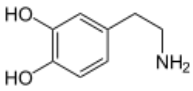
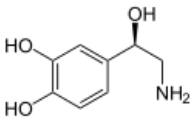
Secretion and physiological effects of catecholamines

Adrenal medulla

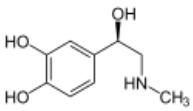
The adrenal medulla is located at the center of the adrenal gland, being the innermost part surrounded by the adrenal cortex. It resembles literally a large sympathetic ganglion. It consists of cells called chromaffin cells which produce and secrete, upon stimulation, catecholamines; epinephrine, norepinephrine and dopamine. The chromaffin cells are modified postganglionic neurones, that have lost their dendrites and axons, receiving sympathetic innervation and stimulation by preganglionic autonomic fibers controlled by the CNS. The chromaffin cells have neuronal properties due to their embryonic-neural crest origin which is different from that of adrenal cortical cells. Thus the adrenal gland is referred as an endocrine gland of dual origin just like hypothalamus. The chromaffin cells form clusters around large and numerous blood vessels a feature that enhances the efficiency amd the velocity of the catecholamine activity. The medullary cells are considered as endocrine cells but in reality they exhibit neuroendocrine properties due to the neural origin of the adrenal medulla. The amount of dopamine secreted by the medulla is relatively small in comparison to the total body dopamine. It is used, however, as a precursor for the production of norepinephirne and eventually epinephrine. The most abundant catecholamine released by the medulla is epinephrine whose amount is five times greater than that of norepinephrine constituting the 80% of total catecholamine amount.



Dopamine



Norepinephrine

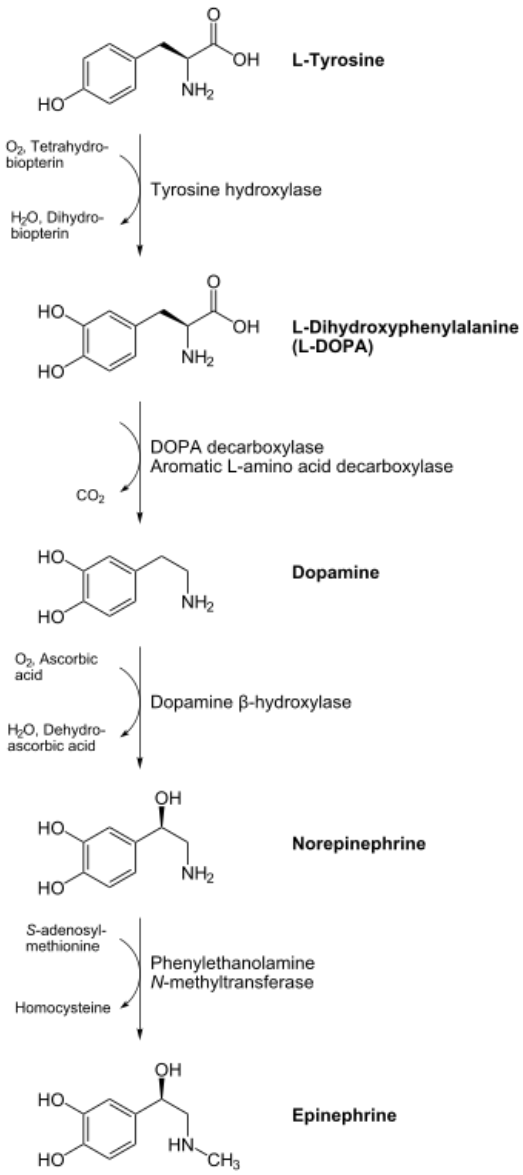


Epinephrine

Catecholamines

Synthesis of catecholamines

The catecholamine hormones are synthesized from the amino acid L-tyrosine. The L-tyrosine is transformed to L-DOPA in presence of the tyrosine hydroxylase enzyme which is the rate limiting enzyme of the whole catecholamine synthetic pathway. The L-DOPA in turn is transformed into dopamine in presence of the DOPA decarboxylase enzyme. The dopamine is transformed into norepinephrine in presence of the dopamine ß-hydroxylase. The norepinephrine is transformed eventually into epinephrine in presence of the N-methyltransferase enzyme. Sympathetic stimulation induces increased concentrations of both tyrosine hydroxylase and dopamine ß-hydroxylase. The hypothalamic CRH (corticotropin releasing hormone) and the hypophyseal ACTH(adrenocorticotropic hormone) help to sustain the levels of these enzymes under stressful conditions. At the same time, cortisol induces the N-methyltransferase and therefore selectively stimulates epinephrine synthesis.

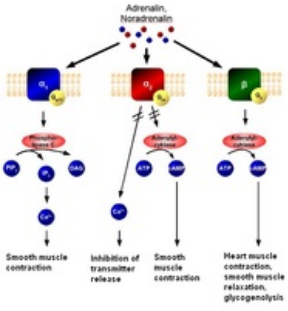


Metabolism of catecholamines

The circulating medullary catecholamines perform similar activity as the sympathetic neurotransmitter norepinephrine having one big characteristic difference. The half life of the circulating medullary catecholamines is only few minutes a time much smaller than that of the sympathetic norepinephrine resulting to a lesser functional efficiency. This results from the presence of two enzymes within the blood circulation that degrade the medullary catecholaminess very fast.They can be degraded either by deamination by the enzyme monoamine oxidase (MAO) or by methylation by the enzyme catechol-O-methyltransferase (COMT).

Catecholamine receptors

- Epinephrine and norepinephrine perform their functions by binding on specific receptors situated on the plasma membrane of target effector cells. These membrane receptors are called adrenergic receptors and divide into two groups; the α and the β adrenergic receptors each of which induces either excitation or inhibition of the target cell according to the receptor subtype of each group. The α receptors are further divided into α_1 and α_2 adrenergic receptor; similarly β receptors are divided into β_1, β_2 and β_3 adrenergic receptors. β_1 and β_2 receptors are coupled to a G protein which activates adenylyl cyclase as soon as the catecholamine-receptor complex is formed. Then increase of intracellular cAMP occurs which acts as a second messenger which in turn activates the protein kinase A enzyme. α_2 receptors are coupled with an inhibitory G protein which decreases cAMP levels as soon as hormone binding occurs. α_1 are coupled to phosphatidylinositol membrane system, Ca^{2+}, and protein kinase C signaling mechanisms.



Adrenergic receptor mechanisms

- The norepinephrine has great effect over α adrenergic receptors, but it has a much smaller affinity for the β adrenergic receptors whereas epinephrine reacts with both α and β receptors with the same great potency.

Physiological effects of catecholamines

1. Both epinephrine and norepinephrine increase glucose levels inducing a hyperglycemic effect. This is achieved directly through stimulation of glycogenolysis and gluconeogenesis in the liver by activation of β and α receptors of the hepatocytes respectively and indirectly through enhancement of glucagon secretion by the α cells of the pancreatic islets of Langerhans. Catecholamines further increase the hyperglycemic effects through inhibition of the insulin mediated glucose uptake by muscle and adipose tissue by blocking the GLUT4 transporters and through inhibition of insulin secretion by the β cells of the pancreatic islets reducing the hypoglycemic effect of insulin. All these effects promote the same objective; an increase of the blodd plasma glucose levels.
2. Epinephrine activates adipose tissue lipase which promotes lipolysis increasing the plasma free fatty acid levels which in turn produce energy in the form of ATP either through gluconeogenesis or β oxidation. This lipolytic effect of catecholamines is of vital importance when there is glucose deficiency and consequently ATP and energy deficiency, thus catecholamines lipids are use as an alternate fuel.
3. Epinephrine increases the basal metabolic rate with consequent increase of the nonfacultative thermogenesis. This is achieved by increasing the O2 consumption a state compensated by increasing the minute ventilation. The minute ventilation augments by increasing the tidal volume rather than the respiratory rate $\dot{V} = V_T \times RR$.
4. Catecholamines a great effect over the cardiovascular system affecting the activity of the heart and blood vessels. The catecholamines increases all four effects of heart activity. Increase of the inotropic effect causes contractility of the cardiac muscle increasing the cardiac output by increasing the stroke volume. Increase of the bathmotropic effect increases the excitability of the cardiac muscle which also increases the cardiac output through stroke volume alteration. Increase of the dromotropic effect increases the AV nodal conduction velocity which increases the cardiac output by increasing the heart rate. Increase of the chronotropic effect increases the SA nodal discharge rate which also increases the cardiac output through heart rate alteration $CO = SV \times HR$. The catecholamines alter the blood pressure by altering the vascular resistance. Control of the vascular resistance is achieved through vasoconstriction and vasodilation. Vasoconstriction is mediated through the α adrenergic receptors in liver, kidney, skin and gut and vasodilation is mediated through β adrenegic receptors in skeletal muscle $\Delta P = \frac{8\mu l\dot{V}}{\pi r^4}$ and $R = \frac{8\mu l\dot{V}}{\pi r^4}$.
5. Catecholamines promote relaxation of the visceral smooth muscle acting through β adrenergic receptors inducing decreased GIT activity, relaxation of the urinary bladder detrusor muscle and bronchodilation

Links

Bibliography

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- Lecture Notes: Prof. MUDr. Jaroslav Pokorný DrSc.