Pharmacology

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ARKAN ACADEMY

Autonomic Nervous System

- Synthesis and release of catecholamines:
  - ***Tyrosine*** enters the axon terminal using ***Na^+-dependent carrier A***
  - Tyrosine is converted into ***dopa*** by ***tyrosine hydroxylase*** (inhibited by *α methyltyrosine*)
    - ✓ It is the rate limiting step
  - Dopa is converted into ***dopamine*** by ***Dopa decarboxylase***
  - Dopamine enter vesicle via ***vesicle monoamine transporter (VMAT)*** (blocked by *reserpine*)
    - ✓ Dopamine is converted into ***Norepinephrine*** (***NE***) inside vesicle, by ***dopamine β hydroxylase***
      - Tyrosine can be converted into NE by a pathway of tyramine and octopamine
      - Monoamine oxidase inhibitors can cause tyramine and octopamine accumulation
    - ✓ NE is converted into ***epinephrine*** (***EPI***) by ***N-methyltransferase***
  - When action potential reaches the terminal, Voltage sensitive Ca^{+2} channels open causing the fusion between vesicle and terminal membrane causing the release (explosion) of vesicle content
    - ✓ Release is blocked by *guanethidine* and *bretylium*
  - After the release neurotransmitters bind a receptor, to produce a response, which is terminated by:
    - ✓ NE diffuses or transported back into the terminal by the ***norepinephrine transporter (NET)*** which is blocked by cocaine and certain antidepressants
    - ✓ NE can diffuse into postjunctional or perijunctional cells

- Catecholamines are metabolized into ***VMA*** (3-methyl-4-hydro-mandelic acid) by:
  - *MAO (monoamine oxidase):* Oxidation of the amino group
  - *COMT (Catechol-O-methyrtansferase):* Methylation of hydroxyl group
    - ✓ Tumors in the adrenal medulla or sympathetic chain can be measured by VMA levels
- Autonomic drugs can reach the specific site of action, but dopamine, NE and EPI can't due to their metabolism in the intestines, bloodstream and brain before reaching the site
- ***Cholinoceptors (Cholinergic):*** Receptors stimulated by *acetylcholine*
  - Include Muscarinic (***alkaloids muscarine***) and nicotinic (***nicotine***) receptors
    - ✓ Muscarinic ***M1***: *Sweat glands* supplied by sympathetic postganglionic neurons
    - ✓ Muscarinic ***M2***: *Myocardium and smooth muscles*
    - ✓ Muscarinic ***M3***: Exocrine *glands* and *vascular smooth muscles*
    - ✓ Muscarinic ***M5***: *Vascular endothelium*
    - ✓ Nicotinic N_N: *Postganglionic neurons*
    - ✓ Nicotinic N_M: *Skeletal* muscle neuromuscular end plate

- ***Adrenoceptors (Adrenergic):*** Receptors stimulated by *catecholamines* (NE, EPI)
  - ✓ *Alpha 1*: *Smooth muscles* (**Contraction**)
  - ✓ *Alpha 2*: *Presynaptic* adrenergic nerve terminals (***Negative feedback***)
  - ✓ *Beta 1*: *Heart* and juxtaglomerular apparatus in the *kidney*

- ✓ *Beta 2*: Smooth muscles of *blood vessels in the skeletal* muscle and bronchi (**Relaxation**)
- ✓ *Beta 3*: *Lipocytes*

- ***Dopamine receptors (Dopaminergic):*** Receptors stimulated by dopamine
  - ✓ D1: renal vascular bed (Vasodilation)

- ***Presynaptic*** β-adrenoceptors when ***activated by NE*** facilitate further NE release (***Positive feedback***)
  - ➢ Receptors of negative and positive feedback are **autoreceptors**
- Some ***vagal*** fibers in the myocardium synapse on sympathetic nerve terminals and ***inhibit NE release***
- ***Serotonin (5-HT)*** stimulation at cholinergic preganglionic sites ***inhibits cholinergic transmission***
- ***Adenosine*** (P1 receptor) and ***ATP*** (P2 receptor) stimulation inhibits adrenergic function
- ***Angiotensin II*** stimulates its receptor (AT2-1) ***stimulates adrenergic transmission***
- ***Up-regulation:*** ↑ Number of receptors upon continued decreased receptor activation by *antagonist*
- ***Down regulation:*** ↓ Number of receptors upon continued increased receptor activation by *agonist*

- Effects of Sympathetic and parasympathetic on:
- **Eye**
  - ➢ **Miosis** by ***Iris circular muscle*** (aka constrictor pili), and accommodation of **near** vision by ***ciliary*** muscle in parasympathetic stimulation (M3)
  - ➢ **Mydriasis** by ***iris radial muscle*** (aka dilator pili), and accommodation of **far** vision by ***ciliary*** muscle in sympathetic stimulation (alpha1 for mydriasis , Beta for far vision)

- **Heart**
  - ➢ *Chronotropic effect:* Pacemaker (***SA*** node)
  - ➢ *Dromotropic effect:* Ectopic pacemaker (***AV*** node)
  - ➢ *Inotropic effect:* Myocardial ***contractility***
  - ➢ All heart functions accelerate and **increase (positive)** in the sympathetic stimulation (Beta 1 and 2) which increases ***cardiac output***, ***systolic blood pressure*** and ***venous return***
  - ➢ All heart functions decelerate and **decreased (Negative)** in the parasympathetic stimulation (M2) which decreases ***cardiac output***, ***systolic blood pressure*** and ***venous return***

- **Bronchi**
  - ➢ **Relaxation** in the sympathetic stimulation (Beta 2)
  - ➢ **Contraction** in the parasympathetic stimulation (M3)

- **Blood vessels**, **sweat glands** and **pilomotor smooth muscle** (only sympathetic)
  - ➢ ***Splanchnic*** (skin) vessels and ***pilomotor muscle***: **Constriction** and **Contraction** (alpha)
  - ➢ ***Skeletal*** muscle vessels: **Dilation** (Beta 2)
  - ➢ ***Renal resistance vessels*** (arterioles): Vasodilation (D1)
  - ➢ ***Sweat*** glands: Activation and **secretion**
    (*Eccrine thermoregulatory*: M3)
    (*Apocrine in palms for psychologic stress*: Alpha)

Constriction: ↑ Arterial resistance (less blood flow)

Vasodilation: ↓ Arterial resistance (higher blood flow)

- **Metabolism** (only sympathetic)
  - ***Liver:* Gluconeogenesis** and **glycogenolysis** (Beta 2, alpha)
  - ***Fat cells***: **Lipolysis** (Beta 3) but inhibited by alpha 2
  - ***Kidney***: **Renin release** (Beta 1)
  - ***K^+ uptake*** into cells (Beta 2)
- **Genitourinary**:
  - ***Bladder wall*** is ***relaxed*** in sympathetic (Beta 2) and ***contracted*** in parasympathetic (M 3)
  - ***Sphincter*** is ***contracted*** in sympathetic (Alpha 1) and ***relaxed*** in parasympathetic (M 3)
  - ***Uterus relaxes*** (Beta 2) and ***contracts*** (Alpha) in sympathetic, ***contracts*** in parasympathetic (M3)
  - ***Penis*** and ***seminal vesicle ejaculate*** in sympathetic (Alpha), and ***erect*** in parasympathetic (M)
- **Endocrine function:**
  - β-receptor stimulation ***increases insulin*** release by pancreas and glucose uptake into cells
  - α2-receptor stimulation ***inhibits insulin*** release
  - β1-receptor stimulation ***increases renin*** secretion
  - αα2-receptor stimulation ***inhibits renin*** secretion.
- ***Sympathomimetics:*** Drugs that **mimic** the actions of EPI (adrenaline) or NE (noradrenaline)
  - ***Norepinephrine*** is mainly released by ***sympathetic nerves*** upon nerve stimulation
  - ***Epinephrine*** is mainly released by ***adrenal medulla*** in response to a variety of stimuli such as ***stress***
- Mode of action:
  - ***Direct stimulation*** of adrenoceptors
  - ***Displacement*** (release) of stored catecholamines from adrenergic endings (*amphetamine*, *tyramine*)
  - ***Inhibition*** of catecholamine ***reuptake*** (*cocaine*, *tricyclic antidepressants*)
- *Diastolic blood pressure* is related to *systemic vascular resistance*
  - Raised (increased) by vasoconstrictors (**α-agonists**)
  - Reduced (decreased) by vasodilators (**β2-agonists**)
- **α-agonists** causes constriction of blood vessels of upper respiratory tract mucosa causing ***decongestion***

Alpha agonists	
Phenylephrine, methoxamine	$\alpha_1 > \alpha_2 >>>> \beta$
Clonidine, methylnorepinephrine	$\alpha_2 > \alpha_1 >>>> \beta$
Mixed alpha and beta agonists	
Norepinephrine	$\alpha_1 = \alpha_2; \beta_1 >> \beta_2$
Epinephrine	$\alpha_1 = \alpha_2; \beta_1 = \beta_2$
Beta agonists	
Dobutamine[1]	$\beta_1 > \beta_2 >>>> \alpha$
Isoproterenol	$\beta_1 = \beta_2 >>>> \alpha$
Albuterol, terbutaline, metaproterenol, ritodrine	$\beta_2 >> \beta_1 >>>> \alpha$
Dopamine agonists	
Dopamine	$D_1 = D_2 >> \beta >> \alpha$
Fenoldopam	$D_1 >> D_2$

- Specific Sympathomimetics (Catecholamines)
  - ***Epinephrine:*** Stimulates *all adrenoceptors* (α1, α2, β1, β2)
    - ✓ Very potent vasoconstrictor and cardiac stimulant
    - ✓ Positive inotropic and chronotropic actions on the heart (β1)
    - ✓ Vasoconstrictor in many vascular beds (α1)
    - ✓ Vasodilator in skeletal muscle blood vessels (β2) to increase blood flow during exercise.
  - ***Norepinephrine:*** Similar to epinephrine except it has *no significant effect on β2* receptors

- ***Dopamine***
  - ✓ Activates D1 receptors causing ***vasodilation*** specially in ***renal vascular bed*** = ↑ renal blood flow
  - ✓ Activates β1 receptors in the heart
  - ✓ At **high concentration**, it activates vascular α receptors leading to *vasoconstriction* including the renal vascular bed
- ***Fenoldopam:*** Is a *selective D1 receptor agonist* causing **peripheral vasodilation**
  - ✓ Very useful intravenously in ***treating severe hypertension***
- ***Dobutamine:*** Is a *selective β1 agonist* which ***increases cardiac output*** (positive inotropic action)

- Non-catecholamines: Phenylephrine, amphetamine, methamphetamine, methylphenidate, Tyramine
  - ***Phenylephrine:*** It is a relatively *pure α 1 agonist* causes *contraction of blood vessels* smooth muscle
  - ***Tyramine:*** Found in high concentration in **wine**, fermented food such as **cheese**
    - ✓ It is readily metabolized by MAO in the liver, and is ***inactive when taken orally***
    - ✓ It produces indirect sympathomimetic action causing *hypertension*
    - ✓ Patients taking MAO inhibitors should avoid tyramine-rich food to avoid hypertensive crisis

- α-Adrenoceptor Antagonists
  - *Prazosin* and *Terazosine* (**α1 > α2**)
  - *Tamsulosin* (**α_{1A} and α_{1B}**)
  - *Phentolamine* (**α1 = α2**) reversible, Phenoxybenzamine (α1 = α2) irreversible

- Block of α1-receptors:
  - In arterioles leads to **vasodilation**, lowering of peripheral vascular resistance and blood pressure
  - In venules leads to **venodilation**, postural hypotension and reflex tachycardia
    - ✓ Tachycardia is more marked with *nonselective α-blockers* due to increased release of NE
  - *Miosis* and *Nasal stuffiness congestion*
  - Decreased resistance to the *outflow of urine* (α_{1A} , α_{1B} receptors in the base of bladder and prostate)

- β-Adrenoceptor Antagonists
  - ***Competitively inhibit*** occupation of these receptors by catecholamines
  - β-Adrenoceptor antagonists are not the same, regarding their antagonism and lipophilicity
    - ✓ ***Lipophilic*** antagonists cross blood brain barrier affecting **CNS**
  - Non-selective (β1 = β2): *Propranolol*, *Timolol*, *Sotalol*
    - ✓ Propranolol undergoes ***extensive hepatic first-pass metabolism***, low bioavailability so the oral dose is much larger than IV dose
  - Non-selective with some alpha blocking activity (β1 = β2 ≥ α1 > α2): *Carvedilol*, *Labetalol*
  - β1- selective or ***cardioselective*** (β1 > β2): *Atenolol*, *Bisoprolol*, *Metoprolol*, *Esmolol*
    - ✓ Metoprolol and carvedilol are metabolized but atenolol is mainly excreted unchanged in urine

- ✓ Its half-life is prolonged in renal failure
- ✓ Bisoprolol is partly exceted unchanged and partly metabolized

- Block of β-receptors:
  - ➢ *Lowering of blood pressure* in patients with hypertension (*Negative inotropic* effect reducing cardiac output, *suppression of RAAS* (renin-angiotensin system) and a *centrally-mediated* effect on CNS)
  - ➢ Negative chronotropic effect à *bradycardia*
  - ➢ *Slow AV nodal conduction*, prolonging its refractory period (***treating supraventricular arrhythmia***)
  - ➢ *Increased airway resistance* (bronchoconstriction) due to block of β2 receptors
  - ➢ ***Timolol*** *reduce intraocular pressure* (***Treating glaucoma***) due to reduced aqueous humor production
  - ➢ Inhibition of lipolysis (β3) and glycogenolysis (β2)
    - ✓ *Impair recovery from hypoglycemia* in insulin-dependent diabetic patients
    - ✓ **Chronic use** increase plasma concentrations of VLDL and decreased concentration of HDL causing ***atherosclerosis*** and increased risk of ***coronary artery disease***

- *Carvedilol* is used in the ***treatment of chronic heart failure***
  - ➢ It inhibits vascular smooth muscle mitogenesis (hypertrophy and hyperplasia)
  - ➢ It is highly metabolized (liver) attenuates oxygen free radical-initiated lipid peroxidation

- ***Esmolol*** is an ultra-short-acting β_1-selective adrenoceptor antagonist
  - ➢ It is rapidly inactivated by red blood cells esterase ($t_{½}$ = 10 minutes)
  - ➢ It is useful in ***controlling supraventricular arrhythmias*** associated with thyrotoxicosis
- Abrupt discontinuation of these drugs leads to rebound effects (exaggeration of the condition they were used to treat) because of upregulation (increased number) of receptors during treatment, therefore, when drugs are to be discontinued, tapering of the dose gradually rather than sudden withdrawal is required

- ***Cholinomimetics:*** Acetylcholine receptor stimulants (Agonists of muscarinic and nicotinic receptor)
  - ➢ ***Direct Cholinomimetics:*** include *choline esters* (***acetylcholine***, ***methacholine***) and naturally occurring *alkaloids* (***muscarine***, ***pilocarpine***)
    - ✓ *Choline esters* are quaternary ammonium compounds, *charged, highly water* soluble (ionized) and insoluble in lipids (***poorly absorbed*** and poorly distributed into most tissues) and they are hydrolyzed in the GIT and ***not active by the oral route***
    - ✓ *Alkaloid pilocarpine* (lipid soluble, tertiary amine) is *well absorbed* from most sites
    - ✓ *Muscarine* is a quaternary amine and is *less completely absorbed* from GIT than tertiary amines but is toxic when ingested

- Most of their effects are similar to the effects of parasympathetic nerve stimulation and the distribution of muscarinic receptors, which include:
  - ➢ ***Miosis***, accommodation for ***near*** vision (**M3**) and ***facilitation of aqueous humor outflow***
    - ✓ Pilocarpine can be used as a ***treatment of glaucoma***

- Reduction of heart rate (***bradycardia***, negative chronotropy), and ***decreased AV node conduction*** velocity (negative dromotropy), and ***decreased contractility*** of atria (negative inotropy)
  - ✓ Effects on ventricles are much less than atria
- Stimulation of ***M3 and M5*** in the endothelium of blood vessels increases synthesis of endothelium-dependent relaxing factor (***EDRF***) which mediates ***vasodilation***, and reduction of blood pressure
  - ✓ ***Pilocarpine (IV)*** causes *hypertension after the initial reduction* in blood pressure due to sympathetic ganglionic discharge caused by activation of postganglionic M1 receptors
- Contraction of smooth muscle of the bronchial tree = *bronchoconstriction* (M3)
- Stimulation of *secretions* of glands in tracheobronchial mucosa (M3)
- *Increased gastric secretions*, *Peristaltic activity* in gut is increased and most *sphincters are relaxed*
- Stimulation of detrusor muscle of the *urinary bladder (contraction)* and promote voiding (urination)
- Human ***uterus contracts*** and its vessels dilate in response to muscarinic agonists, but pregnant uterus is not affected and the penis erect (M receptors)
- Stimulation of secretions of salivary, sweat, lacrimal and nasopharyngeal glands (secretomotor)

- ***Cholinesterase inhibitors (indirect agonists):*** Drugs which *inhibit the hydrolysis* of acetylcholine stimulates cholinoceptors (**not selective**) with increased response and utilize ACh as a neurotransmitter
  - **Edrophonium** simple alcohol bearing a quaternary ammonium group (charged)
  - **Carbamates**, include:
    - ✓ *Neostigmine* (ester of carbamic acid) and is a quaternary ammonium, administered via *injections*
    - ✓ *Physostigmine* is a naturally occurring tertiary amine (lipid soluble)
    - ✓ *Carbaryl* very high lipid solubility, insecticide
  - ***Organophosphates:*** Insecticides, and humanicides (illegal)
    - ✓ *Echothiophate* (thiocholine derivative of clinical value)
    - ✓ *Parathion*, *Malathion* (Paraoxon, Malaoxon) Insecticides
    - ✓ *Soman*, *Sarin* (nerve gases)

- Absorption of *neostigmine* (quaternary ammonium) from the conjunctiva, skin and lungs is ***poor***
  - Distribution into the central nervous system (CNS) is ***negligible***
- *Physostigmine* is ***well absorbed*** from all sites and can be used topically
  - It is also distributed to the ***CNS*** being more toxic than more polar carbamates
- *Carbaryl* is ***very well absorbed*** from all site and distributed to the ***CNS extensively***
- *Organophosphates* (except echothiophate) are well absorbed from skin, lung, gut and conjunctiva
  - They are extensively distributed to all parts of the body including CNS
- *Echothiophate* is ***highly polar*** and is used ***topically*** in the conjunctiva (treating glaucoma)

- Inhibition of cholinesterases increases the concentration of endogenous acetylcholine
  - Edrophonium produces a *short-lived* and reversible inhibition of the enzyme (2-10 minutes)
  - Carbamates produce reversible and *prolonged* inhibition (0.5-6 hours)
  - Organophosphates phosphorylate the active site *covalently and irreversibly (longed lasting, hours)*
    - ***Aging:*** strengthening of the phosphorus-enzyme bond by breaking oxygen-phosphorus bond
    - ***Oximes (pralidoxime)*** are nucleophiles and are able to break the phosphorus-enzyme bond before aging occurs (***Cholinesterase regenerators***)

- These effects are due to ***accumulation of acetylcholine*** at all cholinergic sites
  - The actions are similar, but not identical, to those of the direct-acting cholinomimetic agonists
  - CNS at *low concentrations* cause diffuse activation of CNS and an *alerting response*
    - In *higher concentrations*, they produce generalized convulsions followed by *coma and death*
  - They can stimulate both parasympathetic and sympathetic ganglia (nicotinic receptors), although *parasympathetic activation predominates*
  - ***Sympathetic*** ganglia stimulation on vascular beds is predominant causing ***vasoconstriction***
    - ***At toxic doses*** these agents may cause *tachycardia*, instead of bradycardia
  - Neuromuscular junction (nicotinic receptors):
    - Low concentration *increases the strength* of contraction in skeletal muscle
    - High concentration leads to *fibrillation* of the muscle fibers and muscular *fasciculation*
    - Marked inhibition of acetylcholinesterase my produce neuromuscular blockade

- Cholinoceptor-Blocking Drugs:
  1. ***Antimuscarinic drugs (Muscarinic Receptor-blocking Drugs)***
- Naturally occurring alkaloids: *Atropine* (hyoscyamine, prototype) and *Scopolamine* (hyoscine)
  - Most well absorbed tertiary antimuscarinic drugs (widely distributed including the CNS)
  - Atropine has **sedative** effect on the brain
  - Scopolamine has more marked central effects producing **drowsiness**, **amnesia**
  - These actions make them useful as pre-anesthetic medications
  - At toxic doses, both can produce excitement, agitation, hallucinations and coma
- Quaternary amines for GIT (*peptic ulcer disease*, *hypermotility*): *Propantheline*, *Glycopyrrolate*
  - Quaternary antimuscaring drugs are poorly absorbed after oral administration (poorly cross to brain)
- Tertiary amines for peripheral applications: *Pirenzepine* (*peptic ulcer disease*), *Tropicamide* (*mydriasis* for eye examination), *Dicyclomine* (peptic disease and hypermotility)
- *Quaternary ammonium* (*Ipratropium*, *Tiotropium*) for use in ***bronchial asthma (bronchodilator)***
- *Tertiary amine* for ***Parkinson's disease***: ***Benztropine*** (can cross BBB)
  - Reduce the tremor of Parkinson's disease
- *Tolterodine* for ***hyperactive urinary bladder***

- Antimuscarinic drugs cause reversible and competitive blockade of muscarinic receptors, preventing acetylcholine from binding (can be ***overcome by increasing Ach***)
- Prevention or ***reversal of the vestibular disturbances*** of motion sickness
- Dilation of the pupil (*mydriasis*) due to blockade of the pupillary constrictor muscle
  - Weaken contraction of ciliary muscle (*cycloplegia*) leading to loss accommodation for near vision
  - *Reduction of lacrimal secretions* leading to dry or sandy eyes
- Small doses of atropine produce ***bradycardia*** by stimulation of acetylcholine release by ***blocking presynaptic M1*** autoreceptors
  - Moderate to high doses of atropine produce ***tachycardia*** by blocking ***postsynaptic*** muscarinic receptors in the SA node in the heart
  - Effects on atria and ventricles are minor
- ***Suppress thermoregulatory sweating*** where reducing sweating elevates body temperature
- ***Block vasodilation*** (in coronary arteries and skeletal muscle blood vessels) induced by cholinomimetics despite lack of parasympathetic innervation of blood vessels (but has ***endothelial muscarinic receptors***)
  - ***Cutaneous blood vessel dilation*** due to blocking of sweating causing ***flushing*** at toxic dose
- *Bronchodilation* (M3 receptors) and *reduced respiratory secretions* and *prevention of laryngospasm*
- *Reduce salivary secretions* → ***dry mouth***
  - *Reduction of gastric secretions* – volume and amount of acid, pepsin and mucin
  - Basal secretion is blocked more than that stimulated by food, nicotine or alcohol
  - Pancreatic and intestinal secretions are less affected
  - *Relaxation of smooth muscle* of GIT from stomach to colon where both tone and propulsive movements are diminished
  - *Prolong gastric emptying time* and intestinal transit time
  - Causing ***constipation***
- *Relaxation* of smooth muscle of the *ureters* and *urinary bladder wall* → ***slows voiding*** (urination) and urinary retention

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