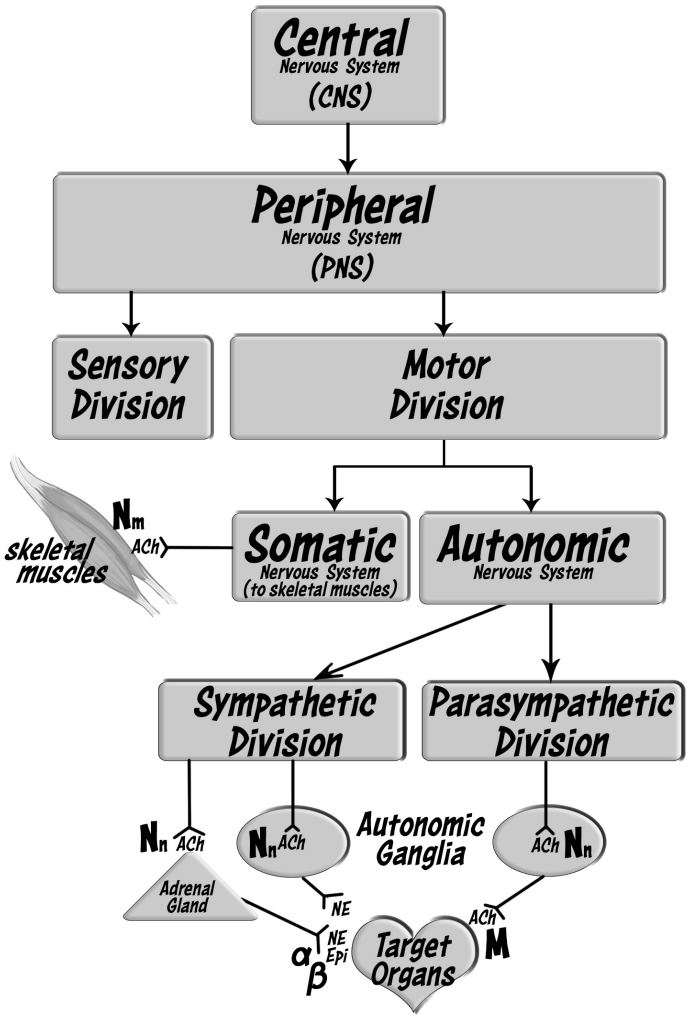
AUTONOMIC NERVOUS SYSTEM

FIRST: PLEASE see/review "GIRL IN THE FOREST" VIDEO at YouTube.com/TaiChiKnees and the relevant Crash Course A&P Lectures

Central Nervous System (CNS)
brain + spinal cord
&
Peripheral Nervous System (PNS)
Sensory + Motor Nerves

Somatic Nervous System
skeletal muscles (acetylcholine binding nicotinic Nm receptors)

Autonomic Nervous System (ANS)
(involuntary) smooth and cardiac muscle
Tissue that can work on its own
(example: frog heart muscle in a dish)
The body only *regulates* how fast/strong the target organ works.



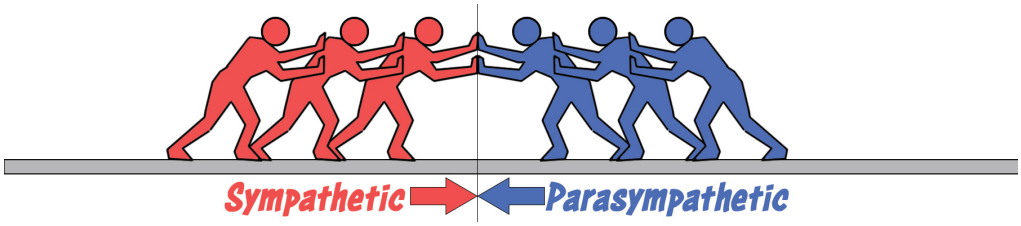
Autonomic Ganglia:
LIGAND: Acetylcholine
RECEPTORS: nicotinic Nn cholinergic
(Note: That is for ganglia going to both the symp. and parasymp. systems!)

Sympathetic NS:
LIGANDS: Norepinephrine & Epinephrine
RECEPTORS: alpha and beta adrenergic

Parasympathetic NS:
LIGAND: Acetylcholine
RECEPTORS: muscarinic M cholinergic

Homeostasis: Maintenance of a stable environment by a tightly regulated balance between different processes in the body.

The Sympathetic vs. Parasympathetic systems are in a perpetual **shoving contest** to control most major organs in the body; both are required constantly to maintain homeostasis.



Adrenergic (alpha & beta) vs. Cholinergic (M)

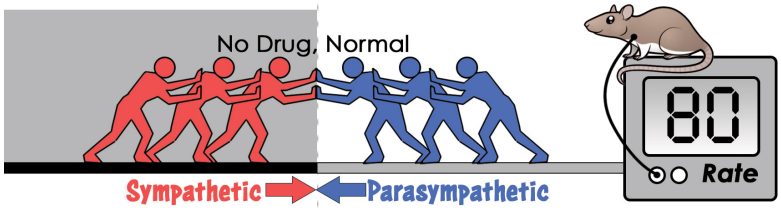
Because of the constant conflict between the homeostatic adrenergic and cholinergic forces on autonomic target organs, the effects of agonists and antagonists are intimately entwined.

Let's do a thought experiment to illustrate this.

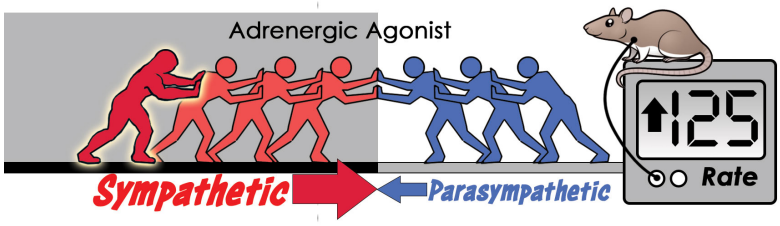
Heart rate speeds up when NE binds beta-1 receptors in the heart (sympathetic).
Heart rate slows down when ACh binds M receptors in the heart (parasympathetic).

So let's measure the heart rate of my pet Beepbeep the Rat every morning for five days after administering one of four drugs.
(We'll do it once a day so we don't have to worry there will be more than one drug in his system at a time.)

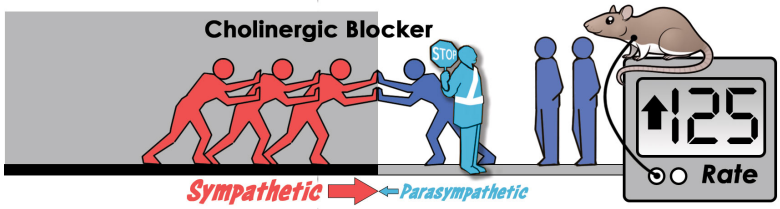
Monday:
At rest the two systems balance and Beepbeep's heart rate is 80.



Tuesday:
If we give Beepbeep a **beta-1 agonist** like dobutamine, the sympathetic side is boosted, and even though the parasympathetic side is no different, the sympathetic side wins.
Heart rate **increases**.

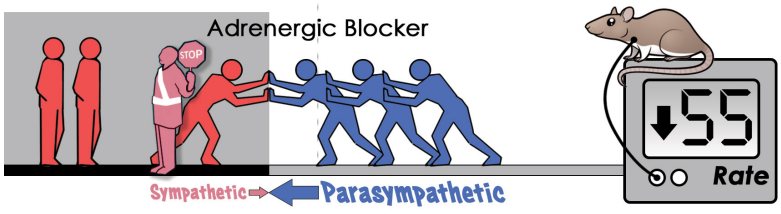


Wednesday:
Today we give Beepbeep atropine, an **anticholinergic**. Now the sympathetic system is behaving normally as it was on Monday, but the parasympathetic side is inhibited, so the sympathetic side wins. Heart rate **increases.**



Thursday:
This morning we administer methacholine, a direct-acting **cholinergic agonist**. Although the sympathetic system's strength is the same as it was Monday or Wednesday, the parasympathetic side is so much stronger that it wins. Heart rate **decreases.**

Friday:
For our last experiment, we give Beepbeep atenolol, a **beta-1 blocker.** The parasympathetic system has returned to normal, but the sympathetic side is inhibited. Parasympathetic side wins.
Heart rate **decreases.**



As you can see, the **effects of a sympathetic agonist = cholinergic antagonist** and the **effects of a sympathetic antagonist = cholinergic agonist,** even though the mechanism of action (and receptors bound) are different! *That's so cool!*

**A normal rat's heart beats extremely fast, but I'm pretending here the rate is more like that of a human!*

Another way we could show the results of our thought experiment would be the table to the top right.

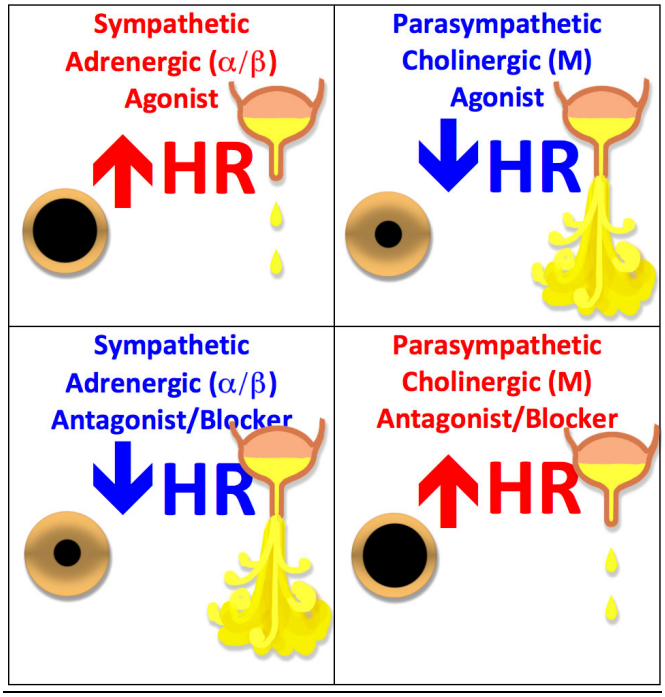
Notice that although the receptors and neurotransmitters involved are completely different in the sympathetic vs parasympathetic side, the net effect of the sympathetic agonist will be the same as the parasympathetic antagonist.

For Heart Rate, the sympathetic action is via beta-1 receptors. The parasympathetic action is through M-2 receptors. So totally different ligands and receptors, but so beautifully complementary!

Sympathetic Adrenergic (α/β) Agonist ↑HR	Parasympathetic Cholinergic (M) Agonist ↓HR
Sympathetic Adrenergic (α/β) Antagonist/Blocker ↓HR	Parasympathetic Cholinergic (M) Antagonist/Blocker ↑HR

You can make a similar table for ALL of the autonomic receptors, target organs and actions.

For example, you can do this with pupil size, or urine flow, or any autonomic action. So now you only have to remember 1/4 the amount of actions of the four drug classes. If you know one, you know them all! Yay!



Critical Thinking: How could we make someone's heart beat even unnaturally faster with drugs?
Answer: Give a Beta-1 agonist + an anticholinergic drug. That would be faster that either drug alone. Right? Of course right!
(The same idea goes for making a patient have ultra-wide pupils: give an alpha-1 agonist + anticholinergic eyedrop!)

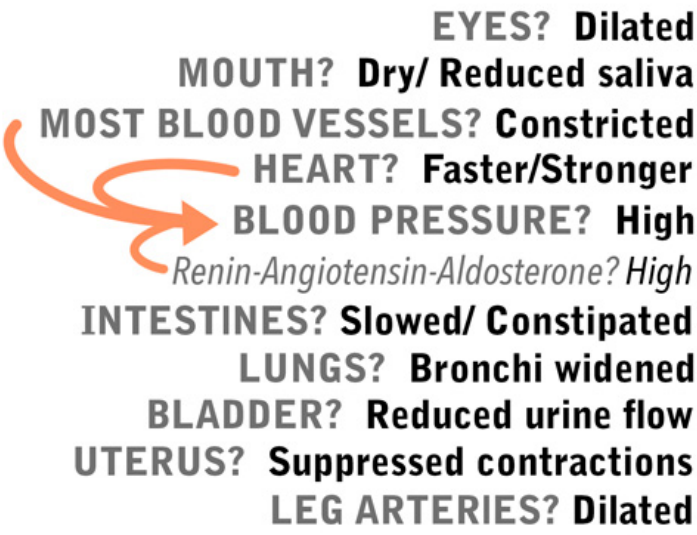
Nomenclature: You may have already noticed that talking about the **Sympathetic** (Fight or Flight) vs **Parasympathetic** (Rest and Relaxation) systems can be confusing because of redundant nomenclature:

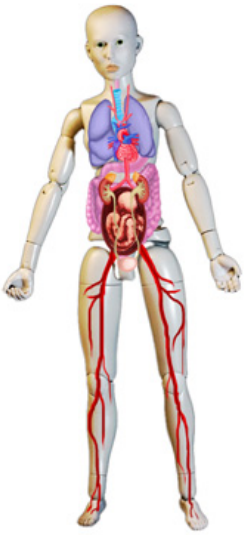
Terminology and Phrases that **mean the same thing**
(the bold-faced terms are the most commonly used terms in modern healthcare)

FIGHT OR FLIGHT Sympathomimetics **Adrenergics** Sympathetic Agonists **Alpha- or Beta-agonists**	**REST & RELAXATION** Parasympathomimetics **Cholinergics** Cholinergic Agonists Parasympathetics
BLOCKERS of FIGHT OR FLIGHT Sympatholytics **Anti-adrenergics** Sympathetic Antagonists Sympathetic Blockers **Alpha- or Beta-blockers**	***BLOCKERS of REST & RELAXATION*** Parasympatholytics **Anticholinergics** Cholinergic Antagonists Parasympathic Antagonists Parasympathetic Blockers

FIGHT OR FLIGHT: SYMPATHETIC NERVOUS SYSTEM:

Imagine a pregnant lady in the forest being chased by a bear at dusk. What happens?
If you can remember this, then you will know almost all the actions of the sympathetic nervous system (and therefore sympathetic agonists).





Sexual Function: Women: Excitement (Parasympathetic), Orgasm (Sympathetic)
Men: Erection (Parasympathetic), Ejaculation (Sympathetic)
*(mnemonic: **P**oint and **S**hoot)*
Note that either sympathetic or parasympathetic blockers can potentially screw up sexual function!

Alertness: Increased with sympathetic stimulation *(Right? Be awake when in danger!)*

Sweating is super weird: The nerves are anatomically sympathetic nerves but they release acetylcholine *(huh?)*
Fortunately there aren't any drugs directed towards sweating yet, so don't worry about it for now…

Terms you should already know:
vasodilation = dilation/widening of blood vessels
vasoconstriction = constriction/narrowing of blood vessels

SYMPATHETIC SYSTEM *(Fight or Flight):*
Norepinephrine, a neurotransmitter, and Epinephrine, a hormone.

Since the **site of action of a drug is determined by the receptor that "catches" that drug out of the bloodstream**, it is easiest to **group the actions of each drug by the TYPE of RECEPTOR it binds**:

MAJOR SYMPATHETIC RECEPTORS on autonomic target organs

TYPE OF RECEPTOR	MAJOR EFFECTS
ALPHA -1* (NE and Epi both bind)	**CONSTRICTS** LEAST CRITICAL BLOOD VESSELS And therefore **INCREASES ⇑ Blood Pressure (BP)** Does most all sympathetic "stuff" other than heart, lung & uterus: Decreases secretions of sinuses – *dries sinuses* Dilates pupils of eyes: *glaucoma risk* Decreases GI secretions: *dry mouth* Decreases GI motility: *constipation* Reduces urine flow from bladder (⇓ bladder *wall* tone ⇑*sphincter* tone)
BETA-1 *(beta-1 receptors are all about blood pressure)* (NE and Epi both bind)	**INCREASES HEART** RATE And increases heart contractility **INCREASES KIDNEY** hormone (renin) to increase **angiotensin** (vasoconstriction through angiotensin receptors) and **aldosterone** (increased water retention in blood vessels via aldosterone receptors) to **increase blood pressure**
BETA-2 (Epi only)	**LUNG**: **dilates** bronchioles (to **widen breathing passages**) **UTERUS: relaxes** uterus to stop contractions (to **stop labor**) Dilates **major SKELETAL ARTERIES** (i.e. legs)

* (There are also "Alpha-2" receptors which mediate NE re-uptake and decrease NE output… *hrm… confusing: another example of the weirdness of receptor subclasses*. Don't worry about this for now; we'll talk about these again in the hypertension unit…)

It turns out that the natural ligands norepinephrine, epinephrine (and weirdly dopamine) all bind the different types of adrenergic receptors with slightly different **affinities.**
SO: NE binds only alpha-1 and beta-1
Epinephrine binds alpha-1, beta-1 *and* beta-2.

The fact that there are different types of receptors helps us in terms of **drug design,** because we can choose which organs we want to target, right? *(See my receptor subtype video)*

The **Adverse/Side Effects** of a given drug class are simply due to activation of receptors on various target organs.

> For example: Since alpha-1 receptors occur in the nonessential vessels inside your nose, if you take an alpha-1 agonist like phenylephrine for a runny nose, you'll also get activation of alpha-1 receptors elsewhere and your side effects will be: high blood pressure (other nonessential vessels), constipation, reduced urinary flow, dry mouth, etc.

So how do we predict what the SYMPATHETIC ***ANTAGONISTS*** will do?

***Direct*-acting** competitive antagonists (we call those α-blockers and β-blockers) *block* the action normally caused by those receptors when NE or Epi bind.

Remembering that the body always tries to maintain homeostasis, blocking those sympathetic agonists leads to the opposite effect, not by any magical means, but just by ***unleashing*** the parasympathetic system (as we saw in our thought experiment with Beepbeep on page 2!).

In other words, when we take away the sympathetic component of the body by blocking its action, the parasympathetic system is free to shove as hard as it likes. So the *clinical* result we see in the patient taking sympathetic blockers is that they display parasympathetic effects.

So, what we call the autonomic *antagonist's* "drug effect" is really the "body's effect."
Go back and look at page 2. Make sure you have this absolutely down; if you know this, then the blood pressure/reflex heart rate aka "dog lab" questions will be easy and you'll be far better prepared for the Heart Drugs and life as a nurse in general!

A NOTE ABOUT DRUGS THAT AFFECT BLOOD PRESSURE

Drugs that affect blood pressure generally cause your body to reflexively try to correct that change a.k.a. push towards homeostasis.
(Remember, the first and ***fastest*** way your body responds to a change in blood pressure is by increasing or decreasing heart rate!)

Two crucial reflexes to mention before we talk about the drugs themselves:

1. Reflex tachycardia (reflexive increase in heart rate) is mediated by firing of sympathetic fibers emerging from the paravertebral sympathetic ganglia (between C2-C7).

> **Reflex tachycardia** occurs when baroreceptors (blood **pressure sensors**) in the **carotids** and aorta **detect a drop in blood pressure**. They stimulate the sympathetic system to increase heart rate, bringing the blood pressure back up to normal.

2. Reflex bradycardia is mediated by the vagus nerve (aka Cranial Nerve X).

> **Reflex bradycardia** occurs when baroreceptors (blood **pressure sensors**) in the **carotids** and aorta **detect an increase in blood pressure**. They stimulate the parasympathetic system to reduce the heart rate, bringing the blood pressure back down to normal.

The vagus nerve (aka cranial nerve X) is the most important nerve of the parasympathetic nervous system that we will talk about in this course.

> The vagus nerve is the only thing that *acutely* keeps your blood pressure in check. Imagine that you are being chased by a bear in the forest, and your sympathetic nerves (NE) and adrenal glands (Epi) are *really* revved up, and squirting out 100% NE & Epi levels. This means your blood pressure would skyrocket and your heart would be beating >200 times a minute. This would be very counterproductive, because once your blood pressure got over 300 or so, you'd burst a blood vessel in your brain and drop dead. Think of it as a safety valve for the fear response.

Reflex tachycardia and reflex bradycardia are the fastest way your body can react to changes in blood pressure, **reacting within one heartbeat** of a BP change! The system is so sensitive that just

the tiny change in blood pressure caused by breathing in and out causes the heart rate to go up and down every time you take a breath. (Go google "sinus arrhythmia" and prepare to have your mind blown.)

Every other process in your body is geared toward increasing your blood pressure. Only the wee little **vagus,** reducing your heart rate **through acetylcholine binding M_2 receptors**, actively pushes your blood pressure down. That's because you can have high blood pressure for a lifetime, but only a few seconds of low blood pressure can mean loss of consciousness and death!

Some example problems

1. If you give an alpha-1 agonist like phenylephrine (that causes vasoconstriction of nonessential vessels and increases BP), your vagus nerve kicks in and slows heart rate (reflex bradycardia) to drive BP back down.

2. If you give a patient an alpha-1 blocker like prazosin (that causes vasodilation of nonessential vessels and therefore drops BP), your body will react by increasing heart rate (reflex tachycardia) to drive BP back up.

So, if a **drug** causes a **blood pressure increase**,
your **body** *(via vagus nerves)* slows your heart rate ***(reflex bradycardia)***
to **decrease blood pressure** back to normal

If a **drug** causes a **blood pressure drop**,
your body (via *sympathetic plexus nerves)* speeds up your heart rate ***(reflex tachycardia)***
to **increase blood pressure** back to normal

When determining the effect of blood pressure drug **combinations**, determine **in this order:**

1) the DRUGS' combined effects on blood pressure
2) the BODY's REFLEX heart rate reaction will be to the BP change caused by the drugs
3) check to see if the body can have the reflex. In other words:
   If the reflex should be tachycardia, be sure there is no beta-1 blocker present.
   If the reflex should be bradycardia, be sure there is no M2-blocker (anticholinergic) present
   If the reflex will be blocked then the reflex cannot occur.

Why are we spending time talking about this? What does a little acute change in heart rate mean to my clinical practice?

Real Life Example: Say you have an older patient Maria who is taking a prescribed beta-1 blocker every day for migraines. One day, she has chest pain and her son takes her to the emergency room. The nurse there gives her a SL nitroglycerin tab because of suspected angina/MI (heart attack). Maria puts the tab under her tongue, stands up to go to the bathroom, passes out, hits her head, gets a concussion with a bleed in the brain and dies. The autopsy shows she had heartburn and the nurse and hospital are sued. What happened?

Answer: Well, let's work through the problem of combined propranolol and nitroglycerin

1) propranolol blocks beta-1 and beta-2 receptors; she takes it every day
   block beta-1 receptors: lowers heart rate - drops BP a lot
   blocks RAAS - drops BP a lot
   block beta-2 receptors: constricts essential vessels a tiny bit: raises BP a tiny bit
   nitroglycerin: dilates coronary vessels and other vessels a lot: drops BP a lot
   Overall: Big drop in blood pressure
2) The **reflex** to a big drop in blood pressure will be to have reflex **tachy**cardia
   Reflex tachy is mediated by NEpi binding Beta-1 in the heart so I have to be sure that can happen.
3) I check for anything blocking beta-1 receptors. Uh oh, that propranolol blocks beta-1!

So the answer here is that there will be a big drop in BP and no reflex change in Heart Rate to balance it. So when Maria stood up to go to the bathroom, her blood pressure was already very low, and standing up dropped that last little bit and she passed out and hit her head. The nurse should have made her lie back or insisted she not get up. The lawsuit will be successful. (Alas, patients often don't listen when you tell them not to get up...)

Remember that these are natural physiologic reflexes that kick in when you administer a **drug**. A drug is an artificial thing. Your body wasn't evolved to deal with pharmacology!

In the *normal* situation, when no drugs are around, and you're in fight-or-flight because of fear or being chased by a bear, sympathetic stimulation leads to increased blood pressure **AND** heart rate, because all the norepinephrine released by sympathetic nerves binds alpha-1 **AND** beta-1!

Norepinephrine vs. Epinephrine:
NE, the *neurotransmitter*, binds alpha-1 and beta-1 receptors after being *released at nerve endings.*

Beta-1 agonists' most important action is to increase blood pressure, right? They
1. increase heart rate and contractility
2. increase renin, which in turn releases angiotensin, which also constricts ***non-essential*** blood vessels *(more on that later),* which in turn: releases aldosterone & ADH to increase blood volume *(more later)*

Epinephrine, the *hormone* (because it goes into the blood stream), activates alpha-1, beta-1 **AND beta-2** by circulating through the bloodstream. I think of epinephrine as only being secreted in more dire emergencies.

> Therefore, I think of beta-2 effects as those last ditch OMG-you're-gonna-die-actions your body wouldn't want to do otherwise: dilating essential vessels (which normally would drop BP), stopping a baby delivery from the uterus, and throwing the bronchi wide (which you wouldn't want to do at rest, because you'd have to take way deeper breaths).

Extra fun happy fun time eye talk with Dr. Boyev, Board-Certified Ophthalmologist:
Eplanation with diagrams of why you shouldn't dilate eyes in patients with glaucoma, and therefore use alpha-1 agonists and anticholinergics with caution in those patients:

http://www.hopkinsmedicine.org/wilmer/glaucoma_center_excellence/book/sec_acg.html

...well, I think it's fun... ;-)

The point is, that when your eyes dilate the iris crumples up like a blanket shoved into the gap under a door to keep out a cold draft. The iris blocks the outflow of the fluid in the eye and it builds up, increasing pressure in the eye and pressure on the optic nerve. Like any nerve, the optic nerve will die if it gets pressed on long enough, and the blindness can be permanent. It also can go unnoticed by the patient because it starts from the outside in. So the patient won't notice it until they accidently run over some toddler they didn't see because they had no side vision. Symptoms of angle closure vary with severity of the attack and can run from mild nausea to severe redness and pain in the eye and vomiting. It is easily treated by an eye surgeon with a lazer, but is an emergency. Always keep this in mind when a patient is taking ANYTHING that can cause anticholinergic or alpha-1 agonist actions. Sometimes the medication is what causes the problem for the first time!

Examples of direct-acting **sympathetic agonists**:

These effects (and side effects) and contraindications should all make sense now… You need to know the drugs in bold-face type.

DRUG CLASS	**Actions**	Drugs	**Indications/ Therapeutic Effect**	**Contra-indications**	Notes*
Alpha-1 Agonists	Constricts nonessential blood vessels, dilates pupils, increases BP, reduces urine flow, causes constipation, CNS effects are activating (can keep people awake and jittery)	**pseudoephedrine** *(Sudafed)* Schedule V in Illinois	Used for **runny nose** (by constricting the blood vessels of the mucous membranes, it lowers leakage)	**Heart disease High BP BPH Glaucoma MAOI***	Topical α-1 agonists cause intense vaso-constriction of small blood vessels, they should ***never be used for more than 2-3 days,*** because in many cases the body will grow new blood vessels!!
		phenylephrine (same drug!) eye or nasal drops (*Neosynephrine*)	To **dilate pupils** or help **runny nose**		
		phenylephrine *(PO: Sudafed-PE)* (IV*: Neosynephrine)*	In cold remedies, To increase BP in **shock** patient or to LOWER heart rate in **arrhythmia** (how?)	Beware extravasation when using IV!	
		tetrahydrazoline drops (*Visine*)	Dilated blood vessels on eyes **(red eyes)**		
Beta-1 Agonists	Increases Heart rate and contractility Increases renin/ angiotensin/ aldosterone	**dobutamine (IV)**	Used in patients who are in **shock**		
		dopamine (IV)	Used in patients in **shock** or codes: Low doses: constricts blood flow to everywhere **but brain and kidney.** High doses: Constricts all blood vessels.		**Dopamine binds its own "D" receptors & weirdly also β-1 receptors** when given at therapeutic doses
Beta-2 Agonists	Relax Lung Bronchioles Relax the Uterus	**albuterol** (*Ventolin*) salmeterol *(Advair)*	**Bronchodilator** "		May cause reflex tachycardia *(How?)*
		metaproterenol (*Alupent*)	Bronchodilator **&** used to **arrest pre-term labor**		
Nonspecific β-1&β-2 Agonist	Stimulates heart/renin & Bronchodilates	**isoproterenol** (*Isuprel*)	Bronchodilator (inhaled or PO)	Cardiac Ischemia (Angina)	**Older drug**. Used for certain arrhythmias
Nonspecific a-1 and b-1 Agonist	Increases BP by vasoconstriction, increased HR and Renin-A-A	IV **norepinephrine** *(Levophed)*	severe drops in BP, shock		NE **must** be diluted and injected into a **large** vein
Non-specific α−1 β−1 β−2 **agonists**	α−1 β−1 β−2	**Epinephrine** ⇑SystolicBP ⇓DiastolicBP ⇑Heart Rate	Used in **cardiac arrest**, **anaphylaxic** shock (Epi-pen), severe acute **asthma**. **Used surgically** to reduce bleeding at surgical sites		Yippee! A great drug because it is a great **rescue** hormone in the body.
	α−1,β−1, β−2	ephedrine	Asthma, narcolepsy, hypotension, myasthenia		Schedule IV in Illinois

*Remember alll ANS drugs potentially screw up sexual function. Note also alpha-2 and beta-3 receptors exist ; more on that later

Examples of direct-acting **sympathetic antagonists** (a.k.a. sympathetic blockers):

DRUG CLASS	Actions	Drugs	**Indications**	Contra-indications	Side Effects (opposite of the agonist effects!)
ALPHA BLOCKERS α1-blocker	Lower Blood Pressure Increase peripheral circulation (Raynaud's Disease) Increase bladder function Increase urinary flow Treat pheochromocytoma Reverse skin necrosis (due to extravasation of vaso-active drugs such as NorEpi)	**prazosin** (*Minipress*) **terazosin** (*Hytrin*) doxazosin alfuzosin **phentolamine** (*Regitine*) "	**Hi BP** (Blood Pressure) **Hi BP** **BPH** (Benign ProstateHypertrophy [drug ⇑s Urinary flow] BPH/Hypertension BPH Pheochromocytoma **Skin necrosis** (due to extravasation of vaso-active drugs)	low blood pressure ("**1st dose syncope**")	orthostatic hypotension, runny nose, constricted pupils, increased salivation, increased urine flow, diarrhea, sexual dysfunction
DRUG CLASS	Actions	Drugs	**Indications**	Contra-indications	Side Effects
Beta-1 Blockers	Reduce heart rate and contractility of heart, leading to a net drop in blood pressure. Also decrease renin release from kidneys & resets baroreceptors to lower BP	**atenolol** *(Tenormin)* metoprolol (*Lopressor*) betaxolol *(Betoptic, Kerlone)*	Hi BP, angina, post-MI, anxiety, others High Blood Pressure angina, post-MI Glaucoma, High Blood Pressure, various Heart probs		orthostatic hypotension, reduced heart rate, reduced exercise performance in athletes, sexual dysfunction
Non-specific Beta-1&-2 Blockers	As above, but β-2 effects also (with concerns about lungs now an issue)	**propranolol** *(Inderal)*	High Blood Pressure Migraine Tremor Angina Post Heart Attack arrhythmias	DON'T USE IN Asthma/ COPD patients, Depression, Heart failure ""	difficulty breathing, depression, Erectile Dysfunction, orthostatic hypotension

*note: most beta-blocker names end with **–olol**

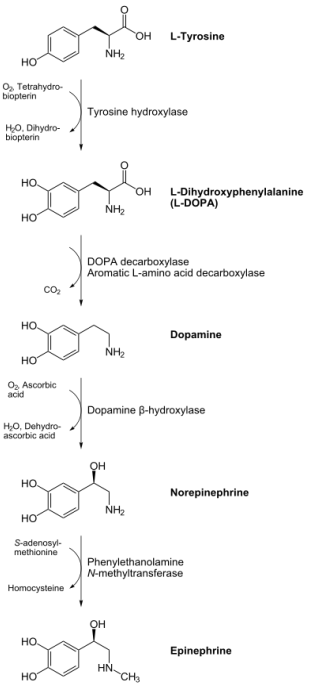
WEIRD alpha-blocker/ beta- blocker combo drugs	cannot always predict action	labetalol (*Normodyne*) **carvedilol** *(Coreg)*	High Blood Pressure Heart Failure		Weirdly helps damaged heart cells align properly

*Note: **all** alpha and/or beta agonists AND antagonists can potentially interfere with sexual performance and/or orgasm.*

Let's go back now to the release of NE from presynaptic nerves.

NE and Epi are catecholamines (aka monoamines), called so due to their similar chemical structure. Since the molecules are shaped the same, it shouldn't be a surprise that they bind some of the same receptors.

Dopamine
Norepinephrine (NE)
Epinephrine (Epi)
(Epi also = "adrenaline")

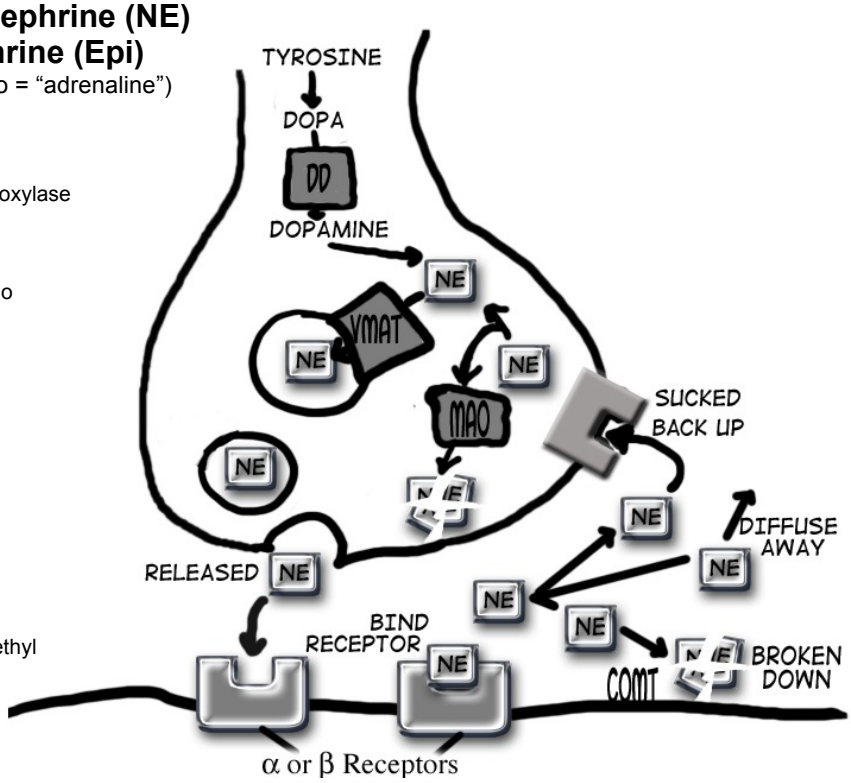


DD=Dopamine Decarboxylase

VMAT=Vescicular Mono Amine Transporter

MAO= MonoAmine Oxidase

COMT=Catechol-O-Methyl Transferase



So look at all the steps required to make norepinephrine!

So you can simulate or increase the action of Norepinephrine (NE) by:

1. Adding more NE (NE can be given I.V.!)
2. Using a drug that acts like NE (a *direct*-acting drug agonist)
3. Stopping the NE from being broken down (e.g. MAO or COMT Inhibitors)
4. Blocking re-uptake so the NE stays in the synaptic space longer (e.g. cocaine, amphetamine)
5. Inducing more NE to be released*, etc…*

Direct vs Indirect: The drugs we've listed on the preceding pages are **direct-acting drugs**; that is, they *directly* bind to the receptor of the natural ligand (in this case norepinephrine and/or epinephrine).

***Indirect*-acting drugs** do not act at the receptor. They **increase or decrease the amount of the natural ligand** (in this case **NE**) via a more indirect approach. Yes, there are ways to mimic or block the sympathetic system other than by binding receptors!

INDIRECT-ACTING* SYMPATHETIC *Agonists:

Amphetamine: Blocks re-uptake of NE (and dopamine) and also promotes release of NE from presynaptic nerves.

Cocaine: Blocks re-uptake of NE (and dopamine) into the presynaptic nerve.

MAOI = MonoAmineOxidase Inhibitor: A class of anti-depressant drugs that inhibits the enzyme MAO and therefore the breakdown of monoamines. By blocking the action of MAO the levels of NE rise. So, for example, MAOIs will increase blood pressure. (See the picture on page 3.) Because it inhibits MAO it leads to hypersensitivity to any type of sympathetic agonist. MAOIs must not be used with sympathetic agonists or disastrous increases in blood pressure can result in stroke. We'll visit this drug again in the CNS handout.

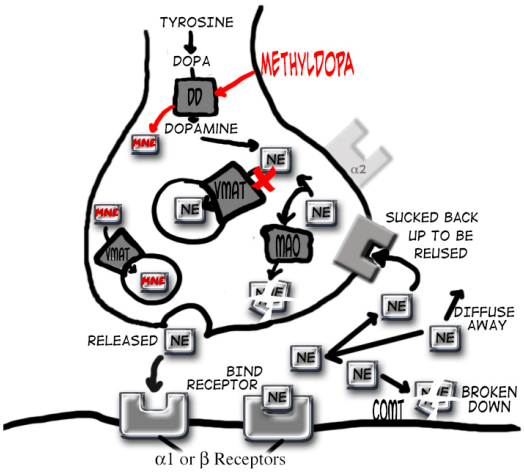
Tyramine: Tyramine is found in many types of food and acts indirectly in the brain to release any stores of norepinephrine. It is not a large effect but can be deadly when combined with MAOIs.

> *I hear you asking, "Wait, I thought agonists specifically bound receptors. These drugs screw around with synthesis and metabolism. WTF? - Yes, and this is a quirk of medical nomenclature. When you talk about direct acting drugs, you are definintely talking about receptor pharmacodynamics. But in CLINICAL PRACTICE, people group drugs by what happens to the patient when they take the drug, that is, what levels of ligand or drug go up or down in the body, and what the clinical efffect looks like. Sorry about that; it wasn't my idea. :-(*

INDIRECT-ACTING* SYMPATHETIC *Antagonists:

Indirect "Antagonists" (or "Blockers"): In contrast, the examples below are indirect antagonists. By reducing the available amount of NE they all lower blood pressure.

Examples:
methyldopa (*Aldomet*): makes "fake" NE, a "false transmitter" which gets into vesicles…So less room for NE, less NE, less NE activity



Concerning the α2 receptor: Let's worry about this later. The α2 receptor has nothing to do with the α1 receptor despite having a similar name. We'll revisit this in the blood pressure handout.

PARASYMPATHETIC SYSTEM *(Rest and Digest)*

Review the figure on page 1.

The main transmitter of the parasympathetic system is Acetylcholine (ACh).

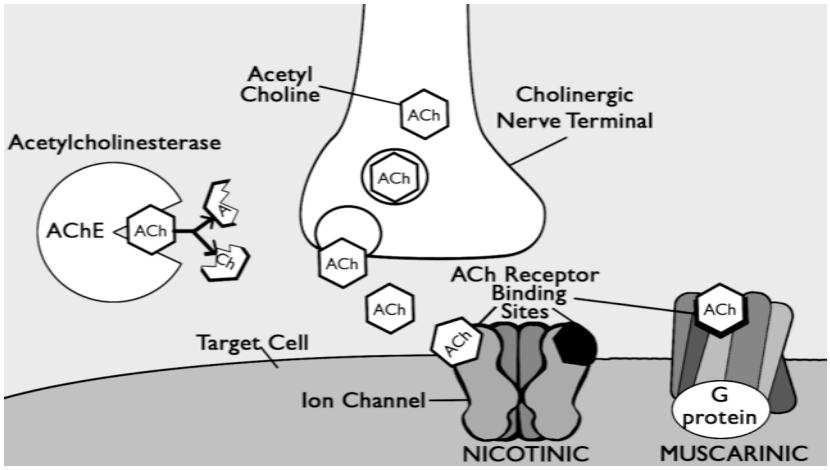
Acetylcholine is a neurotransmitter. ACh is made by nerve endings of the ganglia of both the parasympathetic and sympathetic system, as well as the post-ganglionic parasympathetic nerve endings on target organs. Ach is also the neurotransmitter for nerves for skeletal muscle, right? Since ACh receptors are all over your body,

ACh is *NOT* produced as a hormone and lasts only seconds in the bloodstream

Main classes of cholinergic (acetylcholine) receptors:

Nicotinic receptors are in skeletal muscle (**Nm**), brain and neurons (**Nn**) and are usually stimulatory.

Muscarinic receptors are only in the brain and in parasympathetic target organs (eye, stomach, lung, bladder, heart, pupil, etc). They come in 5 subtypes ($\mathbf{M_1}$-$\mathbf{M_5}$), but fortunately for you there aren't any useful subtype-specific drugs yet.



The actions of the parasympathetic system ***oppose*** those of the sympathetic system:

Increases GI motility (sphincter relaxation, gut contraction)
Increases GI secretions (drool, acid and enzymes)
Increases urinary flow (bladder contraction, sphincter relaxation)
Constricts pupils
Lowers heart rate (via the vagus nerve, remember?)
Lowers blood pressure (physiologically through heart rate, pharmacologically also through vasodilation)
Constricts bronchioles in lungs (and increases secretions)

Basically the cholinergic system makes you all wet and messy, because everything comes out of you!

A popular mnemonic for remembering the effects of the parasympathetic system is "SLUDGE":

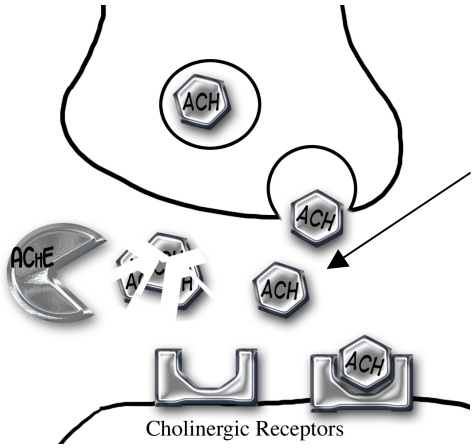
Personally I don't like "SLUDGE" because it doesn't mention small pupils, slow heart rate, shock and bronchoconstriction.
I like the visual of the poor exploding soldier to help

Salivation
Lacrimation
Urination
Defecation
GI Upset
Emesis

Acetylcholine ALSO plays an important role in the brain in memory formation, motor skills and other tasks and has important roles in Alzheimer's disease and Parkinson's disease (more on that later).

Cholinergic Nerve Ending (**Muscarinic *and* Nicotinic receptors; both bind acetylcholine**)

AcetylCholinEster**ase**



PARASYMPATHOMIMETICS (a.k.a. **Cholinergics,** Parasympathetic Agonists)
Note! All of the following types of drugs are, *clinically speaking,* cholinergic agonists:
That is ***they act LIKE Acetylcholine:***

Direct-acting Cholinergic Drugs

Indirect-acting **Anti**cholin**esterases**
Reversible Anticholinesterases
Irreversible Anticholinesterases

Don't get confused by the prefix "anti" you see here! These are, clinically speaking, all cholinergic agonists!

Indirect cholinergic agents increase levels of acetylcholine in the whole body.
So, keep in mind that indirect acting cholinergic drugs will lead to whole body Muscarinic stimulation, and ALSO Nicotinic receptor stimulation

...and don't forget: since current cholinergic agonist drugs non-specifically stimulate all Muscarinic Receptors (no distinction between M1-M5), they also have more side effects than our *sympathetic* specific alpha-1 agonists and beta-2 agonists did. *Why?*

Cholinergic Drugs (Parasympathetic agonists)

DRUG CLASS	Drugs	Indications/ Effects	Notes
Direct-Acting Cholinergics (drugs that non-specifically **bind the ACh M** receptor and stimulate it)	acetylcholine *(Miochol)* topical	Shrinks pupil in cataract surgery	ACh itself is too rapidly destroyed by cholinesterases in the bloodstream, so you can't use it systemically
	carbechol *(Ocupress)*	treats glaucoma shrinks pupil, increases aqueous outflow in eye	eye drops
	pilocarpine (Salagen)	treats glaucoma, dry mouth	topical for either indication
	bethanechol (*Urecholine*)	**i**ncreases urine flow; used for urinary retention after surgery or with spinal cord injury	luckily doesn't slow the heart too much *(how might you explain that?)* Mostly binds M-3 receptors
	methacholine *(Provocholine)*	constricts bronchial airways; used to diagnose occult asthma	only used in a hospital in testing
Indirect-Acting Reversible Acetylcholinesterase enzyme inhibitors "agonists" These inhibit AChE and thereby **increase the ACh concentration** at nerve terminals and in the body That ACh binds all the N and M receptors everywhere!	ambenonium *(Mytelase)* **neostigmine** *(Prostigmin)* edrophonium *(Tesilon)* **pyridostigmine** *(Mestinon)*	All used to diagnose or treat myasthenia gravis, autoimmune disease against Nm receptors.	When using these drugs for the first time to test for Myasthenia, a patient must be on a heart monitor, because you might induce severe bradycardia or even asystole; that is, the heart might beat dangerously slowly or even stop*! (Why?)* In order to minimize autonomic effects of increased ACh on M receptors, often prescribed with atropine. *(Why?)*
	rivastigmine *(Exelon)* galantamine *(Reminyl)* donepezil *(Aricept)*	Increases ACh in the brain to improve function in Alzheimer's Dementia	*If these help Alzheimers Dementia symptoms, then what does that suggest about the cause of the disease?*
	physostigmine *(Antilirium)*	use IV as antidote to overdoses anticholinergics	Can also use as antidote for anticholinergic syndromes caused by TCAs and phenothiazines (see CNS unit)

PLEASE NOTE the difference between the words: **Anticholinesterase and Anticholinergic**

Again: PLEASE NOTE the difference between the words:
Anticholinesterase and Anticholinergic

A note about **Irreversible Anticholinesterases (Irreversible Anti-AChEs)**

These are also cholinergic agonists, from a clinical point of view.
Irreversibly-acting Anticholinesterases are generally poisons, because they permanently inhibit AChE, and you have to wait until your body makes new AChE before you can break down Acetylcholine made all the time throughout your body.

One medically used Irreversible Anti-AChE is
echothiophate iodide *(Phospholine Iodide),* an eyedrop for glaucoma.

But ***most*** Irreversible AChEs are **poisons**. Like the organophosphates.

Organophosphates:
Some **pesticides** and **nerve gas** like "Sarin" nerve gas
They act irreversibly, not competitively by covalently phosphorylating the AChE enzyme so that it is unable to bind Acetylcholine.

Cause a **"cholinergic crisis"** due to massive rise in ACh everywhere in the body
massive S-L-U-D-G-E + low HR + low BP + bronchoconstriction + small pupils

In high enough concentrations ACH will blow out not only the **M**uscarinic receptors, but the **N**icotinic receptors too, and paralyze muscles (including breathing muscles!)

To treat an organophosphate poisoning:
1. ….Can you guess? Right! You would treat them with an anticholinergic. In fact, you might use ***atropine!*** (Atropine is a potent nonspecific anticholinergic that will help block Ach receptors in your whole body!)

2. **oximes:** You also treat *organophosphate poisoning specifically* with **pralidoxime** *(Protopan)*, a drug that removes the phosphate group covalently added to the enzyme by the organophosphate so it can work again.

ANTICHOLINERGICS

Don't forget there are anticholinergics that block the action of **nicotinic (Nm) receptors** at the neuromuscular junction (i.e. such as **Botox®** or **pancuronium.** (See page 17 below)

That being said, **we will focus mainly on anticholinergics that block muscarinic (M) receptors** (a.k.a. Parasympatholytics, Parasympathetic ANTAGONISTS).

In fact, in common parlance**, when a clinician uses the word "anticholinergic", they generally mean anti-muscarinic**.

Parasympathetic anticholinergics

Since these BLOCK the action of the cholinergic drugs, they have the opposite effect:

block vagus nerve so ⇑ heart rate (a double negative!)
⇓ lung secretions
⇓ GI secretions and motility – constipation, dry mouth
⇓ urination (tighten sphincter and relax bladder wall)
Dilate pupils (lose ability to see near & ⇑ eye pressure in some people)
⇓ sweating (dry skin, flushing)

★**CNS: most anticholinergics will cause some degree of drowsiness** ⇐(NOTE!
If you are trying to remember the actions of drugs by rules of opposites, in the CNS things are more complicated. When drugs cross the blood-brain-barrier, **sympathetic drugs generally make you more alert;** anticholinergics make you drowsy. Keep that in mind!)

Anticholinergic overdose: ⇑⇑heart rate, blurred vision, flushed, dry skin, constipation, CNS depression or hallucinations, worsens glaucoma and worsens urine flow. ***Except for the drowsiness,*** atropine poisoning would *clinically* look like epinephrine poisoning, right?

Treat an *anti*cholinergic overdose with the reversible AChE inhibitor **physostigmine** *(Antilirium)*

The following drugs bind/block ***all*** **muscarinic (M) receptors**, but ***not*** nicotinic (N) receptors.

atropine
Is a non-specific Muscarinic Blocker
Used PO, IV, IM, SQ and as eye drops!
Used pre-anesthetic, as an emergency drug (to treat **bradycardia**!), irritable bowel syndrome, **diarrhea** (*Lomotil*), **Parkinson's disease**, enuresis, and kids with amblyopia "lazy eye" (eye drop lasts 7-10 days!) and to treat cholinergic poisoning.
Atropine will show up on every exam in this class in some form. You've been warned!
Questions:
From a clinical point of view, how are atropine's effects different from epinephrine's?

What about phenylephrine?

scopolamine: used for motion sickness (*transderm-Scop*) patch used on cruise lines
-will also cause pupil dilation so wash hands after use

oxybutynin (*Di**trop**an*): used for bladder spasm to help people who are incontinent

homatropine: eye drop (lasts 1-2 days)

tolterodine (*Detrol*) : also used for incontinence

benztropine (*Cogentin*): Parkinson's

ipratropium: anti-cholinergic used for asthma and other lung disorders, or pre-op to dry the lungs

Okay, so what about **NICOTINIC DRUGS?**

1. Remember that the indirect-acting "-stigmines" increase Ach everywhere in the body, so that increased ACh will stimulate ALL nicotinic AND muscarinic receptors.

2. **Nicotine** itself, commonly abused in the form of tobacco or e-cigarettes, or that new thing the kids call "vaping", stimulates muscular Nm receptors and (more importantly for this handout) ***stimulates ganglionic Nn receptors.***

   Look back at page 1: If nicotine stimulates ganglionic Nn receptors, it stimulates sympathetic *AND* parasympathetic nerves.

   It turns out **Sympathetic adrenergic nerves dominate in blood pressure control** and **Parasympathetic cholinergic nerves dominate in digestion**.

   So, nicotine taken as a drug: has some sympathetic effects: ⇑heart rate, ⇑blood pressure
   & has some parasympathetic effects: ⇑GI motility

   Nicotine has very **High First Pass Metabolism**; so it is usually inhaled or topically administered.
   Remember that **nicotine gum's effects are *topical***
   Pregnancy Category **D**

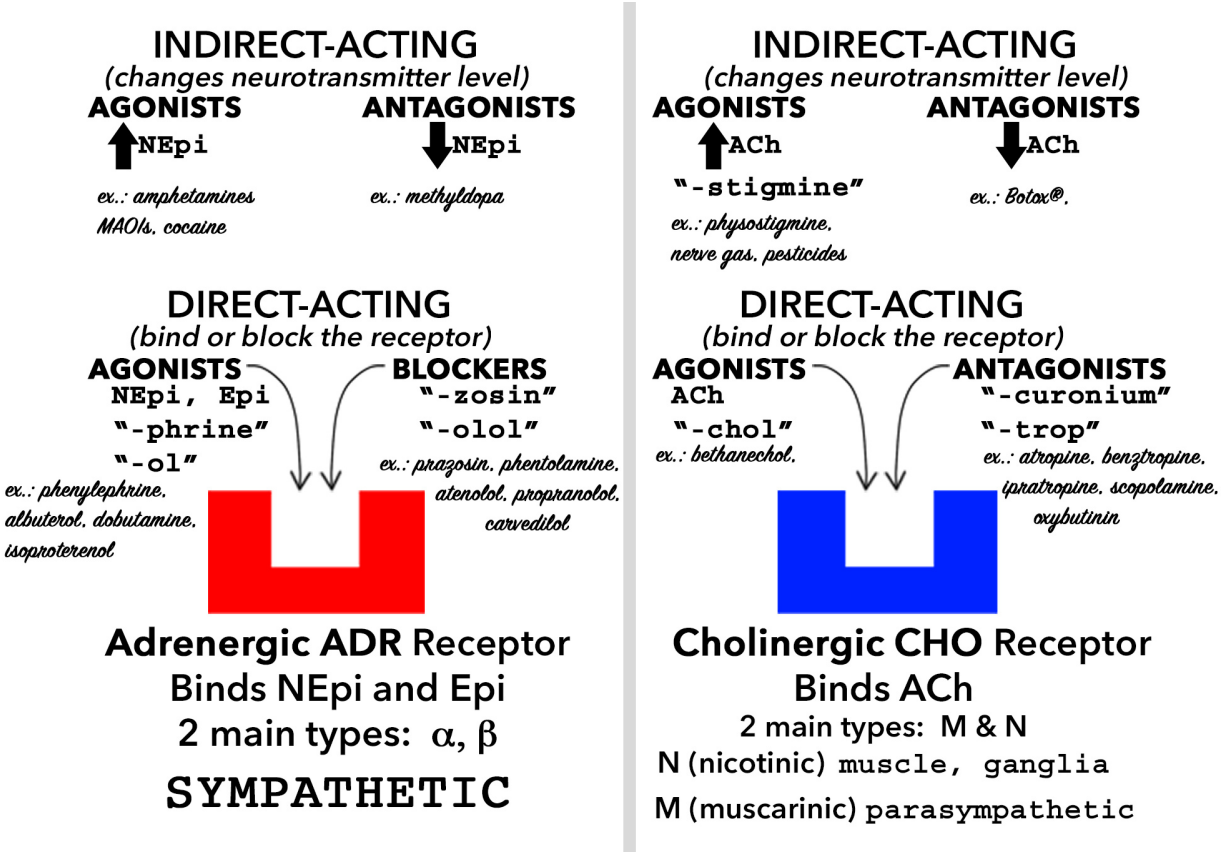
3. **Nicotine-specific BLOCKERS** tend to be drugs aimed at the **neuromuscular junction.**

   ex. Indirect Acting: **botulism toxin** *(Botox)* works as an indirect inhibitor of acetylcholine by inhibiting acetylcholine release. The toxin works by paralyzing skeletal muscle. If your skeletal muscles around your lungs don't work then you can't breathe and if you can't breathe you die.

   ex. Direct acting: **pancuronium** is a derivative of curare, another paralyzing poison. Pancuronium and drugs like it are direct-acting drugs that are used in anesthesia to cause temporary paralysis during surgical procedures so that the patient will not "fight" the ventilator.

GAH!!!! **HOW DO I LEARN ALL THIS?!??!**

So here is a little diagram I've drawn and then made all fancy.
It summarizes all the autonomic drugs described.
Make sure you can draw it too if I give you a blank sheet of paper.



You need to know this handout backwards and forwards.

In other words, you need to know how to match lists of:

Drug Classes and effects
Drug classes and mechanisms
Drug Classes and indications
Drug classes and contraindications
Individual drugs and effects
Individual drugs and mechanisms
Individual drugs and indications
Individual drugs and contraindications
Indications and drug classes
Indications and individual drugs
Indications and drug classes
Contraindications and drug classes
Contraindications and individual drugs
Etc
Etc
Etc
Etc