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Gonadal Hormone Modulation of Hippocampal Neurogenesis in the Adult

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ABSTRACT: Gonadal hormones modulate neurogenesis in the dentate gyrus (DG) of adult rodents in complex ways. Estradiol, the most potent estrogen, initially enhances and subsequently suppresses cell proliferation in the dentate gryus of adult female rodents. Much less is known about how estradiol modulates neurogenesis in the adult male rodent; however, recent evidence suggests that estradiol may have a moderate effect on cell proliferation but enhances cell survival in the DG of newly synthesized cells but only when estradiol is administered during a specific stage in the cell maturation cycle in the adult male rodent. Testosterone likely plays a role in adult neurogenesis, although there have been no direct studies to address this. However, pilot studies from our laboratory suggest that testosterone up-regulates cell survival but not cell proliferation in the DG of adult male rats. Progesterone appears to attenuate the estradiol-induced enhancement of cell proliferation. Neurosteroids such as allopregnalone decrease neurogenesis in adult rodents, while pregnancy and motherhood differentially regulate adult neurogenesis in the adult female rodent. Very few studies have investigated the effects of gonadal hormones on male rodents; however, studies have indicated that there is a gender difference in the response to hormone-regulated hippocampal neurogenesis in the adult. Clearly, more work needs to be done to elucidate the effects of gonadal hormones on neurogenesis in the DG of both male and female rodents. © 2006 Wiley-Liss Inc.

KEY WORDS: adult neurogenesis; dentate gyrus; estradiol; estrogen; testosterone; neurosteroids; male; female; sex differences

INTRODUCTION

Anyone who has gone through puberty, pregnancy, or menopause will be aware of the powerful effects of hormones on both their body and mind. For example, "female hormones," such as estradiol and progesterone, which are primarily released from the ovaries, fluctuate during the menstrual cycle and are crucial for the maintenance of pregnancy; and "male hormones," such as testosterone, which are primarily released from the testes, play a role in aggression and reproductive behavior. These gonadal hormones are important regulators of reproductive and nonreproductive behaviors throughout the lifespan and have multiple neuroprotective effects (Lee and McEwen, 2001).

Gonadal hormones have both organizational and activational effects. Organizational effects result from early exposure to hormones prior to a critical period (usually pre- or peri-natal exposure) and are permanent such as changing the structure of the sexually dimorphic nucleus of the hypothalamus (Morris et al., 2004). Activational effects refer to transient effects on brain and behavior, which are present only while the hormone is present, such as changes in apical CA1 pyramidal cell spine density across the estrous cycle in female rats (Woolley et al., 1990).

Understanding the impact of sex differences in the brain is important for understanding human health and disease. Anytime there are persistent sex differences in a trait (behavior, neurological disorders, physiological process, etc.), this suggests that gonadal hormones are involved. For example, women suffer from neuropsychiatric disorders such as depression and anxiety more then men, while men develop drug dependencies/addictions more than women (Gold, 1998). The study of how hormones influence brain and behavior is complex: hormonal effects are usually curvilinear with either very low or very high levels causing the same effect and some hormones are precursors to other hormones (see Fig. 1 for steroid pathways). Each sex has active levels of both types of gonadal hormones; however, levels of gonadal hormones vary with sex and there are very few sex differences in estrogen or androgen receptor densities throughout the brain.

Neurogenesis is a process that consists of both cell proliferation (the birth of new cells) and cell survival (new cells that survive to maturity). Factors that affect cell proliferation are those that either suppress or induce mitosis in precursor cells. Factors that affect cell survival either promote or prevent the differentiation and/or maturation of cells into mature neurons. Thus, the number of new neurons can be increased not only by increasing cell proliferation but also by enhancing the survival of new neurons. From a functional standpoint, behavior would likely be more immediately influenced by factors that increase the incorporation of immature neurons into existing circuitry than by factors that increase cell division. However, discovering the regulatory mechanisms of *both* cell proliferation and survival is important in neurogenesis research. Certain steroid hormones, such as estradiol and testosterone, have been shown to modulate both cell proliferation and cell survival in the adult hippocampus. In this review, we will concentrate mainly on the role of gonadal hormones in regulating hippocampal neurogenesis. Adrenal hormones, such as corticosterone, can also regulate neurogenesis and will be reviewed in another

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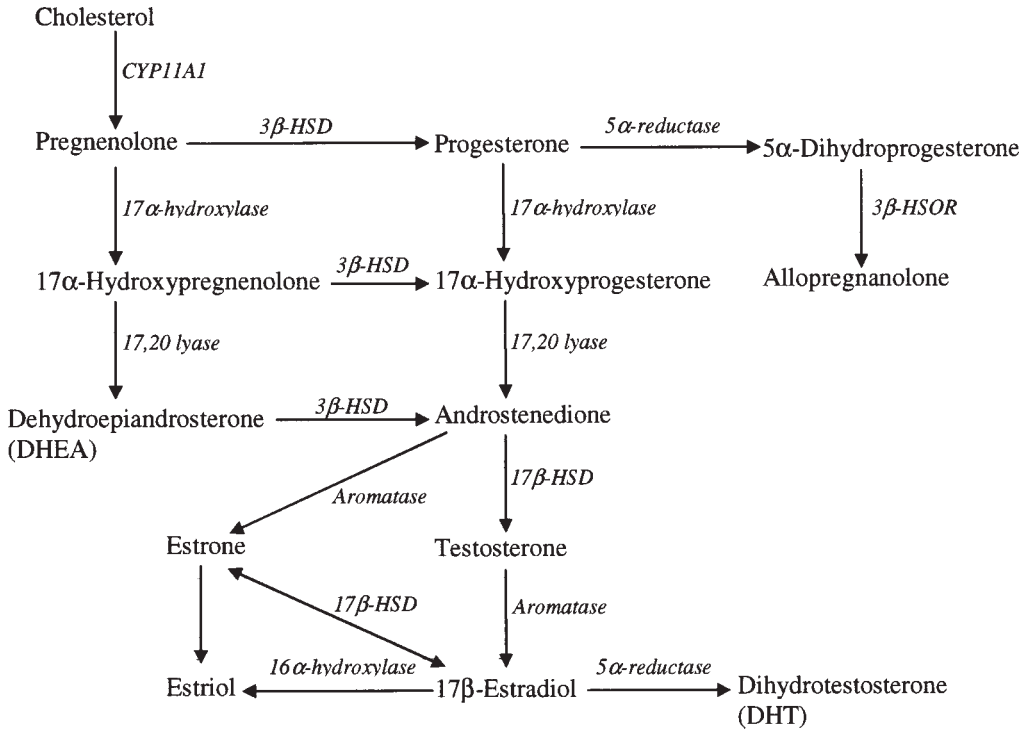

FIGURE 1. Catabolic pathways, with associated enzymes, for androgens, estrogens, and other pregnenolone derivatives. Some enzyme names are abbreviated: 3β-hydroxysteroid dehyrogenase (3β-HSD), 17β-hydroxysteroid dehyrogenase (17β-HSD), and 3β-hydroxysteroid oxidoreductase (3β-HSOR).

chapter. Furthermore, although gonadal hormones also affect embryonic and postnatal neurogenesis in many areas and adult neurogenesis in the subventricular zone, in the interest of space, these data will not be extensively reviewed here.

Estrogens

Estrogens are mainly produced in the ovaries, but are also produced by Leydig cells in the testes, peripheral tissues (Grodin et al., 1973; Hemsell et al., 1974; MacDonald et al., 1979), the brain (Garcia-Segura et al., 1999), and the placenta (Wood, 2005). Estrogens include estradiol (the most potent estrogen), estrone, and estriol. As mentioned earlier, male primates and rodents also have circulating estradiol, as testosterone can be converted to estradiol via aromatase.

Effects of Estrogens on Hippocampal Neurogenesis: Cell Proliferation

Estradiol affects both cell proliferation and cell survival in the dentate gyrus (DG) of the adult rodent. However, these effects differ depending on the time of exposure to estradiol, amount of estradiol, presence of progesterone, species, and sex of subject. Most research on estradiol's effects on neurogenesis has been performed on adult female rodents and therefore much less is known about exposure to estradiol on hippocampal neurogenesis in adult male rodents. Nonetheless, interest in gonadal hormone regulation of adult hippocampal neurogenesis first precipitated from studies showing a sex difference favoring females in level of hippocampal neurogenesis in the adult rodent. Two studies have shown that females have higher levels of cell proliferation, but not cell survival, than males depending on the endocrine state of the female (Galea and McEwen, 1999; Tanapat et al., 1999). For example, only proestrus females have higher levels of cell proliferation than male rats (Tanapat et al., 1999) and proestrus is associated with high estradiol levels. Female meadow voles also have higher levels of cell proliferation than male meadow voles but only during the nonbreeding season (when estradiol levels are low) (Galea and McEwen, 1999). Although these two studies appear contradictory, there are differences between species (laboratory rats vs. meadow voles), duration of exposure to estradiol (a few hours vs. months), and length of exposure to estradiol significantly affects the level of cell proliferation in the hippocampus.

Studies manipulating estradiol levels have found that short-term exposure (2–4 h) to high estradiol in adult female rodents result in enhanced cell proliferation when compared with ovariectomized controls (Tanapat et al., 1999; Banasr et al., 2001; Ormerod and Galea, 2001). Exposure to estradiol initially enhances cell proliferation (within 4 h) but subsequently suppresses cell proliferation after 24–48 h in adult female laboratory rats and meadow voles (Ormerod and Galea, 2001; Ormerod et al., 2003). The estradiol-induced enhancement in cell proliferation was found to be dependent on serotonin, as a serotonin antagonist, PCPA, blocked the ability of estradiol to enhance cell

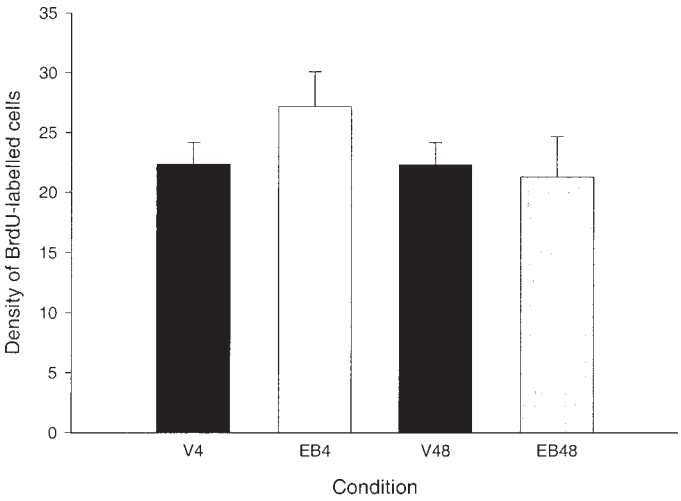

FIGURE 2. Mean (+ standard error of mean) density of BrdU-labeled cells in the DG of adult male rats given BrdU 4 or 48 h after estradiol (E4, E48) or vehicle (V4, V48). Estradiol exposure for 4 h had a nonsignificant tendency to increase the number of BrdU-labeled cells in the DG of adult male rats ($P = 0.15$).

proliferation. Furthermore, the estradiol-induced suppression in cell proliferation is mediated in part by adrenal steroids, as adrenalectomy eliminated but did not reverse the estradiol-induced suppression in cell proliferation in adult female rats. Recent work in our laboratory has shown that the estradiol-induced enhancement in cell proliferation is mediated in part through its effects on the estrogen receptor (Nagy et al., in press), as the estrogen receptor antagonist ICI 182, 780 partially blocked the estradiol-induced enhancement in cell proliferation. Furthermore, we have found that both ERα and ERβ are involved in the estradiol-induced enhancement in cell proliferation in the DG as both ER selective subtype agonists (PPT and DPN) enhance cell proliferation (Mazzucco and Galea, unpublished observations). Intriguingly, neither agonist enhanced cell proliferation to the same extent as estradiol alone (Mazzucco and Galea, unpublished observations), and the ER antagonist ICI 182, 780 did not completely eliminate the estradiol-induced enhancement (Nagy et al., in press). Both these lines of evidence suggest that estradiol may be working through another mechanism independent of its two known ER to up-regulate cell proliferation.

The ability of estradiol to up-regulate cell proliferation appears to be dependent both on the amount of time the rodent has been deprived of its normal circulating levels of estradiol and on the length of time the rodent is exposed to estradiol (acute vs. chronic administration). For example, in ovariectomized rats, estradiol administration does not enhance cell proliferation if administered 4 weeks after ovariectomy, and neither continuous estradiol administration (via silastic pellets) nor estradiol injections every 4 days affect cell proliferation in the DG (Perez-Martin et al., 2003; Tanapat et al., 2005). Also, the estradiol-induced enhancement of cell proliferation is dose-dependent: while a 10 μg and possibly 1 μg dose of estradiol enhanced cell proliferation, a supraphysiologial dose (50 μg) did not result in a significant enhancement of proliferation (Tanapat et al., 2005). Very little is known about the effects of estradiol on male rodents; however, pilot studies in our laboratory suggest that estradiol does not significantly alter cell proliferation in the DG (Pawluski et al., unpublished observations; see Fig. 2) although there is a slight tendency to increase cell proliferation 4 h after exposure to estradiol.

Effects of Estrogens on Hippocampal Neurogenesis: Cell Survival

There are two methods of examining cell survival: investigating the total number of cells surviving after an enhancement in proliferation; and investigating the rate of cell survival independent of any effects on proliferation. The percentage of cells surviving appears to be higher in male when compared with female rats, even though the total number of cells surviving is not significantly different. For example, although there are no significant sex differences in the number of BrdU-labeled cells surviving 14 days after BrdU injection (Tanapat et al., 1999), when one takes into account the percent of cells surviving vs. proliferating, it appears that males have higher levels of cell survival than females (75% in males vs. 47% in females: Tanapat et al., 1999). Curiously, in meadow voles, which have more stable gonadal hormone levels than do rats, both male and female reproductively active voles have higher levels of cell survival than nonreproductively active male or female voles suggesting that constant exposure to gonadal hormones may in fact promote cell survival (Ormerod and Galea, 2001, 2003). The fact that cell survival (total number of cells surviving after estradiol's initial enhancement in proliferation) is not enhanced in female rats may not be surprising, as female rats have a 4–5 d estrous cycle that results in continually fluctuating estradiol and progesterone levels. It remains to be determined what effect, if any, constant levels of estradiol have on cell survival in the hippocampus of adult female rats.

Experiments investigating the effects of estradiol on the rate of cell survival independent of its effects on cell proliferation have found that estradiol does enhance cell survival in the adult male meadow vole (Ormerod et al., 2004). Estradiol administration doubled the number of new neurons in the DG in castrated male meadow voles (Ormerod et al., 2004). This effect was dependent on when during the cell maturation cycle, the new cells were exposed to estradiol. Estradiol enhanced cell survival in males only when administered 6–10 days after BrdU incorporation, which is coincident with the time of axon extension (Hastings and Gould, 1999), but not if administered before or after this phase (Ormerod et al., 2004). Furthermore, there is very likely a sex difference in the effects of estradiol on the rate of cell survival, as unpublished observations in our laboratory have found that estradiol enhances cell survival, independent of its effects on cell proliferation, in the DG of adult female meadow voles at any time point examined (Ormerod and Galea, unpublished observations). In both of these studies (Ormerod et al., 2004; Ormerod and Galea, unpublished observations), BrdU was administered prior to treatment with estradiol, indicating an effect on cell survival independent of its effects on cell proliferation or an effect of estradiol on the rate of cell survival.

Estrogen Receptor Expression in the Hippocampus

Estradiol may not act directly to enhance cell proliferation or survival in the DG. There are regional differences of receptor expression in the rat hippocampus: ERα (mRNA and protein expression) has been identified in the hilus of the DG (Weiland et al., 1997; Orikasa et al., 2000; Blurton-Jones et al., 2004), whereas ERβ protein expression has been identified in the granule cell layer (Blurton-Jones et al., 2004). Additionally, nonnuclear ERα and ERβ protein expression has been identified in the same corresponding areas as their nuclear counterparts in the hippocampus of the adult female rat (Kalita et al., 2005). Thus, both ERα and ERβ are located in areas that could influence estradiol's effects on cell proliferation. Indeed, although ER expression has not been observed on dividing hippocampal progenitors in adult female rats (Tanapat et al., 2005), progenitors harvested from the subventricular zone of fetal and adult rats express both ERα and ERβ (Brännvall et al., 2002), suggesting that estradiol could mediate its effects on cell proliferation directly. Furthermore, Perez-Martin et al. (2003) found that BrdU-labeled cells in the DG were also immunoreactive for ERα and ERβ. In adult male rats, the majority of cells in the subgranular zone that express the endogenous proteins Ki-67 (actively dividing cells) and doublecortin (young, migrating neurons) also express mRNA for both subtypes of ER (Isgor and Watson, 2005). Thus, actively dividing cells and young neurons in the DG should be capable of responding to estrogens. Finally, the presence or absence of the ERα and ERβ does not preclude cells from responding to estrogen via nonclassical ER, including the plasma-membrane-associated putative ER-X (Toran-Allerand et al., 2002) or through another mechanism. Indeed, cells respond via ER to factors other than estrogens to influence hippocampal neurogenesis as the ER antagonist, ICI 182, 780, blocks the increase in cell proliferation induced by insulin-like growth factor-1 (IGF-1), suggesting that IGF-1 acts through the estrogen receptor to promote neurogenesis (Perez-Martin et al., 2003). In addition, estrogens may act through indirect mechanisms involving other endogenous hormones, such as progesterone, which may in turn interact with estrogen or other receptors to augment, offset, or abolish the effects of estrogen on hippocampal neurogenesis (see Progesterone section below).

Androgens

Androgens are produced mainly in the Leydig cells of the testis in males, but in both males and females, small amounts are also produced by the adrenal cortex (Chung and Hu, 2002) and in brain tissue (Baulieu, 1997). The major circulating androgen in vertebrates is testosterone. Within peripheral tissue, testosterone is metabolized into two biologically active steroids: dihydrotestosterone (DHT) and estradiol (Chun and Hu, 2002). Androgens also include dehydroepiandrosterone (DHEA), a steroid produced peripherally in the adrenal cortex, and centrally (Suzuki et al., 2004).

Compared to estrogens, considerably fewer experiments have directly manipulated androgens to determine their effect on adult neurogenesis in the hippocampus. At this time, much of the evidence that androgens may influence hippocampal neurogenesis is inferred. Furthermore, most of the work on androgens and neurogenesis has involved the avian high vocal center (HVC), but the findings with birds seem to corroborate the few studies conducted on the effects of androgens on hippocampal neurogenesis in rodents and have, therefore, been included in this review.

Effects of Endogenous Androgens

Seasonal changes in testosterone levels are associated with seasonal changes in neurogenesis in the hippocampus of rodents and the HVC in birds, providing indirect evidence that testosterone may influence adult hippocampal neurogenesis. Male canaries show seasonal peaks in neuron number within the HVC that corresponds with periods of song learning and high levels of androgens (Alvarez-Buylla and Kirn, 1997) and thus these changes in neuron number may be due to changes in neuron survival caused by fluctuations in testosterone. Specifically, Alvarez-Buylla and Kim (1997) noted that pyknosis within the HVC is highest during periods of seasonal decline in testosterone, and they suggest that low testosterone induces cell death, providing vacancies for newly proliferated cells to grow into. Meadow voles also show seasonal changes in testosterone, with a peak during the breeding season (Galea and McEwen, 1999), and males with higher testosterone levels have larger hippocampal volumes (Galea et al., 1999). Interestingly, these differences in hippocampal volume may be a result of testosterone's effect on cell survival within the DG. Ormerod and Galea (2003) found enhanced survival of ^{3}H-thymidine-labeled cells in the DG of reproductively active male meadow voles (when testosterone levels were high) when compared with reproductively inactive (when testosterone levels are low) male meadow voles. In contrast, reproductively active and reproductively inactive males showed no differences in cell proliferation within the DG (Ormerod and Galea, 2003), suggesting that seasonal fluctuations in androgens may enhance cell survival but not cell proliferation.

Numerous studies have demonstrated that agonistic interactions result in decreased cell proliferation and survival with the dentate gyri of socially subordinate individuals (Gould et al., 1997, 1998; Czéh et al., 2002; Simon et al., 2005). These results are generally attributed to the suppressive effects of stress hormones (corticosterone in rodents and cortisol in primates) on adult neurogenesis among socially stressed individuals. However, not all studies comparing socially dominant and subordinate individuals have documented differences in corticosterone level between groups. Both subordinate chickadees and male rats have lower cell proliferation in the ventricular zone or DG, respectively, than do their dominant counterparts, but in neither study did these groups differ in their corticosterone levels (Pravosudov et al., 2003; Kozorovitskiy and Gould, 2004; Pravosudov and Omanska, 2004). Thus, differences in neurogenesis between dominants and subordinates may be due to differences in testosterone levels, as repeated defeats during agonistic encounters lead to a decrease in testosterone levels among subordinate males (Schuurman, 1980; Blanchard et al., 1993; Stefanski, 2000). To date, no studies of social dominance and neurogenesis have measured testosterone levels.

Effects of Androgen Manipulations

In general, experiments involving birds and rodents suggest that androgens enhance cell survival but have no significant effect on cell proliferation. Fowler et al. (2003) found that testosterone implants in castrated male voles had no effect on hippocampal cell proliferation. However, the testosterone-treated male voles did show an increase in cell proliferation within the amygdala, which seems to be via an estrogen dependent pathway because DHT implants had no effect on cell proliferation and estradiol implants had effects (Fowler et al., 2003). Recent work in our laboratory has shown that castration causes a decrease in cell survival when compared with intact male rats, but has no significant effect on cell proliferation within the DG of adult male rats (Spritzer and Galea, 2005), consistent with the findings in male meadow voles (Ormerod and Galea, 2003). Furthermore, we have found that 30 days of testosterone injections administered to castrated adult male rats result in increased cell survival within the DG (Spritzer and Galea, unpublished data), similar to previous findings with birds (Rasika et al., 1994; Absil et al., 2003). Studies in starlings and canaries have found further evidence that testosterone affects cell survival. Intact male starlings implanted with testosterone showed increased cell survival (21 days) in the ventricular zone and HVC (Absil et al., 2003). Rasika et al. (1994) found that testosterone implants in adult female canaries increased cell survival (after 60 days) in HVC but testosterone did not have any significant effects on cell proliferation in the HVC (Rasika et al., 1994) or ventricular zone (Brown et al., 1993) in adult female canaries. In contrast to these studies, Brännvall et al. (2005) found that intact adult male and female rats injected with the anabolic steroid 19-nortestosterone (15 mg/kg) had decreased cell survival in the DG. These contradictory results may be due to the hormone used (19-nortestosterone vs. testosterone propionate) and/or the dose.

Possible Mechanisms of Androgen Effects

Androgen receptors (mRNA and protein) are expressed in the hippocampus, suggesting that androgens could influence adult neurogenesis directly. Kerr et al. (1995) found that the level of androgen receptor mRNA expressed in the hippocampus of adult male rats was similar to that found in the hypothalamus, where androgen receptor binding drives male sexual behavior. Brännvall et al. (2005) recently demonstrated that the androgen receptors are expressed in neural stem cell cultures developed from cells from the subventricular zone of adult female rats. It remains unknown whether androgen receptors are also expressed by hippocampal progenitor cells, but these results suggest that testosterone or DHT may influence neurogenesis by binding to androgen receptors on progenitor cell populations in the adult brain.

Besides direct effects on androgen receptors, interactions between testosterone and trophic factors provide evidence that testosterone may indirectly lead to changes in neurogenesis. Brain-derived neurotrophic factor (BDNF) is present in the HVC of adult male canaries but not females (Rasika et al., 1999). Female canaries given testosterone implants showed increased BDNF, and BDNF infusions increased cell survival in the HVC (Rasika et al., 1999). Vascular endothelial growth factor (VEGF) plays an intermediary role between testosterone and BDNF in canaries (Louissaint et al., 2002). Specifically, testosterone implants resulted in increased VEGF, which in turn led to increased proliferation of capillary epithelial cells within the HVC (Louissaint et al., 2002). These new epithelial cells were shown to synthesize BDNF, which promoted neurogenesis within the HVC. It remains unclear whether similar interactions between testosterone and trophic factors influence neurogenesis within the mammalian hippocampus, but BDNF knockout mice show reduced cell proliferation and survival within the DG (Lee et al., 2002), and increased expression of VEGF within the rat hippocampus leads to increased cell proliferation and survival (Cao et al., 2004). However, neither DHT nor testosterone implants in aged male rats had an effect on BDNF levels within the hippocampi (Bimonte-Nelson et al., 2003). No studies to date have manipulated testosterone in young male rodents to examine its effects on BDNF or VEGF.

DHEA Stimulates Neurogenesis

Apart from testosterone and DHT, DHEA is another androgen that has been shown to influence adult hippocampal neurogenesis. DHEA is produced primarily by the adrenal cortex, but is also produced as a neurosteriod in the brain (Suzuki et al., 2004). Karishma and Herbert (2002) found that DHEA implants given to intact male rats resulted in increased cell proliferation and cell survival (28 days) in the DG. Furthermore, DHEA prevented the corticosterone-induced suppressing effects on cell proliferation in adult male rats. In vitro, DHEA increases the proliferation of human neural stem cells derived from fetal cortex (Suzuki et al., 2004) and plays a role in increasing cell survival and decreasing apoptosis of cultured neuronal precursors from embryonic rat forebrain (Zhang et al., 2002). Interestingly, DHEA increases the survival of newly proliferated cells through an Akt-dependent pathway and DHEAS, the sulfated derivative of DHEA, has an opposing effect of cell survival, causing an increase in apoptosis and a reduction in Akt activation (Zhang et al., 2002). Therefore, like testosterone, DHEA increases the survival of newly proliferated cells, but unlike testosterone, DHEA seems to cause an increase in cell proliferation.

Other Derivatives of Pregnenolone: Pregnenolone-sulfate, Allopregnanolone, and Progesterone

Recent work has investigated the role of the neurosteroids, pregnenolone-sulfate, and allopregnanolone on neurogenesis in the DG. Pregnenolone is the precursor to steroids both peripherally and centrally, and its derivatives pregnenolone-sulfate, progesterone, and allopregnanolone (3α,5α-tetrahydroprogesterone, which is derived from progesterone) have been suggested to play a role in hippocampal neurogenesis (Vallée et al., 2001).

Pregnenolone-sulfate

Pregnenolone-sulfate has been implicated as a potential player in age-related cognitive decline of hippocampus-mediated tasks (Vallée et al., 1997; Darnaudery et al., 2002; for review see Vallée et al., 2001). For example, Vallée et al. (1997) report that age-related decline on a hippocampus-dependent task is correlated with a decline in concentration of pregnenolone-sulfate in the hippocampus and this cognitive decline can be reversed if pregnenolone-sulfate is administered icv. Recently, Mayo et al. (2005) found that pregnenolone-sulfate enhances hippocampal neurogenesis in vivo: Young adult male rats administered pregnenolone-sulfate icv showed a 63% increase in BrdU-labeled cells and PSA-NCAM expression in the DG 44 h after BrdU injection and a 47% increase in BrdU-labeled cells 3 weeks after BrdU administration. In addition, pregnenolone-sulfate increased the number of BrdU-labeled cells and PSA-NCAM expression in the DG of aged male rats after 44 h (a longer period of survival was not assessed in aged animals). In apparent contrast, Wang et al. (2005) have shown an opposite effect: administration of pregnenolone-sulfate decreases cell proliferation of hippocampal neurons. However, pregnenolone-sulfate was administered to embryonic hippocampal neurons in vitro and thus differences in the effects of pregnenolone-sulfate on cell proliferation may be due to differences in the techniques used and/or age of the neurons.

Allopregnanolone

The role of allopregnanolone on hippocampal neurogenesis, primarily cell proliferation, has also been investigated recently (Mayo et al., 2005; Wang et al., 2005). Allopregnanolone concentration in the brain of Alzheimer's patients is diminished, suggesting that allopregnanolone may also play an important role in cognition and perhaps neuroplasticity (Weill-Engerer et al., 2002). Wang et al. (2005) report that allopregnanolone increased cell proliferation in embryonic hippocampal neurons in vitro and this effect is dose-dependent in a biphasic manner such that doses of allopregnanolone between 100 and 500 nmol significantly increase BrdU incorporation, whereas doses greater than 1000 nmol reversed the increase of proliferation eventually, resulting in a suppression of proliferation at very high doses (Wang et al., 2005). In addition, Mayo et al. (2005) found that allopregnanolone administered icv (6.3 nmol/7 μl) decreased neurogenesis in the DG 44 h after BrdU injection in young adult male rats when compared with controls. The suppression of cell proliferation with allopregnanolone in the Mayo et al. study may be due a number of factors including the dose-dependent curvilinear relationship described in the in vitro study by Wang et al., (2005), differences in experimental design (in vivo vs. in vitro preparations), or to a different cell populations (adult granule cells in vivo vs. embryonic hippocampal neurons in vitro).

Progesterone

Progesterone, a gonadal and neuro-steroid derived from pregnenolone and a precursor of allopregnanolone, has been shown to have a limited effect on hippocampal neurogenesis. Tanapat et al. (2005) have shown that an elevation in progesterone following an elevation in estradiol reduces estradiol's enhancing effects on cell proliferation in the DG of adult female rats. Similarly, Tanapat et al. (2005) have shown that ovariectomized rats treated with a high level of estradiol have enhanced hippocampal cell proliferation, but when ovariectomized rats are treated with estradiol and subsequently treated with progesterone, the estradiol-induced enhancement of cell proliferation is abolished. Unpublished work in our laboratory has found that in ovariectomized rats, a low level of estradiol and progesterone for 3 days followed by a high dose of estradiol and BrdU 4 h later (a regime which normally enhances cell proliferation) significantly suppresses progenitor cell proliferation in the DG of adult female rats (Falconer and Galea, unpublished data). This study and the work by Tanapat et al. suggest that progesterone can significantly alter estradiol's influence on adult neurogenesis. The role of progesterone alone on hippocampal neurogenesis has not been investigated in vivo; however, progesterone was found to enhance cell proliferation in vitro (Wang et al., 2005).

The Role of Fluctuations in Multiple Steroids on Neurogenesis in the Naturally Occurring Events of Pregnancy and Motherhood

The above-mentioned neural and gonadal steroids, as well as other hormones, naturally fluctuate during the lifespan of many species. In particular, pregnancy, parturition, and the postpartum coincide with dramatic fluctuations in steroid and peptide hormones. In the rat, estradiol increases dramatically during late pregnancy and decreases during parturition, while progesterone and allopregnanolone levels increase steadily during pregnancy, peak prior to parturition, and decline thereafter (Rosenblatt et al., 1988; Concas et al., 1998). Because of the dramatic changes in the steroid and peptide hormones during pregnancy and the postpartum, it is perhaps not surprising that pregnancy and/or mothering may alter adult neurogenesis in the hippocampus. Surprisingly, little work has been done in this area. One study found that on day 18 of gestation, PSA-NCAM-ir in the DG was enhanced (Banasr et al., 2001), suggesting that pregnancy may augment hippocampal neurogenesis. Recently, in pregnant mice, it was found that cell proliferation in the subventricular zone (these cells typically migrate to the olfactory bulb) was enhanced during gestational day 7 and postnatal day 7 with no changes in cell proliferation on gestational day 7 in the DG (Shingo et al., 2003). These changes during gestation in the subventricular zone were mimicked by prolactin administration. Preliminary data from our laboratory suggests that motherhood, but not pregnancy, suppresses 21 day cell survival, with BrdU injection given on the day after birth in primiparous rats (Pawluski and Galea, 2005).

CONCLUSIONS

Clearly, gonadal hormones dramatically affect both behavior and adult hippocampal neurogenesis. There are relatively few

studies investigating the effects of hormones on both male and female rodents, despite the fact that both sexes have similar density of hormone receptors. Obviously, more work needs to be done investigating the role of steroid hormones on hippocampal neurogenesis in both adult male and female rodents and the mechanisms that mediate these changes.

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