Part 1: Basic Principles of Autonomic Pharmacology

Adrenergic → Think Adrenaline
- ↳ Action mediated by norepinephrine Noradrenaline
- ↳ Nerve that synthesizes and releases norepinephrine

Receptor Subtypes: Alpha (α_1 and α_2) metabotrophic → GCPR

Beta (β_1 β_2 β_3) metabotrophic → GCPR

α_{1a} α_{1b} α_{1d} → Increase Ca^{2+} and generate IP_3 and DAG as messengers (G_q) * Facilitates physiologic processes

α_{2a} α_{2b} α_{2c} → Inhibit adenylyl cyclase and decrease cAMP * Inhibit physiologic response

β_1, β_2, β_3 → Stimulate adenylyl cyclase and increase cAMP

Where are they expressed?

α_1 - Postsynaptic Sites — Usually facilitates contraction

α_2 - Presynaptic Sites — Inhibition of transmitter release

β_1 - Cardiac muscle — ↑ force + rate of contraction

β_2 - Non-Cardiac tissues — Smooth muscle relaxation

β_3 - Adipocytes — lypolysis

Cholinergic → "Choline" Cholinergic
- ↳ Action mediated by acetylcholine
- ↳ Nerve that synthesizes and releases acetylcholine

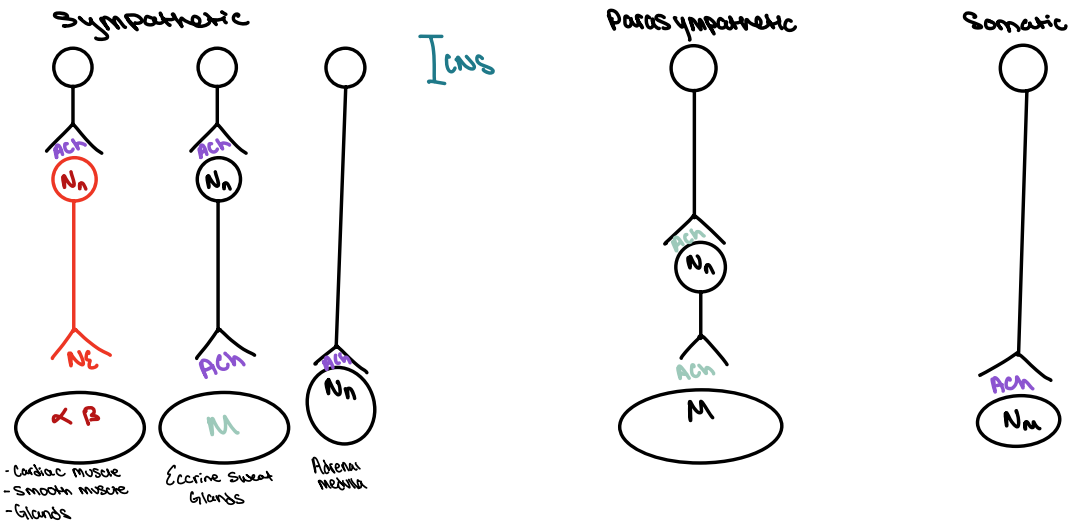
Receptor Subtypes: Nicotinic (N_N and N_M) ionotropic → ligand-gated channels

Muscarinic (M_1 M_2 M_3 M_4 M_5) metabotrophic → GCPR

M_2 M_4 → associated with G_i to inhibit adenylyl cyclase — Some cellular processes inhibited

M_1 M_3 M_5 → associated with G_q to activate Phospholipase C — Initiates cellular changes

Autonomic Neurochemistry



Targets (effectors) of ANS

- Exocrine glands

- Cardiac muscle
  - ↳ B_1 receptor stimulation ↑ HR, contractile force, and conduction velocity
  - ↳ Muscarinic receptor stimulation ↓ HR and contractile force

Smooth muscle
- ↳ α receptor stimulation causes smooth muscle contraction
- ↳ B_2 receptor stimulation causes smooth muscle relaxation
- ↳ Muscarinic receptor stimulation causes smooth muscle contraction

Targets can express more than one subtype

Ex: Vascular beds in different anatomical locations

Skeletal muscle: α_1 and β_1 (slightly more α_1)

Renal vessel: α_1 DA and some β_2

Subcutaneous vessel: α_1 solely

There is also "cross-talk" between sympathetic and parasympathetic neurotransmission

- another way to push the gas or pump the breaks!

Part 2

Does sympathetic activation usually cause vasoconstriction or vasodilation?

- Vasoconstriction typically occurs via activation of synaptic α_1 receptors
- β_2 receptors expressed on vascular smooth muscle cause vasodilation
  - non-synaptic, lower affinity for NE than α_1
  - physiologically activated by circulating catecholamines and systemic admin of β_2 agonist
- At very high levels, epinephrine will also activate alpha receptors

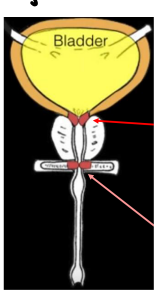
Autonomic Innervation of the eye

Miosis (pupil constriction): Parasympathetic (muscarinic receptors)

Mydriasis (pupil dilation): Sympathetic (α_1 adrenergic receptors)

Autonomic Control of the bladder

Major muscles:



Detrusor muscle: Smooth muscle surrounding bladder
Relaxation = urine retention
Contraction = urine release

Internal urethral Sphincter muscle: Smooth musc. surrounding urethral orifice @ bladder junct.
Relax: urine release
Contract: urine retention

External urethral sphincter
- Skeletal muscle under voluntary control

Sympathetic Innervation of the bladder

Norepinephrine → β_2 - adrenergic receptors activated, detrusor muscle relaxes
- Urine retention

→ α_1 - adrenergic receptor activated, contraction of internal sphincter muscle
- Urine retention

Parasympathetic Innervation of the bladder

Acetylcholine → Activates muscarinic receptors on detrusor muscle
- Contraction of detrusor muscle
→ urine release

Agonist vs Antagonist Review

Direct agonist: binds to and activates receptor

Indirect agonist: ↑ duration of action or availability of neurotransmitter by ↑ 2nd messenger action, ↓ NT degradation, blocking synaptic uptake of NT etc.

Direct antagonist: Binds and competitively inhibits NT binding to receptor

Indirect antagonist: Decreases availability of neurotransmitter

Adrenergic Receptors: α → Agonist; β → Antagonist

Sympathomimetic (produces sympathetic effects)

Sympatholytic (inhibit sympathetic effects)

Sympathomimetics: Amphetamine, Cocaine, Phenylephrine (α_1), Albuterol (β_2)

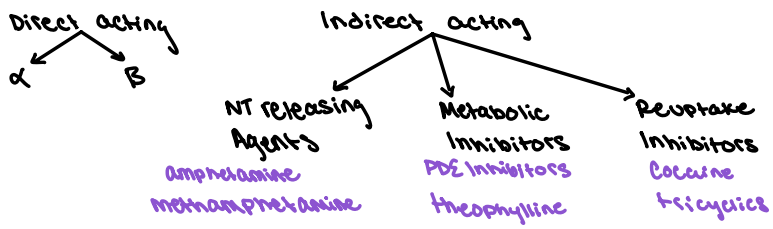
Sympatholytics: Methyltyrosine, Reserpine, Guanethidine, Prazocin (α_1), Atenolol (β_1)

Direct-Acting Adrenergic Drugs

	Agonist	Antagonist
α non-selective	Norepinephrine Epinephrine	Phentolamine Phenoxybenzamine
α_1	Phenylephrine Phenylpropanolamine	Prazosin
α_2	Clonidine Xylazine Dexmedetomadine	Yohimbine

β non-selective	Isoproterenol	Yohimbine
β_1	Dobutamine	Propranolol
β_2	Metaproterenol Albuterol Terbutaline	metaprolol Atenolol Nore

Adrenergic Stimulants



Clinical Uses of Sympathomimetics

Alpha Agonists

α_1 Agonists: Vasoconstriction

- Anaphylaxis - causes low blood pressure (epinephrine)
- Hypotension and shock (norepinephrine)
- Control hemorrhage in superficial surgery (epinephrine)
- Contain local anesthetics (epinephrine)
- Nasal decongestant (phenylephrine)

Smooth muscle Contraction

- Urinary incontinence (phenylpropanolamine) ↑ urethral sphincter tone

Beta agonists

β agonists: Cardiac Stimulation

- Bradycardia and AV block (isoproterenol)
- Cardiac arrest, congestive heart failure (dopamine, dobutamine)

β_2 agonists: bronchial relaxation

- Asthmatic Attack (albuterol and terbutaline)

Alpha Antagonists

α_1 antagonist: Vasodilation

- Hypertension (prazosin, phenoxybenzamine) Phenochromocytoma tx

Beta Antagonists (beta-blockers)

Non-selective β antagonists

- Hypertension (propranolol, sotalol)
- Glaucoma (timolol lowers ocular pressure)

β_1 antagonist: Attenuates cardiac response

- Cardiac arrest, congestive heart failure (atenolol)
- Hypertension (atenolol)

Cholinergic Receptors

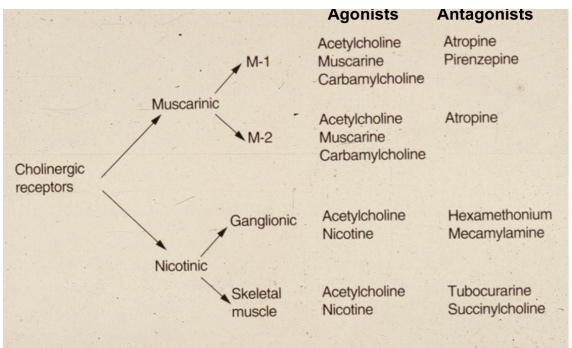
- Nicotinic
- Muscarinic

→ Agonist: parasympathomimetic (produces parasympathetic results)

→ Antagonist: parasympatholytic (inhibits parasympathetic results)

Parasympathomimetics: Nicotinic agonists, muscarinic agonists, cholinesterase inhibitors

Parasympatholytic: Nicotinic antagonists, muscarinic antagonists, choline uptake blockers



Clinical uses of Parasympathomimetics

Glaucoma (want to prolong cholinergic signaling)

Pilocarpine — muscarinic agonist

Physostigmine, ecothiophate — cholinesterase inhibitors

GI Stasis and Urinary retention (in absence of obstruction)

Bethanechol — Physostigmine, neostigmine

Muscarinic agonists, Cholinesterase inhibitors

Myasthenia gravis (Autoimmune disease of neuromuscular junct → weakness and fatigue)

Cholinesterase inhibitor - Edrophonium, physostigmine, neostigmine

Dilate Pupil (to produce mydriasis)

Muscarinic antagonist → causes relaxation of sphincter muscles

Long-acting - atropine, scopolamine

Short-acting - tropicamide, cyclopentolate

Pre-anesthetic medication (to ↓ secretions and/or prevent reflex or drug-induced bradycardia during Sx)

Muscarinic agonist atropine or scopolamine

↓ GI Hypermotility/Spasms of GI/Urinary tract

Antiemesis

Urinary incontinence

Treatment of organophosphate toxicity Muscarinic antagonists (atropine)

Asthma Case Study

- Airways of asthmatic patients are abnormally sensitive to non-specific stimuli
- Problem w/ nerves that regulate smooth muscle contraction

Airway Innervation Pathway: Efferent Pathway: Autonomic nerves
- Parasympathetic
- Sympathetic
- Sensory nerves

Afferent Pathway: Sensory nerves

Excitatory	VS	Inhibitory
Bronchoconstriction		Bronchodilation
Cholinergic (parasympathetic)		Adrenergic (sympathetic)

Dominant Neural control of airways

Non-adrenergic, non-cholinergic excitatory (NANC)
- calcitonin gene-related peptide (CGRP)
- Tachykinins (Sub. P, Neurokinin A and B)

Non-adrenergic, non-cholinergic inhibitory
(Nitric oxide, vasoactive intestinal polypeptide)