ADRENERGIC NEUROTRANSMISSION

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Medicinal Chemistry-I

Anatomy of Sympathetic (thoracolumber) Nervous System

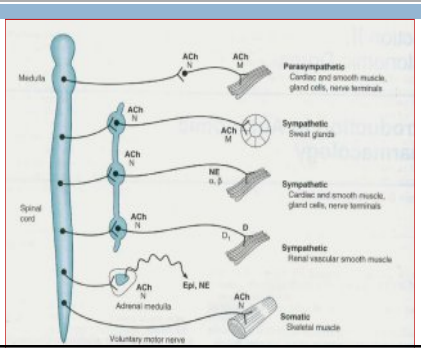
- Nerves arise from spinal cord
- Pre-ganglionic nerve fibers arise from *thoraco-lumber* region of sp.cord (T_1-L_2;containing cell bodies)⇒ terminate in sym. ganglia near spinal column (either sides)
- Post-ganglionic fibers arise form ganglia & reach to organs

Chemical Mediators (neurotransmitters)

Preganglionic sympathetic nerve fibers secrete **Acetylcholine**

Postganglionic sympathetic nerve fibers (except sweat glands) secrete **Noradrenaline**

AUTONOMIC & SOMATIC MOTOR NERVES



Classification of Adrenoceptors

ADRENOCEPTORS

α-adrenoceptors α1 α2

α1A α1B α1D α1L

α2A α2B α2C

β-adrenoceptors β1 β2 β3

Cont.

- All subtypes of α & β belong to G-protein coupled receptor family
- α_1- receptor activate PLC--⇒**IP3 & DAG** as 2nd messenger
- α_2-receptors inhibit adenylate cyclase ⇒ **↓CAMP** formation
- All types of β-receptors stimulate **adenylate cyclase**

Effects of Adrenoceptors

a) α1-receptor activation

Vasoconstriction, relaxation of GI smooth muscle, salivary secretion stimulation & hepatic glycogenolysis

b) α 2-receptors activation

Inhibition of transmitter release (including NA & ACh release for autonomic nerves), platelet aggregation, contraction of vascular smooth muscle, inhibition of insulin release

c) β1-receptors

- Increased cardiac rate & force

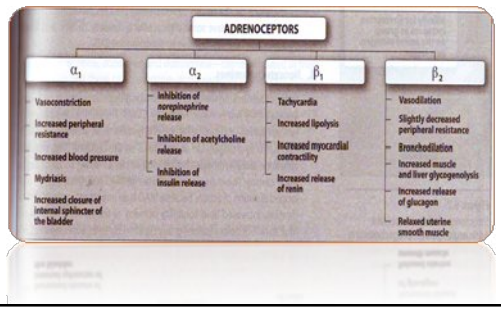
d) β2-receptors

Bronchodilation, vasodilation, relaxation of visceral smooth muscle, hepatic glycogenolysis & muscle tremors

e) β3 receptors

lipolysis

Major effects mediated by α & β adrenoceptors



Neurotransmission at adrenergic neurons

Six stages

- **Synthesis**
- **Storage**
- **Release**
- **Binding to receptors**
- **Termination of action of norepinephrine**
- **Recycling of precursor**

1. Synthesis of Norepinephrine

Tyrosine (precursor) ⇒

Transported (Na-linked carrier) into axoplasm of adrenergic neuron

⇒ hydroxylation to DOPA

⇒ **dopamine**

2) Storage of norepinephrine in vesicles

- Dopamine ➡ transported & stored in vesicles to synaptic vesicle ➡ NE
- Ad medulla= NE (methylated to epinephrine) stored in chromaffin cells
- Ad medulla = release NE (20%) + EP (80%)

3) Release of Noradrnaline

Arrival of action potential at nerve junction

⇒ triggers opening of Ca^{2+} channels

⇒ **passage of Ca^{2+} from extracellular fluid to cytoplasm of neurons**

⇒ **fusion of vesicles with cell memb.**

⇒ **rupture of vesicles**

⇒ **release of NE**

4) Binding to α receptors

- NE ⇒release from synaptic vesicles
- Diffuse across synaptic space
- Binds to either post synaptic receptors on effector organ or to presynaptic receptors on nerve ending

5) Removal of norepinephrine

NE

1) diffuse out of synaptic space & enter general circulation --- OR

2) metabolized by COMT to O-methylated derivatives in synaptic space------OR

3) recaptured by uptake system that pumps back NE into neurons

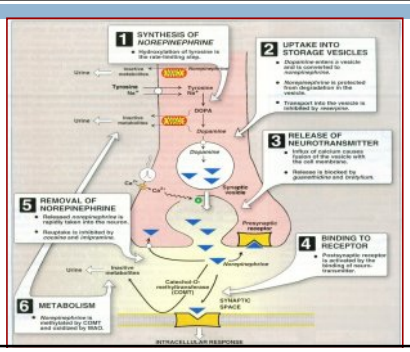
6) Potential fate of recaptured norepinephrine

Once NE reenters cytoplasm of neurons

- *May taken up into vesicles & be sequestered for release by another action potential*
- *It may persist in a pool*
- *It may be oxidized by MAO enzyme*

Inactive NE metabolites = excreted in urine as **vanillylmandelic acid, metanephrine & normetanephrine**

Synthesis & release of norepinephrine from adrenergic neuron



Classification of Adrenoceptor agonists

1) According to their chemical structure

2) By types of adrenoceptor stimulation

3) By direct or indirect action

1.Based on chemical structure

Two groups

- **Catecholamines**
- **Noncatecholamines**

A- Catecholamines

- Drugs contain catechol nucleus in their chemical structure
- Catechol nucleus= OH group at position 3 & 4 on benzene ring

e.g., ***adrenaline*** (Ad), ***noradrenaline*** (NE), ***isoprenaline*** (ISOP) , ***dopamine*** (DA) , ***dobutamine*** (Dob)

Properties of Catecholamines

1. High potency

Highest potency in activating α or β receptors

2. Rapid inactivation

- These catecholamines metabolized by COMT (postsynaptically) + MAO (intraneuronally)
- Also metabolized in liver, gut wall by MAO+COMT
- Given parenterally ; ineffective when given orally

Cont.

3. Poor penetration into CNS

- Catecholamines are polar = not readily penetrate into CNS
- Most have clinical effects attributable to CNS effects= anxiety, tremor & headache

B) Noncatecholamines

- Sympathomimetics do not contain catechol nucleus in their chemical structure

e.g., ***amphetamine, ephedrine, phenylepohrine*** (Phe), ***methoxamine, salbutamol*** (Salb), ***terbutaline, fenoterol***

- Poor substrates for MAO
- Prolonged duration of action
- ↑ Lipid solubility permits greater access to CNS

2) Based on effects of drugs on receptor types

A. Both alpha & beta agonists

e.g., Ad, NE, ephedrrine, amphetamine

B. Mainly alpha agonists

i) Mainly α_1 agonists

e.g., Phe, methoxamine

ii) Mainly α_2 agonists

e.g., clonidine, methyldopa, guanabenz, guanfacine

Cont.

c) Mainly Beta agonists

i) Mainly β1 & β2 agonists

e.g., ISOP

ii) Mainly β1 agonists

e.g., Dob, prenalterol

iii) Mainly β2 agonists

e.g., Salb, terbutaline, ritoderine, fenoterol

iv) Dopamine agonists

e.g., DA, bromocriptine, fenoldopam, ibopamine

3. Based on mechanism of action of adrenergic agonists

A. Direct acting agonists

Act directly on α or β receptors producing effects similar to those that occur following stimulation of sympathetic nerves

e.g., ***Ad, NE, ISOP, Phe, Salb***

B. Indirect acting agonists

- Agents act indirectly
- Their actions dependent on release of endogenous catecholamine

They have either of **two d/f mechanisms:**

a) displacement of stored catecholamines from adrenergic nerve ending

e.g. amphetamine & tyramine

Cont.

b) Inhibition of reuptake of catecholamines already released

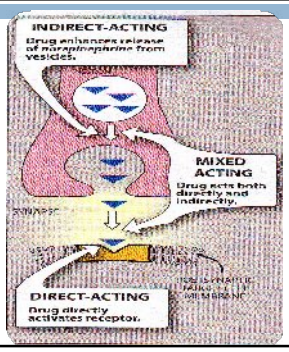
e.g., cocaine, & tricyclic antidepressants

C. Mixed action agonists

They have capacity to stimulate adrenoceptors directly + release NE from adrenergic neurons

e.g., **Ephedrine & pseudoephedrine**

Site of action of direct, indirect & mixed-acting adrenergic agonists



Organ system effects of Sympathomimetic drugs

Cardiovascular system

A. Blood vessels

- Peripheral vascular resistance & venous capacitance is controlled by catecholamines
- Alpha receptors ↑ arterial resistance
- β2 receptors promote sm muscle relaxation
- Skin + splanchnic vessels= predominantly α receptors & constrict by Ad & NE
- Cont.

- Blood vessels of skeletal muscle may constrict or dilate depend on whether α or β receptors are activated
- Overall effects of sympathomimetics on blood vessels depends on activities of that drug at α or β receptors
- D1 receptors promote vasodilation of renal, splanchnic, coronary, cerebral & other resistance vessels

B. Heart

- Direct effect on heart determined by β1

a) Positive chronotropic effect

Beta receptor activation = ↑ Ca flux in cardiac cells
→ ↑ pace maker activity both normal (SA node) & abnormal (purkinje fibers) ⇒ conduction velocity in AV node ↑ + ↓ refractory period

b) Positive inotropic effect

↑ in intrinsic contractility

c) Coronary blood flow ↑

C. Blood Pressure

Sympathomimetics= heart + PVR + venous return

Phe (α agonist) = ↑ peripheral arterial resistance + ↓ venous capacitance ⇔ rise in BP → baroreceptor vagal tone ↑ → slow HR

β-adrenoceptor agonist = stimulation of β-receptors in heart ↑ CO

Cont.

ISOP

Peripheral resistance ↓ by β2 →vasodilation= maintain or slightly ↑ systolic pressure +fall in diastolic pressure

Eye

Alpha stimulants

i) Mydriasis

Phe= activation of radial pupillary dilator muscle on eye

ii) **Out flow of aqueous humor** ↑→ ↓ Intraocular pressure---helpful in glaucoma

Beta agonist = little effect on eye

Cont.

Beta antgonists

- Production of aqueous humor ↓

Adrenergic drugs directly protect neuronal cells in the retina

Respiratory tract

- Activation of β2 receptors of bronchial sm muscles= bronchodilation
- Blood vessels of upper respiratory tract mucosa contain α receptors= decongestant action of adrenergic stimulant – clinically useful

Gastrointestinal tract

β-receptors

- Relaxation (via hyperpolarization) & d/c spike activity in sm muscles

α-selective agonists

- D/c muscle activity indirectly by presynaptically reducing the release of Ach & possibly other stimulants within ENS

α2 receptors

- D/c salt & water flux into lumen of intestine

Genitourinary tract

- Human uterus = α & β2 receptors
- Bladder base, urethral sphincter & prostate contain **α-receptors** ----Mediate contraction ----promote urinary continence
- Bladder wall has **β2** ---mediate relaxation
- Ejaculation depends on normal α-receptors activation in ductus deferens, seminal vesicles & prostate

Exocrine glands

- Adrenoceptors present on salivary glands regulate secretion of amylase & water
- Clonidine =dry mouth symptom
- Adrenergic stimulants- --↑ sweat production (apocrine sweat glands on palms of hands) during stress

Metabolic Effects

- Activation of β3 of fat cells==↑ lipolysis with enhanced release of free FA & glycerol
- α2 receptors of lipocytes– inhibit lipolysis by ↓ intracellular cAMP
- Sympathomimetic ↑ glycogenolysis in liver (by β receptors)--- ↑glucose release into circulation
- Cont.

- ↑ of catecholamine = metabolic acidosis
- β-receptor ⇔ ↑ insulin release
- α2 ⇔ ↓ insulin release

Effects on Endocrine functions & Leukocytosis

- Insulin stimulated by β-receptors & inhibited by α2 receptors
- Renin stimulated by β1 & inhibited by α2 receptors (β-receptor antagonist ↓ plasma renin & BP in HTN by this mechanism)
- Adrenoceptors also modulate secretion of PTH, calcitonin, thyroxin & gastrin
- At high conc. Ad cause leukocytosis

Effect on CNS

- Action of sympathomimetics on CNS vary dramatically depending on ability to cross BBB
- **Catecholamines** ---CNS effects at high doses (nervousness, tachycardia, tremor)
- **Noncatecholamines** with indirect actions (**amphetamine**) → mild alerting with improved attention to boring tasks, elevation of mood, insomnia, euphoria, anorexia, fully blown psychotic behavior

Specific sympathomimetic drugs

Catecholamaines

1) Epinephrine (adrenaline)

- Powerful vasoconstrictor & cardiac stimulant
- It has +ve inotropic & chronotropic actions on heart
- Vasoconstriction due to effect on α receptors
- Also activates β2 receptors in some vessels (sk muscle) –dilation---total Peripheral resistance↓= ↓BP---increased blood flow in sk muscle during exercise

2) Norepinephrine (noradrenaline)

- NE & Ad have similar effects on β1 receptors in heart & similar potency at α receptors
- NE have little effect on β2 receptors -- ↑peripheral resistance-+ ↑ sys & diastolic BP

Isoproterenol

- Very potent β-receptor agonist
- Little effect on α receptors
- +ve chronotropic & inotropic actions (b/c of β-receptor activation)
- ISOP is potent vasodilator
- Marked ↑ in CO associated with fall in diastolic & MAP & lesser d/c or slight ↑ in systolic pressure

Dopamine

- Activates D1 receptors = vasodilation (several vascular beds including renal)
- Activation of presynaptic D2 receptors=suppress NE release
- Dopamine= activates β1 receptors on heart
- Low dose of DA ↓ peripheral resistance
- High doses DA activates vascular α receptors = vasoconstriction (including renal)

Dopamine agonists

- Dopamine agonists with central actions important for treatment of Parkinson's disease & prolactinemia

Dobutamine

- Relatively β1 selective synthetic catecholamine

Fenoldopam

- D1 receptor agonist
- Selectively leads to peripheral vasodilation in some vascular beds
- Intravenous treatment of severe hypertension

Other Sympathomimetics

Phenylephrine

- Pure α-agonist
- Acts directly on receptors
- It is not catechol derivative so not inactivated by COMT
- Much longer duration of action than catecholamine
- Effective mydriatic & decongestant
- Used to raise BP

Methoxamine

- Acts pharmacologically like Phe, acting directly on α1 receptors
- Cause prolonged ↑ in BP due to vasoconstriction
- Vagaly mediated bradycardia

Midodrine

- Prodrug, enzymatically hydrolyzed to desglymidodrine (α_1 receptor selective agonist)
- Used for treatment of postural hypotension, typically due to impaired ANS function

Ephedrine

- Non catechol phenylisopropylamines
- Occurs in various plants
- High bioavailbility
- Long duration of action (hours)
- Its excretion can be accelerated by acidification
- Mild stimulant, gain access to CNS
- Pseudoephdrine---component of many decongestant mixture

Xylometazoline & oxymetazoline

- Direct acting α agonist
- Used as topical decongestant (promote constriction of nasal mucosa)
- Cause hypotension at high doses b/c of central clonidine like effects
- Oxymetazoline has significant affinity for α-**2A** receptors

Amphetamine

- **Phenylisopropylamine**
- Important b/c of its use & misuse as a CNS stimulant
- Readily enter into CNS
- Marked stimulant effect on mood & alertness
- Depressant effect on appetite
- Peripheral actins mediated through release of catecholamines

Methamphetamine (N-methylamphetamine)

- Very similar to amphetamine

Phenmtrazine

- Variant of phenylisopropylamine with ampetamine like effects
- Promoted as an anorexiant
- Popular drug of abuse

Receptor-selective Sympathomimetic Drugs

- Alpha2-selective agonists
- D/c BP through action in CNS
- Direct application to blood vessels cause vasoconstriction

e.g., **clonidine, methyldopa, guanfacine, guanabenz**

All are useful for treatment of HTN