Chapter 1
The Neurohormonal System in Adolescence

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Puberty is a period that begins between childhood and adulthood characterized by intense body transformations; it is a part of the stage of life known as adolescence. Therefore, adolescence is a critical period of development signaled by change.

Several studies [1, 2] (including those using electrophysiological, imaging, pharmacological, and reactivity methods among others) have demonstrated that the brains of adolescents differ from both child and adult brains regarding their morphological and functional features as well as their structures, regions, circuits, and systems. In addition, adolescent brains differ with regard to their gray and white matter, their connectivity among structures, and their neurotransmission.

Adolescence, especially the peripubertal period, is a stage of remarkable development that includes significant brain changes such as synaptic pruning, the emergence of new fibers, and myelination. The different maturation rates of the brain areas related to emotional regulation and executive function might partially account for the remarkable increase in adolescents' engagement in high-risk situations and the search for new situations [3]. Morphophysiological changes occur that derive from the reactivation of the neurohormonal mechanisms in the hypothalamic-pituitary-gonadal axis, which are a part of a *continuum* that begins during intrauterine life and finishes when growth and development are complete. The neuroendocrine system regulates this process and determines its onset, the time required for maturation to occur, and the rate of change.

The age at which puberty is triggered is highly variable across individuals. Although a pattern of pubertal development exists, its actual progression is subjected to several influences, including genetic, ethnic, and racial factors; psychosocial and socioeconomic factors; climatic and geographic factors; the presence or aggravation of diseases; exercise; and the use of drugs or medication [4].

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The central nervous system, especially with regard to brain anatomy and function, undergoes substantial changes from late childhood to adolescence. These changes affect adolescent behavior, are genetically mediated, and are developed during the intrauterine period (the first period of major transformations when millions of synapses are formed) based on the exposures to which individuals are subjected throughout their lives.

One might assert that puberty is the stage of life during which the skills to solve complex problems in a mature manner emerge. The brain, subject to remodeling and learning over at least 10 years, undergoes a massive reorganization that might be considered the basis of the attitudes exhibited by adolescents. Along this process, brain structures and functions undergo the refinement needed for neurocognitive, affective, and social maturation. Such refinement occurs in a progressive manner and along a definite direction: from the posterior portion of the brain to its frontal portion over several years. The occipital lobe, located in the brain's posterior area, is responsible for the most basic functions such as visual perception and processing. The frontal portion is responsible for more complex functions, and it is the last portion to mature, accounting for the most elaborate cognitive and emotional functions such as planning, the production of mental representations of the external world, logical reasoning, and speech production. The cerebellum is related to motor control and learning, the maintenance of the body balance and posture, the perception of music and mathematics, and advanced social skills. The cerebellum exhibits high plasticity and is sensitive to external stimuli; its number of neurons and complex connections increases throughout adolescence [5].

Importantly, the amygdala, which is located in a still-developing prefrontal cortex, is where primary emotions such as fear and anger are activated. Therefore, this structure might account for the impulsiveness and behavioral maladjustments specific to adolescence. Neuronal mechanisms significantly participate in the elaboration of emotions while the adolescent brain undergoes significant changes [6]. Some neuronal evidence indicates an association between the brain's defense systems and the fear-stress-anxiety concept. The reactions or responses of orientation when facing (real or delusory) signals of danger, avoidance, or preparation with regard to confronting danger seem to be associated with anxiety. This process involves the participation of the cyngulate gyrus and the prefrontal cortex on one side as well as the contralateral median raphe nucleus, septum, and hippocampus, which are a part of the brain circuits that integrate emotional responses. Fearful stimuli that trigger active defense patterns restricted to specific situations but that are poorly elaborated induce other emotional states and seem to be associated with basic manifestations of fear. The dorsal periaqueductal gray matter is the major neural substrate for the integration of these brain circuits, and it participates in fear/anxiety responses [7–9].

We make choices all the time; the same is true of adolescents. However, the choices that adolescents make are not always the best response to a given situation because they have not yet processed the repertoire of cognitive-social-emotional experiences that enable them to make the best choices. An awareness regarding the irreversibility of the numerous choices one must make progressively develops over the course of adolescence.

Adolescence is a unique time to explore existential matters such as life and death [10]. In fact, death is one of the causes of fear that adolescents often mention [11–13]. The amygdala also participates in the "reward center" that also includes the hypothalamus, basal ganglia, and certain thalamic areas related to compulsive behavior.

The cortex metabolic rate is high throughout childhood, and it begins to decrease during late childhood to reach adult levels during the second decade of life. Simultaneously, the prefrontal cortex, which is related to the planning and regulation of emotional behavior, continues developing until approximately 20 years old. The anatomical changes that occur in the prefrontal cortex during physical maturation are most likely related to many of the behavioral changes observed throughout puberty [14, 15]. Linear volumetric increases in white matter occur between 4 and 22 years old as a function of the myelination that occurs throughout development, whereas gray matter undergoes more complex changes [16, 17]. Between 2 and 16 years old, cortical synaptic density and neuronal density decrease, and programmed cell death occurs, such that programmed synaptic reduction is associated with the improvement memory [18, 19].

The temporal lobe is related to memory, hearing, and the processing of visual and auditory information; it grows until reaching its maximum by 16–17 years old; greater neuronal communication during this period is favorable for reading activities.

The parietal lobe receives and processes spatial and sensory information from the entire body. Importantly, by 10–12 years old (i.e., the time when most puberty-related body changes occur), the parietal lobe attains its largest volume. Physical appearance plays a significant role in the development of adolescents' self-concepts. During this new process of refinement, an enormous effect on adolescent self-image might take place to promote the adjustment of sensory-motor "maps" of new body proportions.

The changes in the brain's reward system and the newly acquired ability for abstract thinking are the guiding impulses for adolescents to forego old childhood habits and develop interests in music, sports, religion, and philosophy. We might assert that the acquisition of new skills and the development of abstract reasoning lead adolescents to question rules and discover the social, economic, and cultural complexity of life. For that reason, they become impatient, forsake childish pleasures and the safety of their parents' home to look for satisfaction and pleasure in new activities, seek new friends, and expose themselves to risks they might not have even imagined before. The emergence of an explicit interest in sex is related to their hypothalamic-pituitary activity and the release of sexual hormones that increase during puberty.

Diseases such as mania, depression, obsessive-compulsive behavior, and schizophrenia are more common after puberty. That fact might indicate a relationship between these diseases and abnormalities concerning the architectural and functional changes of the brain throughout puberty [20]. A pattern of gray matter loss has been described in certain childhood psychoses that progress along the same direction as brain development during adolescence (i.e., from the posterior to anterior portions).

This pattern corresponds to the structural changes in gray matter characteristic of normal brain development, albeit at an abnormally high rate. Therefore, a pattern of disease reflects a lack of control in the regulation of gray matter maturation [15].

The major biological transitions that adolescents undergo likely make them more vulnerable to stress and the onset of psychopathologies. Stressful experiences during childhood and adolescence are associated with the development of later psychiatric disorders. However, only a small fraction of the adolescents exposed to stress develop psychopathologies [21].

Recently, numerous researchers across many fields have studied adolescence because of its associated intense physical, behavioral, social, and neurologic changes as well as the alarming health statistics relative to this period of life. Researchers have observed that the behavior of adolescents and its related neurological changes bear significant implications for adolescent health. Adolescents are prone to engage in high-risk behaviors with potentially disastrous consequences, including drug abuse, unprotected sex, self-harm, and harm to others, all of which imply a risk of death [22]. According to the 2007 "Youth Risk Behavior Survey" [23], motor-vehicle crashes, unintentional injuries, homicide, and suicide were the most prevalent causes of adolescent mortality, accounting for 72 % of the total; all of these causes are preventable. That study suggested that those deaths were partially because of inadequate choices or risky actions (e.g., crashes) and exaggerated emotiveness (e.g., suicides). These findings reinforce the need to understand the biological basis of emotions and promote research regarding adolescent behavior. Nevertheless, the significant role that environmental influences (e.g., reduced parental supervision) play with regard to risks to which adolescents are exposed should not be overlooked, nor should the increased permission that our society provides to adolescents who engage in high-risk situations.

Major Pubertal Changes Due to Hormone Secretion

Two independent, albeit intertwined, processes are responsible for the increase of the sex hormone secretions that occur during peripuberty and puberty: gonadarche and adrenarche. These processes have a similar timing but are controlled by different mechanisms.

Gonadarche is the reactivation of the hypothalamic-pituitary-gonadotropic-gonadal axis. The sizes of the breasts, uterus, and ovaries increases in girls, and the size of the genitals and testicles as well as the amount of hair increases in boys as a result of the increased levels of sex hormones (i.e., estrogens in girls and androgens in boys).

Adrenarche (i.e., pubarche) is the increase of adrenal androgenesis that occurs 2 years before the development of the gonads, usually at 8 years old. Pubic, axillary, and facial hair appears as a result of the increased adrenal production of androgen.

Puberty begins by quickly elevating the production of sex hormones. From 5 to 9 years old, the adrenal glands start producing an increasing amount of androgens, which plays a significant role in the growth of pubic, axillary, and facial hair. A few years later, girls' ovaries increase their production of estrogens, which stimulates the growth of their genitals and the development of their breasts. Among boys, the production of androgens (especially testosterone by the testicles) increases, thereby stimulating the growth of the genitals, body hair, and muscle mass. Importantly, estrogens and androgens are produced in both genders; however, the production of the former is higher in females, and the latter is higher in males. Testosterone promotes the growth of the clitoris, bones, and pubic and axillary hair in females [5].

The need to achieve a "critical weight" to trigger puberty has been postulated; for example, the adipose tissue is a hormonal tissue, and several neuropeptides play a key role in triggering puberty. One of the neuropeptides most widely studied currently is leptin, a protein hormone secreted by the adipose tissue that plays a well-known role in obesity as well as in triggering puberty [24]. The accumulation of leptin in the bloodstream might stimulate the hypothalamus to signal the pituitary gland, which in turn signals the sex glands to increase the corresponding hormone secretion. This pathway might explain why girls with excess weight tend to enter puberty before their thinner counterparts.

The exacerbation of emotions and the mood instability present at the onset of adolescence are associated with hormonal changes [25]. Nevertheless, the influence of other factors such as gender, age, temperament, and the timing of puberty onset should not be overlooked because they can modulate or even surpass the effects of hormones. In any case, aggressiveness among males as well as aggressiveness and depression among females are associated with hormones. Hormones seem to have a stronger relationship with mood states among males and younger individuals, i.e., precisely those who are adjusting to the changes associated with puberty.

The increases in linear growth (height) and body weight known as the adolescent growth spurt is due to the action of the adrenal and gonadal hormones, combined with the increased secretion of growth hormones, somatomedins (i.e., insulin-like growth factor; IGF), and thyroid hormones (which directly act on the bone growth plate). Growth hormone secretion is pulsatile, episodic, and seasonal; furthermore, it tends to occur at night after the first short period of deep sleep. Somatomedins are produced in the liver and act on cell receptors and bone epiphyses; they are carried by "binding" proteins, which are influenced by stress, nutritional, and hormonal factors [5].

All hormonal actions are synergic, and the regulation mechanisms of hormone secretions exhibit a characteristic pulsatile pattern that reflects their mutual interaction as well as the participation of several neurotransmitters and neuropeptides. All of these factors account for the susceptibility of growth to stress, sleep, and fasting as well as to fevers and infections (as is the case for individuals with chronic diseases).

The Hypothalamic-Pituitary-Gonadal System

The hypothalamus and the pituitary gland (or hypophysis) form an interrelated system such that they might be considered a single entity. United with the hypothalamus, the pituitary gland has a double embryonic origin that results in the anterior (or adenohypophysis) and posterior (infundibulum and inferior pituitary stalk) pituitary. The anterior pituitary produces the growth hormone and prolactin. The cells that produce the luteinizing and follicle-stimulating hormones are scattered across the gland. The cells that produce the thyroid-stimulating and adrenocorticotropic (ACTH) hormones are located in the central mucoid wedge, although some ACTH-producing cells are also found in the lateral wings. The pituitary hormones act on various cells and tissues of the human body, which produce other hormones involved in hypothalamus and pituitary self-regulation. Several factors or substances stimulate or inhibit the secretion of hypothalamic-pituitary hormones. Tension, fear, and other emotional stimuli modulate the endocrine system through the connections between the hypothalamus and the higher brain centers via the limbic system. The sleep-wake cycle is a significant physiological modulator that acts via the central nervous system. Several hormones exhibit a circadian pattern of secretion in which their plasma concentrations increase at night after a period of deep sleep [5].

Chemical neurotransmitters such as acetylcholine, gamma-aminobutyric acid, dopamine, histamine, serotonin, and melatonin also interfere with hypothalamic central control. In addition, drugs and other pharmacological substances might act on the neuroendocrine system with a broad range of possible effects. Puberty might be altered or even interrupted following episodes related to the interaction of environmental factors. Therefore, the use of medication or drugs and other environmental factors (e.g., sleep, exercise, emotional disorders, and nutritional status) behave as exogenous factors and have repercussions on the neuroendocrine system during pubertal development. Situations characterized by chronic stress or environmental risk might trigger severe emotional reactions (e.g., fear, anxiety, depression, existential anguish associated with loss, and emotional pain) and stress adaptation responses that might interfere with the neurohormonal mechanisms that promote growth, nutrition, and sexual maturation during puberty.

The human hypothalamic-pituitary-gonadal system differentiates and is active during fetal life and the onset of childhood; its activity is latent for approximately one decade, showing only a low level of activity until puberty when it is reactivated. Thus, puberty likely represents the reactivation of the neurosecretory cells associated with the arcuate nucleus and their endogenous secretion following a long period of minimal activity. Therefore, the onset of puberty is characterized by the activation of the hypothalamic-pituitary-gonadal axis at several levels including gametogenesis, changes in the peripheral receptivity to sex steroids, gonadal steroid secretion, and gonadotropic secretion.

The Hypothalamic-Pituitary-Adrenal System

The maturation of the hypothalamic-pituitary-adrenal axis precedes that of the brain pathways regulating emotions, cognition, and learning such as the prefrontal cortex, hippocampus, amygdala, and ventral striatum [26]. Intense changes in several brain areas contribute to the peculiar behavior of adolescents.

As emphasized above, significant changes in adrenal function occur approximately 2 years before the first hormonal variations of the hypothalamic-pituitary-gonadal axis and gonadal maturation (gonadarche) become detectable.

Adrenarche (i.e., the growth of the androgenic area of the adrenal cortex) and the progressive increase in the serum androgens concentration (first, dehydroepiandrosterone [DHEA] and DHEA-sulfate; second, delta-4-androstenedione [4]) occur during the prepubertal period at approximately 7–8 years old. The onset of either hormonal or physical puberty occurs only 2 years after the onset of the aforementioned processes.

The androgenic action of DHEA and 4 is weak; these hormones promote the growth of pubic hair, mainly among girls (the action of testosterone prevails in boys), and participate in the development of the apocrine and sebaceous glands and bone growth. Importantly, however, these hormones do not play a significant role in the adolescent growth spurt because the greater spurt exhibited by males is due to the action of testosterone. The development of the adrenal cortex is clinically expressed by the increase in the amount and the particular distribution of axillary and pubic hair, the increase in perspiration, and the appearance of body odor and acne.

The conversion of androgens into estrogens occurs in extraglandular tissues under the action of the enzyme aromatase.

The interaction of androgens and estrogens accounts for the development of secondary sex characteristics, ovulation in females, spermatogenesis in males, and the full process of fertilization.

Many adolescents begin their sexual life during early or mid-adolescence. The average age for sexual initiation in Brazil is 15 to 17 years old in females and 13 to 15 years old in males [27]. Factors including the onset of puberty, low self-esteem, having smoked or consumed alcohol, and the absence of excess weight are strongly associated with early sexual debut among females. In the case of males, an active sexual life is associated with having an older age, having been reared with poor parental relationships and weak family ties, and having smoked [28]. Several studies have found an association between sexuality and testosterone production among males, whereas others have emphasized the effects of social factors on pubertal maturation. The increase in testosterone levels is associated with sexual activity. A similar pattern is exhibited among girls, where the elevation of testosterone levels increases the frequency of sexual thoughts and masturbation. Peers exert a striking influence on masturbation as well as on the progression of sexuality and the transition to first sexual intercourse. However, the association between testosterone levels and sexual activity was not found among a population of white girls who regularly attended religious services. The social pressures include messages that target females, either encouraging or restricting the exercise of sexuality, in very different ways compared with males [5].

Therefore, adolescence is a period of physical, emotional, and social vulnerability; adolescents' particular reactivity to stressful situations, cultural factors, hormonal reactions, and brain immaturity are its possible causes.

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