TRANSFORMATION

Dr. M's SCIENCE NOTES

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HORMONES, part 2: Modes of Action and Specific Examples

Since hormones control all body functions, the secretion and biological function of these specific biomolecule messengers needs to be carefully monitored and ensured for optimal wellness. Based on the various regulatory and biochemical characteristics of hormones mentioned previously (see *Dr. M's Science Notes*, Vol 8, "Hormones, part 1: Basics of Their Biochemistry"), adequate hormone function requires the following:

- Good nutrition to ensure the presence of all building blocks for adequate biosynthesis of the hormone
- Adequate control of catabolic functions that otherwise could impair synthesis of needed hormones
- Good neural function to deliver the initial signaling input at the level of the hypothalamus
- Adequate synthesis of functional hormone molecules
- Good blood circulation to ensure timely delivery of needed hormones to their target organ(s)
- Good antioxidant environments to prevent oxidation of the hormones, their carriers, and/or their receptors
- Normal endocrine gland function to avoid underproduction or overproduction of hormones
- Proper signaling mechanisms for synthesis and shutdown, depending on the case

Hormones are molecules that are synthesized by certain tissues and carried to other tissues or organs, where they elicit a specific biological response. Upon binding to the receptor, the complex directly or indirectly reacts with gene sequences to regulate the expression of certain molecules. Thus, most hormones ultimately impact gene expression. This specific role of hormones in gene regulation makes their biochemistry extremely relevant both to homeostasis and to good health.

The specific mechanisms through which hormones reach the DNA sequences vary. Three different processes could be noted. These are based on the site of interaction of hormones and their receptors and modes of action. Hormones mediate their biological function by binding to receptors located on the plasma membrane, within the cytoplasm, and/or even within the nucleus in a few cases.

The first group of hormones react to receptors located on the surface of the cell membrane. That binding triggers a set of biological reactions, which ultimately transmit the specific hormone message to the targeted DNA sequence. In this particular type, the hormone/receptor complex could either remain on the surface of the cell or become internalized in the cytoplasm to initiate the biological response.

There are several molecular steps that help connect the message to the DNA and control the specific regulation of a gene. One aspect is the involvement of multiple messengers. In this scenario, the hormone is the first messenger. It binds to its receptor on the surface of the cell. The binding then triggers a molecular reaction that leads to the activation of the second messenger (such as cAMP, kinases, or calcium), which triggers a set of reactions that ultimately sends the signal to the nucleus where the genes are located. In some instances, the biological response of the hormone may be to activate or inhibit an enzyme, to facilitate some cellular trafficking of molecules, or to affect protein synthesis. The hormones most representative of this group are the peptide hormones.

Other hormones, following their secretion by their respective glands, cross the cell membrane in a seemingly passive diffusion manner and enter the cytoplasm. It is within the cytoplasm that this second group will bind to their receptors. Once bound to the receptor, that type of hormone (along with its receptor) then moves into the nucleus, where it will bind to a specific DNA sequence region to affect transcription. The hormones most representative of this group are the steroid hormones.

A third set of hormones, mostly represented by the thyroid hormones, passes freely across the plasma membrane into the cytoplasm and from there continues inside the nucleus, where it will bind to nucleoproteins to regulate transcription.

However, irrespective of their mode of carrying their message, one specific condition in the action of hormones is their rate of synthesis. In normal physiological conditions, the body regulates:

- The rate of hormone synthesis
- The rate of receptor synthesis and activity
- The turnover rate of hormone and receptors
- Various other factors related to hormonal function

The regulation of the body's endocrinological activity is a function of factors such as growth and development, the reproductive cycle, digestion, energy metabolism, stress, environment, and other external and internal cues. However, the biological response resulting from hormones depends on several other factors, including:

- The biochemical characteristics of the hormone
- The capacity of the target tissues to respond adequately and specifically to the hormone in question
- The rate of synthesis and concentration of the hormone
- The relative distribution of the hormone within the body
- The presence and effectiveness of the hormone receptor

One of the main reasons for the tight regulation in hormone function is the fact that hormones are involved in gene expression, activation and/or inhibition of some enzymes, and cellular function management. The abundance, untimely expression, or the lack of a hormone could affect the normal homeostasis of the body and even promote the onset of diseases such as cancer. Consider how this is the case in the following examples of hormone modes of action. The specific hormone cases considered here will be thyroid hormone, growth hormone, and cortisol.

Thyroid hormone

Synthesis - This hormone is synthesized from the stimulation of the pituitary gland by the hypothalamus. The hypothalamus secretes a thyrotropin-releasing hormone that acts on the pituitary. Upon stimulation by the hypothalamus, the pituitary then secretes thyroid-stimulating hormone, which will direct the thyroid glands to ultimately produce thyroxine (T4) and triiodothyronine (T3).

Mechanisms of action - The active hormones are thyroid hormones T4 and T3, although T3 is biologically more active than T4. These enter the cell and go directly inside the nucleus, where they bind to a receptor and/or chromatin to affect gene expression.

Biological functions -
- Regulation of cellular differentiation during development
- Regulation of metabolic rates
- Increased oxygen consumption, body temperature, pulse, systolic blood pressure, mental and physical potency, irritability, lipolysis, and weight loss
- Reduction of cholesterol levels
- Enhancing the response to glucagon and catecholamines
- Enhancing protein synthesis
- Increasing gene expression and transcription
- Effect on other hormones

It should be noted that high concentrations of thyroid hormone could affect heart function, create a negative nitrogen balance, impair the mitochondrial energy production, and induce hyperthermia and fatigue. Low thyroid concentrations will undermine some of the functions cited above. Some examples of hypothyroidism manifestations include Hashimoto's disease, increased sensitivity to cold, poor development and growth (as in cretinism), and anemia.

Growth hormone

Synthesis - Growth hormone is a single polypeptide that is mostly synthesized from the anterior pituitary gland. Its release in the system is under the influence of the hypothalamus and its amounts vary according to various factors, including age and stress.

Mechanism of action - It binds to its cell surface receptor and transduces its action within the cell.

Biological functions -
- Lactogenic activity as prolactin or human placental lactogen
- Anabolic effect
- Increased growth and sometimes gigantism (in case of excess)
- Increased transport of amino acids in cells (protein synthesis)
- Increased DNA and RNA synthesis
- Increased collagen synthesis
- Increased lipolysis
- Inhibition of glycolysis (may antagonize insulin in muscle tissues)
- Potential to induce hyperglycemia
- Increased mineral and ion metabolism and absorption
- Stimulation of mammary glands

As a result of its action on nucleic acids (DNA/RNA) and various other biosynthetic processes, its presence or synthesis in the body must be tightly regulated.

Cortisol

Synthesis - Cortisol is synthesized from the adrenal cortex (zona fasciculate) under the influence of the hypothalamus and the pituitary gland.

Mechanism of action - Cortisol is a steroid hormone derived from cholesterol. Upon secretion into blood circulation, it travels to target

cells, where it traverses the membrane and binds to its receptor within the cytoplasm. The cortisol/receptor complex moves into the nucleus where it will bind to the DNA complex and regulate transcription.

Biological functions (especially under high concentrations) -

- Increased RNA synthesis
- Changes in various metabolic pathways
- Catabolism of lymphoid tissues
- Decreased glucose uptake in peripheral tissues
- Increased muscle wasting
- Increased lipolytic activities in adipose tissues
- Increased urea production
- Decreased cellular protective functions, thus acting as anti-inflammatory
- Decreased synthesis of prostaglandins
- Decreased immune responses
- Reduced lymphocyte production and function
- Increased production of hydrochloric acid and pepsin leading to ulcer formation at high concentrations it
- Enhanced osteoporosis and calcium loss
- Increased blood pressure
- Reduced levels of DHEA, growth hormone
- Antagonistic to insulin effects
- Reduced blood supply to digestive system
- Reduced saliva secretion
- Reduced synthesis and secretion of pancreatic digestive enzymes
- Inhibition of GI contractions and absorption of nutrients
- Increased appetite for sugars

It should be noted that cortisol is an important hormone that is secreted daily in the body, with its highest levels in the morning and its lowest at night. Most of the negative effects of cortisol are due to persistent high levels in the system. Thus, any condition that promotes high levels of cortisol in the body could be detrimental to wellness and health. The combined effects of high cortisol lead to poor healing, malnutrition, suppressed immune functions, and increased risks to degenerative diseases.

Conclusion

The concentration of any hormone in the body must be tightly regulated. It is important to assess the body's specific hormone need prior to starting any long term hormone replacement therapy program. Hormones must be adequately synthesized and secreted only when needed.

Additionally, effort needs to be made to control the intake of hormone "look-alike" molecules that are present in the food chain or environment. Although hormones and receptors are generally very specific in their binding and affinities, there are cases where other molecules, including food molecules, phytochemicals, and xenobiotics with similar structure to a hormone could bind to the receptor of that hormone and thus initiate a biological response similar to that of the native and legitimate hormone. The binding of these "look-alike" molecules to specific receptors of a hormone could inhibit the action of that hormone, as its receptors are not available (i.e., "occupied") for further hormone coupling.

Many molecules in the environment or derived from inadequate gastrointestinal microbial metabolism could also act as hormones and disturb the normal hormonal control in the body. For instance, studies have indicated that some microbial by-products could act as insulin-like molecules, ultimately leading to insulin resistance if their levels persist in the body over a period of time. Similar findings were observed with steroid-like molecules synthesized by various organisms from digestive residues in the gut.

Hormones are important molecules that regulate several body functions. Without proper

hormone secretion and effectiveness, various metabolic disorders could occur. Equally important, high levels of hormones in the system could also undermine the normal functioning of the body and lead to health deterioration. This fact is particularly important because several hormones can act to enhance or inhibit the transcription of various genes. Endocrinology is therefore an area where moderation, control, and remaining in tune with the body's needs is very critical.

Enzyme supplementation plays a major role in supporting hormone synthesis and secretion as well as receptor biology. Hormones and receptors are molecules that are mostly synthesized upon demand. Thus, the various building blocks needed for their biosynthesis must be present in a steady and available manner. This condition can be best achieved through an adequate nutrient acquisition process and good blood circulation (see *Dr. M's Science Notes*, Vol 1, "Nutrient Acquisition: The Foundation of Wellness" and *Dr. M's Science Notes*, Vol 3, "Proteolytic Enzymes: Applications and Benefits").