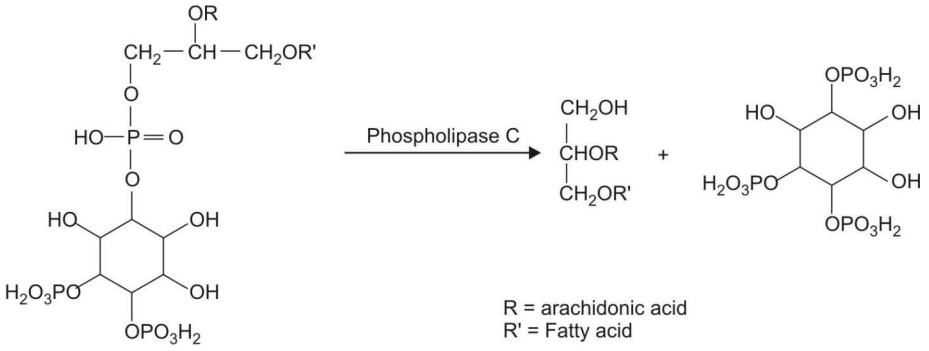
Both α_1- and α_2-adrenergic receptors are guanine-nucleotide-regulatory protein (G-protein) linked receptors. However, they differ in second messenger system. In case of α_1-adrenergic receptor, the Gs-protein is coupled to phospholipase C. Activation of the α_1-receptor results in activation of phospholipase C which hydrolyses phosphatidylinositol-4, 5-diphosphate [PIP_2 , (5)] into diacylglycerol [DAG, (6)] and inositol triphosphate [IP_3, (7)]. Both of these function as second messengers. Production of DAG (6) results in activation of membrane-bound protein kinase C,which causes phosphorylation of protein. IP_3 (7) on the other hand, causes release of Ca^{2+} from intracellular stores, the endoplasmic reticulum. The endoplasmic reticulum is coupled to calcium channel, which open after IP_3 (7) binds to receptor in endoplasmic reticulum. Increased free intracellular Ca^{2+} results in smooth muscle contraction, increased force of contraction of cardiac muscle and transmitter release.



(5) (6) (7)

α_2-Adrenoreceptors are G_i-linked. Activation of these receptors results in inhibition of adenylyl cyclase. This leads to lowering of c-AMP levels.

In summary, the stimulation of α_1-receptors results in vasoconstriction, relaxation of gastrointestinal smooth muscles, salivary secretion and hepatic glycogenolysis, while stimulation of α_2-receptors results in inhibition of transmitter release, both norepinephrine (1) and acetylcholine (2), platelet aggregation, contraction of vascular smooth muscles and inhibition of insulin release.

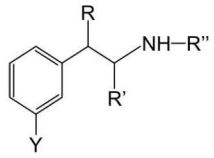
All the three types of β-receptors are linked to guanine nucleotide protein Gs and the second messenger in all the three subtypes of β-receptors is adenylyl cyclase, which catalyzes the formation of c-AMP from ATP. The increased levels of c-AMP result in activation of protein kinase which phosphorylates myosin-light-chain kinase, thereby inhibiting the contraction. Activation of β-receptors also reduces the intracellular Ca^{2+} through its efflux.

The effect of stimulation of β_1-receptors results in increased cardiac rate and force, β_2-receptor stimulation leads to bronchial dilation, vasodilation, relaxation of visceral smooth muscles and hepatic glycogenolysis. The stimulation of β_3-receptors results in lipolysis.

The distribution of various classes of adrenergic receptors and the effect of their stimulation on some organs is summarized in Table 1.1.

Sympathomimetics with Mixed Action

Some the phenylalkylamines have shown to increase the levels of norepinephrine (1) by interacting directly with the adrenergic receptors as well as indirectly by increasing the release of norepinephrine (1) from its storage sites. Some of these are ephedrine (24), metaraminol (25), phenylethanolamine (26), phenylpropanolamine (27), and tyramine (28).

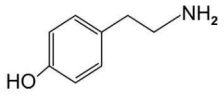


(24), R = OH, R′ = R″ = CH_3, Y = H;

(25), R = Y = OH, R′ = CH_3, R″ = H

(26), R = OH, R′ = R″ = Y = H

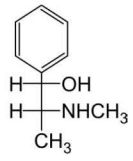
(27), R = OH, R′ = CH_3, R″ = Y = H



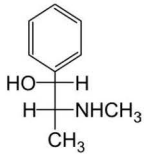
(28)

All of these drugs have very weak action on adrenergic receptors and their main adrenergic action is through action on storage sites of norepinephrine (1) as in case of indirectly acting sympathomimetics, discussed earlier. As is evident from the structures of indirectly acting amines and amines with mixed activity, there does not seem to be stringent structural requirements for the action.

Ephedrine (24) has two asymmetric centres and can exist in 4 stereoisomers, DL-erythro (29) and DL-threo (30). Ephedrine (24) is the naturally occurring D(–)-erythro-isomer. It is 36 times more active than D(–)-threo form, which is commonly called D(–)-pseudoephedrine. The relative pressor activities of D-(–) ephedrine, L-(+)-ephedrine, L-(+)-pseudoephedrine, and D-(–)-pseudoephedrine are 36, 11, 7, and 1, respectively.



(29)



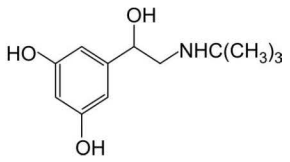
(30)

DRUGS ACTING ON ADRENERGIC RECEPTORS—AGONISTS

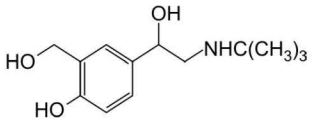
The endogenous catecholamines, norepinephrine (1) and epinephrine (3) are potent stimulants of α- and β-adrenergic receptors. Both drugs are equipotent at β_1-receptor. Norepinephrine (1) is a potent agonist of α-adrenergic receptor and has little action on β_2-receptors, however, it is less potent than epinephrine (3) on the α-receptors of most of the organs.

α_1-Adrenergic Receptor Agonists

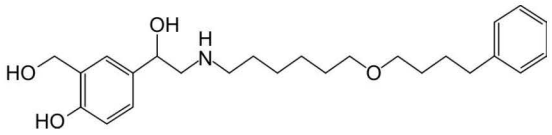
Mephentermine (21) and metaraminol (25) have mixed actions, acting directly by binding to



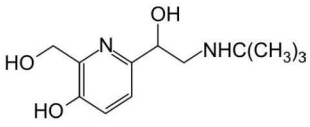
(46)



(47)



(48)



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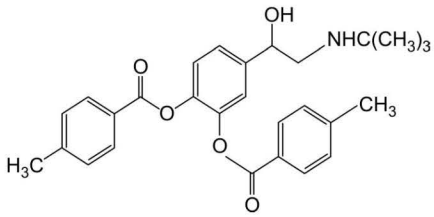
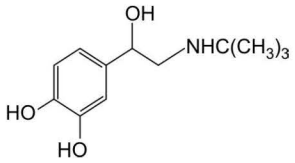


(50)

Increasing of bulk of the alkyl group at amino nitrogen leads to enhanced β-activity as compared to α-activity. All the β_2-agonists have been used for asthama. Since one of the major side effects of antiasthamatics is stimulation of heart caused by β_1-agonist activity, efforts have been made to have selective β_2-agonist. This selectivity has been achieved by having non-catechol moiety attached to ethanolamine residue excepting bitolterol (50). This has also resulted in oral activity as well as longer duration of action because they are not the substrates for enzymes which metabolize catecholamines.

Bitolterol (50) which is catecholamine diester of 4-methylbenzoic acid is actually a prodrug, esterases hydrolyse (50) to colterol (51) which is the active form of bitolterol (50).



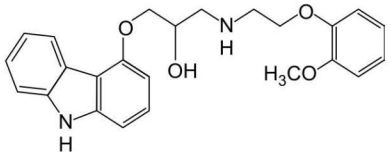
(51)

All the β_2-adrenergic agonists are used in asthma for dilation of bronchi.

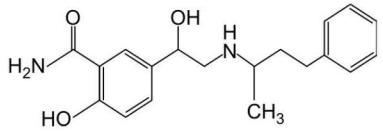
DRUGS ACTING ON ADRENERGIC RECEPTORS—ANTAGONISTS (BLOCKERS)

α_1-Adrenergic Receptor Antagonists (Blockers)

Blockade of α_1-adrenergic receptors results in vasodilation (inhibition of vasoconstriction by



(86)



(87)

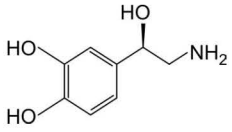
The (*S*)-isomer of carvedilol (86) possesses the β-blocking activity while as the α_1-blocking activity resides in (*R*)-isomer. It is also reported to possess antioxidant activity.

INDIVIDUAL COMPOUNDS

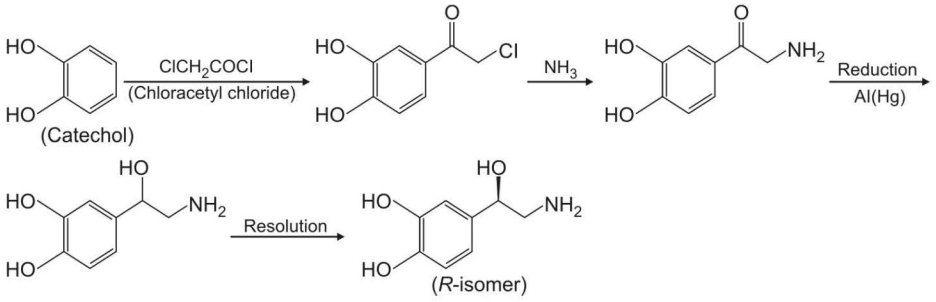
ENDOGENOUS CATECHOLAMINES

Norepinephrine

(*R*)-1-(3,4-Dihydroxyphenyl)-2-aminoethanol



Synthesis



Norepinephrine is more active at α-receptor. It is used to maintain the blood pressure in acute hypotensive states such as shock, hemorrhage. It is administered by intravenous route, sodium bisulphite is used as an antioxidant in the formulation.

Epinephrine

(*R*)-1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol