

# Endocrine Modulation of the Adolescent Brain: A Review

Pilar Vigil MD, PhD<sup>1,2,\*</sup>, Renán F. Orellana LicSc<sup>1</sup>, Manuel E. Cortés LicSc<sup>1,3</sup>,  
Carmen T. Molina LicMedT<sup>1</sup>, Barbara E. Switzer BA<sup>4</sup>, Hanna Klaus MD<sup>5</sup>

<sup>1</sup>Unidad de Reproducción y Desarrollo, Departamento de Fisiología, Facultad de Ciencias Biológicas, Santiago, Pontificia Universidad Católica de Chile, Chile

<sup>2</sup>Fundación Médica San Cristóbal, Santiago, Chile

<sup>3</sup>Departamento de Ciencias Animales, Facultad de Agronomía e Ingeniería Forestal, Pontificia Universidad Católica de Chile, Santiago, Chile

<sup>4</sup>Florida State University College of Medicine, Tallahassee, Florida

<sup>5</sup>Natural Family Planning Center of Washington, DC, and Teen STAR Program, Bethesda, Maryland, USA

## ABSTRACT

Neurophysiological and behavioral development is particularly complex in adolescence. Youngsters experience strong emotions and impulsivity, reduced self-control, and preference for actions which offer immediate rewards, among other behavioral patterns. Given the growing interest in endocrine effects on adolescent central nervous system development and their implications on later stages of life, this article reviews the effects of gonadal steroid hormones on the adolescent brain. These effects are classified as organizational, the capacity of steroids to determine nervous system structure during development, and activational, the ability of steroids to modify nervous activity to promote certain behaviors. During transition from puberty to adolescence, steroid hormones trigger various organizational phenomena related to structural brain circuit remodelling, determining adult behavioral response to steroids or sensory stimuli. These changes account for most male-female sexual dimorphism. In this stage sex steroids are involved in the main functional mechanisms responsible for organizational changes, namely myelination, neural pruning, apoptosis, and dendritic spine remodelling, activated only during embryonic development and during the transition from puberty to adolescence. This stage becomes a critical organizational window when the appropriately and timely exerted functions of steroid hormones and their interaction with some neurotransmitters on adolescent brain development are fundamental. Thus, understanding the phenomena linking steroid hormones and adolescent brain organization is crucial in the study of teenage behavior and in later assessment and treatment of anxiety, mood disorders, and depression. Adolescent behavior clearly evidences a stage of brain development influenced for the most part by steroid hormones.

**Key Words:** Adolescence, Adolescent behavior, Adolescent brain, Steroid hormones, Neurotransmitters, Psychological disorders

## Introduction

A series of changes take place during human development; those occurring over adolescence are particularly noteworthy. In this stage, a number of physiological variables promote the manifestation of sexual characteristics, determining both gender phenotype (male or female) and the capacity for fertility of the individual. The cognitive variations experienced in puberty have been widely studied in this context over the past years. It has been suggested that, in adolescents, various mental faculties are still developing. Therefore, they appear exacerbated or diminished in youngsters as compared to adults. The purpose of the present review is to offer evidence of the effects on brain development exerted by gonadal steroid hormones, which increase during adolescence. Hence, this stage can be understood as a unique opportunity in which the changes taking place in the encephalon might determine character as well as certain behavior patterns in later stages such as adulthood.

The authors do not have any potential conflicts of interest to disclose associated with this article.

\* Address correspondence to: Pilar Vigil, MD, PhD, Unidad de Reproducción y Desarrollo, Departamento de Fisiología, Facultad de Ciencias Biológicas, Pontificia Universidad Católica de Chile, Av. Alameda B. O'Higgins 340, Santiago, Chile

E-mail address: [pvigil@bio.puc.cl](mailto:pvigil@bio.puc.cl) (P. Vigil).

## Puberty, Adolescence and their Associated Endocrine Changes

Adolescent growth and development are influenced by a series of highly regulated and coordinated endocrine changes which start in puberty or shortly before; in fact, the latter is defined as the period in which an individual becomes sexually mature.<sup>1</sup> Puberty generally begins at age 8–10 and culminates in menarche at age 12–13 in females.<sup>2</sup> In males, puberty generally begins one year later than in females and culminates at completion of spermatogenesis, with the full development of the spermatogenic line.<sup>3</sup> During puberty hormonal changes culminate in expulsion of mature oocytes from the ovary<sup>4</sup> and of mature spermatozoa from the testes. Recently, numerous studies have focused on this topic; however, the endocrine mechanisms underlying the onset of puberty remain to be elucidated. It is known that one of the main hormonal signals linked to puberty corresponds to an increase in the levels of leptin, a protein hormone thought to be one of the key signalling agents involved in triggering puberty. Leptin is a fundamental regulator of lipid homeostasis and, therefore, of adiposity. Thus, an increase in leptin is related to the rise in adiposity associated with puberty.<sup>5</sup> While the hormonal mechanisms triggering puberty have not been fully described yet, it is certain that one of the events signalling the onset of puberty is the activation of the hypothalamic-hypophyseal-gonadal axis.<sup>6,7</sup> As a component

of this axis, the hypothalamus starts releasing pulses of gonadotropin-releasing hormone, which exerts its stimulating effect on the hypophysis. This stimulation causes the adenohypophysis to release the follicle-stimulating hormone and the luteinizing hormone, which exert their multiple functions on the gonads increasing biosynthesis and secretion of steroid hormones, mainly estrogens, progesterone, and testosterone<sup>6</sup>; this is considered another biological marker for puberty. The increased hormonal levels cause the expression of secondary sexual characteristics, e.g., breast development in women and facial hair in men.<sup>8</sup> Most probably the levels of several other hormones also vary at the onset or throughout puberty, among them an increase in growth hormone.<sup>9</sup> Recent reports have also found fluctuations in the levels of insulin, insulin-like growth factor 1, kisspeptin,<sup>10</sup> and ghrelin,<sup>9,11</sup> among others, but further research is needed in order to understand their role at the beginning and progression of puberty.

On the other hand, adolescence—from the Latin *adolescere*, meaning “to grow into maturity”—is the period of transition from childhood to adulthood, and involves a number of changes in the psychological, social, and physiological development of a particular individual, including capacity for mature sexual behavior.<sup>6,12</sup> The physical changes associated with puberty begin as early as 7 or 8 years of age and are generally completed by age 16–18, while the psychological changes associated with adolescence occur between the ages of 12 and 21. The modulation of the limbic-cortical circuits which leads to the acquisition of adult cognition and the establishment of information pathways to promote social development in the individual is characteristic of adolescence.<sup>12</sup>

### Some Considerations on Adolescent Behavior

The transition from puberty to adolescence is a complex period from the perspective of the individual; during adolescence youngsters evidence a wide variety of behavioral patterns that often disappear in adulthood. The rapid succession of changes in their psychic and physical development is often confusing to teens, leading to erratic behavior. Youngsters often make irrational decisions and take risks exploring consumption of addictive substances, participating in extreme sports or adventures, and early—sometimes promiscuous—sexual activity, with the subsequent danger of sexually transmitted diseases and unplanned pregnancies. In this period, individuals are easily overcome by stressful situations and show great difficulty in performing tasks that demand inhibition of impulsive behavior.

Adolescents are also characterized by egocentrism. This has been defined as the inability to differentiate boundaries in subject-object interactions<sup>13,14</sup>; others are viewed as an extension of oneself. Elkind<sup>15</sup> has suggested that during adolescence in particular, youngsters' egocentrism is characterized by the belief that they are special and unique, and that others are excessively focused on their appearance and behavior.<sup>15</sup> Egocentrism is distinguished both by a lack of ‘common sense’ in decision making and rigidity in reasoning, related to being unable to integrate information

correctly. Coupled with this egocentrism there is considerable excitability, which leads to emotionally basing their decision-making. These aspects are signs of developing cognitive maturity, a process which is seldom smooth.

Behaviors can originate from outside the person (exogenously) or within the person (endogenously). Exogenous behavior is generated by external stimuli, such as sensory perceptions or emotional responses to perceived situations which may or may not be factual. Contrary to a reflex act produced by the stimulation of the spinal cord, exogenous behavior involves the immediate participation of brain regions in response to external stimuli, generating spontaneous behavior. On the other hand, endogenous behavior is triggered by cognitive control involving antecedent goal-directed planning behavior. Endogenous behavior requires the participation of a higher number of brain regions<sup>16</sup> and is a behavior acquired in the early stages of the individual's development. It continues to develop during adolescence and probably throughout life. Luna<sup>17</sup> states that adolescents can be expected to present predominantly exogenous behavior since their endogenous behavior is still developing.<sup>17</sup>

Each stage of development is characterized by possessing a certain speed for processing sensory information. This processing speed begins to decrease in infancy and during adolescence, until it reaches adult levels.<sup>18,19</sup> Both exogenous and endogenous behaviors require a precise processing speed to guarantee the correct emission of responses. The optimal speed for processing information is reached during adolescence leading to an adequate balance between endogenous and exogenous behaviors<sup>17,18</sup>; for this reason some cognitive/logic tasks appear to be specially difficult during this stage of adjustment.

Another characteristic of adolescent behavior is impulse control. Impulsive behavior interferes with the execution of behavior aimed at reaching a certain goal, e.g., good school performance. In order to acquire this capacity, the individual needs to be able to regulate his impulsive and irrational behavior by selectively blocking the generated responses.<sup>20</sup> This process involves discriminating the information received. During adolescence, youngsters appear to be unable to perform this selective inhibition; this inability inclines teens toward behaviors which yield immediate gratification even if risky, but which appear to be more attractive than those activities with long-term rewards.<sup>17</sup>

In brief, during adolescence there is an incomplete development of the encephalic functions that determine endogenous (voluntary) behavior. In addition, there is an exacerbated influence of immediate or short-term incentives. This generates limitations to discriminate information errors, to maintain a voluntary state of control, and to feel motivation towards a future reward. This set of processes is still developing, which explains the greater part of typical adolescent behaviors.

### Characteristics of the Adolescent Brain

Neurological development in adolescence is associated to the acquisition of cognitive control and affective

modulation. It has been observed,<sup>21</sup> by functional magnetic resonance imaging, that the encephalic regions normally activated in an adolescent during elaboration of an answer differ from those used in an adult, who would require fewer regions to elaborate the same answer. Therefore, it is possible to suggest a suboptimal use of the brain on the part of teenagers.<sup>20</sup> Moreover, sleep deprivation, so common in this period, has been shown to aggravate this situation by altering the normal activation of certain brain regions. This affects information processing, leads to behavioral modification, and generates a number of emotional problems.<sup>22</sup>

During adolescence, the connections that determine endogenous behavior are still immature. It has been suggested that humans may possess a "motivational circuit," where the limbic-cortical routes interact. In this circuit, the cortical system would act as a filter to the stimuli sent by the limbic system, inhibiting the stimuli that lead to risky or inconvenient actions, and consciously responding to any stimuli favorable to the individual and his immediate environment. During late adolescence, the connections which regulate this circuit mature.<sup>18</sup> This route, immature in adolescents, is based on the "selection" on the part of the cortical system of the motivational behaviors generated by the limbic system. This circuit contains a neuron population with a defined activation pattern which is part of the connection pathways between the prefrontal and the ventral striate cortex, then the thalamus, and finally back to the cortex.<sup>23</sup>

The links in the motivation circuit develop during adolescence; in this period, the limbic-cortical systems are weakly connected, presenting limited cross-communication regarding the adequate selection of motivational behaviors. Impulsivity decreases throughout childhood and adolescence, secondary to maturation of the prefrontal cortex.<sup>24,25</sup> At the same time, the regions linked to emotional behavior, generation of feelings, and affective information (nucleus accumbens and amygdala) show increased activity compared to the same regions of children and adults.<sup>26</sup> Even though both the cortical regions and the limbic system are still under development, it has been suggested that in this stage the activation of the limbic system exceeds that of the cortical systems, leading to the predominance of the emotional component of behavior.<sup>27</sup> Towards the end of adolescence, neural activity in both systems reaches similar values, affording the balance needed to issue adequate integrated responses to the stimuli elicited by the limbic-cortical system.<sup>24</sup> Thus the systems that control the prefrontal cortex are required to inhibit inappropriate responses, favouring the execution of planned behavior.

The previously described conditions lead us to conclude that adolescent behavior is the result of a set of neural connections that are still being established, determining a series of behavioral differences that will be acquired at the beginning of adult life. In addition to these variations in neural connection networks, there are molecular events occurring in this stage which may also explain some patterns of conduct in teenagers. One of the main differences found in people this age is related to the molecular mechanism of action of gamma-aminobutyric acid (GABA). GABA constitutes the main inhibitory neurotransmitter of the central

nervous system. Binding to its membrane receptors triggers the opening of the associated chloride channel. When this anion enters the neuron, chloride produces hyperpolarization, preventing synaptic transmission of nervous impulses. This way, the GABAergic system can be used as an "interrupting mechanism" to control the excitability of the nervous system.<sup>28</sup> Thus, an increase in GABAergic activity would reduce excitation of the individual, whereas an inhibition of such activity would produce increased neural excitement (and probably anxiety) in the individual. Shen et al<sup>29</sup> have described replacement of the  $\alpha 1$  subunit of the GABA receptor by its homologous  $\alpha 4$  during adolescence,<sup>29</sup> the latter possesses an arginine residue which causes a decrease in chloride intake altering normal inhibition in the nervous system. This particular function of the GABAergic system in adolescence may be responsible for the excitement phenomena observed due to the action of 17-hydroxyprogesterone (17OHP, a hormone (neurosteroid) that acts by binding GABA receptors) during this stage of life, as opposed to the inhibitory episodes caused by the same compound in adult life.<sup>30</sup> According to some authors,<sup>30</sup> this role is especially relevant in this period for development of the audacious behaviors necessary in this stage. Thus the thoughtlessness involved in adolescent decision making could be seen as a survival mechanism necessary for species adaptation.<sup>30</sup> For example, many young individuals need to risk their lives to learn to hunt for survival. In some adults "excitatory adolescent GABA receptors" may continue to bind 17OHP as in adolescence. In these cases, 17OHP would continue to exert an excitatory response instead of the inhibitory response expected to be present in adult life. This could explain the anxiety and depression which some women experience at certain stages of the menstrual cycle and upon ingestion of steroid hormones for hormone replacement therapy or contraception,<sup>31</sup> because the 17 OHP would bind to this form of "excitatory adolescent" GABA receptor still present in adulthood. Thus teenage behavior can be partially explained by processes of neural connectivity, but the explanation must also include differences at the molecular signalling level which determine the post-synaptic regulatory responses of the central nervous system.

#### **Current Evidence of the Effects Exerted by Gonadal Steroid Hormones on the Brain**

Steroid hormones such as estrogens, progesterone, and testosterone exert a role on the central nervous system, as has been described for 17OHP. Some studies<sup>32</sup> have made it possible to classify the effects of these hormones as organizational or activational. Activational effects of sex steroids modify neural activity to favor a certain conduct in a specific context.<sup>32</sup> Activational effects are not permanent, but appear only in the presence of the hormone. Organizational effects, in turn, are related to the capacity of sex steroids to determine the structure of the nervous system during its development. These effects are permanent, remain after exposure to the steroid, and allow for the generation of activational responses to hormones in adulthood.<sup>32</sup>

During embryonic development the nervous system is highly sensitive to gonadal steroid hormones. It is in this stage that organizational modifications occur.<sup>33</sup> However, it has been observed that a series of important processes involving organizational development of the nervous system also occur during adolescence.<sup>34</sup> During this period, sex steroids produce a structural remodelling of the circuits that determine the behavioral response to hormonal or sensory stimuli in adulthood.<sup>32</sup> For this reason, adolescence represents a second stage of development of the nervous system in which the gonadal hormones secreted during puberty exert a series of organizational changes.

### Sexual Dimorphism

The brain is an organ which presents sexual dimorphism; its morphology varies depending on the sex of the individual.<sup>35</sup> Over the past three decades, our understanding of the characterization of mammalian brain structures as related to being male or female, man or woman, has increased considerably. These advances have subsequently led to a deeper knowledge about the role of steroid hormones in the development of the human being. In mammals, brain sexual dimorphism appears during exposure to different concentrations of gonadal steroid hormones.<sup>36</sup> In males, the level of androgens such as testosterone present in perinatal life organizes the nuclei of the limbic and hypothalamic systems as well as that of the dorsal cord, influencing a given behavior in later stages of life. Thus if androgen levels are below those considered to be normal for the species at this stage of development, formation of different nuclei will be altered, as is the case with the corpus callosum which connects the cortical hemispheres and facilitates the rapid transfer of information between cortical areas,<sup>37,38</sup> rather than being one homogeneous bundle of fibers, subsections of the corpus callosum vary dramatically in quantitative characteristics of axon density, size, and degree of myelination.<sup>39</sup> In the male macaque and the rat, corpus callosum also is larger than in females due to a higher density of axons (around 10 million more).<sup>39,40</sup> Some authors<sup>41</sup> maintain that during embryonic development, exposure to fetal testosterone during critical periods of fetal brain development slows the maturation of the left hemisphere, thus allowing the right hemisphere to achieve dominance. The delayed development of left hemisphere functions in males may explain many of the observed trends: accelerated language development in females, males' enhanced performance of visuospatial tasks, and their higher incidence of left-handedness. The organizational effects caused by steroid hormones cause variations in the volume of certain brain regions, the number and density of neurones, the extent and ramification of synaptic connections, among others.<sup>42</sup>

Sexual dimorphism is not only determined during the perinatal period. Several recent studies have shown that some of these differences may have their origin or even their complete development in adolescence.<sup>43</sup> The female brain presents a proportionally higher volume in regions such as Broca's and Wernicke's areas,<sup>44</sup> associated with

language and communication skills; as well as the corpus callosum;<sup>45</sup> the hippocampus,<sup>46</sup> which participates in the formation of memory; the locus coeruleus<sup>47</sup> which is related to panic and stress behavior; and the periventricular anteroventral nucleus,<sup>48</sup> which is associated with feedback regulation of gonadotrophic hormone secretion. At the same time, the male brain has other areas of comparatively greater volume than the female brain such as: the inferior parietal lobule, an area of integration of sensory-motor information;<sup>49</sup> the visual cortex, in charge of processing the visual information from the retina;<sup>50</sup> the amygdala, linked to the processing of emotions;<sup>43</sup> the stria terminalis, which participates in the integration of the amygdala to cortical regions;<sup>51</sup> and the sexually dimorphic nucleus of the preoptic area, involved in sexual behavior.<sup>52</sup>

The sexual dimorphism of the brain and the endocrine differences between males and females may explain the differential prevalence of mood disorders in sex and gender of the individuals. It is known that certain mood and anxiety disorders are more frequent among women.<sup>53</sup> This could be explained on the basis of the hormonal and organizational characteristics of women.

### Hormones and the Brain

#### *Basic Neurobiological Concepts*

Far from being considered a rigid system, the brain is currently understood as a dynamic structure with neural networks which frequently interact and are able to modify themselves, generating great structural and functional complexity. One of the most frequently studied changes affecting the brain relates to the variation in white and gray matter. Through the use of magnetic resonance images, it has been possible to establish that there is a linear increase of white matter and a net reduction of gray matter during adolescence.<sup>54</sup> In fact, several periods have been identified in which the encephalon is more susceptible to undergo both organizational and activational changes. During a normal individual's life, his brain will present great neural plasticity during the embryonic period and puberty. The organizational changes which occur in the brain during adolescence are based on four functional mechanisms, myelination, neural pruning, apoptosis, and dendritic spine remodelling:

#### *Myelination*

Myelination is the process by which axons are covered by myelin sheaths; myelin is mainly lipid, allowing for the saltatory conduction of the nerve impulse which gives the system a higher transmission speed. In the central nervous system, myelin is supplied by the oligodendrocytes; whereas in the peripheral nervous system, this electric insulator is provided by Schwann cells. In the central nervous system this process can be influenced by the action of gonadal steroid hormones.<sup>55</sup> Both estradiol and progesterone facilitate myelination in the female, inducing synthesis of the basic myelin protein in oligodendrocytes,<sup>56</sup> while in the male testosterone is crucial to the process of myelination, partly because administration of testosterone

to oligodendrocytes induces their maturity and myelin formation.<sup>57</sup>

#### *Neural Pruning*

During development, both the number of neurons and the number of connections among them vary. Synaptic density (i.e., number of synapses per unit of brain tissue volume) increases during the early development of an individual, known as synaptogenesis; there is a subsequent critical decrease towards adolescence, called neural pruning,<sup>17</sup> in which the most frequently used connections are strengthened and preserved, while synapses which have shown scarce activation degenerate. Thus the system acquires a more efficient synaptic configuration as only the regions directly involved in responding to a given task are activated.

#### *Apoptosis*

Programmed cell death affects neurons. Apoptosis allows for variation of both the volume of different brain areas and the number of available neurons, and is also considered a mechanism of the neural plasticity which operated mainly during embryonic development. Estradiol presents a dual mechanism as regards apoptosis, acting as an anti-apoptotic agent capable of promoting cell division and cell proliferation in brain cortical neurons in rats,<sup>58</sup> and as a pro-apoptotic agent, triggering a decrease in the volume of the preoptic area in some mammals.<sup>59</sup>

#### *Dendritic Spine Remodelling*

Neural dendrites are covered by small extensions called dendritic spines, which correspond to the anatomical site where synapses occur.<sup>60</sup> These structures are dynamic and can grow, persist, or degenerate; hence each dendrite presents different spinal remodelling. Exogenous elements i.e., pathologies, aging, and gonadal steroid hormones can alter remodelling.<sup>61</sup> In mammals, the number of dendritic spines changes over the course of the female hormonal cycle; neurons present a higher density of synaptic spines in proestrus than in estrus and diestrus.<sup>62</sup>

#### *Organizational Window*

Brain organizational modifications were first thought to occur only during embryonic development, whereas only (hormonally mediated) activational effects took place during puberty. However, recent studies<sup>1,34,63</sup> have suggested that both activational and organizational changes occur in puberty.

Among current experimental models, one of the most representative is based on a reproductive behavioral study in rodents, in which male hamster copulatory behavior in the presence of female hamsters was assessed. This pattern is commonly observed among adult individuals and is evidenced in copulation. In this experiment, prepubertal subjects who had received testosterone did not copulate. Similarly, adult male hamsters who had been castrated in the prepubertal period, and who had been given testosterone, also failed to copulate in the presence of female hamsters. But administration of testosterone to male adult hamsters castrated during the postpubertal period immediately generated copulatory responses.<sup>63</sup>

Schulz's study<sup>63</sup> shows that copulatory behavior in adult rodents requires the presence of testosterone both in puberty and in adult life. Therefore, the copulatory sexual response corresponds to an activational hormonal effect. However, this behavior can only occur through a prior organizational change triggered by exposure to testosterone during puberty which coordinates the neural circuits needed to effect sexual behavior in the presence of steroid hormones and a female individual. It can be claimed that these organizational events did not occur during prenatal development because those hamsters did not present such sexual behavior in the same circumstances in the prepubertal period.<sup>63</sup> The copulatory sexual behavior was only present in adults who, in their pubertal period, had functional gonads capable of secreting physiological amounts of steroid hormones. For this reason, prepubertal gonadectomy abolished an adult rodent's copulatory behavior; while postpubertal gonadectomy had no effect on the subjects after administration of testosterone.

Sexual behavior is evident only in adult rodents who have been subjected to physiological concentrations of steroid hormones during puberty. Based on this evidence, one can suggest that certain organizational processes take place during adolescence. Scores on a spatial ability test<sup>64</sup> were higher in control (normal) human subjects than in subjects with prepubertal idiopathic hypogonadism and postpubertal acquired hypogonadism. Testosterone administration after puberty did not affect the scores obtained by the subjects in either of the hypogonadic groups.<sup>64</sup> These results suggest that the organizational changes which determine the development of spatial abilities in an individual are also activated during adolescence and that physiological levels of testosterone produced by functioning gonads are required. As in the example of the copulatory behavior in hamsters, the absence of effect on the acquisition of spatial abilities due to testosterone administration during the postpubertal period implies the existence of a defined period for the occurrence of these modifications.<sup>64</sup>

According to these data adolescence can be viewed as a window of opportunity when structural (organizational) modifications necessary for the acquisition of certain activational effects occur. This window of opportunity is time limited. There are organizational effects of steroid hormones which cannot be exerted except within this interval. Hence, it is possible to suggest that puberty is a critical period when diverse modifications which affect the encephalon determine the adult individual's behavior.

Regardless of the mechanism of brain organization, the effect exerted by steroid hormones on this process is due to the interaction of these molecules with the neural receptors and, later, to the coordination and subsequent execution of a certain cell response. A better understanding of these phenomena can be approached through the study of intracellular signalling pathways used by steroid hormones in other cell types. Over the last years it has been proposed that steroidal hormones possess two signalling pathway components: the genomic effects and the non-genomic effects. The former correspond to the classic mechanism of action of these hormones, according to which there are

cytoplasmic receptors capable of interacting with them, dimerizing, translocating to the nucleus, and transcribing the required genes.<sup>65,66</sup> The non-genomic effects are generated by the interaction of steroidal hormones and membrane receptors, which act through the classical second messengers such as  $\text{Ca}^{2+}$ , phosphatidylinositol triphosphate, and diacylglycerol, among others.<sup>67</sup> Non-genomic effects can be observed within minutes, whereas genomic effects take hours to develop.

Currently, further analysis is needed as regards the study of the effects of steroidal hormones before being able to determine whether the observed effects are genomic or non-genomic. For this type of approach, the spermatozoon constitutes a model of study.<sup>68,69</sup> During development this cell loses its ability to transcribe genes; therefore, only the non-genomic signalling pathways are available to the spermatozoon.<sup>68,69</sup>

Another advantage presented by this model of non-genomic pathways is that mammalian spermatozoa and neurons are strikingly similar as far as their receptors are involved,<sup>70</sup> suggesting that both types of cell possess a comparable ability to react to the same hormonal changes in the milieu. It has been recently proposed that steroid hormones—specifically estrogens and progesterone—would act at the cellular level in the spermatozoon regulating the occurrence of the acrosome reaction (AR)<sup>68</sup> a modification that is necessary so that it can go through the zona pellucida, penetrate the oocyte and fuse with it, constituting a crucial event for reproduction.<sup>68</sup> It has been observed that the responses of spermatozoa and neurons to the interactions between steroid hormones and the GABAergic system are similar.<sup>69</sup> In the light of this evidence, it seems reasonable to think that the changes in the levels of sex steroids play a part in puberty, influencing not only the reproductive system, but also having a certain impact on brain development and organization taking place in this period. According to this hypothesis, puberty and adolescence are intrinsically linked in so far as the brain constitutes a target for steroid hormones. GABA, a neurotransmitter generally associated to inhibitory action in the central nervous system, and progesterone, a neuroactive steroid, would influence mood swings in women undergoing hormonal replacement therapy;<sup>31</sup> besides, both induce AR in human spermatozoa.<sup>69,71</sup> Progesterone and GABA would act in a similar way, both in neurons (negative mood) and in spermatozoa (AR inductor). Estradiol, in turn, presents the opposite effect to those of progesterone and GABA, both in the nervous system and in spermatozoa, since it causes a state of euthymia and inhibits AR in spermatozoa.<sup>31</sup>

On the basis of the aforementioned data one may propose that, in certain cases, steroid hormones and the GABAergic system would interact in analogous ways, both in spermatozoa and in neurons. Future research could use the spermatozoon as a model to understand the non-genomic effects involved in the molecular interaction between the above compounds.

The increase of steroid hormones during puberty is linked to the individual's development of secondary sexual characteristics. However, during adolescence hormones are

also exerting a role in the development of the nervous system through the neural plasticity mechanisms previously described. One of the main milestones of adolescence is the organizational development of the brain by the sex hormones secreted in puberty. Taking into consideration the above, puberty and adolescence are closely linked in considering the brain as a target organ which responds to the presence of several hormones.

#### *Psychological Alterations Associated with Endocrine Disorders*

Current knowledge regarding the effects of gonadal steroid hormones on behavior is limited; however, the presence of endocrine disorders and their connection with behavior point to some link between them. Over the pre- and postnatal period, the organizational effects taking place in the brain will help determine the behavior of the individual in his adult life.<sup>72</sup> Similarly, during adolescence steroid hormones modify both the structure of the nervous connections and the number of neurotransmitter receptors present in the neurons. These changes could exert a role in the ability of the nervous system to respond to endogenous or exogenous variables, leading to mood and affective disorders.<sup>72,73</sup> This concept is supported by studies which show that free testosterone (the bioactive form of this hormone) is related to premenstrual syndrome and depression in women.<sup>74–77</sup>

An example of a pathology that may be associated to psychological alterations is polycystic ovary syndrome (PCOS), an endocrine disorder defined as an ovulatory dysfunction caused by hyperandrogenism and/or hyperandrogenemia and which can frequently be linked to metabolic diseases such as insulin resistance.<sup>78</sup> It is diagnosed mainly among fertile women, with a prevalence of 5–10%.<sup>79</sup> Even though this pathology is considered to be characteristic of the reproductive age, some of its manifestations have been known to appear in early stages of life, and even in the intra-uterine period.<sup>80</sup> Women suffering from PCOS show a high correlation between their abnormal androgen levels and the incidence of mood disorders, ranging from affective problems to alterations in sexual identity and depression.<sup>81–83</sup> A Rorschach study on PCOS subjects<sup>84</sup> showed that PCOS women evidenced distortions in the configuration of the physical and psychological self: the women tend to think they are at a disadvantage compared to others, and tend to be hypercritical of themselves and intolerant of factors outside the norm.<sup>84</sup> These characteristics could result from their hormonal imbalance.

Although steroid hormones exert some degree of control on mood, they also are capable of predisposing to certain psycho-affective disorders. The appearance of such problems may be related both to the organizational effects produced in the perinatal period and adolescence and to activational effects produced by the steroids secreted during puberty.

The incidence of exogenous factors in this brain/hormone dynamic could affect the organizational processes which take place in adolescence. Sleep deprivation together with consumption of nicotine, alcohol, steroid hormones, and various types of drugs during adolescence may

generate alterations in brain organization, and could manifest themselves as behavioral and psycho-affective disorders in adult life.<sup>76,77</sup>

## Conclusions

Adolescent behavior, associated with irrational decisions, thoughtlessness, and lack of emotional control, among others, reflects a particular neurological state. In this period of life, two important events take place: a rise in the levels of gonadal steroid hormones, which will have a systemic effect generating the secondary sexual traits; and the timely occurrence of a “window” in which certain organizational brain processes can be carried out. Both events are closely linked since the impact of hormones on adolescents at physiological level will allow for the opportune and adequate remodelling of the brain circuits; this, in turn, will determine the manifestation of activational effects in adulthood. Thus, several behavioral patterns of adulthood, such as copulatory sexual behavior and spatial ability, are influenced by a process of organizational development during the perinatal period or during adolescence.

To date, various mechanisms of neural plasticity have been described by means of which sex steroids could exert organizational changes in the brain. Steroid hormones affect the occurrence of phenomena such as myelination, apoptosis, and remodelling of dendritic spines. These processes, together with neural pruning, could exert changes at different levels in the nervous system originating a particular structure. The effect of external and internal factors capable of altering hormonal balance during adolescence is worth considering. These factors could have an effect on organizational alterations of the nervous system, leading to permanent effects which will be evident in adult life.

## Acknowledgments

Renán F. Orellana and Manuel E. Cortés thank CONICYT (Chile) for the scholarship granted for PhD studies.

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