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Module 1, Video 3: Sex Hormone Synthesis and Mechanism of Action

Hormones are specialized chemical messengers that are secreted directly into the blood, where they are carried to different cells throughout the body and exert specific stimulatory or inhibitory effects. There are many different types of hormones: proteins, steroids, and amino acid derivatives, and these hormones play critical roles in diverse physiological processes including survival, stress, injury, metabolism, inflammation and reproduction.

In this video, we will discuss the synthesis and mechanism of action of one class of steroid hormones, called gonadal hormones or sex hormones. We will also present an example of how sex hormones can change behavioral responses to fear learning and generalization.

At the basic level, sex hormones include androgens, estrogens and progestins, all of which are present in both males and females, just in varying amounts. Like all steroid hormones, sex hormones are synthesized in the mitochondria from cholesterol, through a common precursor pregnenolone. Pregnenolone then diffuses into the cytosol, where it is further converted into various other steroid hormones through enzymatic reactions [1].

All sex hormones are primarily produced in the testes, ovaries and adrenal cortex. After synthesis, they are released from the gonads or adrenal glands and transported through the blood via carrier proteins to various target tissues. Sex hormone receptors are present in both males and females throughout the body, including all areas of the brain. They are also present in both nuclear and non-nuclear compartments, including mitochondria.

The brain itself also has the capacity to generate sex hormones independent of the gonads and adrenal glands. [2-5]. Sex hormones produced in the brain are called neurosteroids because they are synthesized and show activity in the central nervous system. Neurosteroids are synthesized through two mechanisms: The first is de novo from cholesterol using the same pathway as in the periphery. This is possible because the neurons and glia of several brain regions possess the necessary enzymatic machinery to produce sex hormones directly from cholesterol. The second is through the transformation of circulating peripheral hormones, which cross the blood brain barrier and act as the precursors for neurosteroid synthesis. Some regions of the brain appear more capable of synthesizing steroids de novo than others, but this variation remains poorly understood.

Regardless of where they are synthesized, sex hormones must bind to specific receptors and exert their effects. Sex hormones act on target cells through either genomic or non-genomic signaling:

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For genomic signaling, steroid hormones enter the cell by diffusing across the cell membrane or through the assistance of a transporter protein. They then bind to and activate an intracellular hormone receptor, which in turn binds to a DNA response element, resulting in either gene repression or activation. Activation initiates transcription and protein translation. This mechanism has a relatively long latency of onset, in the magnitude of hours [6, 7].

In contrast, non-genomic sex hormone signaling occurs rapidly—on the order of seconds to minutes—allowing for quick adaptation to local changes in the extracellular environment. Non-genomic signaling occurs when sex hormones bind to either classical or non-classical membrane bound receptors. When bound to classical receptors, a second-messenger cascade is activated [6, 8], which can lead to downstream genomic effects. Sex hormones can also bind to non-classical membrane receptors, which results in calcium influx through other second messenger systems.

Both the genomic and non-genomic actions of sex hormones in the brain play critical roles in important processes such as synaptic plasticity, memory, mood and cognition [8].

To illustrate how nongenomic and genomic effects may differ, we will use the example of fear conditioning and fear generalization. Sex steroids are known to differentially affect contextual fear conditioning and fear generalization. Fear conditioning is a behavioral paradigm in which an environment is paired with an unconditioned stimulus, such as a foot shock.

This pairing elicits a conditioned response, generally freezing, when the animal is returned to the same environment. Using this paradigm, rodents learn to associate fear with a specific environment [9] as well as generalize their fear to other unfamiliar environments. Activation of androgen and estrogen receptors during fear conditioning results in opposing effects. When androgen receptors in the hippocampus are activated by testosterone and dihydrotestosterone, fear memory is reduced, meaning male rodents are less likely to recall the context in which they received the foot shock [10]. By comparison, activation of intracellular estradiol receptors in the same brain region by estradiol increases contextual fear memories and fear generalization, meaning that female rodents are more likely to express fear in a neutral context [11]. As will be discussed in later videos, this has important implications for disorders such as PTSD, a condition that effects twice as many women as men.

Our current understanding of sex steroids and their mechanisms of action has rapidly evolved. We now know that sex hormones have other important functions beyond reproduction, including regulating critical neuronal and glial features. The capacity to locally synthesize sex steroids de novo in the brain is critical to their rapid, non-genomic responses as well as their ability to mediate transcriptional activation or repression. The relative contribution to physiology and behavior of locally synthesized steroids versus those of sex origin is still being

investigated [12]. In the following videos in the module, we will discuss in more detail how sex hormones acting in the brain are able to modulate neuronal and behavioral actions differentially in males and females.

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