(SECOND)

#11
adrenergic agonist & antagonist

MADE BY LAITH SOROUR
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Pre-lecture (min 3.0)
* last lecture we talked about parasympathetic nervous system about cholinergic drugs(agonists) & anti-cholinergic drugs(antagonists)
* we call the cells that accept Ach cholinergic cells
(min 5.30)
- in general adrenergic receptors we have alpha & beta receptors
alpha has alpha-1 & 2 beta has 1&2 we talked about them in the last lecture 
you should know where each neurotransmitter binds(((Ach→cholinergic receptors in cholinergic cells and pre-ganglions, noradrenaline and adrenaline in adrenergic receptors)))
and the function of each receptor and the agonists and antagonists and how they bind direct & indirect

Adrenergic agonist (sympathomimetic or adrenergic drug): 
(min 7.25)

-Agents that mimic actions of sympathetic system & stimulate adrenergic receptors (adrenoceptors)
- Adrenergic neurons release norepinephrine as primary neurotransmitter
- Adrenergic neurons are found in CNS & sympathetic nervous system SNS (as links between ganglia & effector organs)

Classification of adrenergic agonists:

**Direct-acting: (8.30)
means go direct to the receptor and works as NA & A
have two types:
1- Selective (salbutamol, dobutamine)
means recognize certain receptor (alpha-1 or 2,beta 1 or 2)
is important because can give us certain activity without toxicity(adverse effect)
* if affinity of the drug increased for more than one receptor it gives more side effect
alpha 1 & 2 are related to each other by shape but some drugs can distinguish between them(selective) but other drugs can’t even distinguish between alpha and beta(non-selective)
* for example a drug that works on beta-1 & 2(non-selective) can give us a side effect because b-1 increases the heart rate and b-2 dilates airway passages and adrenaline binds t them when someone is running or scared
2- Non-selective (adrenaline, noradrenaline) *these are found naturally in the body
*when released in body they bind to all adrenergic receptors
*in drugs we only give them in emergencies because it can give high side effects
*A works on all receptors\NA works on a-1,b-1,a-2

**Indirect-acting: min 9.55

- **Releasing agents (amphetamine→(*CNS stimulator))**
  makes the releasing of Adrenaline & NA more

- **Uptake inhibitors (cocaine, tricyclic antidepressants)**
  uptake means taking(absorb) the neurotransmitter from pre-synaptic cleft
  so when we inhibit the uptake more A & NA stays in the cleft near the receptors so
  we prolong the action

- **MAO Inhibitors**
  mono-amino oxidase recycles neurotransmitters and are used and anti-depressant
  MAO blockers increases the concentration of neurotransmitters

**Mixed-acting(ephedrine, pseudoephedrine)**
works direct & indirect

**Actions of adrenergic agonists:**

- These are mediated through stimulation of alpha, beta & dopaminergic
  adrenoceptors
- All these adrenoceptors are metabotropic receptors (G protein-coupled receptors)
  *g protein-coupled receptor is 7-helix on membrane which releases second
  messenger and gives a cascade of actions until the biological effect

**Inhibitors of noradrenaline pathway in body:**

- Synthesis: metyrosine useful in treatment phaeochromocytoma
- Storage: is blocked by reserpine
- Binding: by alpha & beta-blockers
- Reuptake: by cocaine & tricyclic antidepressants (TCAs) (imipramine)
Sympathomimetics:

They are also classified into:

- **Catecholamines**: (adrenaline, NA, dopamine, dobutamine & isoprenaline)
  *catechol: benzene group + 2 OH

**Pharmacokinetics:**
* rapid onset action \(\rightarrow\) works fast and eliminated fast
* brief duration of action \(\rightarrow\) short half-life
* not administered orally(used during emergency parenteral)
* don’t penetrate BBB \(\rightarrow\) Poor penetration into CNS
* Enzymatic metabolism by MAO & COMT

- **Non-catecholamine**: (synthetic alpha-agonists & beta- agonists, e.g. phenylephrine, ephedrine, amphetamine)

**Pharmacokinetics:**
* Slower onset & longer duration of action
* can be administered orally or via inhalation or parenteral
* Less enzymatic degradation \(\rightarrow\) because doesn’t have catechol group(enzyme goes to catechol group)
* More central effects (CNS effects) \(\rightarrow\) because when no catechol less OH groups \(\rightarrow\) less H-bond \(\rightarrow\) more lipophilicity \(\rightarrow\) can cross BBB

*More the ethyl groups more the affinity so more binding occurs and effect increases so the specificity increases

**Alpha-adrenoceptors**

- \(\alpha_1\) present on postsynaptic membrane of organs supplied by sympathetic system
- \(\alpha_2\) present presynaptically on adrenergic nerve terminals & post-synaptically in certain sites
*alpha 2 makes balance by negative feedback inhibition
- Presynaptic \(\alpha_2\) are autoregulatory; controlling release of NA from nerve endings. \(\alpha_2\) stimulation inhibits NA release
  high NA conc. Inhibits its release
  alpha2 reveres the sympathetic action although it’s a receptor for it because it is regulatory

**Alpha1-Adrenoceptors:**
- Vascular smooth M \(\rightarrow\) Vasoconstriction
- Radial M. of iris \(\rightarrow\) Mydriasis
- Bladder sphincter \(\rightarrow\) Contraction
Intestine sphincter → Contraction
Male sex organs → Ejaculation
Inhibits entry of K into cells → Hyperkalemia (high K in blood)
Increase peripheral vascular resistance
(blood moves in dilated veins easier)
if it is very high makes hypertension

Alpha2-adrenoceptors:
Presynaptic → Inhibits NA release
Platelets → Enhances aggregation
Islet cells → Inhibits insulin release of pancreas
*alpha2 blockers increase insulin

alpha-stimulants:
Pressor agents:
- Phenylephrine
Mucosal decongestants:
- Pseudoephedrine, Oxymetazoline
Alpha 2-agonists:
- Clonidine & alpha-methyldopa

1- Pressor agents:
These are non-catecholamines that increase peripheral vascular resistance (PVR) & arterial blood pressure (both SBP & DBP)
Heart rate may decrease due to reflex vagal stimulation secondary to increase in ABP
They reduce renal blood flow (RBF) & splanchnic blood flow due to α1-vasoconstriction

**Phenylephrine:**
- Is a direct acting, synthetic adrenergic drug
- It has predominantly direct α1-agonist effect, a vasoconstrictor & It is used as:
  Pressor agent
  Nasal decongestant agent (makes vasoconstriction for nasal vessels)
  Mydriatic agent (makes the iris wider)
  Vasoconstrictor agent with local anesthetics (LA)
*local anesthesia dilates the vessels so the absorption increases this leads to short anesthesia so we give a phenylephrine so it constricts the vessels and make longer effect of anesthesia

2-Mucosal decongestants: (Pseudoephedrine, Oxymetazoline)
-* Useful in allergic rhinitis, common cold & sinusitis (التهاب الجيوب)
Oxymetazoline is used in Ophthalmic drops for relief of redness of eye associated with swimming, colds or contact lens
*if the face is red means its vasodilated \blue→constricted

** Avoid:
- Prolonged use (rebound congestion→means when we stop taking the drug the problem returns so we give it 3 days and stop)
- In hypertensive patients→in hypertension the vessels are already constricted
- Children below 2 years of age
- Therapy with MAOI or with tricyclic AD→those drugs increase the conc. Of neurotransmitters so when I give an agonist overdose happens and leads to shock

3. Alpha 2-agonists (clonidine & alpha-methyldopa)
- centrally acting antihypertensive drugs: clonidine & alpha-methyldopa (Aldomet)
- these act acentrally to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery
- they are rarely used because of risk of rebound hypertension on withdrawal of therapy

Adrenergic Antagonist (blockers or sympatholytic agents): 32.00

- These drugs act by either reversibly or irreversibly attaching to the receptor, thus preventing its activation by endogenous catecholamines
- They are classified according to their relative affinities for α or β receptors:
  - β-blockers
  - α-blockers
Beta-adrenergic blocking agents
*are found everywhere but B1 majorly concentrated in heart\B2 majorly concentrated in lungs
They are divided into:
- Non-selective: act at both β1 and β2 receptors
- Cardioselective: block β1 receptors
} The names of all β-blockers end in “-olol” except for labetalol and carvedilol

Therapeutic use: min 34.00
- Hypertension (HTN)→(the drug either dilate the vessels or decrease heart rate)
- Angina
- Cardiac arrhythmias
- Myocardial infarction (MI)
- Congestive heart failure (CHF)
- Hyperthyroidism→(happens because of very active heart work)
- Glaucoma
*anti-adrenergic drugs are almost same as cholinergic drugs
- Prophylaxis of migraine headaches
*one of the reasons of headache is vasodilation so beta-blockers constricts it

A. Propranolol: { 38.00
- Inderal, Indicardin
- A nonselective β antagonist
- Is the prototype β-adrenergic antagonist and blocks both β1 and β2 receptors

actions:
A. Cardiovascular:
- Negative inotropic & chronotropic effects (decrease cardiac output, bradycardia, decrease oxygen consumption)
B. Peripheral vasoconstriction:
- Reduction in cardiac output leads to decreased blood pressure. This hypotension triggers a reflex peripheral vasoconstriction
C. Bronchoconstriction
D. Increased Na+ retention
E. Hypoglycemia

Therapeutic effects:
1. Hypertension
2. Migraine (prophylaxis)
3. Hyperthyroidism
4. Chronic stable angina (not for acute attacks)
5. Myocardial infarction: (protect form second attack, reduce infarct size, sudden arrhythmic deaths)
6. Anxiety
7. Essential tremor

Adverse effects:
- Bronchoconstriction
- Cardiac arrhythmias (sudden withdrawal)
because of reflux tachycardia
also reflux peripheral vasoconstriction happens
- Sexual impairment ➔ because less blood flow
- Hypoglycemia
}

B. Timolol, Nadolol
- Nonselective β antagonists
- Are more potent than propranolol
- Nadolol has long duration of action (14-24 hrs)
- Timolol is used topically in treatment of chronic open-angle glaucoma. It reduces production of
aqueous humor by ciliary body
- Occasionally, for systemic treatment of hypertension (in progressed situations because non-selective)

C. Selective B1 antagonists:
- Acebutolol, atenolol (hypoten, tenormin), metoprolol, esmolol
- Cardioselective β-blockers
- Are useful in hypertensive patients
- Are useful in diabetic hypertensive patients
- Have less effect on peripheral vascular β2 receptors, coldness of extremities, a common side effect of β-blocker therapy, is less frequent

D. Antagonists of α- & β-adrenoceptors:
- Labetalol & carvedilol
  - Are reversible β-blockers with concurrent α1-blocking actions that produce peripheral vasodilation, thereby reducing blood pressure
  - Carvedilol also decreases lipid peroxidation and vascular wall thickening, effects that have benefit in heart failure.

Labetalol:
- Labetalol is useful for treating the elderly or black hypertensive patient
- Labetalol is employed as an alternative to methyldopa in treatment of pregnancy-induced hypertension
- I.V labetalol is used to treat HTN emergencies, because it can rapidly lower blood pressure

Ψ Adverse effects:
- Orthostatic hypotension and dizziness are associated with α1 blockade
  *orthostatic according to standing pose
  pressure to position (higher to slower):
sleeping → sitting → standing

Alpha-adrenergic blocking agents:
) Drugs that block α-adrenoceptors profoundly affect blood pressure

alpha 1 blockers:
) Prazosin, terazosin, doxazosin, alfuzosin, and tamsulosin
) Are selective competitive blockers of α1 receptor
) They decrease peripheral vascular resistance (PVR) & lower arterial blood pressure (ABP) by causing relaxation of both arterial and venous smooth muscle
  - smooth muscles are involuntary so inhibition of receptor makes dilation (relaxation)
Therapeutic uses:

- Treatment of Hypertension
- Benign prostatic hypertrophy (BPH)

Prazosin, terazosin, doxazosin (alphapress, cardura) are useful in the treatment of hypertension.

- The first dose of these drugs produces an exaggerated orthostatic hypotensive response that can result in syncope (fainting).
- This action, termed a “first-dose” effect, may be minimized by reducing dose and giving drug at bedtime.
- Tamsulosin (omnic) and alfuzosin (xatral) are indicated for the treatment of benign prostatic hypertrophy (also known as benign prostatic hyperplasia or BPH).
  - have been used as an alternative to surgery in patients with symptomatic BPH.
  - Blockade of the α receptors decreases tone in the smooth muscle of the bladder neck and prostate and improves urine flow.
  - Tamsulosin is a more potent inhibitor of α1A receptors found on smooth muscle of prostate.

**Adverse effects:**

- Dizziness, a lack of energy, nasal congestion, headache, drowsiness, and orthostatic hypotension
  - the more the pressure decreases the more fatigue one is

alpha1- & alpha2- blockers:

- Phenoxybenzamine
  - Nonselective, block both α1-postsynaptic and α2-presynaptic receptors
  - is used in treatment of pheochromocytoma, a catecholamine-secreting tumor of cells derived from adrenal medulla.
  - Adverse effects: postural hypotension, nasal stuffiness, nausea, vomiting, inhibit ejaculation.
  - if someone have ejaculation problems first thing you ask does he take anti-hypertensive drugs

*For tables and pictures go back to slides

*next week only pharma

*the week next the doctor is flying so we will take micro

Good luck }}