylamine – ***blockers*** *Primarily **used for lowering BP**; blocking autonomic NS reflexes.* ***Ganglionic blockers will block a reflex brady/tachycardia after a vasoconstricting/dilating agent is given (α1, β2 agonist), but it will NOT block a directly induced brady/tachycardia by a β1 or M2 agonist!***	Succinylcholine – ***depolarizing neuromuscular blocker*** Tubocurarine, Pancuronium, Rocuronium, Mivacurium – ***nondepolarizing NMB*** *(endotracheal intubation, relax skeletal muscles during surgery, facilitate ventilation in ICU patients)*

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PARASYMPATHETIC NERVOUS SYSTEM – Direct Cholinomimetic Drugs

DRUG	RECEPTOR	LOCATION	ALL ACTION = DUMBBELSS	INDICATIONS	NOTES
ACETYLCHOLINE *Major NT*	Muscarinic & Nicotinic agonist		Neuron depolarization → influx of Ca^{2+} ions → exocytosis of ACh Synthesized by **ChAT**	**No therapeutic implications** – diffuse action (more adverse effects) & rapid hydrolysis	*Choline Ester* *Metabolized by **acetylcholinesterase** & butyryl cholinesterase*
METHACHOLINE	Muscarinic agonist	Lungs	↓HR	**DIAGNOSIS of bronchial hyperactivity & ASTHMA condition** – *has no effect in patients without asthma!* **Very short lived so not very useful therapeutically**	*Choline Ester*
CARBACHOL ***Resistant to AChE***	Non-selective **MUSCARINIC & NICOTONIC AGONIST** *Can release EPI from adrenal medulla*	GIT & Urinary bladder	Miosis – constriction of pupil	**Glaucoma – ↓IOT** (MIOTIC) *EYE DROP – *not absorbed into the blood so no systemic side effects*	*Choline Ester* *At doses used for ophthalmological purposes, **little or no side effects** due to lack of systemic penetration*
BETHANECHOL ***Resistant to AChE***	**MUSCARINIC AGONIST** ***No nicotinic actions***	GIT & Urinary bladder	Stimulates **atonic bladder** (M3) ↓ G_q	**NON-OBSTRUCTIVE** urinary retention – *neurogenic bladder* (postpartum/postoperative) Congenital megacolon Paralytic ileus	*Choline Ester* ***Adverse effects:** cholinergic overacting (sweating, salivation, flushing, ↓BP, nausea, abdominal pain, diarrhea, bronchospasm)*
PILOCARPINE ***Resistant to AChE***	Muscarinic agonist ***No nicotinic actions***	Eye **Penetrates CNS at therapeutic doses (uncharged)**	Applied topically to the cornea to produce rapid miosis & contraction of ciliary muscle **(spasm of accommodation – near vision)** +M3 → Miosis → ↑outflow of Aqueous Humor = ↓IOP	**Emergency lowering of IOT of both *narrow-angle* & *wide-angle* GLAUCOMA** (EYE DROPS) Promotes salivation in patients with **Xerostomia** resulting from **irradiation** of head & neck & **Sjogren's Syndrome**	*Tertiary amine (CNS entry)* ***Adverse effects:** profuse sweating (diaphoresis) & salivation; can enter brain & **cause CNS disturbances – convulsion with high doses***

Choline Esters – poorly absorbed from the stomach, poor lipid solubility, poor BBB penetration; *short-lived*

Cholinesterases { acetyl → SYNAPSE
pseudo → PLASMA

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Inhibit Acetyl Cholinesterase = ↑ACh in the Synapse

PARASYMPATHETIC NERVOUS SYSTEM – Indirect Cholinomimetic Drugs (AChE Inhibitors)

DRUG	MECHANISM	ALL ACTION - DUMBBELSS	INDICATIONS	NOTES
EDROPHONIUM *Short-acting*		**Duration: 10-20 minutes**	**DIAGNOSIS of Myasthenia Gravis (TENSILON TEST)** **Differentiates myasthenia from cholinergic crisis** **Reverse effects of competitive NMJ blockers*	
NEOSTIGMINE *Intermediate-acting carbamate* 4° Amine → No CNS action	**REVERSIBLE AChE inhibitor** *Stimulates muscarinic & nicotinic sites by ↑ concentration of ACh;*	**Duration: .5-2 hours**	Paralytic ileus/Congenital megacolon Urinary retention **MYASTHENIA GRAVIS** **Antidote for Tubocurarine** (& competitive NMJ blockers)	Quaternary amine (no CNS)
PYRIDOSTIGMINE *Long-acting*		**Duration: 3-6 hours (P)**	**CHRONIC MYASTHENIA GRAVIS!!!** Urinary retention Paralytic ileus/Congenital megacolon	
PHYSOSTIGMINE *Intermediate-acting carbamate* 3° Amine → enters CNS	**REVERSIBLE AChE inhibitor** *Can cross BBB*	**Duration: 2-4 hours**	**Glaucoma**: miosis; ↓IOT (EYE DROPS) **Bladder & intestinal atony**: ↑intestinal & bladder motility **Antidote in Atropine OD:** DOC bc crosses the BBB ★	Tertiary amine (enters CNS) **Naturally occurring alkaloid** Oral absorption is good ***Adverse effects:*** *convulsions*
DEMECARIUM	REVERSIBLE AChE inhibitor		Chronic open-angle & closed-angle glaucoma	Quaternary amine (no CNS)
TACRINE **DONEPEZIL** **RIVASTIGMINE** **GALANTAMINE**	REVERSIBLE AChE inhibitor CEREBROSELECTIVE		**Alzheimer's Disease** *"Will come again when we discuss this disease."*	Lipid soluble (CNS entry)
ORGANO-PHOSPHATES PARATHION MALATHION DIAZINON (TIK-20) SOMAN **SARIN** TABUN	ORGANOPHOSPHATES = Irreversible Inhibitors of AChE (by Phosphorylation) **IRREVERSIBLE AChE inhibitors** *Insecticide: Parathion/Malathion* *Nerve gas poison: Sarin*		**Acute Organophosphate Toxicity** ***Muscarinic effects: DUMBBELSS*** *Diarrhea, Urination, Miosis, Bradycardia, Bronchoconstrict, Excitation (CNS+Muscle), Lacrimation, Salivation, Sweating* **IMMEDIATE ANTIDOTE: ATROPINE*** ***Nicotinic effects:*** *skeletal muscle excitation followed by paralysis + CNS stimulation*	**ANTIDOTE: PRALIDOXIME*** **(Cholinesterase Reactivator)**
ECHOTHIOPATE (ORGANOPHOSPHATE)		Generalized cholinergic stimulation, paralysis of motor function (breathing difficulties), & convulsions **Intense miosis**	Chronic open-angle glaucoma: miosis **(Only use when nothing else works; not 1st line treatment. The *ONLY organophosphate that is used therapeutically*. And it does NOT cause cycloplegia!)**	*Potential risk of cataracts limits the use of Echothiphate* **ANTIDOTE: PRALIDOXIME**

TOXICITIES TO KNOW

① ★**Organophosphates irreversibly inhibit AchE** – Phosphate group covalently binds to serine-OH group in the active site of AchE, thus rendering the enzyme permanently inactive. **ATROPINE** counteracts the muscarinic & CNS effects of OP poisoning by protecting muscarinic receptors (competitive inhibition) from increased levels of Ach & thus preventing overstimulation. Atropine is given ASAP. **PRALIDOXIME** (2PAM) is used to **REACTIVATE** the inhibited AchE. It should be given *before the "aging" process* of the organophosphate-AchE complex is complete (within 24 hours). *Pralidoxime binds to the anionic site of AchE – this is why it will not work for carbamate poisoning because the anionic site is not open in carbamates.*

② Mushroom toxicity → Muscarinic Agonist ⟹ DUMBBELSS → Rx: Atropine

③ Atropine toxicity → Anti-DUMBBELSS

Competitive Muscarinic Antagonist = Reversible by ↑ACh (will compete w/ Atropine) → Give AChE⊖ = PHYSOSTIGMINE

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PARASYMPATHETIC NERVOUS SYSTEM – Anti-Cholinergic: Muscarinic Blockers (TROP)

DRUG	RECEPTOR	ACTION	INDICATIONS	NOTES
ATROPINE	**Muscarinic antagonist** *CNS & peripherally*	– **HEART:** **tachycardia** (blocks M2 on SA Node), AV conduction; ***NO MARKED EFFECT ON BP*** – **EYE:** **mydriasis** + ***cycloplegia*** *(paralysis of accommodation by blocking M3 =* **BLURRY VISION***)* – **GIT:** peristalsis inhibited = **CONSTIPATION** – **BRONCHUS:** dilation – **URINARY BLADDER: URINARY RETENTION** – **GLANDS (M3):** ↓**SECRETION** of salivary glands, sweat glands, tracheobronchial tree, **STOMACH ACID**, & lacrimal gland; ↑**body temperature**-**FEVER** (detrimental in children) – **CNS (HIGH DOSES):** restlessness, excitement, hallucinations, disorientation –	**Organophosphorus poison + Pralidoxime** **Pre-anesthetic medication**: to dry up secretions to prevent aspiration Bradycardia (Acute MI) ***Contraindicated in glaucoma & urinary retention (esp. BPH patients)***	Tertiary amine (enters CNS) Absorbed from the GIT Freely penetrates the cornea Half life = 4 hours ***Adverse effects:*** **"Dry as a bone, Red as a beet, Hot as a hare, Blind as a bat, Mad as a hatter"** *Antidote in atropine poisoning is Physostigmine (AchE inhibitor)*
SCOPALAMINE	Muscarinic antagonist	Inhibits vestibular disturbances	Motion sickness (TRANSDERMAL PATCH)	*Scopalamine differs from atropine in its longer duration of action & more potent CNS effects.*
IPRATROPIUM	Muscarinic antagonist	*SEE ASTHMA & COPD CHARTS	Bronchial asthma & COPD	
TROPICAMIDE	Muscarinic antagonist		Mydriatic & cycloplegic agent for **opthalmoscopic examinations**	
BEZTROPINE **TRIHEXYPHENYDYL**	Muscarinic antagonist CNS		**Parkinson's Disease** – *the tremors in Parkinson's are due to overactive ACh – this is why you give anti-muscarinic* Drug-induced extrapyramidal dysfunction	*Will learn in CNS Pharm*
IMIPRAMINE	Blocks NET	Blocks reuptake of NE	Tricyclic antidepressant (TCA)	
CHLORPROMAZINE			Antipsychotic agent	
DIPHENDYDRAMINE	Histamine (H_1) blocking			

Atropine & Atropine-like drugs used for: antispasmodic (slow gastric motility), antisecretory (pre-anesthetic medication), bradycardia

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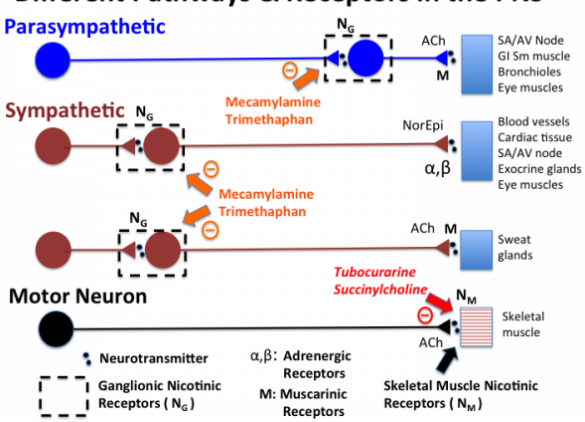
No 2nd messengers

PARASYMPATHETIC NERVOUS SYSTEM – Anti-Cholinergic: Nicotinic Blockers

DRUG	RECEPTOR	LOCATION	ACTION	INDICATIONS	NOTES
HEXAMETHONIUM **TREMETHAPHAN**	**Competitive N_N ganglionic blocker**	Preganglionic	Ganglionic blocker of PNS + SNS → *reduces the predominant tone* ★ – Blocks **REFLEX bradycardia** from α1 agonistic (Phenylephrine) vasoconstriction or REFLEX tachycardia from β2 agonistic vasodilation (Isoproterenol)		***Adverse effects:*** *orthostatic HTN due to blocking of reflexes*
MECAMYLAMINE	**N_N ganglionic blocker**			Moderate to severe HTN Anti-addictive drug	
BOTULINUM TOXIN	N_M blocker	Postganglionic	Blocks ACh release; **Spasmolytic** Degrades **SNAP-25**: req'd for vesicular fusion & ACh release *Block ACh release = flaccid paralysis of skeletal muscle + reduced activity of cholinergic synapses*	Direct acting muscle relaxant: Chronic migraine prophylaxis Blepharospasmep Cervical dystonia Hyperhydrosis Several cosmetic surgeries	***COMPLICATION: Respiratory paralysis***
SUCCINYLCHOLINE	N_M blocker ***Behaves as cholinergic agonist***	Post-ganlionic	Remains bound to receptor for prolonged period of time. Depolarizes NMJ Inhibits muscle contraction	*Endotracheal intubation*	*Short-acting due to rapid hydrolysis by plasma cholinesterases*
TUBOCURARINE	Competitive N_M antagonist		Blocking nicotinic receptors at NMJ	*Pre-surgical drug that produces skeletal muscle relaxation*	*Antidote in Tubocurarine overdose Is Neostigmine (AchE inhibitor) – increases Ach concentration which competes with tubocurarine at NMJ)*

Different Pathways & Receptors in the PNS



GANGLIONIC BLOCKING AGENTS (HEXAMETHONIUM, MECAMYLAMINE) – *Block predominant tone*

SITE	PREDOMINANT TONE	EFFECT OF GANGLIONIC BLOCKADE
Arterioles	Sympathetic (adrenergic)	Vasodilation; increased peripheral blood flow; hypotension
Veins	Sympathetic (adrenergic)	Dilation: peripheral pooling of blood; decreased venous return; decreased cardiac output
Heart	Parasympathetic (cholinergic)	Tachycardia
Iris	Parasympathetic (cholinergic)	Mydriasis
Ciliary muscle	Parasympathetic (cholinergic)	Cycloplegia—focus to far vision
Gastrointestinal tract	Parasympathetic (cholinergic)	Reduced tone and motility; constipation; decreased gastric and pancreatic secretions
Urinary bladder	Parasympathetic (cholinergic)	Urinary retention
Salivary glands	Parasympathetic (cholinergic)	Xerostomia
Sweat glands	Sympathetic (cholinergic)	Anhidrosis
Genital tract	Sympathetic and parasympathetic	Decreased stimulation

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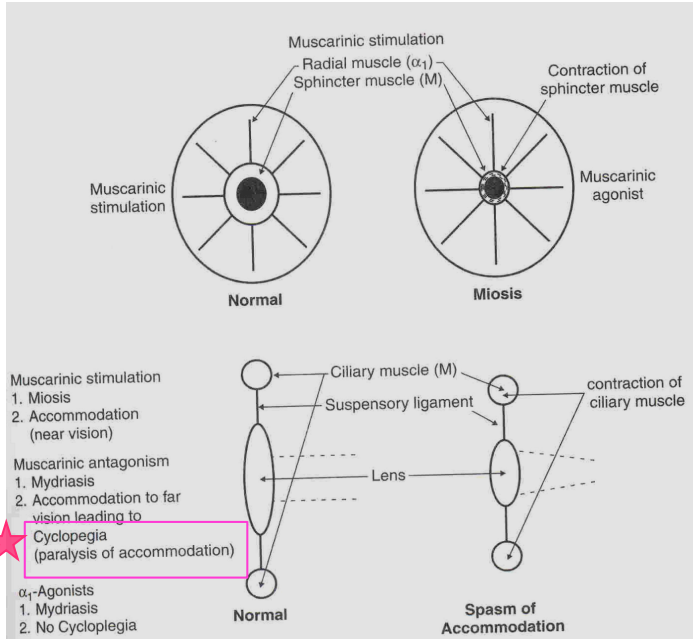
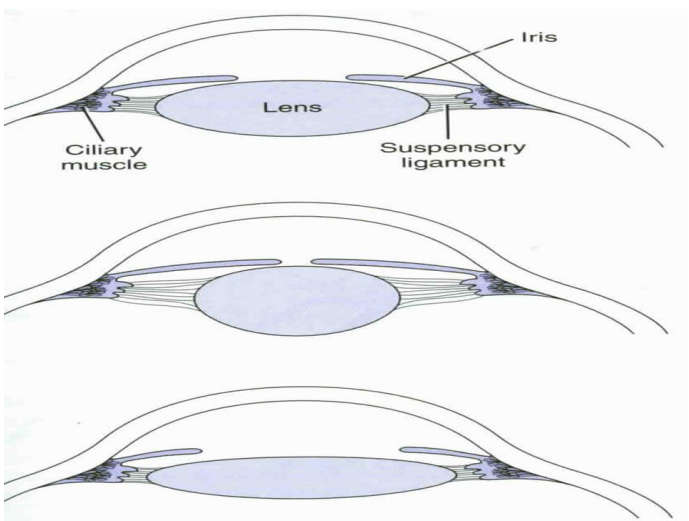
AUTONOMIC NERVOUS SYSTEM – Pupillary Size/Accommodation Reflex



MIOSIS

Constriction of Sphincter Muscle
Muscarinic Agonists
Anticholinesterases

Relaxation of Radial Muscle
α1 Adrenergic Antagonists
Adrenergic Neurone Blockers



MUSCARINIC AGONIST
Miosis & Spasm of Accommodation

MUSCARINIC ANTAGONIST
Mydriasis & Cycloplegia

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GLAUCOMA

The angle refers to the area between the iris & the cornea, through which the aqueous humor must flow to escape via the trabecular meshwork.

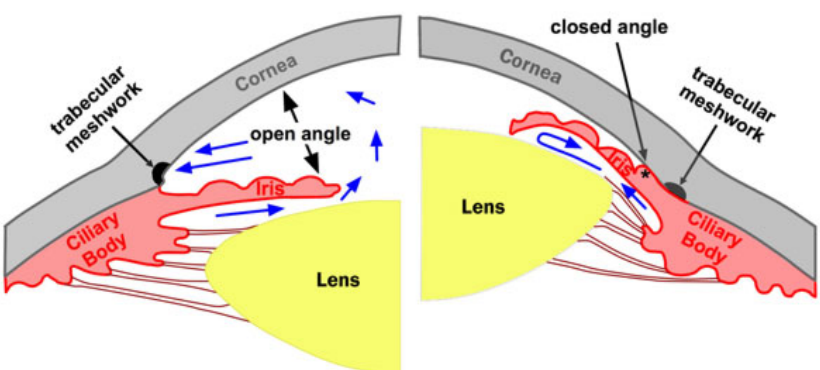
OPEN/WIDE-ANGLE tends to progress at a slower rate & patients may not notice they have lost vision until the disease has progressed significantly.

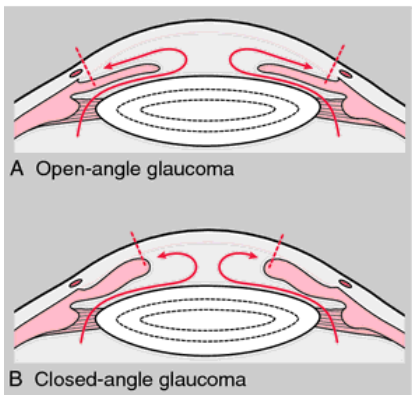
- Topical **Pilocarpine** *(muscarinic agonist)* is the DOC for emergent reduction of IOT – *muscarinic agonists cause constriction of the pupil (miosis), which increases the angle and allows for better outflow of aqueous humor, thus decreasing the intraocular pressure.*
- **Carbachol** (*muscarinic agonist)* is also indicated in treatment of glaucoma.

CLOSED/ACUTE-ANGLE can appear suddenly & is often painful.

- Topical **Pilocarpine** *(muscarinic agonist)* is the DOC for emergent reduction of IOT – *muscarinic agonists cause constriction of the pupil (miosis), which increases the angle and allows for better outflow of aqueous humor, thus decreasing the intraocular pressure.*
- Topical β-blocker (i.e. **Timolol**): β-blockers reduce intraocular pressure by decreasing production of aqueous humor

Anti-muscarinics (atropine) can precipitate an emergent situation in patients with narrow-angle glaucoma. Anti-muscarinics will cause mydriasis (dilation of the pupil), which will in turn push the iris back, decreasing the angle, and blocking the outflow of aqueous humor (fluid). This would result in an increase in intraocular pressure, a medical emergency.





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