Adrenal Medulla

Lecture Goal(s): To describe the production of catecholamines by the adrenal medulla, the actions of catecholamines in the body and the metabolism of catecholamines. Abnormalities of catecholamines, and their metabolites, will be correlated with pheochromocytoma.

Lecture Objectives: Upon completion of this class material each student will be able to do the following:

1. Cog/I List the hormones produced by the adrenal medulla and the percentage of these hormones produced in the adrenal medulla as compared to elsewhere in the body.

2. Cog/I Recognize the chemical structure of epinephrine and norepinephrine and explain the chemical characteristics of the catecholamines group.

3. Cog/II Describe the synthesis of catecholamines by the adrenal medulla noting the enzymes necessary in this process.

4. Cog/II Describe the following effects of catecholamines once they are released from the adrenal medulla.

   a. glycogenolysis in the liver and skeletal muscle
   b. mobilization of free fatty acids
   c. the metabolic rate
   d. force and rate of heart contraction
   e. vasoconstriction and vasodilation
   f. "fight-or-flight" response

5. Cog/II Describe the metabolism of catecholamines and the enzymes involved.

6. Cog/III Evaluate the following parameters in cases of pheochromocytoma.

   a. serum epinephrine/norepinephrine levels
   b. 24-hr. urine metanephrines
   c. 24-hr. urine vanillylmandelic acid

I. **Adrenal Medulla -** is the functionally distinct inner portion of the adrenal gland.

A. **The adrenal medulla produces the class of hormones known as catecholamines.** These primarily include:

1. **Norepinephrine (noradrenaline is an older name)** - approximately 10 - 20 percent of the norepinephrine in the body comes from the adrenal medulla (the rest comes from neuronal synthesis)
2. **Epinephrine (adrenaline is an older name)** - Approximately, 80 - 90 percent of the epinephrine in the body comes from the adrenal medulla (the rest comes from neuronal synthesis)
3. **Dopamine** - about ½ of the dopamine produced in the body comes from the adrenal medulla

B. **Function of catecholamines -** Known as hormones in cases where this chemical is produced by the adrenal medulla and then transported in the blood to a distant target organ in order to stimulate a specific response or action

1. Catecholamines serve primarily as neurotransmitters in other cases.

C. **Chemical Nomenclature** - Norepinephrine, epinephrine, dopamine, and L-DOPA are classified as catecholamines.

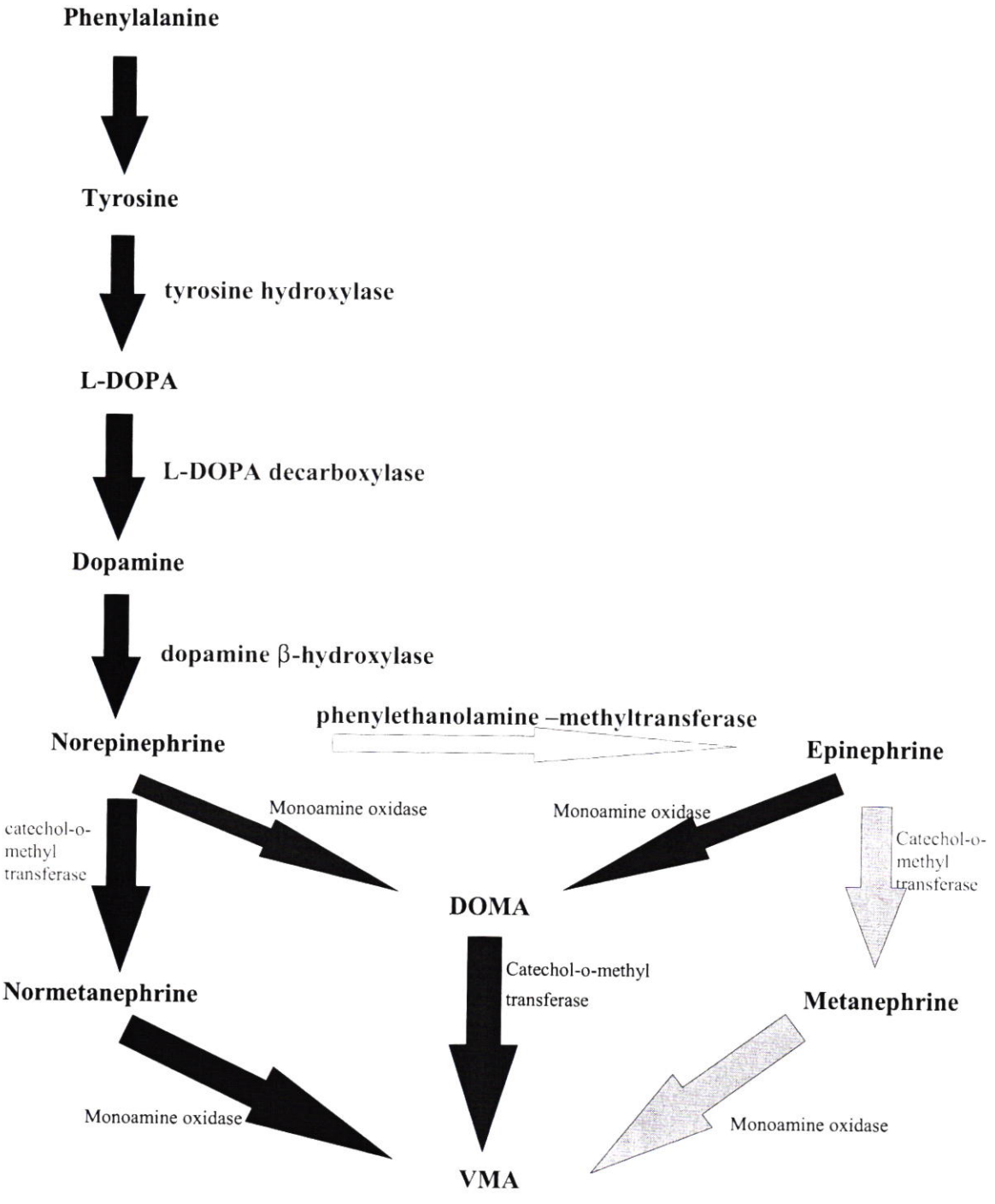
1. **Catecholamines refers to a group of chemical compounds that possess a catechol function and an amine function.**
   - **a.** The catechol function is a dihydroxybenzene function.
   - **b.** The amine function is NH_2.

Synthesis of Medullary Hormones -

A. The sequence of steps in the synthesis of adrenal medullary hormones is illustrated on page 18-4. The chemical structures of the compounds involved in the synthesis of these hormones are illustrated in Figure 46-4, page 883 in Kaplan. Tyrosine is considered to be the main precursor for this synthetic pathway, but the process may actually begin with phenylalanine.

1. The first step involves the hydroxylation of tyrosine which is catalyzed by the enzyme tyrosine hydroxylase. This reaction results in the formation of dihydroxyphenylalanine (DOPA). The physiologically active form of DOPA is the L-form, thus one typically sees this intermediate abbreviated as L-DOPA.
2. L-DOPA is decarboxylated to form dopamine by the enzyme L-DOPA decarboxylase. Finally, dopamine may undergo another hydroxylation in the formation of norepinephrine. This step is catalyzed by the enzyme Dopamine β-hydroxylase.
3. In the final step, we have the formation of epinephrine. Norepinephrine is converted to epinephrine by a methylation process catalyzed by phenylethanolamine N-methyltransferase.
   a. Phenylethanolamine N-methyltransferase - Phenylethanolamine N-methyltransferase occurs primarily in the adrenal medulla and in a few nerve endings in the heart and uterus. This methylating enzyme is not found elsewhere in the body. This explains why it was noted earlier that 80 - 90 percent of the epinephrine produced in the body comes from the adrenal medulla.

Biosynthesis and Metabolism of Adrenomedullary Hormones



These hormones are produced in the mitochondria of the cells of the adrenal medulla. Here they are stored in secretory granules until their secretion is initiated by the neurotransmitter acetylcholine. Once their action is complete, they are removed from the circulation by liver metabolism.

In the liver there are two basic pathways for metabolism. These pathways are illustrated on the preceding diagram.

The first pathway involves the methylation of both epinephrine and norepinephrine by the enzyme catechol-o-methyl transferase (COMT) to form metanephrines. These metanephrines may be excreted directly into the urine or they may be further metabolized to vanillylmandelic acid (VMA) which is excreted into the urine. This second metabolic step of the first pathway is catalyzed by the enzyme monoamine oxidase.

The second pathway of metabolism involves the action of monoamine oxidase directly on epinephrine and norepinephrine, leading to the formation of 3,4-dihydroxymondelic acid (DOMA). DOMA is then acted upon by the enzyme catechol-o-methyl transferase to produce VMA.

Both of these metabolic pathways are present in the liver. Metanephrines (i.e., metanephrine and normetanephrine) and VMA are serve no physiologic function in the body. Thus, they are considered to be physiologically inert.

Approximately 80 percent of catecholamines are excreted as VMA and approximately 20% are excreted as metanephrines (i.e. only one metabolic step). There may also be some free epinephrine and norepinephrine present in the urine, but usually a very small amount (<2%).

Physiologic Actions of Catecholamines

Physiological actions of the catecholamines are diverse. Norepinephrine functions primarily as a neurotransmitter. Both norepinephrine and epinephrine have influences in the vascular system, whereas epinephrine influences metabolic processes such as carbohydrate metabolism. The physiological actions of the catecholamines are initiated through their interaction with two different types of specific plasma membrane receptors, alpha- and beta-adrenergic receptors. These receptors have different affinities for norepinephrine and epinephrine and cause opposing physiological effects. Norepinephrine primarily interacts with alpha receptors, whereas epinephrine interacts with both alpha and beta receptors.

Stimulation of alpha-adrenergic receptors results in vasoconstriction, decreasing in insulin secretion, sweating, piloerection (hair standing on end), and stimulation of glycogenolysis in the liver and skeletal muscle, leading to an increase in blood glucose concentration. Stimulation of beta receptors, however, leads to vasodilation; stimulation of insulin release; increased cardiac contraction rate; relaxation of smooth muscle in the intestinal tract, and bronchodilation by relaxation of smooth muscles in bronchi; stimulation of renin release, which enhances sodium resorption from the kidney; and enhanced lipolysis.

Diseases of the Adrenal Medulla

In a histology lab, one would find that the adrenal medulla stains brown with chromic acid. This is why it is often referred to as chromaffin tissue. Tumors in the adrenal medulla, or in sympathetic neurons, produce excessive amounts of epinephrine and norepinephrine. This disease is known as pheochromocytoma (chromaffinoma - older name). Pheochromocytoma is the only significant adrenal medullary disease.

Approximately 90 percent of the pheochromocytomas occur in the adrenal gland. Pheochromocytoma is a rare cause of hypertension. It is responsible for approximately 0.5 percent of the cases of hypertension. Pheochromocytoma can cause death by an acute hypertensive attack. In the case of pheochromocytoma, one would expect to see an elevation of both metanephrines and VMA in the urine.

Testing for Pheochromocytoma - There are two schools of thought for testing for pheochromocytoma.

1. One approach involves the use fluorometric or RIA techniques to measure epinephrine and norepinephrine levels directly in the plasma.
2. The second approach involves the use of a 24-hour urine for the measurement of VMA and metanephrine levels.
3. As discussed with adrenocortical hormones, measurement of the hormone itself can be affected by a variety of factors and may not reflect the patients true level of the hormone while collection of a 24-hour urine may provide a more true picture of hormone.