

SNS: Pharmacotherapeutics, Medication, and Neuropharmacology

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ENDOGENOUS NEUROMEDIATORS

Released by sympathetic post ganglionic neurons.

Exceptions: Sweat Glands

- norepinephrine (levarternol, noradrenalin)
- epinephrine (arterenol, adrenalin)
 - stimulates metabolic activity
 - promotes blood flow to skeletal muscle
 - Skeletal muscles have alpha and beta receptors.
 - epinephrine is released from chromaffin cells

Termination of the Physiological and Pharmacological action:

- Nor-epinephrine / epinephrine
 - METABOLIC BIOTRANSFORMATION:
 - catechol-O-methyl transferase (COMT) = extraneuronal
 - monoamine oxidase (MAO) = neuronal hepatic
 - Dietary amines are destroyed in the liver, before they can do harm.
 - Liver (MAO)
 - Intraneuronal - Preventing build-up of nor-epinephrine inside neuron (housekeeping)

ADRENERGIC RECEPTORS

- alpha = smooth muscle contraction
- beta₂ = smooth muscle relaxation
- Further breakdown :
 - Beta-1 (cardiac effect)
 - Beta-2 (smooth muscle effect)
- alpha and beta do not work in opposition to each other

ALL adrenergic drugs can be shown to possess both alpha and beta activity, but the activity ratio may vary significantly:

- phenylephrine
- norepinephrine
- epinephrine
- isoproterenol

EFFECTS of EPI and NE

- high doses/low doses - effects of epi and NE
- bronchioles
- nasopharyngeal
- CNS
- metabolic activity of Epi and NE:
- Catalytic action of Epinephrine: Glycogen=>Glucose
- Triglycerides=>Free Fatty Acids

DISEASES ASSOCIATED WITH CATACHOLAMINES

- Pheochromocytoma
- Essential Hypertension - Cause is not known, however, in a certain percentage of the population having hypertension, there will be an increase in circulating catacholamine.

CATACHOLAMINE EFFECTS ON OTHER SYSTEMS

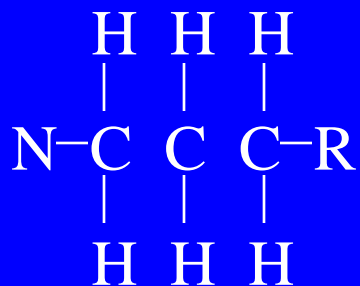
- Glands: Thick saliva secretions
- Sweat Glands: No effect

ADRENERGIC PHARMACOLOGY

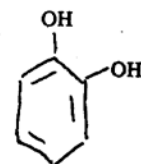
- Classification of adrenergics by mechanism of action:
 - Direct Acting - Interact with receptors (alpha and/or beta)
 - Indirect Acting - 2 types
 - Those that cause release of endogenous catecholamines, ie. amphetamine
 - Those that inhibit catecholamine reuptake mechanism, ie. cocaine (prototype)
- Mixed Action - Act by combining direct and indirect mechanisms from above.

ADRENERGIC STRUCTURES AND SAR's

- Aliphatic Amines - Generally low sympathomimetic potency and not to important.

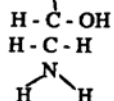


Aromatic Amines- Basic structure is beta-phenyl-ethyl amine



THESE TWO HYDROXYL GROUPS PERMIT RAPID METABOLISM BY COMT

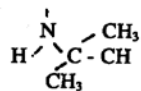
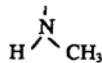
PRESENCE OF THESE TWO HYDROXYL GROUPS ENHANCE ALPHA ACTIVITY



SUBSTITUTION ON THIS ALPHA CARBON RETARDS METABOLIC BIOTRANSFORMATION

Because of rapid metabolism by COMT, which converts the -OH to -CH₃ due to metabolic biotransformation, it is orally ineffective and has a short duration.

ALKYL SUBSTITUTION ON THE "N" ATOM TEND TO ENHANCE BETA ACTIVITY



CLINICAL USES OF ADRENERGIC DRUGS

Vasoconstrictors

- Uses:
 - nasal decongestants, hypotensive states, hemostatic action
- Route of Administration:
 - drops, nasal insufflation, snorting, systemic
- Mechanism of action (describe):
 - medical terms used - rhinorrhea (runny nose)
 - coryza (acute rhinitis)
 - If vasoconstriction is too severe (from overuse), extreme vasoconstriction may occur.
 - severe vasoconstriction ischemia secondary hyperemia

Uses (cont.)

- Children:
 - CNS stimulation vs. drowsiness / coma
- OTC Uses:
 - examples of catecholamines used.

Hypotensive States (due to vasodilation)

- Lowered BP for example from allergic reaction, response to anesthesia, etc.
- Alpha adrenergics will constrict blood vessels, therefore we can use these to treat certain kinds of shock
 - **LOW VOLUME SHOCK:** Shock due to a reason other than loss of blood.
 - examples of drugs used: epinephrine, dopamine
 - Dobutamine has become popular because it increases BP without effecting the kidneys.

Hemostatic Action

- Epinephrine - locally
 - systemic absorption, local blood flow during Surgery
- Ophthalmic-Reduces formation of aqueous humor

Mydriatics

- These offer advantage over Belladonna (ie.cycoplegia)
 - Topical Epinephrine
 - Hydroxyamphetamine

Bronchodilators

- describe mechanism of action alone, and in combination with theophylline.
- Cardiac side effects
 - Isoproterenol-Pure beta
 - Epinephrine- alpha activity/secretions
 - Ephedrine
- Terbutaline-primarily beta₂ activity
 - **ALSO FOR TOCOLYSIS**
- Albuterol (Ventolin, Proventil)
- Famoterol (Foradil)

Bronchial Asthma

- During Bronchial Asthma we see:
 - Hypertension (Why then use epinephrine ?)
 - Hyper-secretions
- In addition to adrenergic agonists (sympathomimetics), xanthine derivatives, anticholinergics (parasympatholytics) such as ipratropium Br, expectorants and other agents are used as well.

Contra-indications for adrenergic agonists

- Hypertension
- Heart Disease
- Hyperthyroidism- hyper-susceptible
- Diabetes
- Pheochromocytoma

Cardiac Stimulants

- 1st, 2nd, and 3rd degree heart block
- Severe bradycardia

Cardiac antiarrhythmics (1)

- Bretylium Tosylate (Bretylol) - Inhibits NE release by depressing adrenergic nerve terminal excitability, inducing a chemical sympathectomy-like state.
- Catecholamine stores are not depleted, but the drug causes an early release of NE from the adrenergic postganglionic nerve terminals.
- Therefore, tachycardia and hypertension are seen shortly after use.

Cardiac antiarrhythmics (2)

- Amiodarone (Cordarone) - M/A is due to at least two activities:
 - A prolongation of of the myocardial cell-action potential during and after the refractory period.
 - Non-competitive alpha and beta inhibition

Cardiac antiarrhythmics (3)

- beta blockers -
- Also used for migraines, reflex sympathetic dystrophy, hypertension, PTSD, performance anxiety, etc.

CNS Stimulant Effect

- Anorexants - amphetamines
- Anti-depressants
- Analeptics
- Narcolepsy
- Hyperkinesia
- Epilepsy - Adjunct to barbiturate therapy
- Parkinson's Disease

Agents Used in Parkinson's Disease

The table below summarizes the drug therapy available for parkinsonism:

Drug Therapy for Parkinsonism						
Drugs	Indications					Usual daily dose range (mg)
	Post-encephalitic	Arterio-sclerotic	Idiopathic	Drug/chemical induced	Adjunct to Levodopa/Carbidopa	
Anticholinergics						
Procyclidine	✓	✓	✓	✓		7.5-20
Trihexyphenidyl	✓	✓	✓	✓	✓	1-15
Benztropine	✓	✓	✓	✓		0.5-6.5
Biperiden	✓	✓	✓	✓		2-8
Ethopropazine	✓	✓	✓	✓		50-600
Diphenhydramine	✓	✓	✓	✓		10-400
Dopaminergic Agents						
Levodopa	✓	✓	✓	✓ ¹		500-8000
Carbidopa/levodopa	✓		✓	✓ ¹		10/100-200/2000
Amantadine	✓	✓	✓	✓		200-400
Bromocriptine	✓		✓			12.5-100
Pergolide					✓	1-5
Selegiline					✓	10

¹ Not effective in drug-induced extrapyramidal symptoms.

SUMMARY OF SELECTED PHARMACOLOGICAL EFFECTS OF ADRENERGIC AGENTS

<u>EFFECTOR ORGAN</u>	<u>RECEPTOR</u>	<u>DIRECT RESPONSE</u>
Heart		
S-V node	BETA	Tachycardia
A-V node	BETA	Incr.conduction;;decr refract. period
Atria and Ventricles	BETA	Positive inotropy
Blood Vessels		
General	ALPHA	Contraction (constriction)
Skeletal Muscle-----	ALPHA	Contraction
-----	BETA	Relaxation (dilation)
Gastrointestinal	BETA	Inhibited motility
	ALPHA	Inhibited motility
Eye		
Radial muscles	ALPHA	Contraction (mydriasis)
Nictitating membranes	ALPHA	Contraction (for lab reference)

CARDIOVASCULAR EFFECTS OF EPINEPHRINE AND NE

EPI and NE have similar effects at moderate to high doses, but differ somewhat at low doses.

Cardiovascular effects of small (and larger) doses of NE in man

- | | |
|--------------------------|--------------------------------------|
| 1. peripheral resistance | Increased (vasoconstriction) |
| 2. diastolic pressure | Increased (result of preceding) |
| 3. systolic pressure | Increased (follows from preceding) |
| 4. mean pressure | Increased (follows from preceding) |
| 5. heart rate | Decreased (reflex response from 1-4) |
| 6. cardiac output | Decreased (result of 5, primarily) |

Cardiovascular effects of small doses of Epi in man

- | | |
|--------------------------|---|
| 1. peripheral resistance | Decreased (NET vasodilation) |
| 2. diastolic pressure | Decreased (NET vasodilation) |
| 3. systolic pressure | Increased (result of cardiac stimulation) |
| 4. mean pressure | Unchanged (combination of 2 and 3) |
| 5. heart rate | Increased (direct stim.;lack of reflex) |
| 6. cardiac output | Increased (result of cardiac stim.) |

AMPHETAMINES

- M/A: An indirect acting adrenergic

Receptor Blockers (1)

- alpha and beta blockers = epinephrine reversal
- Alpha adrenergic blocking agents
 - equilibrium type: phentolamine, tolazoline
 - non-equilibrium type: phenoxybenzamine, dibenzamine - too many irreversible side effects
 - other: methyldopa (centrally acting alpha agonist)
 - clonidine (similar m/a to above)

Receptor Blockers (2)

- Beta adrenergic blocking agents:
- Propranolol - competitive antagonist
 - membrane stabilizing activity
 - decreased cardiac output
 - decreased mean atrial pressure
 - decreased myocardial oxygen consumption

Receptor Blockers (3)

ACTIVITY:

- Propranolol may also be used for renin dependent HT
- Propranolol interferes with reflex tachycardia
- Propranolol interferes with glycogenolysis
- Contra-indications:
 - Bronchospasm
 - Cardiac depression
 - A-V block
 - 2nd/3rd degree heart block

Receptor Blockers (4) USES:

- Antiarrhythmic
- Angina Pectoris
- Hypertrophic Subaortic Stenosis
- HT
- Pheochromocytoma
- Thyrotoxicosis

Receptor Blockers (4) DI's:

- Drug Interactions:
 - Insulin and other hypoglycemics
 - Digitalis glycosides
 - Adrenolytics (Catecholamine-depleting agents, ie. reserpine)
 - Anti-hypertensives in general
 - Skeletal Muscle Relaxants - d-tubocurarine's duration of action is significantly prolonged.
- **ABRUPT PROPRANALOL WITHDRAWAL MAY CAUSE HEART ATTACK**

ADRENERGIC AMINE DEPLETORS

- Reserpine and Guanethidine - Unprotected release of NE
 - Amphetamine and Tyramine cause a protected release of NE
- Bretylium - Causes inhibition of protected release.
- Cocaine and Imipramine - Primary effect is the blockade of the reuptake mechanism, which intensifies sympathetic stimulation.
- MAO inhibitors - M/A