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 adaptations 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

CNS

Norepinephrine

Adrenergic receptor

Acetylcholine

Muscarinic receptor

Sympathetic (a)

Nicotinic receptor

Parasympathetic (b)

Somatic Motor (c)

Acetylcholine

Nicotinic receptor

Nicotinic and muscarinic receptors = cholinergic receptor
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 cranial sacral 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
  - Muscarinic 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.

Summary of General Principles

- **Alpha 1**: Vasculature constriction, ejaculation
- **Beta 1**: Heart stimulation, Juxtaglomerular 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.

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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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