# ADRENAL MEDULLA

The adrenal medulla is a specialized part of the sympathetic nervous system that secrets catecholamines. The sympathetic nervous system typically secretes **norepinephrine** as a local neurotransmitter directly in target organs. In comparison, the adrenal medulla is important for its secretion of **epinephrine** and other substances into the general circulation of widespread distribution and effect. Although the adrenal medulla is not critically necessary for survival, its secretion of epinephrine and other compounds helps maintain the body's homeostasis during stress.

**Pheochromocytomas:** are tumors that arise from the adrenal sympathetic ganglia. These tumors can secrete excessive amounts of *epinephrine* and *norepinephrine*, causing a dangerous exaggeration of the stress response.

In humans, the adrenal medulla occupies a central position of the gland. There is no clear demarcation between the cortex and medulla. The adrenal medulla constitutes about one tenth of the weight of the gland.

The **chromaffin cells, or pheochromocytes,** of the adrenal medulla contain large numbers of vesicles or granules containing catecholamines. The adrenal medulla also contains some sympathetic ganglion cells. The cells of the adrenal medulla are innervated by preganglionic fibers of the sympathetic nervous system, which release acetylcholine and enkaphlins at the synapse.

In mammals, the enzyme that catalyzes the conversion of norepinephrine to epinephrine is induced by cortisol. The chromaffin cells containing epinephrine therefore receive most of their blood supply from the capillaries draining the cortical cells, whereas cells containing predominantly norepinephrine are supplied by arteries that directly supply the medulla.

## Hormone of the Adrenal medulla

### Catecholamines

**Biosynthesis:** catecholamines are molecules that have catechol nucleus (benzene with two hydroxyl groups) plus a side chain amine. Catecholamines include dopamine, epinephrine, and norepinephrine (Fig. 11-2). In mammals, epinephrine is synthesized mainly in the adrenal medulla, whereas norepinephrine is found not only in the adrenal medulla but also in the CNS and in the peripheral sympathetic nerves. Dopamine, the precursor of norepinephrine, is found in the adrenal medulla and in noradrenergic neurons. It is present in high concentration in the brain and in specialized interneurons in the sympathetic ganglia where it serves as a neurotransmitter.

The catecholamines are synthesized from tyrosine, which may be derived from ingested food or synthesized from phenylalanine in the liver. Tyrosine is converted to L-dihydroxyphenylalanine (L-dopa) by tyrosine hydroxylase, which is transported to the nerve terminal. Tyrosine hydroxylase is the rate-limiting step in catecholamine synthesis. α-Methyltyrosine is an effective inhibitor as is sometimes used in the therapy of malignant pheochromocytomas.

Dopa is converted to dopamine by the enzyme dopa decarboxylase. Dopamine enters granulated storage vesicles where it is hydroxylated to norepinephrine by the enzyme dopamine β-hydroxylase (DBH), which is found within the vesicle membrane. Norepinephrine is then stored in the vesicle. The granulated storage vesicle migrates to the cell surface and secretes its contents via exocytosis; both norepinephrine and DBH are released during exocytosis. After secretion, most norepinephrine is recycled back into the nerve. Normally, most circulating norepinephrine originates from diffusion out of nonadrenal sympathetic nerve cells.

Norepinephrine can diffuse into the cytoplasm and is converted to epinephrine by the enzyme 4-phenylethanolamine–N-methyltransferance (PNMT). Epinephrine can then return to the vesicle. High concentrations of cortisol enhance the expression of the gene encoding PNMT. Cortisol is present in high concentrations in most areas of the adrenal medulla. This accounts for the fact that in the adrenal medulla about 80% of the catecholamine content is epinephrine while only 20% is norepinephrine.

The enzyme PNMT is found in many tissues like the lungs, kidneys, pancreas, and cancer cells. Therefore, a nonadrenal tissue is capable of synthesizing epinephrine if norepinephrine is available as a substrate. PNMT is found in human lung; in vivo exposure of bronchial epithelial cell lines to dexamethasone increases the expression of PNMT. Thus, glucocorticoids could potentially increase local concentration of epinephrine in the lung; this might be one potential mechanism for the effectiveness of systemic and inhaled glucocorticoids in asthma.

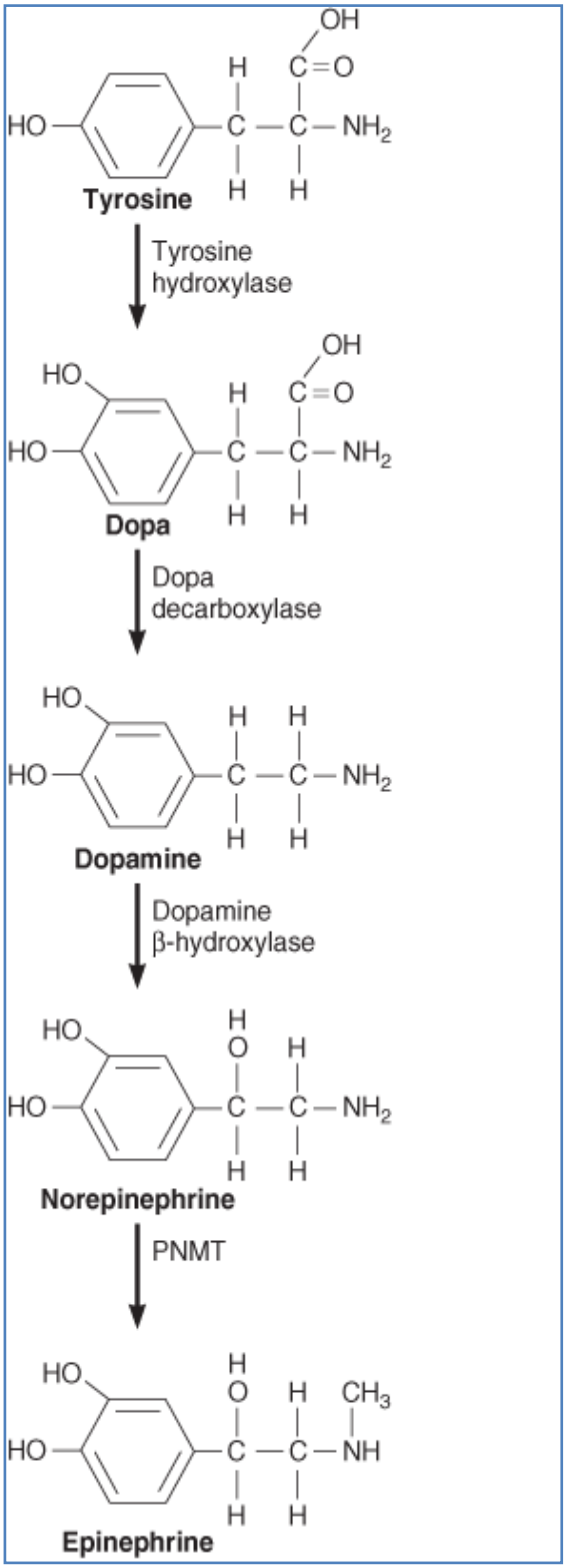


**Figure 11-2**. Biosynthesis of catecholamines (PNMT, phenylethanolamine-*N*-methyltransferase).

**Secretion:** adrenal medullary catecholamine is increased by exercise, angina pectoris, myocardial infarction, hemorrhage anesthesia, surgery, hypoglycemia, asphyxia, and many other stressful stimuli. Secretion of the adrenal medullary hormones is mediated by the release of acetylcholine from the terminals of preganglionic fibers. The resulting depolarization of the axonal membrane triggers an influx of $Ca^{++}$. The contents of storage vesicles are released by exocytosis by the calcium ion increase.

**Metabolism and Inactivation of Catecholamines**: Catecholamines are quickly metabolized into inactive compounds, including metanephrine, vanillylmandelic acid (VMA), and conjugated catecholamines (Fig. 11-3). Excess intracellular norepinephrine is inactivated primarily by deamination, catalyzed mainly by monoamine oxidase (MAO). Peripheral circulating norepinephrine is metabolized largely to normetanephrine by Catechol-O-methyltransferase (COMT). Epinephrine is similarly catabolized to metanephrine, some of which is then converted to VMA (Fig. 11-3). Catecholamines and metabolites are excreted in the urine; 50% metanephrines, 35% VMA, 10% conjugated catecholamines and other metabolites and <5% free catecholamines.

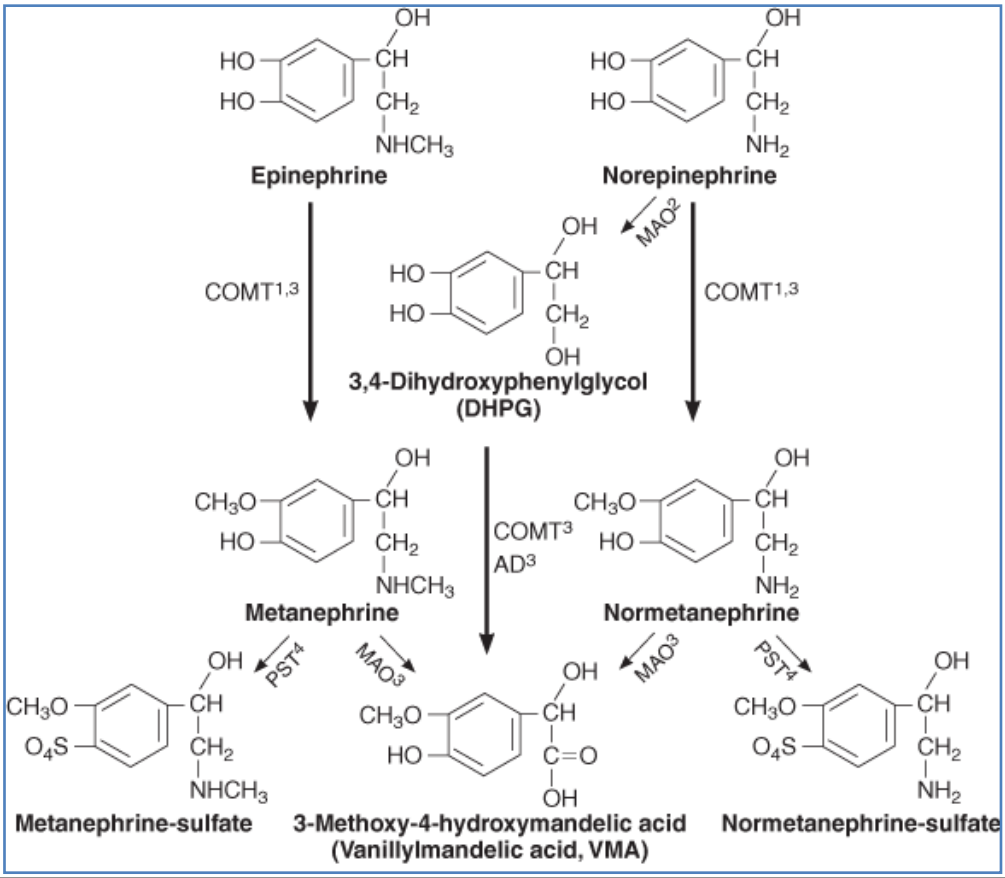


**Figure 11-3**. Metabolism of catecholamines: by catechol-*O*-methyltransferase (COMT), monoamine oxidase (MAO), aldehyde dehydrogenase (AD), and phenol-sulfotransferase (PST). (1) Adrenal medulla or pheochromocytoma; (2) Sympathetic nerves; (3) Liver and kidneys; (4) GI, platelets, lungs.

**Adrenergic Receptors:** Adrenergic receptors were first classified by the relative potencies of a series of adrenergic agonists and antagonists. Each of the subtypes is now known to be coded for by one or more separate genes (Table 11-3). The physiologic effects mediated by then are summarized in Table 11-4. The adrenergic receptors are transmembrane proteins coupled to G proteins. The G proteins consist of α,β and γ subunits. There are many G proteins that have different α subunits while the β and γ subunits are similar. When hormone binds to the receptor, the β and γ subunits dissociate from the α subunits allowing GDP to the replaced by GTP on the α subunits and causing the β and γ subunits to dissociate from it. The GTP-bound α subunits activate the post receptor pathways (Fig. 11-5).

| Table 11–3. Catecholamine Receptor Types and Subtypes.[1] | | | |
|---|---|---|---|
| **Receptor** | **Relative Agonist Potency** | **Effects** | **Gene on Chromosome** |
| **Alpha$_1$ type** | Nonepinephrine > epinephrine | ↑$IP_3$, DAG common to all | |
| Alpha$_{1A}$ | | | C5 |
| Alpha$_{1B}$ | | | C8 |
| Alpha$_{1D}$ | | | C20 |
| **Alpha$_2$ type** | Nonepinephrine > epinephrine; clonidine | ↓cAMP; ↑$K^+$ channels; ↓$Ca^{2+}$ channels | |
| Alpha$_{2A}$ | | | C10 |
| Alpha$_{2B}$ | Nonepinephrine > epinephrine | ↓cAMP; ↓$Ca^{2+}$ channels | C2 |
| Alpha$_{2C}$ | | ↓cAMP | C4 |
| **Beta type** | Epinephrine > nonepinephrine; Isoproterenol; dobutamine | ↑cAMP | |
| Beta$_1$ | | | C10 |
| Beta$_2$ | Epinephrine >>> nonepinephrine; terbutaline | ↑cAMP | C5 |
| Beta$_3$ and putative beta$_4$ | BRL37344; CGP12177A | ↑cAMP | C8 |

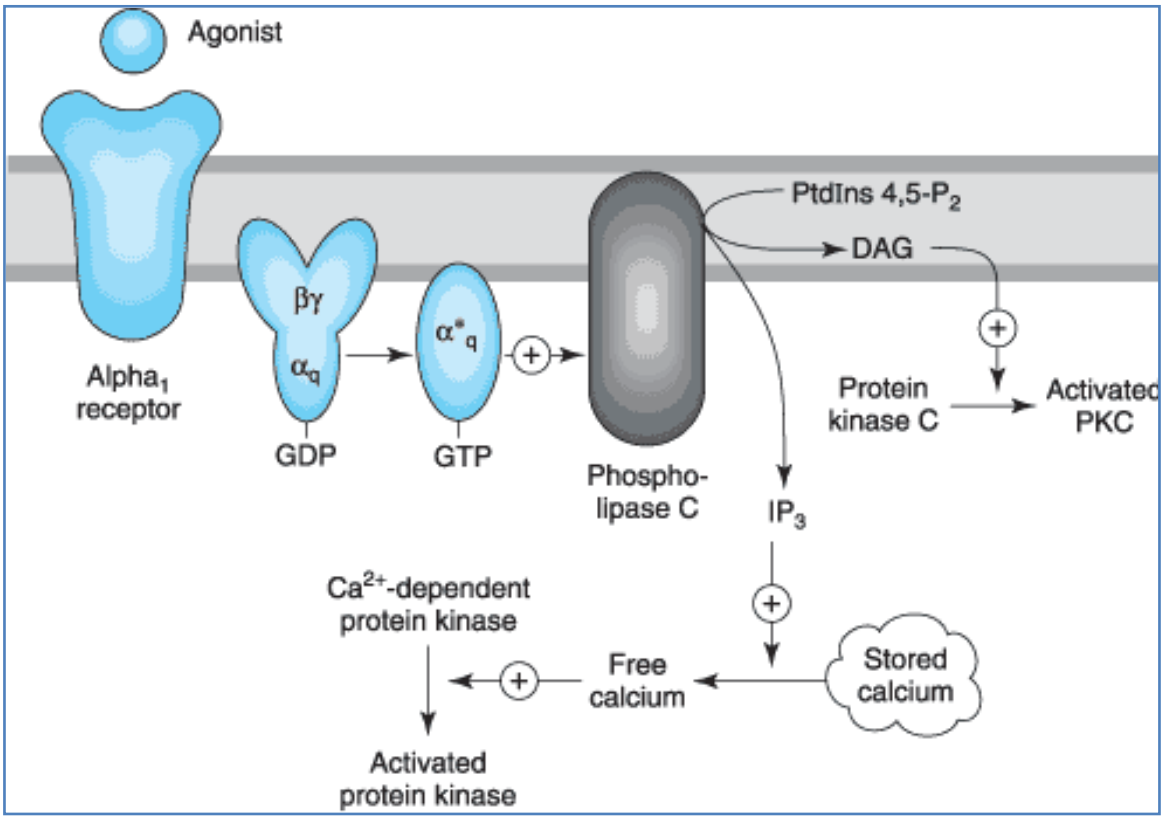


**Figure 11-5**. Activation of $\alpha_1$ adrenergic responses. Stimulation of $\alpha_1$ receptors by catecholamines leads to the activation of a $G_q$ subunit. The subunit of this G protein activates the effector, phospholipase C, which leads to the release of $IP_3$ (inositol 1,4,5-trisphosphate) and DAG (diacylglycerol) from phosphatidylinositol 4,5-bisphosphate (PtdIns 4,5-$P_2$). $IP_3$ stimulates the release of sequestered stores of calcium, leading to an increased concentration of cytoplasmic $Ca^{2+}$. $Ca^{2+}$ may then activate $Ca^{2+}$-dependent protein kinases, which in turn phosphorylate their substrates. DAG activates protein kinase C.

| **Table 11–4**. Catecholamine Receptors: Location and Actions. | | |
|---|---|---|
| **Type of Catecholamine Receptor** | **Tissue Location** | **Action following Receptor Activation** |
| Alpha$_1$ | Vascular smooth muscle | Increases vasoconstriction (increases blood pressure) |
| | Liver | Increases glycogenolysis and gluconeogenesis |
| | Eye | Increases ciliary muscle contraction (pupil dilation) |
| | Skin | Increase pilomotor smooth muscle contraction (erects hairs) |
| | Prostate | Increases contraction |
| | Uterus | Increases contraction |
| Alpha$_2$ | Pancreatic islet cells | Decreases release of insulin and glucagon |
| | Blood platelets | Increases platelet aggregation |
| | Adipose cells | Decreases lipolysis |
| | Preganglionic and postganglionic nerves | Decreases release of neurotransmitter (negative feedback inhibition) |
| Beta$_1$ | Myocardium | Increases force and rate of contraction |
| | Kidney (juxtaglomerular apparatus) | Increases secretion of renin |
| | Most tissues | Increases calorigenesis |
| | Nerves | Increases conduction velocity |
| Beta$_2$ | Intestinal smooth muscle | Decreases intestinal motility |
| | | Increases sphincter tone |
| | Bronchiolar smooth muscle | Decreases contraction (bronchial dilation) |
| | Liver | Increases glycogenolysis and gluconeogenesis |
| | Pancreatic islet cells | Increases release of insulin and glucagon |
| | Adipose tissue | Increases lipolysis |
| | Muscles | Increases potassium uptake (prevents hyperkalemia) |
| | Liver and kidney | Increases peripheral conversion of $T_4$ to $T_3$ |
| | Uterus smooth muscle | Decreases uterine contraction (uterine relaxation) |
| Beta$_3$ | Adipose cells | Increases lipolysis |
| Dopamine$_1$ | Renal artery smooth muscle | Decreases vasoconstriction (dilation of renal artery) |
| Dopamine$_2$ | Nerve terminals | Controls neurotransmitter release |

A. **Alpha–Adrenergic Receptors:** The $\alpha_1$ subtypes are postsynaptic receptors that typically mediate vascular and other smooth muscle contraction. When agonist binds to this receptor, $G_q$ is released and activates phospholipase C. Epinephrine and norepinephrine are potent agonists for this receptor, while isoproterenol is weakly active. $\alpha_2$ receptors were first identified at the presynaptic sympathetic nerve ending and, when activated, served to inhibit the release of norepinephrine. However, these receptors have been found in platelets and postsynaptically in nervous system, adipose tissue, and smooth muscle. Agonist binding to the $\alpha_2$ receptor release $G_i$ $\alpha$, which inhibits adenylyl cyclase. Prazosin is a selective antagonist at the $\alpha_2$, whereas phentolamine and phenoxybenzamine act at both.

B. **Beta–Adrenergic Receptor**: Agonist binding to the beta-adrenergic receptors activates adenylyl cyclase via the Gs $\alpha$ subunit. There are three major beta-receptor subtypes. The $\beta_1$ receptor, which mediates the direct cardiac effects, is more responsive to isoproterenol than to epinephrine or norepinephrine. The $\beta_2$ receptor mediates vascular, bronchial, and uterine smooth muscle relaxation, probably by phosphorylating myosin light chain kinase. Isoproterenol is also the most potent agonist at this receptor, but epinephrine is much more potent than norepinephrine. The $\beta_3$ receptors regulate energy expenditure and lipolysis. Homozygous mutations in the $\beta_3$ gene in Pima Indians are associated with earlier onset of type 2 diabetes. In the heart, $\beta_3$ stimulation causes decreased ventricular contraction by increasing nitric oxide.

C. **Dopamine Receptors:** Dopaminergic receptors are found in the CNS presynaptic adrenergic nerve terminals pituitary, heart, renal, and mesenteric vascular beds. Five subtypes of the dopaminergic receptor, $D_1$ to $D_5$.

   The binding affinity of the $D_1$ receptor is greater for dopamine than for haloperidol; the reverse is true for the $D_2$ receptor. The effect of the D1 receptor is greater for dopamine than for haloperidol; the reverse is true for the $D_2$ receptor. The effects of the $D_1$ receptor are mediated by stimulation of the adenylyl cyclase system and are found postsynaptically in the brain. Those in the pituitary are $D_2$ receptors that inhibit the formation of cAMP, open $K^+$ channels, and decrease $Ca^{++}$ influx.

**Regulation of Activity:** the major physiologic control of sympathoadrenal activity is exerted by alterations in the rate of secretion of catecholamines. However, the receptor and postreceptor events serve as sites of five regulations. Norepinephrine released during presynaptic nerve stimulation binds to $\alpha$ receptors and reduced the amount of norepinephrine released. The number of receptors on the effector cell surface can be reduced by binding of agonist to receptor "down-regulation". The mechanisms involved in some of these changes are known. For example, phosphorylation of the beta-adrenergic receptor by beta-adrenergic receptor kinase results in their sequestration into membrane vesicles internalization and degradation. The phosphorylated receptor also has a greater affinity of $\beta$-arrestin, another regulatory protein, which prevents its interaction with $G_s\alpha$.