Adrenoceptors

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Adrenoceptors are adrenergic receptors.

The adrenergic drugs affect receptors that are stimulated by norepinephrine or epinephrine.

Some adrenergic drugs act directly on the adrenergic receptors by activating it and are said to be sympathomimetic.

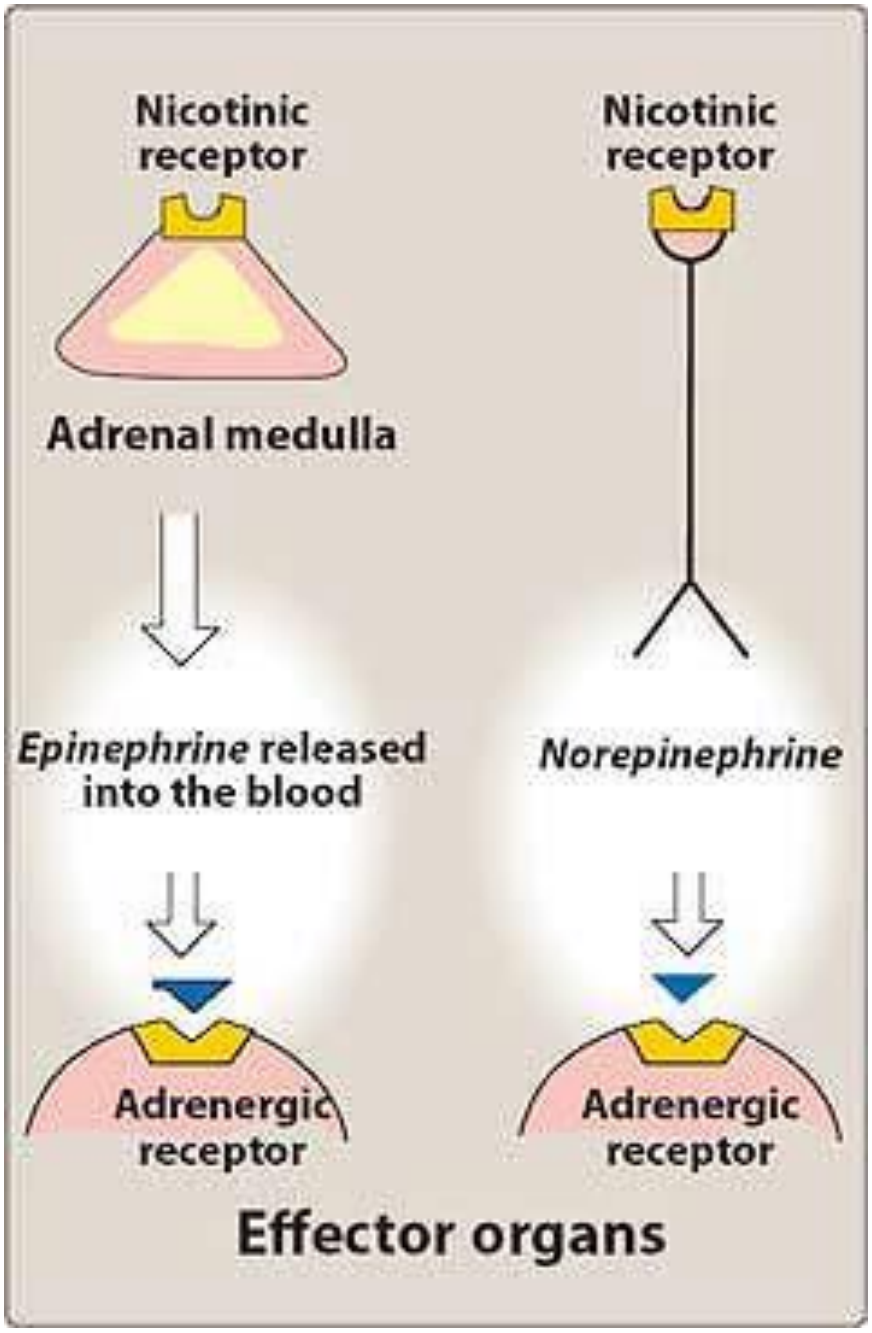
Others block the action of the neurotransmitters at the receptors and are said to be sympatholytics.

The Adrenergic Neuron

Adrenergic neurons release norepinephrine as the primary neurotransmitter.

These neurons are found in the central nervous system and also in the sympathetic nervous system, where they serve as links between ganglia and the effector organs.

The adrenergic neurons and receptors, located either presynaptically on the neuron or postsynaptically on the effector organ, are the sites of action of the adrenergic drugs.


Nicotinic receptor
Nicotinic receptor
Adrenal medulla
Epinephrine released into the blood
Norepinephrine
Adrenergic receptor
Adrenergic receptor
Effector organs

Neurotransmission at adrenergic neurons

Neurotransmission in adrenergic neurons closely resembles that already described for the cholinergic neurons, except that norepinephrine is the neurotransmitter instead of acetylcholine.

Neurotransmission takes place at numerous bead-like enlargements called varicosities.

The process involves five steps: synthesis, storage, release, and receptor binding of norepinephrine, followed by removal of the neurotransmitter from the synaptic gap.

Synthesis of norepinephrine:

Tyrosine is transported by a Na^+-linked carrier into the axoplasm of the adrenergic neuron, where it is hydroxylated to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase.

This is the rate-limiting step in the formation of norepinephrine.

DOPA is then decarboxylated by the enzyme dopa decarboxylase to form *dopamine* in the cytoplasm of the presynaptic neuron.

Storage of norepinephrine in vesicles:

Dopamine is then transported into synaptic vesicles that is also involved in the reuptake of preformed norepinephrine.

This carrier system is blocked by *reserpine*.

Dopamine is hydroxylated to form norepinephrine by the enzyme dopamine β-hydroxylase.

Synaptic vesicles contain *dopamine* or norepinephrine plus ATP and β-hydroxylase as well as other cotransmitters.

In the adrenal medulla, norepinephrine is methylated to yield *epinephrine*, and on stimulation, the adrenal medulla releases about 80 percent *epinephrine* and 20 percent norepinephrine directly into the circulation.

Release of norepinephrine:

An action potential arriving at the nerve junction triggers an influx of calcium ions from the extracellular fluid into the cytoplasm of the neuron.

The increase in calcium causes vesicles inside the neuron to fuse with the cell membrane and expel (exocytose) their contents into the synapse.

This release is blocked by drugs such as *guanethidine.*

Binding to a receptor:

Norepinephrine released from the synaptic vesicles diffuses across the synaptic space and binds to either postsynaptic receptors on the effector organ or to presynaptic receptors on the nerve ending.

The recognition of norepinephrine by the membrane receptors triggers a cascade of events within the cell, resulting in the formation of intracellular second messengers that act as links in the communication between the neurotransmitter and the action generated within the effector cell.

Adrenergic receptors use both the cyclic adenosine monophosphate (cAMP) second-messenger system, and the phosphatidylinositol cycle, to transduce the signal into an effect.

Removal of norepinephrine:

Norepinephrine may 1) diffuse out of the synaptic space and enter the general circulation, 2) be metabolized to O-methylated derivatives by postsynaptic cell membrane associated catechol O-methyltransferase (COMT) in the synaptic space, or 3) be recaptured by an uptake system that pumps the norepinephrine back into the neuron.

The uptake by the neuronal membrane involves a sodium/potassium activated ATPase that can be inhibited by tricyclic antidepressants, such as *imipramine* or *cocaine*.

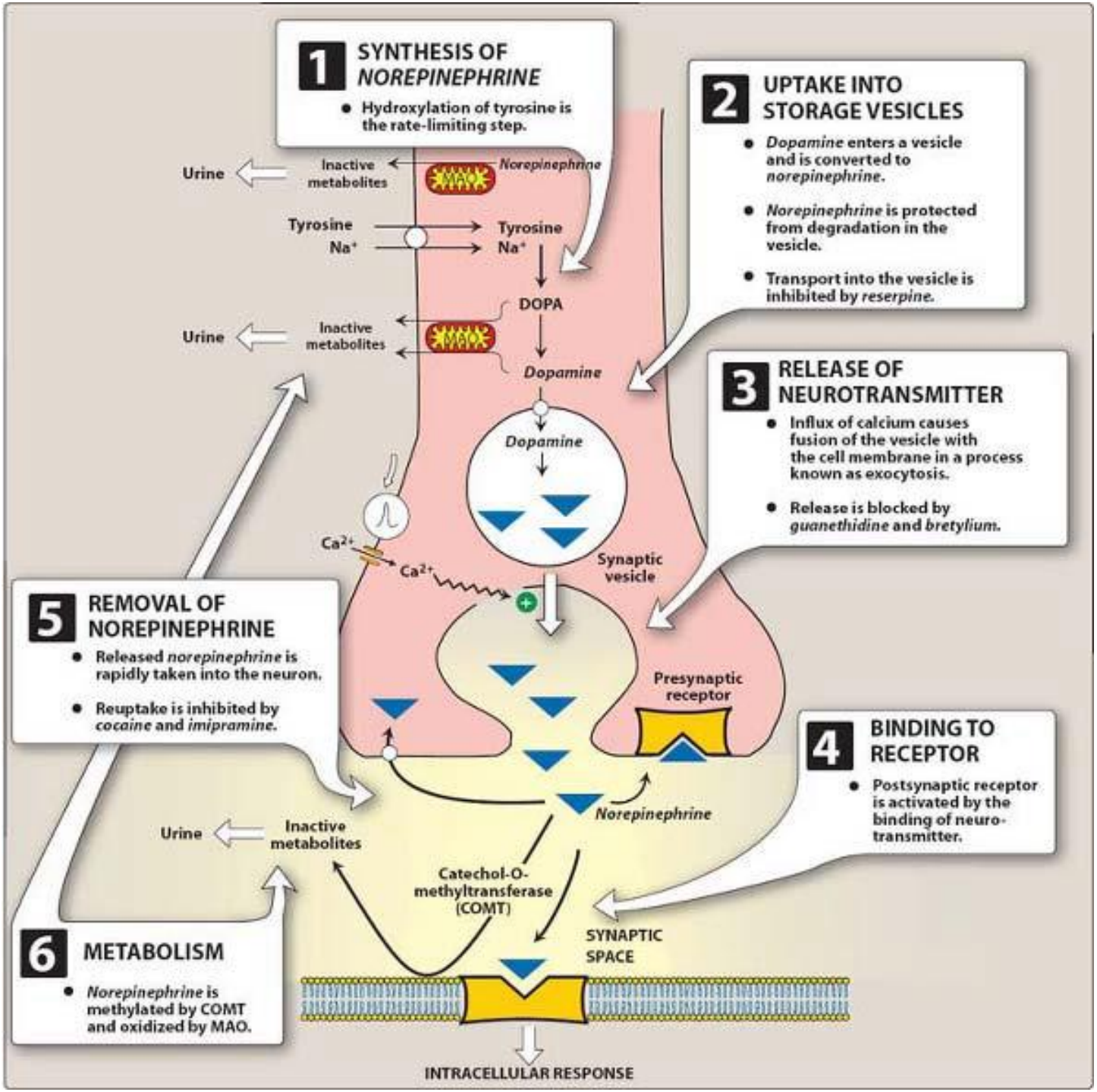
Uptake of norepinephrine into the presynaptic neuron is the primary mechanism for termination of norepinephrine*'s* effects.

Potential fates of recaptured norepinephrine:

Once norepinephrine reenters the cytoplasm of the adrenergic neuron, it may be taken up into adrenergic vesicles via the amine transporter system and be sequestered for release by another action potential, or it may persist in a protected pool.

Alternatively, norepinephrine can be oxidized by monoamine oxidase (MAO) present in neuronal mitochondria.

The inactive products of norepinephrine metabolism are excreted in the urine as vanillylmandelic acid, metanephrine, and normetanephrine.


1 SYNTHESIS OF NOREPINEPHRINE
Hydroxylation of tyrosine is the rate-limiting step.
2 UPTAKE INTO STORAGE VESICLES
Dopamine enters a vesicle and is converted to norepinephrine.
Norepinephrine is protected from degradation in the vesicle.
Transport into the vesicle is inhibited by reserpine.
3 RELEASE OF NEUROTRANSMITTER
Influx of calcium causes fusion of the vesicle with the cell membrane in a process known as exocytosis.
Release is blocked by guanethidine and bretylium.
4 BINDING TO RECEPTOR
Postsynaptic receptor is activated by the binding of neurotransmitter.
5 REMOVAL OF NOREPINEPHRINE
Released norepinephrine is rapidly taken into the neuron.
Reuptake is inhibited by cocaine and imipramine.
6 METABOLISM
Norepinephrine is methylated by COMT and oxidized by MAO.
Urine
Inactive metabolites
MAO
Norepinephrine
Tyrosine
Na+
DOPA
Dopamine
Ca2+
Synaptic vesicle
Presynaptic receptor
Catechol-O-methyltransferase (COMT)
SYNAPTIC SPACE
INTRACELLULAR RESPONSE

In the sympathetic nervous system, several classes of adrenoceptors can be distinguished pharmacologically.

Two families of receptors, designated α and β, were initially identified on the basis of their responses to the adrenergic agonists *epinephrine*, *norepinephrine*, and *isoproterenol*.

α-Receptors: The α-adrenoceptors show a weak response to the synthetic agonist *isoproterenol*, but they are responsive to the naturally occurring catecholamines *epinephrine* and *norepinephrine*. For α receptors, the rank order of potency is *epinephrine* >> norepinephrine >> *isoproterenol*. The α-adrenoceptors are subdivided into two subgroups, α_1 and α_2, based on their affinities for α agonists and blocking drugs. For example, the α_1 receptors have a higher affinity for *phenylephrine* than do the α_2 receptors. Conversely, the drug *clonidine* selectively binds to α_2 receptors and has less effect on α_1 receptors.

β-Receptors: β-Receptors exhibit a set of responses different from those of the α-receptors.

These are characterized by a strong response to *isoproterenol*, with less sensitivity to *epinephrine* and norepinephrine.

For β-receptors, the rank order of potency is *isoproterenol* >> *epinephrine* >> norepinephrine.

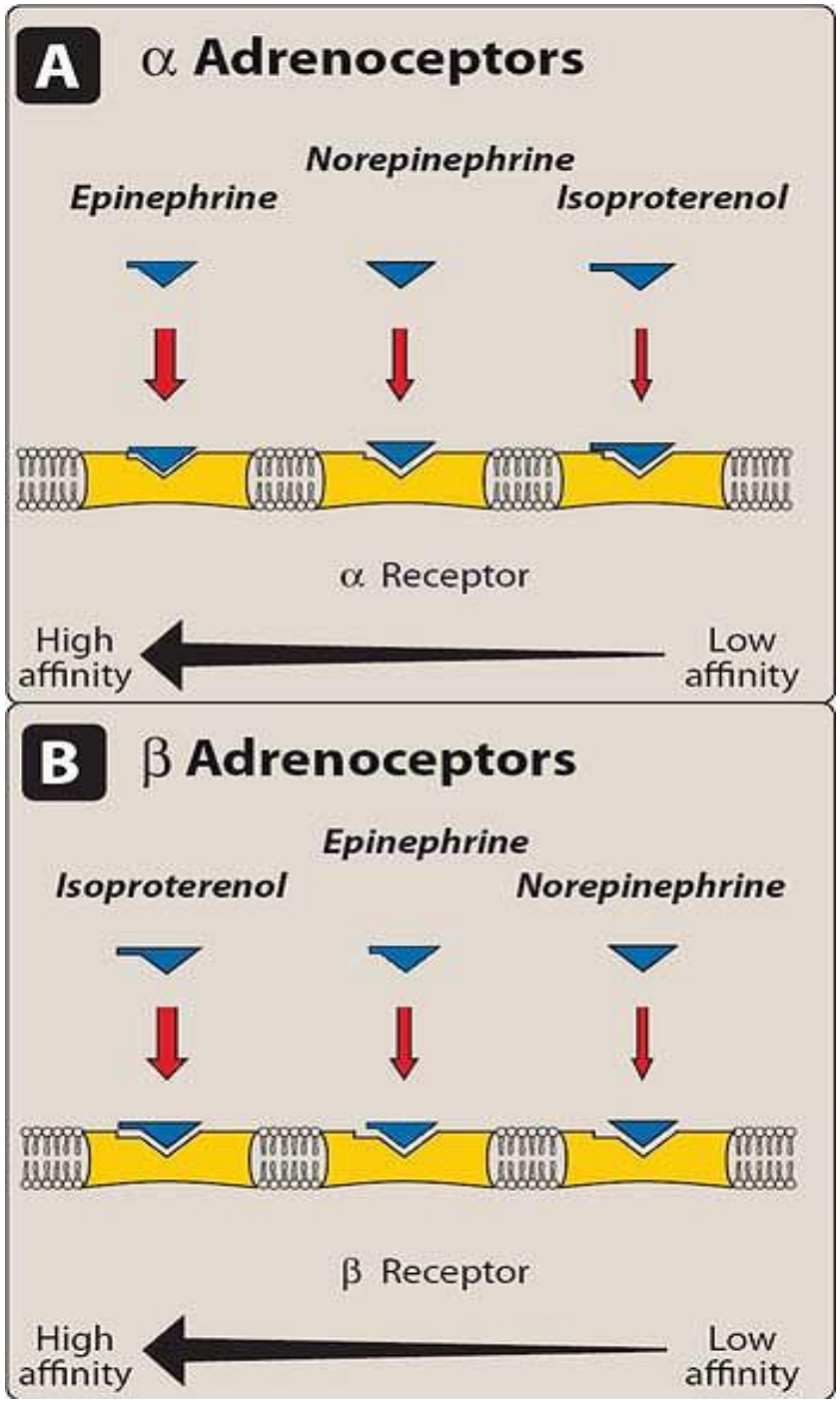
The β-adrenoceptors can be subdivided into three major subgroups, β_1, β_2, and β_3, based on their affinities for adrenergic agonists and antagonists.

It is known that β_3 receptors are involved in lipolysis but their role in other specific reactions are not known.

β_1 Receptors have approximately equal affinities for *epinephrine* and norepinephrine, whereas β_2 receptors have a higher affinity for *epinephrine* than for norepinephrine.

Thus, tissues with a predominance of β_2 receptors (such as the vasculature of skeletal muscle) are particularly responsive to the hormonal effects of circulating *epinephrine* released by the adrenal medulla.

Binding of a neurotransmitter at any of the three β receptors results in activation of adenylyl cyclase and, therefore, increased concentrations of cAMP within the cell.


A
α Adrenoceptors
Norepinephrine
Epinephrine
Isoproterenol
α Receptor
High affinity
Low affinity
B
β Adrenoceptors
Epinephrine
Isoproterenol
Norepinephrine
β Receptor
High affinity
Low affinity

Distribution of receptors:

Adrenergically innervated organs and tissues tend to have a predominance of one type of receptor.

For example, tissues such as the vasculature to skeletal muscle have both β_1 and β_2 receptors, but the β_2 receptors predominate.

Other tissues may have one type of receptor exclusively, with practically no significant numbers of other types of adrenergic receptors.

For example, the heart contains predominantly β_1 receptors.

Characteristic responses mediated by adrenoceptors:

It is useful to organize the physiologic responses to adrenergic stimulation according to receptor type, because many drugs preferentially stimulate or block one type of receptor.

As a generalization, stimulation of α1 receptors characteristically produces vasoconstriction (particularly in skin and abdominal viscera) and an increase in total peripheral resistance and blood pressure.

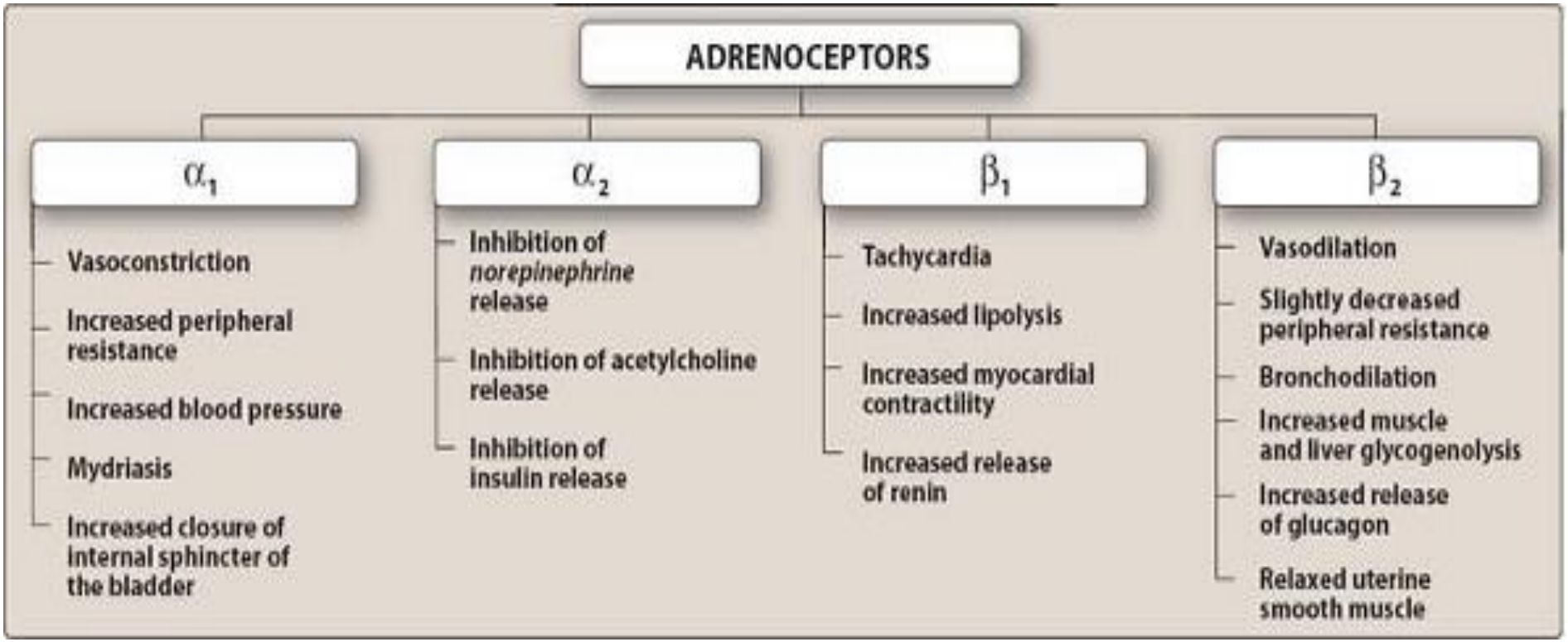
Stimulation of β_1 receptors characteristically causes cardiac stimulation, whereas stimulation of β_2 receptors produces vasodilation (in skeletal vascular beds) and bronchiolar relaxation.

Desensitization of receptors:

Prolonged exposure to the catecholamines reduces the responsiveness of these receptors, a phenomenon known as desensitization.

Three mechanisms have been suggested to explain this phenomenon:

1) Sequestration of the receptors so that they are unavailable for interaction with the ligand.
2) Down-regulation, that is, a disappearance of the receptors either by destruction or decreased synthesis.
3) Inability to couple to G protein, because the receptor has been phosphorylated on the cytoplasmic side by either protein kinase A or β-adrenergic receptor kinase.


ADRENOCEPTORS
α1
Vasoconstriction
Increased peripheral resistance
Increased blood pressure
Mydriasis
Increased closure of internal sphincter of the bladder
α2
Inhibition of norepinephrine release
Inhibition of acetylcholine release
Inhibition of insulin release
β1
Tachycardia
Increased lipolysis
Increased myocardial contractility
Increased release of renin
β2
Vasodilation
Slightly decreased peripheral resistance
Bronchodilation
Increased muscle and liver glycogenolysis
Increased release of glucagon
Relaxed uterine smooth muscle