Topic 10-2 Drugs of the Nervous System-Adrenergic

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Part VI- Nervous system -Corey
1. Nerve Transmission

Peripheral nervous system

- Brain
- Spinal cord
- Peripheral nerves
- Muscle
- Heart
- Gastrointestinal tract (GIT)
- Peripheral nerves
1. Nerve Transmission

Peripheral nervous system

CNS (Somatic) — Ach (N)

CNS (Autonomic)

- Sympathetic
  - Synapse — Ach (N)
  - Adrenal medulla — Adrenaline
  - Synapse — NA

- Parasympathetic
  - Synapse — Ach (N)

Skeletal muscle

AUTONOMIC

- Smooth muscle
- Cardiac muscle
1. Nerve Transmission

Synapses
100-500A
Nerve impulse
Nerve

Receptors
Vesicles containing neurotransmitters

Release of neurotransmitters

Receptor binding and new signal

New signal

Adrenergic endogenous agonists: catechols

Adrenaline

Noradrenaline

In adrenal medulla

Catechol ring system
1. Nerve Transmission

α and β adrenergic G-protein receptors—many overlapping functions

In General:

• β adrenergic receptors
  • Relax smooth muscle (except heart muscle)
  • β1 blockers slow heart muscle contraction, lowers BP

• α adrenergic receptors
  • Contract smooth muscle (except gut)
  • α1 agonists -used for vasoconstriction in local anesthesia, α2 for glaucoma
  • α1 antagonists relax smooth muscle for hypertension and angina
1. Nerve Transmission

α and β adrenergic G-protein receptors-

- Nerve signal
- Target cell
- Vesicles fuse and release transmitter
- Receptor binding and new signal
- Neurotransmitter departs receptor
- Neurotransmitter reabsorbed by active transport
- Neurotransmitter repackaged or metabolized

- Receptor
- Uptake protein
- Vesicle containing noradrenaline
1. Nerve Transmission

Noradrenalin (norepinephrine) system drug targets

- Negative feedback system
- Prostaglandins
- Cholinergic receptor
- Presynaptic adrenergic receptor
- Prostaglandin receptor
- Postsynaptic adrenergic receptor
- Activation of receptor reduces noradrenaline release

NA  Noradrenaline
Adrenergic Binding Site

TM6
Phe-290

H-bonding group

Ser-207

Ser-204

TM5

TM3

Asp-113

meta

para

Important binding groups

HQ

HO

OH

NHR₂

R
Adrenergic Binding Site: $\alpha$ vs. $\beta$

Stimulates $\beta$, not $\alpha$ due to bulky groups
Adrenergic Binding Site: spec. $\beta_2$ agonists and asthma

selective $\beta_2$ agonists, adrenalin is less specific
α Adrenergic antagonists:

- Carvedilol
- Labetalol

- General α/β for antihypertension
- α1 for urinary tract relaxation prostate enlargement treatment

- Mirtazepine (Remeron) α2 blocker for depression-increases serotonin and NA
β-adrenergic blockers: cardiovascular drugs for BP

Isoprenaline

Dichloroisoprenaline

Pronethalol

Partial β agonists
specific β adrenergic blockers: cardiovascular drugs for BP

Extra ring converts agonist to antagonist
specific $\beta$ adrenergic blockers: cardiovascular drugs for BP

$\beta$–blockers effects

- Reduce cardiac output
- Reduce renin release from kidneys (which produces Angiotensin I and II)
- Reduces general activity of CNS
specific $\beta$ adrenergic blockers: cardiovascular drugs for BP

$\beta$-blockers side effects

- Bronchoconstriction due to $\beta_2$ blocking
- Lethargy
- Dizziness, dreams from bbb passage of hydrophobic propanolol
- Potential heart failure
More selective $\beta_1$-blockers - Next generation

$\beta_1$ receptor
More selective $\beta_1$-blockers-3rd generation!
Other Adrenergic drugs

- Biosynthesis “dummies” down regulate adrenergic system

\[
\begin{align*}
\text{α-Methyltyrosine} & \xrightleftharpoons{\text{Dopa decarboxylase}} \text{α-Methyl-m-tyramine} & \xrightarrow{\text{Dopamine β-hydroxylase}} \text{Metaraminol} \\
\text{α-Methyl-dopa} & \xrightarrow{\text{Dopa decarboxylase}} \text{Dopamine} & \xrightarrow{\text{β-monoxygenase}} \text{α-Methylnoradrenaline}
\end{align*}
\]

α-methyl tyrosine: a fake amino acid
Other Adrenergic drugs

- The tricyclic antidepressants
- NA reuptake inhibitors-desensitize a2 receptors leading to more serotonin and NA released to get effect.

![Chemical structures of Desipramine, Imipramine, and Amitriptyline](image)

Similar 3D structure to NA

- Desipramine
- Noradrenaline

Overlay
Other Adrenergic drugs

- Newer antidepressants
- Bupropion (Welbutrin) and others inhibit reuptake of both NA and dopamine in CNS.
- Reuptake inhibitors also used for ADHD (Ritalin, Strattera)
Other Adrenergic drugs

- Cocaine-inhibits NA uptake in peripheral nervous system and dopamine in CNS
Other Adrenergic drugs

- Amphetamine-inhibits NA carrier uptake in CNS
  
  ![Amphetamine structure](image)

- Monoamine oxidase inhibitors-increase [catecholamine] by stopping breakdown
  
  ![Noradrenaline metabolism](image)