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Review

Puberty and the maturation of the male brain and sexual behavior: recasting a behavioral potential

Russell D. Romeo, Heather N. Richardson, Cheryl L. Sisk*

Department of Psychology and Neuroscience Program, Michigan State University, East Lansing, MI 48824, USA

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Abstract

The pubertal transition from the juvenile to adult state requires significant changes in behavior to meet the demands for success and survival in adulthood. These behavioral changes during puberty must be mediated by changes in the structure and/or function of the central nervous system. Despite the profound consequences of puberty on an animal's behavioral repertoire, the mechanisms underlying pubertal maturation of the nervous system remain largely unknown. In this review, we provide a synthesis of neural development during puberty as it relates to maturation of male reproductive behavior. We first outline neuroendocrine events associated with puberty and review work from our laboratory that identifies pubertal changes in the neural substrate controlling male reproduction by comparing the neural responses of prepubertal and adult males to steroids and female chemosensory cues. We then raise the question of whether puberty is a sensitive period in which gonadal hormones influence the structural and functional organization of neural circuits underlying male reproductive behavior. The central thesis of this review is that the development of the nervous system during puberty alters the way in which the male responds to social stimuli, involving the restructuring of neural circuits that integrate steroidal and sensory information and ultimately mediate steroid-dependent social behaviors in adulthood.

Keywords: Puberty; Steroid hormones; Sexual behavior; Amygdala; Hypothalamus; Pheromones; Chemosensory; Neural development

Contents

1. Introduction

The pubertal transition from the juvenile to adult state requires significant changes in behavior to meet the demands for success and survival in adulthood. Adult cognition, social behaviors, and responses to environmental stimuli and stressors differ remarkably from those of the juvenile [1]. Some adult behaviors, such as those related to reproduction and parenthood, emerge as the result of normal development of the nervous system during puberty. The emergence of other behaviors during human adolescence, such as eating disorders and substance abuse, suggests that environmental factors and experience can

* Corresponding author. Tel.: +1-517-355-5253; fax: +1-517-353-1652.
E-mail address: sisk@msu.edu (C.L. Sisk).

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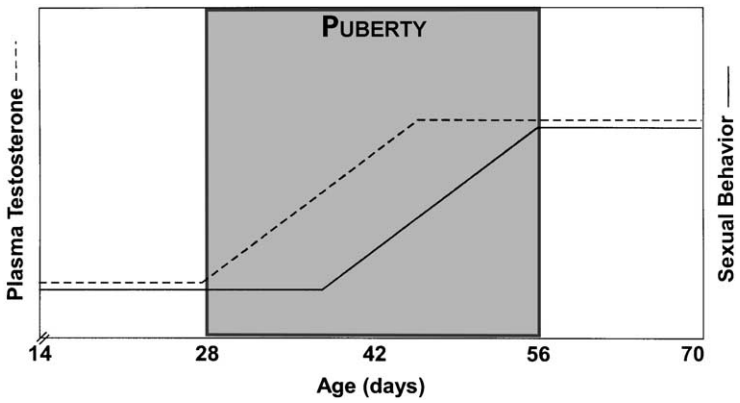

Fig. 1. Schematic time line of the pubertal increases in plasma testosterone secretion and male reproductive behavior in male Syrian hamsters.

interact with developmental processes during puberty to result in behavioral pathologies as well. Despite the profound consequences of puberty on an animal's behavioral repertoire, the mechanisms underlying pubertal maturation of the nervous system remain largely unexplored.

The nervous system is progressively shaped over the life span by endogenous signals, exogenous or experiential factors, and interactions between the two. During sensitive or critical periods, the nervous system is especially susceptible to agents that organize neural circuits and determine responses to stimuli at later stages of development. One of the best-studied critical periods in rodents spans the perinatal period, when gonadal steroids masculinize the nervous system in males. Just before and after birth, differential exposure of male and female brains to steroids leads to sexual differentiation of neural circuits and determines the potential for behavioral responses to steroids in adulthood [2]. However, the brain clearly retains a significant capacity for organizational modifications well beyond this early critical period, and puberty is another important window of development when the nervous system undergoes further and dramatic change to support the expression of adult behaviors [3–6].

We have studied reproductive behavior in the male Syrian hamster (*Mesocricetus auratus*) as a model for understanding neural mechanisms of pubertal behavioral maturation of a steroid-dependent social behavior. Reproductive behavior is unique to adult animals of all species, and its expression is the result of complex interactions among social, sensory, and hormonal signals that impact behavioral neural circuits. For several reasons, the Syrian hamster is an ideal model for addressing pubertal maturation of reproductive behavior. First, the full suite of mating behaviors in the adult male hamster depends on both steroidal hormones and chemosensory cues from the female [7–9], allowing one to study how behavioral and neural responses to one or both cues are regulated during puberty. Second, the developmental profile of endocrine and behavioral events associated with puberty in this species has been well characterized [10,11] (Fig. 1). Finally, the neural substrate and hormonal determinants of mating behavior in adult hamsters have been identified [8,12–22]. Initial studies from this laboratory demonstrated that male hamsters are unable to express the full complement of reproductive behaviors prior to puberty, even when given the appropriate steroid and sensory cues [23]. This finding strongly implies that the neural responses to gonadal steroids and/or sensory stimuli change during puberty.

The objective of this review is to provide a synthesis of neural development during puberty as it relates to maturation of male reproductive behavior. We first outline neuroendocrine events associated with puberty and review work from our laboratory that begins to identify pubertal changes in the neural substrate controlling male reproduction by comparing the neural responses of prepubertal and adult males to steroids and female chemosensory cues. We then raise the question of whether puberty is a sensitive period in which gonadal hormones influence the structural and functional organization of neural circuits underlying male reproductive behavior. Our central thesis is that development of the nervous system during puberty alters the way in which the male responds to social stimuli, involving the restructuring of neural circuits that integrate steroidal and sensory information and ultimately mediate steroid-dependent social behaviors in adulthood.

2. Pubertal maturation of the hypothalamic-pituitary-gonadal axis

Puberty is associated with a variety of physiological and behavioral changes brought about by testicular maturation and the production of adult levels of testosterone [24–26]. These events are the result of re-activation of the gonadotropin releasing hormone (GnRH) neuronal system, which after a brief perinatal period of activation, is quiescent throughout early postnatal life. In the juvenile state, animals are infertile and will not engage in mating behavior. At the onset of puberty, GnRH is released more frequently into the median eminence of the hypothalamus [27,28], signaling

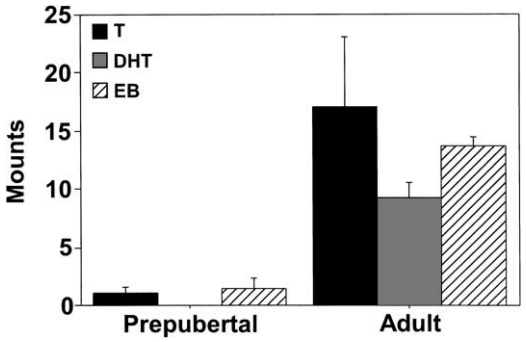

Fig. 2. Adult male castrates treated for 1 week with either 2.5 mg testosterone (T), 1000 μg DHT, or 0.05 mg estradiol benzoate (EB) engage in significantly more mounting behavior than similarly treated prepubertal male castrates. All values are means ± SEM obtained from 15 min tests with a receptive female. Data are taken from Refs. [23,40,41].

the release of the pituitary gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH govern gamete and steroid hormone production in the gonads. The primary steroid secreted from the testes is testosterone, and plasma levels of testosterone gradually rise throughout pubertal maturation (Fig. 1).

Testosterone indirectly regulates its own production by inhibiting activity of the hypothalamic-pituitary-gonadal (HPG) axis via a classic endocrine negative feedback loop. During puberty in male Syrian hamsters, inhibition of the HPG axis by testosterone decreases [29,30]. Prior to puberty onset, LH secretion is attenuated by just a small amount of testosterone, keeping circulating levels of testosterone low in juveniles. However, at about 4–5 weeks of age, a change in the negative feedback set point releases the HPG axis from steroid inhibition [30], allowing the pubertal rise in GnRH, gonadotropin, and testosterone secretion.

The initiation of increased GnRH secretion at puberty onset occurs *before* the pubertal rise in testosterone secretion. This observation suggests that the pubertal change in the set point for negative feedback is a developmentally timed event that occurs independently of the pubertal rise in steroid hormones. Further development of the nervous system during puberty probably involves additional steroid-independent maturational events combined with organization of neural circuits by the pubertal rise in steroid hormones.

3. Pubertal maturation of male sexual behavior

3.1. Hormonal regulation of behavior

The pubertal rise in testosterone secretion precedes the maturation of mating behavior [10,23,31,32] (Fig. 1), but elevated testosterone levels do not fully explain the expression of sexual behavior in adulthood. For instance, when prepubertal male rats [31,33,34], ferrets [35], or hamsters [23] are exposed to doses of testosterone that activate mating behavior in adults, juveniles engage in little or no sexual behavior. Therefore, in addition to the increase in steroid hormone levels during pubertal development, behavioral responsiveness to hormones increases as well.

Although testosterone is the primary steroid released by the testes, the behavioral effects of testosterone are due in large part to the combined actions of estradiol [19,20,36–38] and dihydrotestosterone (DHT) [19,21,22,38,39]. These estrogenic and androgenic metabolites of testosterone are formed locally in the brain by the intracellular enzymes aromatase and 5α-reductase, respectively, [38]. We have shown that testosterone, estradiol, and DHT all activate certain components of mating behavior in adults, but none of the hormones activates these behaviors in prepubertal males [23,40,41] (Fig. 2). Thus, prepubertal males are behaviorally unresponsive to both the estrogenic and androgenic actions of testosterone in the regulation of male mating behavior.

Steroids affect behavior by acting on target cells in the central nervous system. Receptors for both androgens and estrogen are found in amygdalar and hypothalamic cell groups that form the forebrain component of the neural circuit mediating male sexual behavior [42–45]. Intracerebral application of steroids into either the hypothalamus [46–55] or amygdala [55–57] causes an increase in mating behavior in castrated adult males. Together these studies demonstrate that testosterone, in conjunction with its androgenic and estrogenic metabolites, acts in steroid receptor-containing limbic regions to facilitate copulation.

Since androgen receptors (AR) mediate the intracellular actions of testosterone and DHT, we initially hypothesized that the differential behavioral responsiveness to androgenic steroids before and after puberty is mediated by differential expression of the AR in prepubertal and adult males. This hypothesis predicted that the ability of testosterone and DHT to activate behavior in adults but not juveniles would be correlated with a greater number of ARs in the adult, since androgens increase AR [58–60]. To test this hypothesis, we examined brain AR-immunoreactivity in testosterone- and DHT-treated adult and prepubertal hamsters. We focused on AR expression in the medial amygdala (MeA), the bed nucleus of the stria terminalis, and the preoptic area (POA), all part of the steroid-sensitive neural circuit that mediates mating behavior [14]. Contrary to our hypothesis, we found that testosterone and DHT comparably increased AR in both prepubertal and adult males [23,41] (Fig. 3). In fact, in some brain regions, testosterone increased the number of AR-ir cells to a greater degree in prepubertal males compared to adults. These data clearly indicate that the lack of behavioral responsiveness to both testosterone and DHT in prepubertal males is not caused by an inability to increase AR. Furthermore, the ARs present in the prepubertal mating circuit appear to be functional, since an increase in hypothalamic aromatase activity, which is an AR-dependent response [61], was also shown to be equivalent in testosterone-treated prepubertal

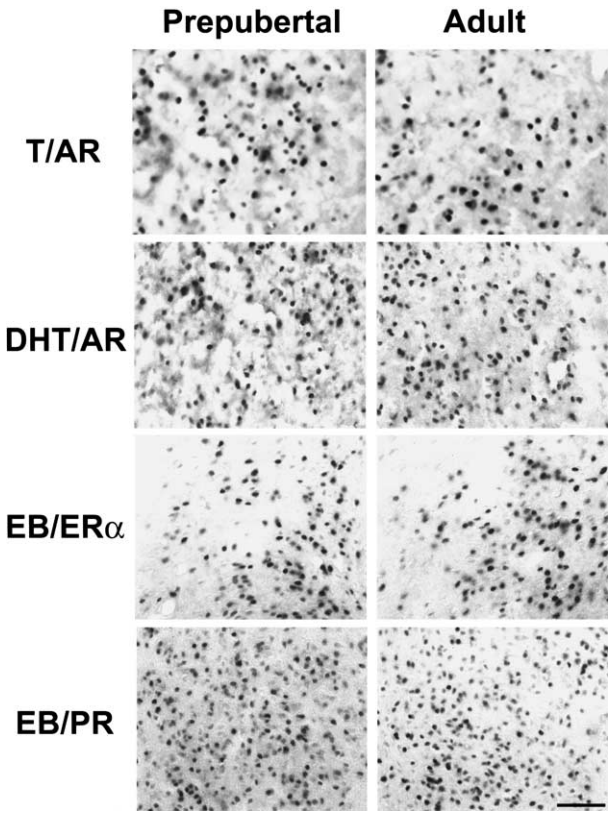

Fig. 3. AR, ER-α (ERα), and PR immunoreactivity in the medial preoptic nucleus is similar in prepubertal and adult male castrates treated for 1 week with either 2.5 mg testosterone (T), 1000 μg DHT, or 0.05 mg estradiol benzoate (EB). Data are from Refs. [23,40,41]. Bar = 50 μm.

and adult males [62]. Thus, while an increase in functional ARs in the mating circuit may be necessary, it is not sufficient to mediate the pubertal increase in male reproductive behavior.

Reproductive behavioral responses to estrogen are mediated by the nuclear estrogen receptor (ER) [38]. There are two known forms of the ER, ERα and ERβ. ERα appears to be the predominant ER responsible for the activation of mating behavior, since male mice lacking the ERα gene, but expressing the ERβ gene, engage in little reproductive behavior [63]. Because prepubertal males also show a reduced behavioral response to estrogen, we examined the expression of ERα in prepubertal and adult males. We found ERα immunoreactivity in the amygdala and hypothalamus to be equivalent in castrated and estrogen-treated prepubertal and adult males [40,64] (Fig. 3). Furthermore, estradiol treatment induced a significant increase in progesterone receptor (PR) levels in the POA of both prepubertal and adult male hamsters [40] (Fig. 3). Since ERα primarily mediates estrogen-induced PR in the hypothalamus [65–67], the ERα present in the POA of prepubertal males is capable of activating transcription. Thus, similar to our findings with the AR, neither expression nor function of ERα appears to explain the lack of reproductive behavior in prepubertal males.

Several lines of evidence indicate that progesterone or activation of the PR has a role in male reproductive behavior in adult rats [68,69], mice [70], and lizards [71–74]. We showed that intact adult male hamsters treated with the PR antagonist onapristone engage in significantly less mounting behavior than oil-treated controls, indicating that PR also plays a role in adult mating behavior in male hamsters [75]. A significant increase in plasma progesterone occurs during pubertal development in both intact [11] and castrated male hamsters (Romeo, unpublished observation). The source of circulating progesterone is most likely both the testes and adrenals, since neither castration nor adrenalectomy alone significantly reduces progesterone titers [76]. Therefore, insufficient levels of progesterone and testosterone (or aromatized testosterone) could preclude activation of PR and expression of reproductive behavior prior to puberty. However, when prepubertal males were castrated and treated with both estrogen (in order to upregulate PR) and progesterone (to activate PR), still no male mating behavior was seen [75]. Thus, although activation of the PR, along with AR and ER, contributes to the display of male sexual behavior in adulthood, similar activation of these receptors in prepubertal males fails to support mating behavior. Moreover, our results suggest that activation of the PR by progesterone is not the rate-limiting factor in the pubertal maturation of male reproductive behavior.

Our studies have focused on pubertal regulation of steroid receptors in limbic and hypothalamic components of the neural circuit mediating adult male reproductive behaviors. Pubertal alterations have been noted in more peripheral steroid-sensitive components of this circuit, such as the lumbar spinal motor neurons that innervate the penis muscles, [77], the pelvic ganglion [78], and penile musculature [79]. Thus, these structures may not be sufficiently developed in the prepubertal male to support the penile reflexes necessary for intromissions and ejaculations. However, mounting is an appetitive behavior mediated by forebrain structures, and is distinct from the more peripherally mediated consummatory behaviors [38]. Thus, the inability of steroids to activate mounting behavior prior to puberty cannot be explained by immaturity of spinal or peripheral systems.

In summary, we have demonstrated that adult-typical behavioral responses to testosterone, DHT, estradiol, and progesterone cannot be evoked in prepubertal males. The lack of a behavioral response to steroids prior to puberty is not due to reduced expression of steroid receptors within the forebrain circuit that mediates sexual behavior. Furthermore, the ARs and ERαs in the mating circuit appear to be functional. While we cannot rule out the possibility that an absence of other steroid receptor-related proteins required for behavioral activation, such as steroid receptor cofactors, accounts for the failure of steroids to activate sexual behavior in prepubertal animals, the fact that other AR- and ER-dependent neural responses occur in prepubertal males suggests that something apart from differences in

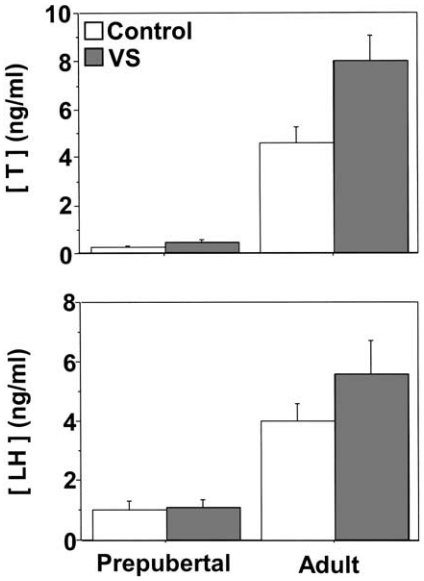

Fig. 4. Adult males exposed to female VS have higher circulating plasma testosterone (T) and LH concentrations than prepubertal males exposed to VS. Blood samples were obtained one hour after exposure to VS [92,93].

the intracellular steroid signaling machinery accounts for differences in behavioral responses to steroids in juvenile and adult males. These findings point instead to the possibility that neural responses to the sensory stimuli required for male mating behavior in the hamster differ in prepubertal and postpubertal males.

3.2. Chemosensory regulation of behavior

Reproductive physiology and behavior in rodents are profoundly influenced by olfactory stimuli [80]. For example, the odor of an estrous female alone causes erection and seminal emission in adult males [81,82]. Neural processing of female olfactory cues is obligatory for expression of male reproductive behaviors in hamsters, since adults will not copulate if they are made anosmic, either by inactivation of olfactory receptors or removal of the olfactory bulbs [8,9,80]. Furthermore, Wood and colleagues have shown that central implants of testosterone activate reproductive behavior in adult hamsters only when the olfactory bulb is intact [7,9].

Male hamsters begin to show an interest in female odors during pubertal development at about 40 days of age [83], and the emergence of selective attention to these chemosensory signals appears to be primarily under androgenic regulation [23,41,84,85]. Thus, chemosensory cues from the female are integral for the initiation of reproductive behavior and the male's interest in the sensory cues is influenced by his age. We have demonstrated that chemoinvestigatory behaviors toward the female are activated in both castrated adult and prepubertal males treated with testosterone, DHT, and to a lesser extent, estrogen [23,40,41]. Yet only the steroid-treated adults progress to mounting and intromissive behaviors with receptive females. Thus, despite similar interest in the female, steroid-treated adult and juvenile males appear to process the chemosensory information from the female differently.

When adult male hamsters are exposed to estrous female vaginal secretions (VS), which contain pheromones, cell groups within the amygdala, bed nucleus of the stria terminalis, and POA express the immediate-early gene product Fos [86–90]. This suggests that VS causes an increase in neuronal activity in brain regions that mediate chemosensory processing and male mating behavior in the adult hamster [91]. We tested the hypothesis that the greater amount of sexual behavior displayed by adult males is due to a greater degree of VS-induced neuronal activation. Contrary to our prediction, we found that the Fos response to VS is equivalent at the two stages of development [92], indicating that VS is detected and induces comparable neuronal activation in juvenile and adult males. Despite the equivalent increase in Fos expression, exposure to female pheromones elicits a rise in LH and testosterone secretion *only* in adults [92,93] (Fig. 4). Activation of the HPG axis by pheromones is a neuroendocrine reflex that does not depend on sexual experience. Thus, during pubertal maturation of mating behavior, female chemosensory cues become salient stimuli for the induction of hormone secretion, suggesting a change in sensory processing, and perhaps in how such stimuli are integrated in the brain with endogenous steroidal information.

In addition to the different neuroendocrine response, a neurochemical response to female chemosensory cues also changes with puberty. Adult male rats and hamsters respond to the scent of an estrous female with an increase in dopamine secretion in the POA [94,95]. Dopaminergic responses in the POA are not dependent on sexual experience and have been linked to the male's motivation to engage in reproductive behavior [94,96]. Pharmacological blockade of dopamine receptor activation reduces expression of reproductive behavior in sexually inexperienced adults [97,98]. In contrast to adults, pheromone-exposed prepubertal male hamsters do not show an increase in dopamine secretion in the POA [95]. The absence in prepubertal males of both neurochemical and neuroendocrine responses to chemosensory cues from the female indicates that such cues are not transduced prior to puberty into neural events that lead to male sexual behavior.

3.3. Neural integration of steroids and chemosensory stimuli

Although it is clear that steroids and chemosensory cues are both necessary for expression of male reproductive behavior, the neural substrate of integration of these two signals remains elusive. The integration of endogenous and exogenous signals may occur at multiple sites within the behavioral neural circuit. Steroid-sensitive and chemosensory pathways related to reproductive behavior converge

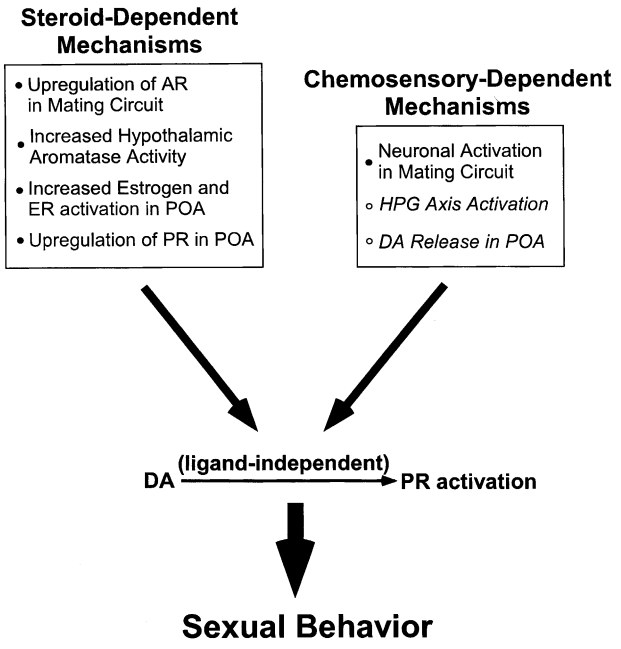

Fig. 5. A schematic diagram of known and hypothesized events underlying pubertal maturation of male reproductive behavior. Italicized chemosensory-dependent events occur in adults, but not in prepubertal males. Thus, prepubertal males have adult-typical neural responses to steroids, but do not have adult-typical neuroendocrine and neurochemical responses to female chemosensory cues. A dopamine-mediated, ligand-independent activation of the PR is a proposed hypothetical mechanism for the neural integration of steroidal and chemosensory cues. This hypothesis predicts that the absence of a dopaminergic response to female chemosensory stimuli in prepubertal males underlies the inability of steroid hormones to facilitate male reproductive behavior prior to puberty.

in the POA, which is one probable site of integration. Collectively, our studies suggest that when prepubertal males are treated with testosterone, AR is upregulated and activated, and aromatase enzyme activity is increased. The resulting local increase in estradiol activates constitutively expressed ER, which leads to upregulation of PR. Steroid treatment of prepubertal males also increases their investigatory behavior of the female, whose chemosensory stimuli activate neurons within the behavioral circuit. In adults, but not in prepubertal males, exposure to the female results in an increase in dopaminergic activity in the POA. We hypothesize that dopamine released in response to the female activates PR in the POA via a ligand-independent mechanism. This hypothesis stems from studies in estrogen-primed female rodents, in which dopamine can facilitate lordosis in the absence of progesterone via a PR-mediated process that involves D1 receptor-activated second messenger systems [99]. If an analogous interaction between female-stimulated dopamine release and PR activation occurs in the male POA, then the POA may serve as a neural substrate for integrating the steroidal and chemosensory cues required for expression of male reproductive behavior. A corollary is that these integrative processes within the POA are not operative prior to puberty because the absence of a dopaminergic response to female pheromones in the POA of prepubertal males precludes facilitation of behavior by steroid hormones (Fig. 5). Experimental testing of this hypothesis is a focus of future work in this laboratory. In any case, it is clear that neural maturation must occur during pubertal development to allow sensory and hormonal cues to evoke a biologically relevant response (i.e. male reproductive behavior).

4. Is puberty a sensitive period for the organization of neural circuits underlying male reproductive behavior?

The dramatic behavioral changes that accompany puberty provide evidence that puberty is a period of neural development during which responses to sensory stimuli are shaped and neural circuits are organized to allow expression of reproductive behavior in adulthood. Our experiments have led us to conclude that pubertal maturation of reproductive behavior requires maturational processes that alter responses to female chemosensory cues. Whether these maturational processes require the presence of steroid hormones specifically during the time of puberty is not known, although it is clear from our studies that exposure to steroids prior to puberty does not yield adult-typical neural responses to females.

In this section, we consider the evidence that puberty is a sensitive period of neural development during which steroid hormones permanently organize the nervous system. Two important questions are addressed. First, what is the evidence for structural reorganization of the nervous system by steroids during puberty, particularly within the circuit mediating male reproductive behavior? Second, must the brain be exposed to steroid hormones specifically during puberty for maturation of reproductive behavior, or can behavioral maturation occur in males deprived of steroids during puberty but subsequently exposed to steroids afterward? If the former is true, then puberty may be viewed as a critical period for the organization of behavioral circuits underlying male reproductive behavior.

4.1. Is there evidence for structural reorganization of the brain during puberty?

Studies from this laboratory demonstrate pubertal changes in hypothalamic and limbic structures related to reproductive behavior in the male hamster. In one set of experiments, several nuclei within the hypothalamus and amygdala were examined both before and after puberty and in adulthood under photoperiods that mimic summer or winter day-lengths. Of particular interest were the comparisons between prepubertal males and adults housed in short days (i.e. those that mimic winter day-lengths). Exposure to short days returns the adult male to a prepubertal-like state in which the gonads regress and circulating levels of testosterone are low [100]. Furthermore, similar to prepubertal males, short day-housed adults do not display reproductive behavior when treated with exogenous

testosterone [101,102]. Our anatomical studies found some structural similarities between prepubertal and short day-housed adults in the amygdala. The cross-sectional area of the postero-dorsal portion of the medial amygdala (MePD) increased with puberty along with a significant increase in the average somal size of cells in this region [103]. This pubertal increase in size could be reversed in adults by exposure to short days. In contrast, cross-sectional area of the anterior portion (MeA) significantly *decreased* with pubertal development, and this structural change was *not* reversible by photoperiod manipulation in adulthood. The decrease in MeA area was not due to reduced cell number or somal size, suggesting that changes in neuronal and/or glial processes may account for the decrease in MeA size with puberty. Thus, while both MeA and MePD undergo structural change during puberty, MePD appears to retain the capacity for seasonal change in adulthood, whereas MeA size remains fixed in adulthood, even when circulating steroids are altered by photoperiod. Since the size of MeA in a short day-housed and prepubertal male is different, yet neither one expresses reproductive behavior, the relationship between MeA size and behavior is not clear. It is also not known whether the pubertal decrease in size of MeA is due to exposure to steroid hormones during puberty. Nevertheless, the finding of an irreversible developmental decrease in MeA size provides evidence for permanent structural change in the MeA during puberty.

In a second set of experiments, we found that the number of AR-expressing cells in several hypothalamic nuclei is influenced by the presence or absence of gonadal hormones during pubertal development [104]. There were fewer AR-expressing cells in males that went through puberty with gonads intact, compared to adult males gonadectomized prior to puberty. Thus, gonadal steroids may act during puberty to influence either cell death or cell phenotype with enduring effects on tissue responsiveness to androgens. The functional consequence of reduced AR immunoreactivity when gonadal steroids are present during puberty is unknown. Although this finding appears paradoxical in light of enhanced behavioral responses to androgen after puberty, it may reflect a refinement of neural circuits analogous to the initial exuberance and subsequent pruning of synaptic connections characteristic of early neural development.

Structural changes in the nervous system during puberty are not limited to cell groups related to reproductive behavior. For example, in rats, the number of cells in the adult visual cortex is greater in males than in females, and this sex difference is the result of a greater degree of apoptosis in females [105]. The period of apoptosis extends through pubertal development, and the degree of apoptosis in females can be reduced by ovariectomy just prior to puberty, indicating a role of steroid hormones in the pubertal emergence of this sex difference [105]. Recent neural imaging studies suggest that hormones may also influence pubertal development of human cortex. A longitudinal study showed that cortical gray matter volume increased around the time of puberty and thereafter decreased, along with an increase in white matter volume, as the subjects approached young adulthood [106]. Another group reported a similar reduction in cortical gray matter volume after adolescence [107]. These changes occurred at an earlier age in girls than in boys, corresponding to the sex difference in average age at the onset of puberty [106]. The increase and subsequent decrease in gray matter volume may represent brain region-specific synapse proliferation and elimination and increased myelination during the time of puberty, and may underlie pubertal changes in human cognition. These reports are just a few examples of the many structural and functional changes in the central nervous system during human adolescence, which have been described and reviewed elsewhere [108,109].

4.2. Must the brain be exposed to steroids specifically during puberty for maturation of male reproductive behavior to occur?

An important question for pubertal maturation of behavior is whether a sustained rise in gonadal steroids must occur specifically during the time of puberty for the behavior to be appropriately expressed in adulthood. If so, then puberty could be viewed as a critical period for steroid hormone-dependent organization of the nervous system. Puberty does appear to be a critical period for steroid-dependent organization of a non-reproductive social interaction used as an index of anxiety in rats. When tested in a novel environment, adult male rats show less interaction with another male and less open-field ambulation (more anxiety) than prepubertal males [110,111]. If males are castrated before puberty and tested in adulthood, they display the high levels of social interaction and open-field ambulation (less anxiety) characteristic of prepubertal males, and testosterone treatment in adulthood does not result in the adult-typical pattern of behavior. Conversely, if animals are castrated after puberty, they engage in the same amount of social interaction and open-field ambulation as gonad-intact adults, whether or not testosterone is given in adulthood [4,5]. These results provide evidence that testosterone acts specifically during puberty to organize the adult pattern of this behavior.

Potential organizational effects of steroids on male reproductive behavior during puberty are not likely to be as dramatic as those on social interaction in a novel environment, because numerous studies have established the perinatal period as the primary critical time for organization of neural circuits underlying male reproductive behavior [38]. Indeed, male ferrets that were gonadectomized *after* the neonatal critical period but before puberty displayed male-typical reproductive behaviors when treated with testosterone in adulthood [112]. Clearly the presence of gonadal steroids during puberty is not an absolute requirement for expression of male reproductive behavior if perinatal sexual

differentiation has occurred normally. However, the literature is not definitive on whether more subtle aspects of the behavior might be influenced by the action of steroid hormones during pubertal development. In one study, male rats castrated prior to puberty and then treated with hormones in adulthood initially responded behaviorally to an estrous female as if they were prepubertal, but quickly developed adult-typical behavioral patterns [34]. In contrast, another study found that depriving the brain of steroids during puberty resulted in a permanent reduction in sensitivity of behavioral circuits to androgens [113], providing evidence for puberty as a critical period for the fine-tuning of the organization of male reproductive behavior by steroids.

Although the evidence on whether exposure to testosterone after puberty is sufficient for normal development of male reproductive behavior is inconclusive, our studies provide compelling evidence that exposure to testosterone *prior* to puberty is insufficient for expression of adult behavior. Because of the short period of time between weaning and the onset of puberty in male Syrian hamsters, our studies have been limited to treating prepubertal males with steroids for a relatively brief period of time (i.e. 1 week). Thus, it is possible that a more extended period of prepubertal hormone treatment could activate behavior prior to puberty. However, two lines of evidence suggest that the limited period of steroid treatment does not fully explain the absence of behavior prior to puberty. First, studies of male ferrets, which have a much longer juvenile period, showed that 2 weeks of hormone treatment was insufficient to activate mating behavior in prepubertal males [35]. Second, only 1 week of testosterone treatment is necessary to activate male reproductive behavior in long-term castrated adult rats [114] and hamsters (our unpublished observations). Thus, it seems likely that prepubertal male hamsters do not engage in mating behavior, even when treated with steroids, because other maturational processes, probably related to perception or interpretation of sensory stimuli or that render neural circuits susceptible to organization or activation by steroid hormones, have not yet occurred.

5. Speculations, future directions, and possible implications

Puberty is a developmental period during which the nervous system undergoes considerable maturation, allowing for expression of the adult behavioral repertoire. Without proper neural development during puberty, it appears that social, sensory, and hormonal signals are not appropriately integrated within the neural circuits. Puberty may be a critical period for organizational effects of steroids on certain steroid-dependent behaviors. For the maturation of other adult behaviors, including male reproductive behavior, both steroid-independent neural maturation during puberty and steroidal shaping of neural circuits may be necessary, but may not need to occur coincidentally. If so, this feature of the maturation of reproductive behavior may be an adaptive mechanism by which individual variation in the timing of gonadal maturation is not detrimental to behavioral maturation, since a temporal dissociation between these two events would still allow for propagation of the species. On the other hand, a temporal dissociation between gonadal maturation and pubertal maturation of the nervous system may have a maladaptive impact on behaviors for which puberty is a critical period for behavioral organization.

In humans, the timing of exposure of the developing nervous system during puberty to elevations in steroid hormones can be either unintentionally altered by delayed or precocious gonadal development, or artificially altered through the use of steroids. Such situations could impact behavioral maturation. For example, what are the behavioral consequences in adulthood of delayed reproductive maturation as a result of exercise or anorexia nervosa, in which the nervous system is not exposed to steroids until after pubertal maturation of the brain, or of anabolic steroid use by preteens, in which the nervous system is exposed to steroids before pubertal maturation of the brain? Male hamsters treated with an androgenic-anabolic steroid cocktail during pubertal development demonstrate increased aggression in adulthood. Furthermore, these behavioral effects appear to be mediated by long-lasting alterations in serotonergic input to the hypothalamus [115]. The potential for perturbations in the normal timing of elevated steroid hormone levels in humans underscores the importance of understanding the neurobiology of puberty, and how alterations in the timing of pubertal development influence the expression of adult behaviors.

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