Chapter 4

The Adrenal Medulla

Introduction

Induction of cortisol production requires several minutes, and full elaboration of cortisol action requires several hours. In contrast, the adrenal medullary hormones are intended for much more rapid responses, and are primary mediators of the "fight or flight" response. This is possible because the adrenal medulla is essentially an extension of the central nervous system. The cells of the adrenal medulla are modified sympathetic ganglia. Acetylcholine from sympathetic neurons causes the release of epinephrine and norepinephrine; in effect, this is a translation from a neural to a hormone signal.

In contrast to cortisol, which is synthesized and released without storage, the medullary hormones are synthesized and stored in vesicles called chromaffin granules. This creates a pool of ready-made hormone which can be released immediately upon stimulation. **The rate of release** is usually the major factor in controlling serum catecholamine levels.

Catecholamine Synthesis

The two most important hormones of the adrenal medulla are the catecholamines epinephrine and norepinephrine (Figure 1). The synthesis pathway for norepinephrine is identical to that used by adrenergic neurons. However, the adrenal medulla expresses an additional enzyme, phenylethanolamine-N-methyl-transferase (PNMT), that the adrenergic neurons do not. This is because only the adrenal medulla is exposed to sufficiently high levels of cortisol (due to the centripetal blood flow from the cortex) to allow induction of PNMT gene expression. PNMT catalyzes the final step in the synthesis pathway, the conversion of norepinephrine to epinephrine.
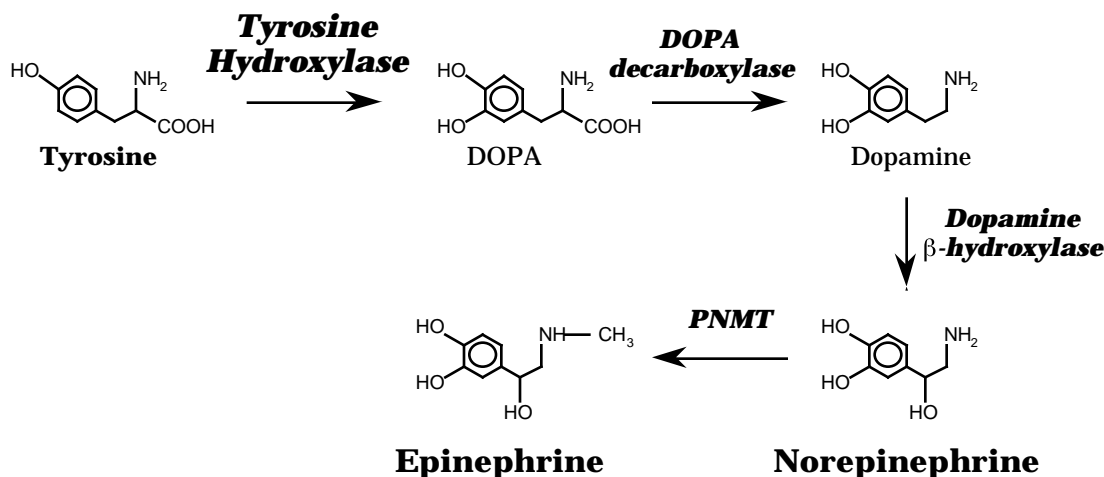

Figure 1. The biosynthesis of the catecholamine hormones.

The biosynthesis pathway begins with the amino acid tyrosine. The first step in the pathway is the committed step for catecholamine synthesis. **Tyrosine hydroxylase catalyzes the rate limiting step** for the production of epinephrine and norepinephrine, the conversion of tyrosine to dihydroxyphenylalanine (DOPA). Phosphorylation by cAMP-dependent protein kinase stimulates tyrosine hydroxylase; this is a rapid activation step. In addition, tyrosine hydroxylase expression increases after long-term stimulation of the adrenal medulla. Finally, tyrosine hydroxylase is feedback inhibited by norepinephrine.

Dihydroxyphenylalanine is converted to dopamine by DOPA decarboxylase. Norepinephrine is produced from dopamine by dopamine -hydroxylase (DBH). DBH requires ascorbic acid as a cofactor; this may be the reason for the large stores of this vitamin in the adrenal cortex.

The human adrenal medulla produces and releases about 80% epinephrine and 20% norepinephrine, with a small amount of dopamine. While the adrenergic neurons are responsible for the majority of norepinephrine production, the adrenal is the source of essentially all of the epinephrine produced in the body.

The term "catechol" means "*ortho*-dihydroxybenzene". Epinephrine and norepinephrine are ethanolamine derivatives of catechol; a catecholestrogen is related to the corresponding estrogen, but has an additional hydroxyl on its A ring. The prefix "nor-" means "without the methyl"; thus, norepinephrine is missing the methyl added in the PNMT catalyzed reaction.

Epinephrine and norepinephrine are often referred to as adrenaline and noradrenaline; these names are actually trademarked terms belonging to the drug company that first synthesized the two hormones.

Chromaffin Granule Contents

Epinephrine and norepinephrine are stored in the chromaffin granules at very high concentrations (about 0.5 M). The DBH-catalyzed reaction occurs in the chromaffin granules; the other reactions occur in the cytoplasm of the cells, with the catecholamines and their precursors being actively transported from one compartment to the other. The granules also contain fairly high concentrations of ATP and ADP (about 0.1 M), probably to supply energy for the active transport mechanisms.

The chromaffin granules also contain other hormones, and hormone-like peptides. The roles of most of these compounds are not understood, although they are probably involved in some aspect of stress response. Compounds known to be present are Neuropeptide Y (a neuromodulator), Calcitonin gene related protein (a vasodilator), and Chromogranins A, B, and C (function unknown, although they may be involved in intracellular traffic direction). Also present are methionine and leucine enkephalin, two 5 amino acid peptides known to bind to opiate receptors, which have been proposed to act as analgesics as part of the stress response, or to act as feedback signals to the adrenal medulla to inhibit further synthesis and

release of catecholamines.

The entire contents of the granule are released upon stimulation of the chromaffin cell by acetylcholine from the sympathetic nervous system. The release signal is triggered by stressors, such as anxiety, fear, pain, trauma, hemorrhage or other fluid loss, changes in pH of the blood, increased energy demand (especially for exercise), hypoglycemia, or exposure to excessive heat or cold. Most, if not all, of the granule contents play some role in preparing the body to respond to these types of stress.

Inactivation of Catecholamines

A number of reactions are involved in catecholamine inactivation. However, there are two enzymes that are especially important. The first is catechol-O-methyl transferase (COMT), which adds a methyl group to the hydroxyl at the 3 position of the catechol ring, and the second is monoamine oxidase (MAO), which catalyzes an oxidative deamidation reaction, leaving an aldehyde in place of the amino group. Figure 2 shows these reactions using epinephrine as an example.
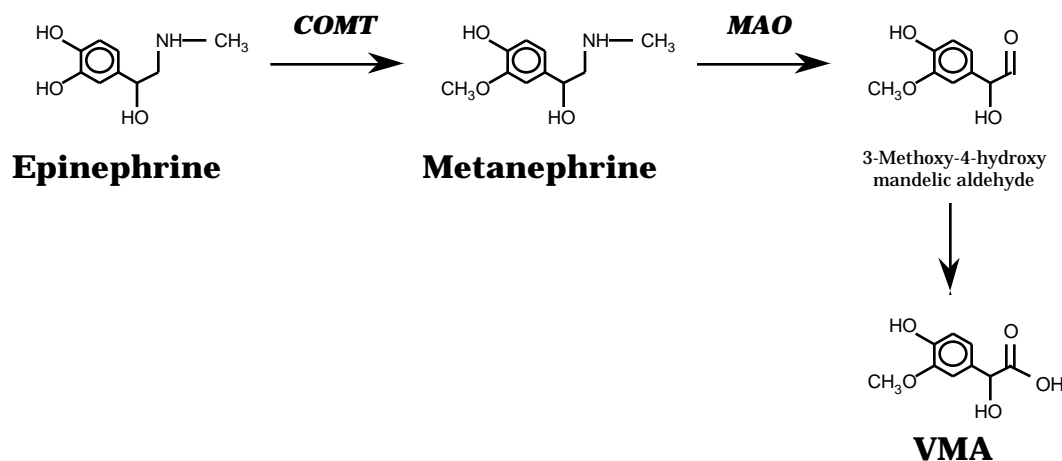

Figure 2. Examples of catecholamine inactivation reactions.

Most of the metabolism of the catecholamines occurs in the liver, which contains COMT and MAO, and a number of other enzymes. The adrenergic nerve terminals lack COMT, and use MAO for neurotransmitter inactivation. Note that COMT and MAO can use norepinephrine, epinephrine, dopamine, and their metabolites as substrates.

Two of the epinephrine and norepinephrine metabolites are major excreted products: the metanephrines (3-methoxyepinephrine and 3-methoxynorepinephrine) make up about 15% of urinary catecholamine residues, and VMA (vanillylmandelic acid = 3-methoxy-4-hydroxy-mandelic acid) is a product of both epinephrine and norepinephrine, and accounts for ~85% of the urinary excretion for these catecholamines.

Actions of Norepinephrine and Epinephrine

The simplest way to view the effects of the adrenal medullary catecholamines is to consider them as hormones that prepare the body for exercise: the classic "fight or flight" response. The effects are mediated by two major sub-types of adrenergic receptor: α and β receptors. The β adrenergic receptors bind both catecholamines. The β adrenergic receptors, and especially the β_2 receptor, are primarily receptors for epinephrine. The β_2 receptor is the prototypical adenylyl cyclase-linked receptor, and like the β_1 receptor uses cAMP as a second messenger; the α_1 receptor stimulates phosphatidyl inositol hydrolysis, while the α_2 receptor acts by inhibiting adenylyl cyclase.

Although norepinephrine and epinephrine are released together by the adrenal medulla, some of their effects are divergent due to their differential affinities for the different adrenergic receptors. For example, epinephrine has direct effects on the heart, causing an increase in heart rate. In contrast, norepinephrine decreases heart rate indirectly, as a result of reflex bradycardia due to its vasoconstrictive effects.

The combined effects of norepinephrine and epinephrine are to increase cardiac output, heart rate, blood pressure, and respiration (epinephrine is a powerful bronchodilator). They also increase blood flow to the muscles, while decreasing the splanchnic and renal blood flow. Finally, they increase alertness (chronic stimulation results in anxiety). The net effects are to reroute blood to the muscles, and to prepare the brain to control the anticipated physical activity.

Direct Effects of Epinephrine on Energy Metabolism

Epinephrine (and to some extent norepinephrine) has effects in all of the major tissues involved in energy metabolism.

In the liver, these hormones stimulate glycogen and lipid breakdown. Epinephrine stimulates glycogen breakdown by activation of phosphorylase (the system in which the concept of the second messenger was first developed). Epinephrine also stimulates gluconeogenesis by inactivating pyruvate kinase, and by increasing fructose-bis-phosphatase and decreasing phosphofructokinase activity, and stimulates glucose release into circulation. The combination of the effects is a large increase in glucose availability, which can lead to hyperglycemia in cases of prolonged stimulation.

In skeletal muscle, epinephrine also stimulates glycogen breakdown. However, in muscle, epinephrine slightly stimulates glycolysis (the muscle and liver contain different isozymes of the glycolytic and gluconeogenic enzymes, and as a result the effects of cAMP-dependent protein kinase are different). The effect of epinephrine in muscle is a preparation for the demands of exercise – without exercise, the increase in glycolysis in muscle is fairly limited. The effects of exercise and of catecholamine action on glucose metabolism are discussed further in Chapters 5 and 6.

In adipose tissue, epinephrine stimulates lipolysis by increasing the activity of hormone-sensitive lipase.

In adipose tissue, epinephrine has been known for some time to have lipolytic effects, primarily as a result of -receptor-mediated stimulation of the hormone-sensitive lipase. However, 2-receptor mediated antilipolytic effects are also thought to occur. These antilipolytic effects may be partially responsible for the decrease in catecholamine-stimulated lipolysis observed during dieting and fasting, although other effectors such as prostaglandin E and adenosine are also thought to be involved. Exercise appears to enhance the lipolytic effects and reduce the antilipolytic effects, probably by altering post-receptor responses.

Indirect Effects of Epinephrine on Metabolism

Epinephrine and norepinephrine decrease pancreatic production of insulin. By lowering insulin, the primary hormone responsible for decreasing serum glucose levels, epinephrine potentiates its effects on other tissues, since the effects of insulin and epinephrine are opposite. This reduction of insulin secretion may also protect the pancreas from exhaustion in conditions of chronic stress, by reducing the necessity for insulin production to compete with production of adrenal hormones. This is potentially important, because, unlike the adrenal, which responds to increased demand for its hormones by increasing its ability to produce those hormones, the pancreas has only a limited capacity for increasing insulin secretion rates. (In untreated Cushing's Syndrome, for example, prolonged high levels of cortisol result in diabetes, possibly as a result of exhaustion of insulin producing cells in the pancreas; high levels of cortisol also inhibit insulin secretion and induce insulin resistance.) The inhibition of insulin secretion by catecholamines is an -adrenergic effect. Although specific -adrenergic agonists alone stimulate insulin release, stimulation of the pancreas by physiological levels of norepinephrine and epinephrine inhibits insulin release.

Interactions of Epinephrine and Cortisol

You will recall from Chapter 3 that cortisol has actions in most of the same tissues as epinephrine. However, the mechanisms by which the two hormones have their effects are quite different. The two hormones have a variety of interactions, depending on the tissue, with some of the effects being complementary and some opposing.

Cortisol is a relatively long term effector: it has a half-life measured in hours, and its effects last even longer. Epinephrine is an immediate-response hormone: it has a short half-life, and its effects disappear rapidly if the hormone is no longer present. This difference is a consequence of the mechanism by which the hormones act. Cortisol increases (or decreases) the *amount* of a given enzyme. Epinephrine acts by modulating the activity of *existing* enzymes.

In the liver the effects of the two hormones are generally complementary: both hormones increase glucose synthesis and glucose release, although the effects on glycogen production are opposite. In adipose tissue, the primary effects of the two hormones are complementary; both hormones act to increase hormone-sensitive lipase activity, with cortisol stimulating the production of the enzyme, and epinephrine increasing the activity of the enzyme.

In contrast, in muscle, the two hormones have opposite effects. Cortisol decreases glucose utilization and uptake by the muscle, and increases protein breakdown, while epinephrine stimulates glucose use.

Finally, cortisol is required for PNMT expression, and therefore for epinephrine synthesis. In addition, cortisol decreases COMT activity, and potentiates -receptor mediated catecholamine action in target tissues. As a result, cortisol potentiates epinephrine effects by increasing epinephrine synthesis and inhibiting catecholamine breakdown, and has permissive effects in many tissues.

Remember that humans do not consist of a variety of different systems acting in isolation. Instead, a human is an organism, with the different systems interacting in many ways. The effect of epinephrine in the absence of cortisol is vastly different from that observed in the presence of cortisol. The net effect on the body is due to the sum of all of the individual effects of the different hormones, and of the interactions among the different hormones.

Clinical Manifestations of the Adrenal Medulla

There are no direct clinical consequences of adrenal medullary insufficiency. An adrenalectomized patient requires supplementation with glucocorticoids and mineralocorticoids, but suffers no apparent ill effects from lack of epinephrine. The reason for this is unknown. It is possible that norepinephrine release from the sympathetic nervous system yields sufficient circulating catecholamine to maintain normal functioning. Alternatively, other systems have somewhat similar effects, especially on glucose homeostasis, and these other systems may compensate for lack of epinephrine.

Uncontrolled excessively high levels of catecholamines are usually the result of a relatively rare tumor of the chromaffin cells called a pheochromocytoma. These tumors may occur in the adrenal or in peripheral locations. A pheochromocytoma may release catecholamines continually, or the release may be episodic. The usual treatment involves surgical removal of the tumor; in cases where this is impossible, patients are generally treated with catecholamine antagonists.

Thyroid hormone potentiates the action of catecholamines by stimulating the production of adrenergic receptors and probably also intensifies post-receptor effects. Symptoms that reflect high levels of catecholamine action (*e.g.*, nervousness and hyperactivity) may therefore be secondary to hyperthyroidism rather than due directly to excessive catecholamine secretion. It is, however, often beneficial to alleviate the symptoms with catecholamine antagonists during attempts to resolve the thyroid disorder (see chapter 7).

References

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