Pharmacology

Subject: A.N.S 5 Slides & Sheet!

Done by: Abdullah F. Masri + Slides

Doctor: Muneer Gharaibeh.

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Structure Activity Relationships

- Substitution on the Benzene Ring
- Substitution on the Amino Group
- Substitution on the Alpha Carbon

A modification in the structure will lead to a change in the following:
- Pharmacokinetics
- Pharmacodynamics
- Receptor selectivity
Substitution on the Benzene Ring:

- Maximal $\alpha$ and $\beta$ activity is found with catecholamines, i.e. drugs having $-\text{OH}$ groups at the 3 and 4 positions on the benzene ring.
- The absence of one or the other of these groups, particularly the hydroxyl at $C_3$, without other substitutions on the ring may dramatically reduce the potency of the drug. For example, phenylephrine is much less potent than epinephrine; indeed, $\alpha$-receptor affinity is decreased about 100-fold and $\beta$ activity is almost negligible.

No $-\text{OH}$ groups on the ring means:

1- COMT is not effective, so the drug is effective orally.

2- Lipid solubility increases, so the drug has a CNS effect. For example, ephedrine and amphetamine are orally active, have a prolonged duration of action, and produce central nervous system effects not typically observed with the catecholamines.

Most of orally administered hormones+ epinephrine will be degraded by COMT (Catechol O Methyl Transferase), if COMT isn’t effective, the drug will be effective orally (if the drug has no $\text{OH}$).

They are CNS drugs, not ANS.
Substitution on the Alpha Carbon

- Substitutions at the $\alpha$ carbon, block oxidation by monoamine oxidase (MAO) and prolong the action of such drugs, particularly the noncatecholamines.
- Ephedrine and amphetamine are examples of $-\alpha$ carbon substituted compounds.

Another enzyme that breaks down sympathomimetics, won’t recognize catecholamines and oxidize them.
Effects of Sympathomimetics

• Effects depend on:
  • Relative selectivity for $\alpha$ or $\beta$ adrenoceptors.
  • Pharmacologic actions at those receptors.
  • Compensatory “baroreflex” mechanisms aimed at restoring homeostasis.

Sitting, lying down, standing up will elicit the baroreceptor reflex mechanisms to restore blood pressure and vice versa. e.g. if you increase blood pressure; vagal stimulation will occur leading to bradycardia, eventually dropping heart rate.

Relative selectivity of alpha and beta adrenoceptors: not all are the same, you'll face some confusing difference, but the point you should focus on is: Does the drug works on alpha or beta, or more alpha than beta and vice versa (know this for all drugs).
Cardiovascular Effects of Alpha1-Receptor Activation

- A relatively pure alpha agonist such as phenylephrine causes arterial and venoconstriction, increases peripheral arterial resistance and decreases venous capacitance.
- The enhanced arterial resistance usually leads to a dose-dependent rise in blood pressure.
- The rise in blood pressure elicits a baroreceptor-mediated increase in vagal tone with slowing of the heart rate, increased blood pressure with decreased heart rate.
- Cardiac output may not diminish, since increased venous return may increase stroke volume.
- If baroreflex function is removed by pretreatment with the ganglionic blocker trimethaphan, the pressor effect of phenylephrine is increased approximately tenfold, and bradycardia is no longer observed. because the reflex will be interrupted if vagus was cut or inhibited
Note:
- If you use phenylephrine which is a pure α agonist it will reduce the heart rate indirectly (reflexly) through activation of the vagus nerve.
- Phenylephrine will work as pure alpha agonist raising blood pressure.

CAPACITANCE:
In venous circulation; if you increase venous capacitance (AKA venous pooling, احتواء الأوردة) this will cause decreased venous return reducing the cardiac output.
If you decrease it, the blood will return to the blood, i.e. increased venous return and cardiac output.

NOTE FOR THE NEXT SLIDE:
- The adrenal gland could be considered a part of the sympathetic system (because it responses together with the sympathetic system in the process of exercise at stress), and - at the same time- might also be considered an endocrine gland, because nervous stimulation produces minute amounts of the transmitter (works locally). While nervous stimulation of pure endocrine gland induce large amount of the hormone which will work on distant places.

- In stress, adrenal gland and the sympathetic nervous system will work the same way, sympathetic will secrete norepinephrine while the adrenal will secrete 80% epinephrine, 20% norepinephrine.
Effects of Alpha1-Receptor Activation

- Vasoconstriction in the:
- Skin vessels
- Splanchnic vessels.
- The blood vessels of the nasal mucosa and this explains their decongestant action.
- During exercise, epinephrine is secreted from the adrenal gland not the sympathetic nervous system.

- Epinephrine also activates \( \beta_2 \) receptors in skeletal muscle blood vessels, leading to their dilation. Consequently, total peripheral resistance may actually fall. Only with epinephrine not with phenylephrine.

- Activation of \( \beta_2 \) receptors in skeletal muscle contributes to increased blood flow during exercise. The “fight” mode.

- Under physiologic conditions, epinephrine released from the adrenal gland, functions largely as a hormone by acting on distant cells.
Vascular Effects of Alpha2-Receptor Activation

- Alpha2 adrenoceptors are present in the vasculature, and their activation leads to vasoconstriction.
- This effect, however, is observed only when α₂ agonists are given locally, by rapid intravenous injection, or in very high oral doses.
- When given systemically i.e. low doses, these vascular effects are obscured by the central effects of α₂ receptors, which lead to inhibition of sympathetic tone and blood pressure.

Directly applied α₂ agonist on the blood vessels will cause constriction, but if it was given the chance to go to the CNS it’ll produce an indirect effect on blood pressure (work on the vasomotor center to reduce the blood pressure).

- Hence, α₂ agonists are used as sympatholytics in the treatment of hypertension.

Works on the brain to inhibit the vasomotor center (inhibiting sympathetic system by acentral mechanism), i.e. opposite to the effect of phenylephrine (α₂ agonist).
Effects of Beta-Receptor Activation

- Stimulation of $\beta$ receptors in the heart increases cardiac output by stimulating contractility (inotropic effect) and by a direct stimulation of the sinus node to increase heart rate (chronotropic effect).

- Also, conduction velocity in the atrioventricular node is increased (dromotropic effect), and the refractory period is decreased.

- Beta agonists also decrease peripheral resistance by activating $\beta_2$ receptors, leading to vasodilation in certain vascular beds.

- Physiologic stimulation of the heart by catecholamines tends to increase coronary blood flow.

Actually not related to the action of the sympathetic nervous system. It’s rather due to accumulation of metabolites. Increased heart activity will give metabolites that are local vasodilatory substances like adenosine (homeostatic function of the blood of the coronary arteries, depends on the metabolic state of the heart). But the direct effect of catecholamines on beds of vessels in constriction!

- Isoproterenol is a nonselective $\beta$ agonist; it activates both $\beta_1$ and $\beta_2$ receptors. The net effect is to maintain or slightly increase systolic pressure and to lower diastolic pressure, so that mean blood pressure is decreased.

Read the note in next slide about this
Effects of Dopamine-Receptor Activation

- Intravenous administration of dopamine promotes vasodilation of renal, splanchnic, coronary, cerebral, and perhaps other resistance vessels, via activation of D1 receptors.

- Activation of the D1 receptors in the renal vasculature may also induce natriuresis. i.e. Secretion of sodium

- The renal effects of dopamine have been used clinically to improve perfusion to the kidney in situations of oliguria (abnormally low urinary output).

Isopretanolol: does not affect α receptors, its action on β1 stimulates the heart, but its action on β2 stimulates vasodilation, resulting in the net effect (mean BP is slightly decreased).

Or in cases of renal failure due to decreased renal perfusion.
- If dopamine was used, this will cause renal dilation leading to enhancement of renal perfusion and consequently improvement of the renal function.
Effects of Dopamine-Receptor Activation

- Dopamine activates $\beta_1$ receptors in the heart.
- At low doses, peripheral resistance may decrease.
- At higher rates of infusion, dopamine activates vascular receptors, leading to vasoconstriction, including the renal vascular bed (by working on alpha receptor).
- Consequently, high rates of infusion of dopamine may mimic the actions of epinephrine.

In cases of renal impairment we give low doses of dopamine to increase the renal blood flow. But in cases of shock (hypotension) we can decrease the dose to stimulate the heart and to increase the peripheral vascular resistance.

Let’s assume a drug works on $\alpha$, $\beta$, and even muscarinic receptors, but MAINLY on $\alpha$ receptors. This means that it has the highest affinity to $\alpha$ receptors, and less much affinity of $\beta$ and so on.

- Dopamine –by definition- works mainly on $D$ receptors, reducing blood pressure in low doses. If you increase the dose it’ll work on the $\beta$ receptors increasing blood pressure.
- Dopamine works mainly on $D_1$, $\beta_1$, and $\alpha_1$ receptors.
Noncardiac Effects of Sympathomimetics

- Activation of $\beta_2$ receptors in bronchial smooth muscle leads to bronchodilation, and $\beta_2$ agonists are important in the treatment of asthma.

- In the eye, $\alpha$ receptor activation by drugs, such as phenylephrine, causes mydriasis.

- Alpha agonists also increase the outflow of aqueous humor from the eye and can be used clinically to reduce intraocular pressure.

- In contrast, beta agonists have little effect, but beta antagonists decrease the production of aqueous humor. These effects are important in the treatment of glaucoma, a leading cause of blindness.

Treated with $\beta$ blockers.
Noncardiac Effects of Sympathomimetics

- The **genitourinary** organs, the bladder base, urethral sphincter, and prostate contain **alpha receptors** that mediate contraction and therefore promote urinary continence (control of urination).
- Urinary incontinence, is any involuntary leakage of urine, a case common with elderly people.

- The specific subtype of $\alpha$ receptor involved in mediating constriction of the bladder base and prostate is uncertain, but $\alpha_{1A}$ receptors probably play an important role.

- Alpha-receptor activation in the ductus deferens, seminal vesicles, and prostate plays a role in normal ejaculation.
Noncardiac Effects of Sympathomimetics

• Insulin secretion is stimulated by $\beta$ receptors and inhibited by $\alpha_2$ receptors.

  This means that using $\beta$ blockers will interfere with the insulin secretion, as well $\alpha_2$ agonists may inhibit insulin secretion.

• Similarly, renin secretion is stimulated by $\beta_1$ and inhibited by $\alpha_2$ receptors.
CNS Noncardiac Effects of Sympathomimetics

- The catecholamines are almost completely excluded by the blood-brain barrier. Because of presence of a large group on the amine [substitution of the amine]

- Peripheral effects of β-adrenoceptor agonists, such as tachycardia and tremor, are similar to the somatic manifestations of anxiety.

  Mydriasis, tremor, sweating, nervousness, tachycardia, urinary retention (When you’re anxious you’ll forget about your urinary and bowel movements!)

  Anxiety is a disease caused by a defect in the CNS, and the ANS is a part of the PNS, but it’s found that the symptoms associated with anxiety are similar to the manifestations associated with the sympathetic nervous system activation, although they aren’t related!
Noncatecholamine sympathomimetics, with indirect actions, such as amphetamines, can readily cross the BBB, and produce qualitatively very different central nervous system effects. These actions vary from mild alerting, with improved attention to boring tasks; through elevation of mood, insomnia, euphoria, and anorexia; to full-blown psychotic behavior. These effects are not readily assigned to either β- or α-mediated actions and may represent enhancement of dopamine-mediated processes or other effects of these drugs in the central nervous system.
Metabolic Effects of Sympathomimetics

- Activation of $\beta_3$ adrenoreceptors in fat cells leads to increased lipolysis with enhanced release of free fatty acids and glycerol into the blood.

- Sympathomimetic drugs enhance glycogenolysis in the liver, as well as the muscles, which leads to increased glucose release into the circulation, mainly by $\beta_3$ receptors.

- Activation of $\beta_2$ receptors promotes the uptake of potassium into cells, leading to a fall in extracellular potassium.

- This may lead to a fall in the plasma potassium concentration during stress and protects against a rise in plasma potassium during exercise.

- $\beta$ receptors increase insulin secretion, while $\alpha_2$ receptors decrease insulin secretion. However, the major regulator of insulin release is the plasma concentration of glucose.

  - The sympathetic can regulate it, but it’s not the main.
Epinephrine (adrenaline)

- Is an agonist at both $\alpha$ and $\beta$ receptors.
- It is very potent vasoconstrictor and cardiac stimulant.
- The rise in systolic blood pressure that occurs after epinephrine release or administration is caused by its positive inotropic and chronotropic actions on the heart (predominantly $\beta_1$ receptors) and the vasoconstriction induced in many vascular beds ($\alpha$ receptors).

Naturally occurring neurotransmitter in the sympathetic nervous system and in the adrenal gland, released in large amounts in response to stress. It is a metabolite of norepinephrine (by adding a methyl group).

Causes vasoconstriction, cardiac stimulation, contractility stimulation, electrical activity stimulation.

This is regarding epinephrine as an administered drug not as a neurotransmitter.
Norepinephrine (levarterenol, noradrenaline)
• Is an agonist at both $\alpha_1$ and $\alpha_2$ receptors. Norepinephrine also activates $\beta_1$ receptors with similar potency as epinephrine, but has relatively little effect on $\beta_2$ receptors.  

Consequently, norepinephrine increases peripheral resistance and both diastolic and systolic blood pressure.

• Compensatory baroreflex activation tends to overcome the direct positive chronotropic effects of norepinephrine; however, the positive inotropic effects on the heart are maintained. Only the chronotropic effect is blocked by reflex vagal stimulation and the heart rate is reduced, so BP is increased but the heart rate is decreased.

Norepinephrine works mainly on $\alpha_1$, $\alpha_2$, and $\beta_1$. Whereas Epinephrine is not that specific.

Won’t work on bronchi.
Dopamine

• Is the immediate precursor in the synthesis of norepinephrine

• Endogenous dopamine may have more important effects in regulating sodium excretion and renal function.

• Its deficiency in the basal ganglia leads to Parkinson's disease, which is treated with its precursor levodopa.

  Levo-rotatory dopa. Dopamine is not administered in this case because it won’t cross the BBB and will have peripheral action only. While a good amount of L-Dopa will reach the brain before metabolized.

• Dopamine receptor antagonists are also targets for antipsychotic drugs. e.g. Schizophrenia
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