Pharmaceuticals, Heart Rate Variability & the Nervous System

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Health is our greatest commodity that requires a dynamic nervous system capable of adapting to the environment.

- Sympathetic Mode
  - VS: increased BP, P
  - Increased cortisol
  - Muscle cramps
  - Nervousness
  - Decreased libido
- Parasympathetic Mode
  - Healing
  - Digestion
  - Sleep

ANS Balancing

- Chiropractic
- Meditation
- Vagal nerve stimulation
- Message
- Chanting/music

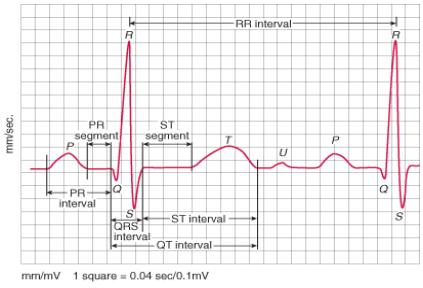
- Determinants
  - Underlying disease
  - **Medications**
  - CV fitness
    - Can detect risk of overtraining in athletes
  - Stress
  - Sleep
  - Pain
    - Trigger point in muscle spindles triggered by unbalanced ANS in favor of sympathetic output
  - Diet
  - Circadian rhythms

Heart Rate Variability (HRV)

A good proxy for stress response & resilience

Time Domain Measurements: Standard Deviations of normal R waves on ECG

- High frequency
  - Emotional regulation
  - Positivity
  - Subjective well-being
  - Executive function
- Low frequency
  - All cause morbidity & mortality
  - Depression
  - Anxiety
  - Aging



HRV: measures the beat to beat variations in R-R intervals

- Variable space between heart beats at rest insures adaptions that ideally keep blood pressure stable.
- Variable BP measurements at rest is a sign of pathology.
- R-R intervals naturally become more evenly spaced with exercise (metronome quality)
- R-R intervals can become evenly spaced with:
  - Disease states (diabetes etc.)
  - Chronically elevated sympathetic tone
  - Poor vagal tone/breaking

HRV/ Biofeedback Measurement Used to improve vagal tone for conditions that are associated with reduced heart rate variability; often the same conditions for which prescriptions are written.

- Asthma
- Functional abdominal pain
- Hypertension
- Chronic muscle pain
- Anxiety
- Sleep disturbance
- Depression

Pharmaceutical Principles

Pharmacokinetics: How the body responds or processes the drug/chemical. Gives direction on dosing and timing of administration.

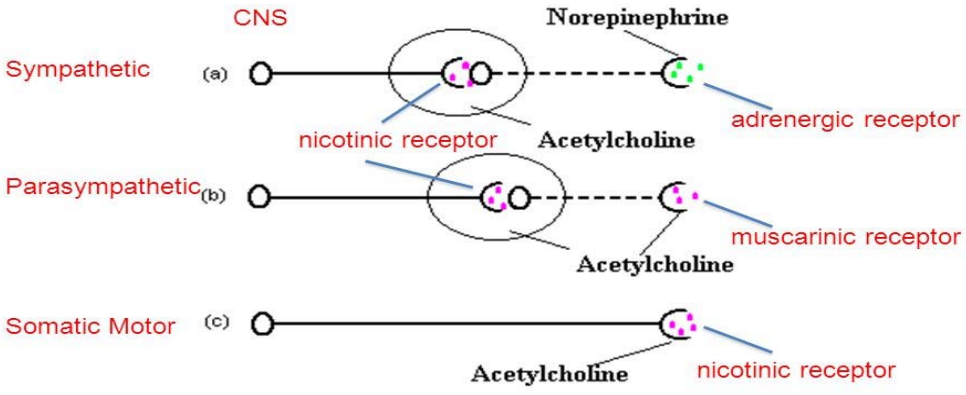
1. Absorption
2. Distribution
3. Metabolism
4. Elimination

Pharmacodynamics: How the drug creates a reaction in the body. Gives clues to expected side effects.

Receptor

activation/signaling

Peripheral Nervous System: Neurotransmitters & Receptors



nicotinic and muscarinic receptors = cholinergic recepto

Autonomic Nervous System: A Complementary System

- Consists of:
  - Sympathetic arm: fast reacting mobilizing responses & originates from T1-L3 spinal cord
  - Parasympathetic arm: slower modulating or breaking responses & has cranialsacral origins including Cranial nerves III, VII, IX, X & S2-S4 spinal cord
  - Enteric nervous system

Sympathetic Arm

- Sympathetic ganglia
  - Chromaffin cells in adrenal medulla
  - Prevertebral ganglia
    - Celiac, superior mesenteric, inferior mesenteric, aorticorenal
  - Paravertebral ganglia of the sympathetic chain
    - Cervical, thoracic, lumbar, sacral

Parasympathetic Arm

- Ganglia of head
  - CN III synapsis pupillary constriction
  - CN VII synapses at submandibular and pterygopalatine
  - CN IX synapses with otic ganglion for parotid secretions
  - CN X & sacral nerves S2, S3, and S4 synapse with ganglia near target organs in the thorax and abdominal cavities

Summary Functions of Parasympathetic Arm

- Increase blood flow & peristalsis in the gut
- Bronchoconstriction of airways
- Cardiac branches
- Pupillary constriction for visual accommodation
- Increase salivary gland secretion
- Erection of genital tissues

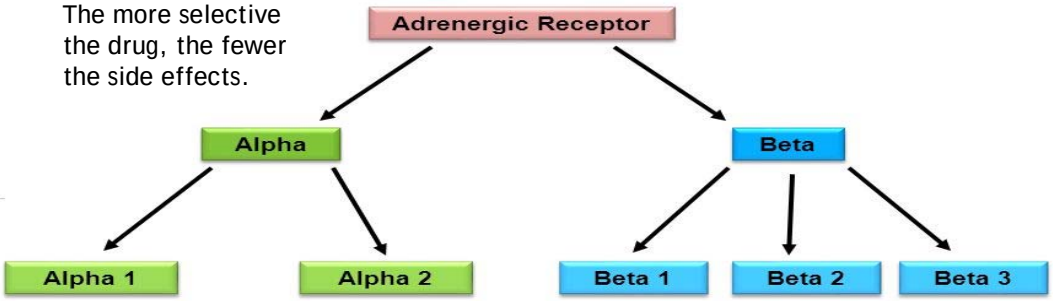
Receptors: located on blood vessels and target organs for cellular signaling

- Adrenergic: Sympathetic neurotransmitter release for "fight or flight responses; stimulated by stress & adrenergic drugs.
  - Sensitive to Norepinephrine & epinephrine
  - Two classes: alpha & beta
  - Subtypes:
    - Alpha 1 & alpha 2
    - Beta 1, beta 2, & beta 3
- Cholinergic: parasympathetic for rest & digest functions
  - Sensitive to acetylcholine
  - Muscurinic G-protein coupled
    - M1, M2, M3, M4, M5
  - Nicotinic Ligand gated ion channels
    - NN-located on neurons in autonomic ganglia of PNS & CNS
    - NM-located on skeletal muscle at neuromuscular junctions; somatic motor neurons

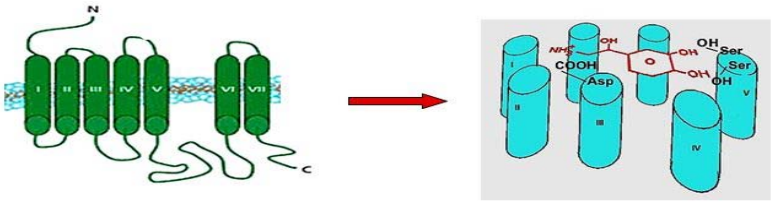
Autonomic Nervous System Drugs

- Sympathomimetics
- Sympatholytics
- Parasympathomimetics
- Parasympatholytics

The more selective the drug, the fewer the side effects.



Adrenergic receptors are seven-pass transmembrane proteins.



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Summary of General Principles

Alpha 1	•Vasculature constriction •ejaculation
Beta 1	•Heart stimulation •Juxtoglomerular cells of kidney to increase BP
Beta 2	•Vascular relaxation •Bronchodilation •Decreased GI peristalsis & secretions •Mobilization of glucose and fat stores
Beta 3	•Adipose tissue •Detrusor muscle of bladder

Drug: Mechanism of Action (MOA)

Agonists: increase the expected response

- Parasympathomimetics
  - Cholinergic: stimulate nicotinic or muscarinic receptors or slow Ach breakdown (nicotine)
- Sympathomimetics
  - Alpha or beta agonists
  - Selective or nonselective

Antagonists: impair or block the expected response

- Sympatholytic
  - Adrenergic antagonists or blockers
- Parasympatholytics
  - Anti-cholinergics

Adrenergic Drugs: Sympathomimetics & Parasympatholytics

- Agonists-sympathomimetics used for:
  - Alpha-agonists
    - Phenylephrine: decongestants
    - Amphetamines: ADHD
    - Pseudoephedrine: Sudafed
  - Beta-agonists
    - Salbutamol/Albuterol/ventolin inhalers
- Antagonist-Anticholinergic Parasympatholytics used for:
- Most act on the muscarinic Ach receptor
- Examples:
  - Diphenhydramine(Benedryl) allergies
  - Oxybutynin: bladder spasms
  - Tricyclic antidepressants
  - Scopolamine: motion sickness
  - Doxepin: depression, anxiety, sleep
  - Dextromethorphan: cough suppressant
  - Bupropion: depression, smoking

Categorical Adrenergic & Anti-cholinergic Side Effect Profile

- Hypertension
- Tachycardia
- Tremors, sweating, anxiety
- Bronchodilation/reduced secretions
- Sleeplessness
- Pupil dilation
- Dry mouth
- Dry eyes
- Urinary retention
- Constipation
- Sexual dysfunction
- Delayed gastric emptying/indigestion/constipation
- Carbohydrate dysregulation/worsening of diabetes
- Cognitive impairment including memory & attention

Adrenergic Receptors: Alpha 1

- Blood vessels: Helps to control blood flow through vasoconstriction when activated by contraction of tunica media
- Skin: cold pale skin; erector pili contraction with hair follicles creating goosebumps
- GIT: decreased splanchnic circulation decreasing absorption & peristalsis/Pancreas to effectively increase blood glucose by stimulating alpha cells to release glucagon & beta cells to decrease insulin
- Eye: dilator pupillae to increase light coming into the eye
- Salivary glands blood vessels to decrease water/electrolytes & increase viscosity of secretions

Adrenergic Receptors: Alpha 1 Continued

GI	• Stimulates pyloric sphincter and internal anal sphincter contraction
Urinary system	• Internal urethral sphincter contraction
Reproduction	• Smooth muscle contraction in epididymis, vas deferens, seminal glands, and prostate • Myometrium contraction

Adrenergic Receptors: Beta 1

Heart: increases HR, BP, contractility, Stroke volume, and cardiac output	Myocardium SA & AV node, bundle of HIS
Juxtaglomerular cells of kidney to release renin and activate angiotensin/aldosterone to increase blood pressure.	
Ghrelin secretion?	

Adrenergic Receptors: Beta 2

- Airway to cause bronchodilation
- Skeletal muscle vasodilates for increased work & muscle spindle activation for proprioception resulting in tremors
- Myocardium to autoregulate with oxygen and adenosine levels
- CNS myogenic blood pressure autoregluation
- Bladder detrusor muscle relaxation
- Eye ciliary muscle relaxation to flatten lens for distant vision
- Salivary glands increase mucous

Adrenergic Receptors: Beta 3

Bladder detrusor muscle relaxation → Adipose tissue resulting in lipolysis

Receptors: located on blood vessels and target organs for intracellular signaling

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Cholinergic Receptors: Activated by Acetylcholine for Rest & Digest Functions

- Exocrine glands
  - including bronchus, pancreas, lacrimal, salivary glands, gastric glands, GI tract
- Bladder
  - M3 receptors for bladder detrusor muscle contractions
  - M3 receptors on ciliary eye muscle for pupillary constriction and near vision accommodation
- Heart
  - M2 receptors on SA node & AV node
- CNS
  - M1, M4, M5 receptors
  - Memory, arousal, analgesia

Sympatholytics & Parasympathomimetics

- Antagonist:anti-adrenergic used for:
  - Alpha blockers: HTN
    - Prazosin
  - Beta blockers: HTN, anxiety, stage fright
    - Propranolol
    - Nadolol
    - Timolol
    - Atenolol
    - Metoprolol
- Agonist-Cholinergic used for:
  - Bethanechol: urinary retention & GI ileus
  - Nicotine
  - Carbachol: glaucoma
  - Cisapride: gastric stasis
  - Metoclopramide: nausea & vomiting

Categorical Cholinergic & Anti-adrenergic Side Effects

- Bronchoconstriction in asthmatics
- Hypotension
- Bradycardia
- Dispepsia/nausea
- Diarrhea
- Urinary urgency
- Skin flushing
- Sweating
- Increased salivary & lacrimal secretions
- Miosis (pupil constriction)

Why does one drug have so many side effects?

One drug; indiscriminant binding to receptors on multiple targets throughout the body. Understanding pharmacodynamics makes most side effects predictable.

Autonomic Nervous System Drugs

- Sympathomimetics
- Sympatholytics
- Parasympathomimetics
- Parasympatholytics

No need to know the names of so many available medications. Just knowing the pharmacodynamics of drug classes will help you predict their impact on your efforts.

https://www.drugs.com/

https://www.rxlist.com/drugs/alpha_a.htm

Thank You

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