ADRENOCEPTORS-ACTIVATING AND OTHER SYMPATHOMIMETIC DRUGS

Sympathomimetics are drugs that mimic the actions of epinephrine or norepinephrine. Epinephrine and norepinephrine regulate the activities of the sympathetic nervous system via the stimulation of sympathetic nerves.

Classification of sympathomimetics

They can be classified base on their mode of actions and the receptors (adrenoceptors) they activate.

Direct acting sympathomimetics: They act directly with and activate adrenoceptors e.g. epinepherine and norepinephrine.

Indirect acting sympathomimetics: Their effects depend on the release of endogenous catecholamines. Indirect acting have two modes of actions:

(a) They can act through the displacement of stored catecholamines from adrenergic nerve ending e.g. amphetamine and tyramine.

(b) Through the inhibition of the reuptake of catecholamines from adrenergic nerve endings. Some sympathomimetics have both direct and indirect effects.

Sympathomimetics and receptor interaction

Sympathomimetics mediate their effects by interacting with adrenoceptors (alpha, beta and dopamine receptors).

Alpha adrenoceptors

Alpha adrenoceptors are divided into 3 subtypes; $\alpha_{1,}$ α_{2} and $\alpha_{3.}$

Activation of α_1 receptor will stimulate the hydrolysis of polyphosphoinositide leading to the production of inisitol 1, 4, 5 triphosphate (IP_3) and diacylglycerol (DAG). IP_3 promotes the release $Ca^{2}+$ from intracellular stores which increases the cytoplasmic concentration of free $Ca^{2}+$ and the activation of various dependent protein kinase.

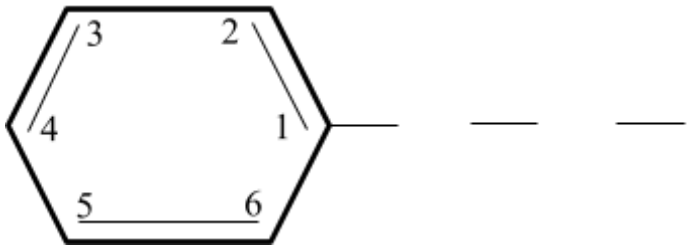
Beta-adrenoceptors (β)

They are further divided into β_1, β_2 and β_3 receptors. β_1 has equal affinity for epinephrine and norepinephrine. β_2 has higher affinity for epinephrine than norepinephrine. The activation of β_1, β_2 and β_3 receptors by sympathomimetics (adrenergic agonist) will lead to the activation of adenylyl cyclase and increase conversion of ATP (Adenosine triphosphate) to cAMP (cyclic adenosine monophosphate) leading to cascade of events. Diacylglycerol (DAG) activates protein kinase c, which modulate activities of many signaling pathways.

Dopamine receptors (D)

Activation of dopamine receptor will lead to the stimulation of adenylyl cyclase. Induced smooth muscle relaxation is due to cAMP accumulation in the smooth muscle of those vascular beds which dopamine is a vasodilator. D_2 receptors have been found to inhibit adenylyl cyclase activity, open potassium channels and decrease calcium influx.

Chemistry and pharmacokinetics of sympathomimetic drugs



Phenyl ethylamine

Above is the structure of phenyl ethylamine, it may be considered as the parent compound which other sympathomimetics are derived from. It has a benzene ring with an ethylamine side chain. On the phenyl ethylamine structure, substitution can be made at: (1) the terminal amino group (2) on α and β carbon and (3) on the benzene ring. Sympathomimetic drugs known as catecholamines are produced due to substitution by -OH groups at positions 3 and 4. Modifications are made on phenyl ethylamine so as to change the affinity of the drug for α and β receptors, and the pharmacokinetics parameters.

Substitution on the amino group

There is increase in β -receptor activity with increase in the size of the alkyl substituents on the amino group e.g. methyl substitution on norepinephrine produces epinephrine and increases activity at β_2 receptor. Activity at beta-receptors can be further increased with isopropyl substitution at the amino

nitrogen (isoproterenol). The larger the substituents at the amino group the lower the activity at α-receptors.

Substitution on the alpha carbon

Substitutions at the α- carbon prevent oxidation by monoamine oxidase (MAO) and increase duration of action. Examples of α -substituted drugs are ephedrine and amphetamine.

Substitution on the beta carbon

Direct-acting agonists (eg epinephrine) have a hydroxyl group (OH) at the β carbon. This increases activity and also facilitates storage of sympathomimetic amines in neural vesicles.

Substitution on the benzene ring

Catecholamines having OH groups at positions 3 and 4 on the benzene ring have maximum α and β activities.

Organ effects of sympathomimetic drugs

Blood vessel

The action of a sympathmimetic drug depends on its activity on α or β-receptor and the anatomical site of the vessels affected. Skin vessels have more of α-receptor and constrict in response to epinephrine and norepinephrine. Skeletal muscle vessels may constricts or dilate depending on the activation of either α or β-receptor.

Heart

Direct effects of sympathmimetics on the heart largely depend on β-receptor and to a lesser extent α -receptor. β -receptor activation in the heart increases influx of calcium into the heart, which produces mechanical and electrical activities. Pacemaker activity is increased (positive chronotropic effect) while intrinsic contractility increases (positive inotropic effect) and relaxation is accelerated.

Blood pressure

The actions on blood pressure depend on their effects on the heart, peripheral vascular resistance and venous return. For example, phenylepinehrine a pure α agonist increases peripheral vascular resistance and decreases venous capacitance thereby increasing blood pressure. The increase in blood pressure will lead to decrease in heart rate due to baroreceptor-mediated responses and also decrease in cardiac output.

Eye

The iris contains α-receptor, activation by sympathomimetics e.g. phenylephedrine causes mydriasis. Stimulation of α-receptor by α-agonists will increase the outflow of aqueous humour from the eye leading to increase in intraocular pressure.

Respiratory

The bronchial smooth muscles contain β_2-receptors which when activated will cause relaxation resulting in bronchodilation.

Metabolic effects

Activation of β-adrenoceptors in fat cells leads to increased lypolysis and the release of fatty acid and glycerol into the blood. Sympathomimetic drugs increase glycogenolysis in the liver stimulating the release of glucose into the blood.

Central nervous system

Sympathomimetics have limited ability to cross the blood-brain-barrier hence do not have central nervous system effects. However, at highest rate of infusion, they produce effects which include nervousness and feeling of impending disaster.

Specific sympathomimetics

Epinephrine

It is a potent vasoconstriction and cardiac stimulants. It increases blood pressure due to its positive chronotropic and inotropic effects on the heart at β_1 receptor.

Norepinephrine

Norepinephrine and epinephrine have similar effects on $\beta_1$receptor in the heart and similar potency at α-receptor.

Dopamine

It is the immediate precursor of norepinephrine; it activates D_1 receptor in vascular beds causing vasodilation.

Fenoldopam

It stimulates D_1 receptor leading to peripheral vasodilation in some vascular beds. It is administered intravenously in the treatment of severe hypertension.

Isoproterenol (isopronaline)

It is a β-receptor agonist that has little effect on α - receptor, it has a positive chronoscopic and inotropic actions.

Uses of sympathomimetics

1. Catecholamines such as isoproterenol and epinephrine are used in the emergency treatment of heart block and cardiac arrest.

2. Sympathomimetic such as terbutaline, albuterol are used for the management of bronchial asthma.

3. Epinephrine is used for the treatment of anaphylactic shock (Type 1) associated with IgE mediated reactions.

4. Phenylephrine is use as a mydriatic agent to facilitate the examination of the retina. It is also used as a decongestant for minor allergic hyperemia and inching of conjuctival membranes. Sympathomimetics are also used for the treatment of glaucoma.

5. Ritodrine and terbutaline have been use in the suppression of premature labor