Gonadal Hormones Organize the Adolescent Brain and Behavior

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Abstract Sexual differentiation of the nervous system and behavior occurs through organizational effects of gonadal hormones acting during early neural development and again during puberty. In rodents, a transient elevation in testosterone around the time of birth masculinizes and defeminizes the male brain, creating structural sexual dimorphisms and programming sex-typical responses to gonadal hormones in adulthood. A second wave of sexual differentiation occurs when levels of gonadal hormones are elevated at the time of puberty. At this time, both testicular and ovarian hormones further masculinize and feminize the male and female brain, respectively, fine-tuning sex differences in adult behavior. To test the hypothesis that the peripubertal period is a sensitive period for hormone-dependent sexual differentiation that is separate and distinct from the perinatal period, exposure to testosterone was experimentally manipulated in male Syrian hamsters to occur either prepubertally, during puberty, or in young adulthood. This experiment revealed that the perinatal and peripubertal periods of masculinization of male sexual behavior are not two separate critical periods of sensitivity to organizing effects of testosterone. Instead, the two periods of masculinization are driven by the two naturally occurring elevations in gonadal hormones. To explore possible neural mechanisms of peripubertal organizational effects of gonadal hormones, cell birth-dating experiments in male and female rats revealed sex differences in the addition of new cells, including both neurons and glia, to sexually dimorphic cell groups in the hypothalamus and medial amygdala. These sex differences in cell addition were positively correlated with sex differences in the volume of these cell groups. Prepubertal gonadectomy abolished sex differences in the pubertal addition of new cells. These experiments provide evidence that gonadal hormone-dependent sex differences in pubertal cytogenesis contribute to the establishment or maintenance of sexual dimorphisms in the adult brain.

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The transition from childhood to adulthood begins with the onset of puberty and the ensuing rise in sex steroid hormones, and it is completed by the end of adolescence. This period of development comprises extraordinary gain of function: individuals acquire the capacity to procreate, function independently within their social realm, and provide for themselves and their offspring. The metamorphosis of behavior is the product of a metamorphosis of underlying neural circuits, which necessarily occurs along different trajectories in females and males. In fact, adolescence can be regarded as a period of further sexual differentiation of brain and behavior, which is mediated in part by the actions of sex steroid hormones in the brain. This paper highlights research from my laboratory that has uncovered roles for gonadal hormones in shaping sex-specific behavioral and brain development during puberty and adolescence. I will first review experiments that establish that testicular hormones, acting during puberty, organize neural circuits underlying male social behaviors. Next I will present evidence that hormonal regulation of pubertal neuro- and gliogenesis is a potential mechanism for the establishment or maintenance of structural sex differences in the brain during adolescence.

Hormonal Organization of Male Social Behaviors During Puberty

The 1959 landmark paper by Phoenix et al. first posited the organizational-activational hypothesis of hormone-driven sex differences in brain and behavior. Within this framework, a transient rise in testosterone during prenatal or early postnatal development masculinizes and defeminizes neural circuits in males, whereas the absence of testosterone in females results in development of a feminine neural phenotype. Upon gonadal maturation during puberty, testicular and ovarian hormones act on previously sexually differentiated circuits to facilitate expression of sex-typical behaviors in particular social contexts. Research in the 1960–1970s identified a sensitive period for hormone-dependent sexual differentiation that occurs during late prenatal and early neonatal development (Baum 1979; Wallen and Baum 2002). Thus, the original conception was that gonadal steroid hormones organize brain structure during an early, developmentally sensitive period and activate behavior during puberty and into adulthood. Our work has refined the organizational-activational hypothesis to extend organizational effects of testicular hormones to the pubertal period. This second wave of brain organization builds on and refines the circuits that were sexually differentiated during early neural development.

Using the Syrian hamster as an animal model, we established that testicular hormones, acting during puberty and adolescence, organize male social behaviors. In these studies, we employed an experimental paradigm in which male hamsters were castrated at weaning, i.e., after the perinatal period of sexual differentiation and before the onset of puberty. In adulthood, testosterone was replaced and, 1–2 weeks later, social interactions with a receptive female or an intruder male were studied. The behavior of these hamsters was compared to that of other hamsters that were similarly treated, except that castration and hormone replacement occurred in

adulthood, several weeks after the pubertal elevation in testicular hormones. Thus, the two groups of hamsters differed in when they were deprived of testosterone, either during the normal time of puberty or in adulthood. This design allowed us to assess whether the presence of testicular hormones specifically during puberty and adolescence programmed behavioral responsiveness to testosterone in adulthood. In these experiments, we found that levels of sexual behavior, aggressive behavior, and flank-marking were all reduced in males in which testicular hormones were absent during adolescent brain development (i.e., males castrated before puberty), as compared to the behavior of males in which endogenous testicular hormones were present during adolescent brain development (i.e., males castrated after puberty; Schulz et al. 2004, 2006; Schulz and Sisk 2006). Even a prolonged period of testosterone replacement in adulthood failed to normalize behavior in males castrated before puberty. Thus, testicular hormones during puberty enhanced subsequent hormone activation of male social behaviors and masculinize behavioral responses in adulthood, outcomes similar to those of perinatal exposure to testosterone and indicative of organizational effects.

These findings prompted us to propose a two-stage model of behavioral development in which the perinatal period of steroid-dependent sexual differentiation is followed by a second wave of steroid-dependent neural organization during puberty and adolescence (Sisk et al. 2003; Sisk and Zehr 2005; Schulz and Sisk 2006; Fig. 1). During the second wave, pubertal hormones first organize neural circuits in the developing adolescent brain and then facilitate the expression of sex-typical adult behaviors in specific social contexts by activating those circuits. We view

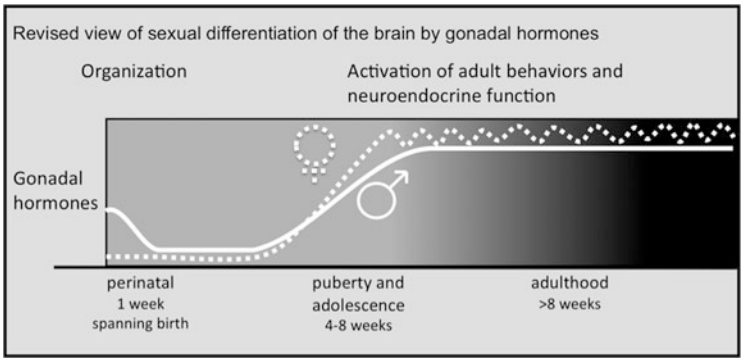

Fig. 1 Contemporary view of the sexual differentiation of brain and behavior by gonadal hormones in rodents. Two phases of sexual differentiation occur during natural developmental elevations in gonadal hormone secretion. The perinatal phase involves the masculinization and defeminization of the brain by a transient rise in testosterone secretion in males. The ovary is quiescent at this time. The pubertal phase involves the masculinization and feminization of the brain by the pubertal rise in gonadal hormones. Testicular and ovarian hormones both play an active role during this phase of sexual differentiation, which builds on the sex differences that were created during perinatal development. The transition from *gray* to *black* shading depicts the decreasing ability for gonadal hormones to exert organizational influences on brain and behavior (Reprinted from Juraska et al. 2013)

hormone-driven adolescent organization as a refinement of the sexual differentiation that occurred during perinatal neural development. That is, what occurs during perinatal brain organization determines the substrate upon which pubertal hormones act during adolescent organization. During the adolescent phase of organization, steroid-dependent refinement of neural circuits results in long-lasting structural changes that further program adult behavioral responses to hormones and socially relevant sensory stimuli.

We next asked whether the perinatal and peripubertal periods of hormone-dependent organization involve two discrete periods of enhanced sensitivity to hormones. We know that a window of sensitivity opens in rodents during late embryonic development to permit the initial sexual differentiation of the brain organized by testicular hormones (Wallen and Baum 2002). We also know that a window of developmental sensitivity to hormone-dependent organization closes (or nearly so) by the end of adolescence, because a prolonged duration of testosterone replacement does not reverse or ameliorate the adverse consequences of the absence of testosterone during puberty on adult social behaviors (Schulz et al. 2004). What was not clear is the extent to which the perinatal and peripubertal windows overlap: does the perinatal window close before the peripubertal window opens, or do the perinatal and peripubertal windows overlap enough to be considered a single period of sensitivity to hormone-dependent organization of the nervous system?

To address these questions, we manipulated the time during postnatal development that male hamsters were exposed to testosterone. If puberty marks the opening of a unique sensitive period for testosterone-dependent behavioral organization, separate from the perinatal sensitive period, then males exposed to testosterone during the normal time of puberty and adolescence, but not males exposed to testosterone before or after, should display the full complement of adult-typical mating behaviors. Male hamsters were castrated after the perinatal window of sensitivity to organizing influences of testosterone on postnatal day (P; P0 = day of birth) 10 and were implanted with testosterone-filled or empty Silastic capsules on P10, P29, or P63. Capsules remained in place for 19 days and then were removed on P29, P48, or P82, respectively. Thus, the groups receiving testosterone-filled capsules were exposed to testosterone either before (P10–29), during (P29–48), or after (P63–82) the normal time of puberty and adolescence (roughly P30–P50). Twenty-eight days after the removal of testosterone or blank pellets, when hamsters in all groups were in young adulthood, all males were implanted with testosterone pellets to activate mating behavior and were tested with a sexually receptive female 7 days later.

We found that testosterone treatment before and during adolescence, but not after, facilitated mating behavior in adulthood (Schulz et al. 2009; Fig. 2). In addition, prepubertal testosterone treatment more effectively facilitated adult mating behavior than at any other age. These findings extend our knowledge of neurobehavioral development by demonstrating (1) adolescence is not a sensitive period for testosterone-dependent behavioral organization distinct or separate from the neonatal period but rather adolescence is part of a protracted sensitive period that likely begins perinatally and ends in late adolescence; and (2) the

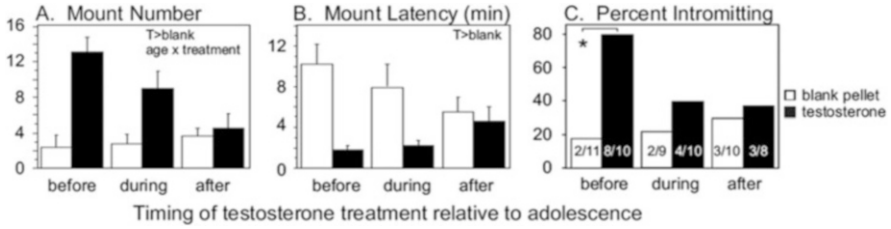

Fig. 2 Effects of periadolescent testosterone exposure on adult reproductive behaviors. Testosterone treatments were designed to simulate early, on-time, and late pubertal development, and all behavior testing occurred in adulthood after a 1-week treatment with testosterone-filled or blank subcutaneous pellets. Only before- and during-adolescent testosterone treatments facilitated mounting behavior in response to testosterone in adulthood. The percentage of male hamsters that showed intromissions was increased only by before-adolescent testosterone treatments. These data suggest that early testosterone treatments enhance behavioral responsiveness to testosterone in adulthood. *Asterisk* indicates a significant difference ($p < 0.05$) between groups (Reprinted from Schulz et al. 2009)

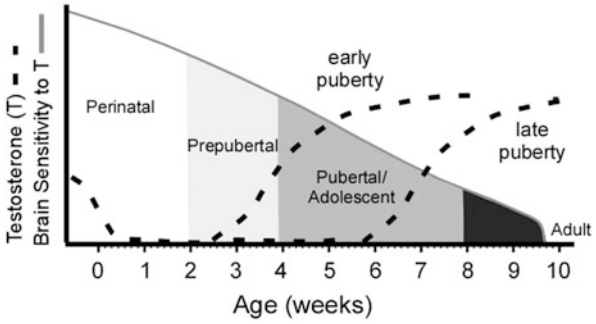

Fig. 3 Illustration depicting the results of our study investigating the effects of early, on-time, and late adolescent testosterone treatments on adult mating behavior. On the y-axis, the *dashed line* approximates testosterone secretion across development, whereas the *solid line* depicts decreasing sensitivity to the organizing actions of testosterone across development. Shading approximates the timing of perinatal, prepubertal, adolescent, and adult periods in the Syrian hamster. Given that early adolescent testosterone treatment was initiated immediately following the period of sexual differentiation (postnatal day 10), our data suggest that adolescence is part of a protracted sensitive period for the organizing actions of testosterone (area under the *solid gray curve*). In addition, because early adolescent treatments most effectively organized adult mating behavior, we propose that sensitivity to the organizing actions of testosterone decreases across postnatal development. If sensitivity to the organizing actions of testosterone decreases with time, then differences in the timing of pubertal onset may result in differences in brain development and adult behavior (Reprinted from Schulz et al. 2009)

timing of testosterone secretion within this postnatal window programs expression of adult mating behavior, with the earlier exposure to testosterone, the greater impact on behavior. Thus, these data have prompted us to revise the two-stage model to include a large postnatal window of decreasing sensitivity to the organizing actions of testosterone (Fig. 3). Importantly, the original two-stage model of

hormone-dependent organization is still relevant, but the stages are not defined by distinct windows of sensitivity to steroid hormones but instead by the two periods of elevated hormone secretion within a prolonged postnatal window of sensitivity to organizational effects of gonadal steroid hormones.

Sexual Differentiation of Brain Structure During Adolescence

In addition to proposing that sexually differentiated adult behaviors are organized by testosterone during early development, Phoenix et al. (1959) also correctly surmised that these early developmental effects of testicular hormones must involve organizational effects on the structure of the developing nervous system. Over the three decades following this seminal paper, an enormous literature emerged describing numerous sexual dimorphisms in the adult nervous system and uncovering the developmental processes by which these sex differences come to be. Structural sexual dimorphisms are typically manifested as sex differences in cell group volume, neuron or glial cell number, soma size, dendritic arborizations, dendritic spine density, degree of myelination, or some combination of these features. One principle derived from early studies of developmental mechanisms of sexual dimorphisms was that testicular hormones drive the perinatal creation of sexual dimorphisms in nervous system structure. This principle was based in large part on experiments showing that either pharmacological blockade or surgical removal of testicular hormone influences during the perinatal period was sufficient to prevent both masculinization and defeminization of sexually dimorphic hypothalamic regions (reviewed in Cooke et al. 1998). In contrast, removal of the ovaries immediately after birth did not have robust consequences on sexual differentiation, which is not surprising given that ovarian hormones are not secreted at this time. These studies led to the idea that, in the absence of testicular hormones, the default phenotype is essentially female and ovarian hormones are not actively involved in early sexual differentiation of the nervous system. Another principle was that the period of sexual differentiation of the nervous system structure is confined to a sensitive period during prenatal and early postnatal life, which in rodents constitutes a week bracketing the day of birth. This principle rested on studies in rodents showing that manipulation of testicular hormones after P7 failed to alter the adult phenotype of sexually dimorphic hypothalamic regions (reviewed in Cooke et al. 1998).

Each of these tenets began to be challenged as scientific interest in adolescent brain development gathered speed in the late twentieth century. Evidence began accumulating in the 1990s that testicular hormones, acting during puberty, masculinize male social behaviors, including male–female interactions, male-male

interactions, and scent-marking (Primus and Kellogg 1990; Bloch et al. 1995; Romeo et al. 2002; Schulz and Sisk 2006). Then came reports that ovarian hormones, acting during puberty, feminize food-guarding behavior and behavioral responses to metabolic challenge (Field et al. 2004; Swithers et al. 2008). These behavioral data encouraged investigations of the potential organizational effects of gonadal hormones on the masculinization and feminization of behavioral circuits during puberty and adolescence and a re-examination of the role of pubertal ovarian hormones in sexual dimorphisms in brain structure (reviewed in Juraska et al. 2013). Here I will discuss experiments from my laboratory that provide evidence that (1) ovarian hormones contribute to sexual differentiation of the brain during puberty, and (2) sex differences in cytogenesis are a potential mechanism for establishment or maintenance of structural sexual dimorphisms in the adolescent brain.

Sexual Differentiation of Hypothalamic Regions During Adolescence: The Anteroventral Periventricular Nucleus (AVPV) and Sexually Dimorphic Nucleus of the Preoptic Area (SDN)

The AVPV and SDN of adult rats are sexually dimorphic, with the AVPV being larger in females than in males (female-biased) and the SDN being larger in males (male-biased). The AVPV is essential for the generation of the preovulatory surge of gonadotropins (Wiegand and Terasawa 1982; Petersen and Barraclough 1989), a neuroendocrine event displayed by female rats only after puberty and never displayed by male rats (Hoffman et al. 2005). SDN function is linked to male sexual behavior, particularly partner preference (Kondo et al. 1990; Baum et al. 1996). Sex differences in the AVPV and SDN were among the first forebrain cell groups to be studied with respect to the mechanisms of sexual differentiation. It was established that the perinatal surge of testosterone secretion in males promotes survival of SDN cells, while simultaneously promoting death of AVPV cells during early postnatal development. Conversely, the absence of testosterone in females favors cell death in the SDN and cell survival in the AVPV (Dohler et al. 1982, 1984; Jacobson et al. 1985; Murakami and Arai 1989; Arai et al. 1994, 1996; Davis et al. 1996a, b). For both AVPV and SDN, then, adult sexual dimorphisms are hormonally programmed during perinatal brain development, with testosterone (or a metabolite) playing the primary role in masculinization and defeminization of these cell groups.

In spite of the evidence that neonatal testosterone promotes cell death in the AVPV during the perinatal period, an early investigation of sex differences in AVPV volume indicated that the female AVPV does not become larger than the male AVPV until puberty; between P30 and P90, AVPV volume grows in females but remains stable in males (Davis et al. 1996a). This finding suggests that the

perinatal programming of sex differences in AVPV volume is not immediately manifested and that pubertal processes contribute to the sexual dimorphism present in adulthood. To determine whether the pubertal increase in AVPV volume is due to the addition of new cells, we used the cell birthdate marker bromo-deoxyuridine (BrdU) to label cells born during puberty in male and female rats (Ahmed et al. 2008). BrdU was administered to rats that were at a prepubertal (P20), early-pubertal (P30), or mid-pubertal (P40) stage, and BrdU-labeled cells were quantified 3 weeks later, allowing time for the new cells to mature and potentially differentiate. Across all ages at which BrdU was administered, more BrdU cells were found in the female than in the male AVPV. Phenotyping studies revealed that some of these AVPV cells that had been born during puberty had differentiated 3 weeks later into mature neurons (Fig. 4). BrdU-labeled cells were also found in the SDN, with greater numbers of pubertally born cells in males than in females. However, in the SDN, there was no evidence for co-labeling of BrdU with either mature neuron or astrocyte markers, so the phenotype of pubertally added SDN cells remains unknown. It is possible that 3–4 weeks is insufficient time for these cells to fully differentiate as mature neurons or glial cells, as reported for cortical interneurons (Cameron and Dayer 2008). The results of these studies offer a novel mechanism for establishing and/or maintaining sexual dimorphisms in the hypothalamus during puberty, when new, sex-specific physiological functions and behaviors are acquired as the transition to adulthood proceeds.

A role for gonadal hormones in the addition of new cells during puberty is evident from additional experiments showing that prepubertal gonadectomy of male and female rats completely abolished the sex differences in the pubertal

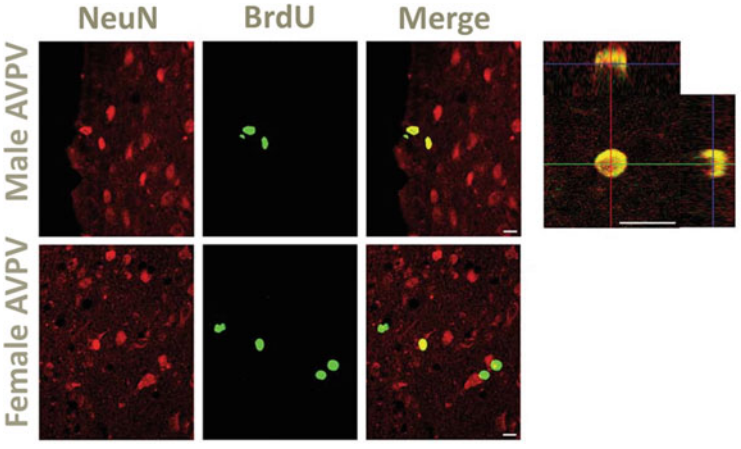

Fig. 4 Confocal images of cells in male and female rat AVPV. Sections were processed for double-label BrdU (*green*) and the mature neuron marker NeuN (*red*); colocalization is *yellow*. Orthogonal views (*right*) of confocal images verify colocalization of BrdU and NeuN in the female AVPV of a neuron that was born on P30–32. Scale bars: 10 μm (Reprinted from Ahmed et al. 2008)

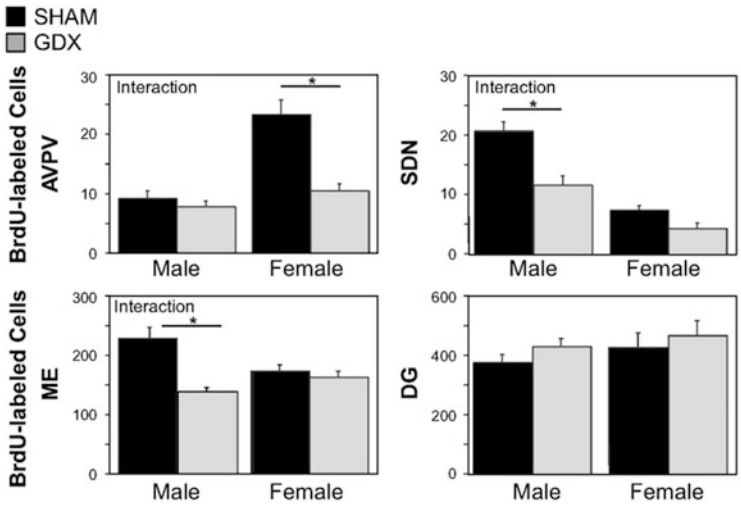

Fig. 5 The effect of prepubertal gonadectomy (GDX) on the number of BrdU-labeled cells depends on sex and brain region. Male and female rats were gonadectomized or sham gonadectomized at 20 days of age ($n = 8$/sex and treatment). A daily injection of BrdU was given on 30–32 days of age and brain tissue was collected at 50 days of age. Prepubertal GDX significantly decreased the number of BrdU-labeled cells in female but not male AVPV (interaction between sex and treatment). Prepubertal GDX decreased the number of BrdU-labeled cells in male but not female SDN and ME (interaction between sex and treatment). Prepubertal GDX did not affect BrdU-labeled cells in the dentate gyrus (*DG*) of either males or females. Data are presented as means ± SEM. *Asterisks* indicate $p < 0.05$ (post hoc Fisher test between groups) (Reprinted from Ahmed et al. 2008)

addition of new cells to the AVPV and SDN (Ahmed et al. 2008; Fig. 5). Prepubertal ovariectomy reduced the volume of the AVPV of females to a volume similar to males, and this reduction in volume was accompanied by a significant reduction in stereological estimates of total neuron number to a number similar to that of males. In contrast, prepubertal gonadectomy had no effect on the volume or pubertal addition of new cells to the AVPV of males. The effects of prepubertal castration on cell addition to the SDN paralleled those for the AVPV, but in a reverse direction. That is, prepubertal gonadectomy of male rats eliminated the sex difference in the number of BrdU-labeled cells in the SDN, reducing the number of pubertally added cells in males to the number observed in females. In contrast, prepubertal ovariectomy did not affect the number of BrdU-labeled cells added to the female SDN. Thus, ovarian hormones during puberty (or just before) feminize the AVPV but do not appear to actively feminize the SDN at this time. And, conversely, testicular hormones further masculinize the SDN during puberty but do not appear to actively masculinize the AVPV.

Sexual Differentiation of the Posterodorsal Medial Amygdala (MePD) During Adolescence

The rodent MePD evaluates chemosensory stimuli from conspecifics and integrates this information with the internal hormonal milieu, thereby coordinating the external and internal signals that regulate social behaviors. MePD volume is larger in adult male rats than in female rats, with this sex difference being more pronounced in the right hemisphere than in the left (Cooke and Woolley 2005; Cooke et al. 2007; Morris et al. 2008). This adult sexual dimorphism is the product of two successive phases of masculinization, one during early postnatal life and one during puberty. At P25, still before the onset of puberty, the rat MePD is already larger in males than in females (Cooke et al. 2007; Johnson et al. 2008, 2012a). Between the time of puberty and young adulthood, the sex difference in the MePD volume becomes even more exaggerated (Johnson et al. 2008, 2012a). BrdU cell birth dating studies corroborate these findings by showing that, during puberty, more cells are added to the male than to the female MePD (Ahmed et al. 2008). Some of these pubertally added cells are neurons and some are astrocytes (Ahmed et al. 2008), but it is not known at this time whether there are either sex or hemispheric differences in the pubertal addition of neurons vs astrocytes to the MePD. It does appear that pubertally born cells in the MePD become functionally integrated into behavioral circuits, as some pubertally born cells in the male hamster MePD express the immediate-early gene product fos after a sociosexual interaction with a receptive female (Mohr and Sisk 2013).

The pubertal phase of sexual differentiation of the MePD appears to involve, at least in part, testicular hormones acting via androgen receptors. The evidence comes from comparing the pubertal development of MePD in wildtype (wt) male and female rats with that of male rats carrying the testicular feminization mutation (tfm) of the androgen receptor, which confers androgen insensitivity. These studies show that the pubertal increase in MePD astrocyte number and astrocytic branching seen in wt male rats does not occur in male tfm rats, indicating that an androgen receptor-dependent mechanism is normally involved in these pubertal processes (Johnson et al. 2012a, b). Furthermore, the sex difference in the pubertal addition of new cells to the MePD is abolished by prepubertal gonadectomy of male rats, indicating that testicular hormones normally promote proliferation and/or survival of pubertally added cells in the male MePD (Ahmed et al. 2008). In contrast, prepubertal ovariectomy does not alter the number of pubertally added cells to the female MePD (Ahmed et al. 2008). Thus, the MePD provides a solid example of a region in which sex differences arise during early development but are magnified during puberty, and in the MePD the sexual differentiation that occurs during puberty involves a testicular hormone-, androgen receptor-dependent mechanism that promotes the addition of new neurons and astrocytes and astrocyte branching in males.

Future Directions

Our work demonstrates that sexually differentiated social behaviors and their underlying neural circuits are further masculinized and feminized during puberty and adolescence by gonadal hormones. Our future work will investigate the mechanisms by which the pubertal elevation in testosterone organizes male social behaviors. For example, are social information processing, social learning, and/or executive regulation of behavior under the organizational influences of testosterone during puberty, and if so, what neural circuits and neurotransmitters are involved and how are they permanently changed by testosterone? What are the roles of pubertally born neurons and glial cells in the adolescent maturation of sexually differentiated behaviors? We hope that elucidation of the mechanisms underlying typical sexual differentiation of the brain and behavior during puberty and adolescence will inform our understanding of the etiology of sex-biased psychopathologies that emerge during this period of development.

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