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Neurosteroid s'effects and mechanisms for social, cognitive, emotional, and physical functions

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Summary

Hormones are trophic factors that integrate central and peripheral nervous system functions, and can influence social, cognitive, emotional and physical (SCEP) processes. Greater understanding of behavioral and neurobiological underpinnings of mental, cognitive, and/or physical changes with maturation is becoming increasingly important as the world's population ages. There are individual differences in how people age, but the factors that influence these differences are not well understood. Social supports are one factor that may influence the trajectory of age-related processes. The loss of close relationships, especially among older persons, is one of the greatest risk factors for mental and physical decline. Progesterone, secreted by the ovaries, or produced *de novo* in the brain, is readily converted centrally to 5 α -pregnan-3 α -ol-20-one (3 α ,5 α -THP), and can influence SCEP, through rapid, non-classical steroid-mediated actions. Our hypothesis is that 3 α ,5 α -THP is a key trophic factor in SCEP and development. Our research has demonstrated that 3 α ,5 α -THP facilitates social and sexual behavior of rodents, which evokes further increases in 3 α ,5 α -THP in midbrain and hippocampus, brain areas involved in SCEP. The role of 3 α ,5 α -THP to influence social and/or sexual experience, and thereby SCEP, is discussed in this review. Further understanding of these neurobiological and/or behavioral factors may lead to findings that ultimately can promote health and prevent disease.

Keywords

Neurosteroids; non-genomic; allopregnanolone; lordosis; THP

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1. Introduction

Steroid hormones, such as progesterone (P), play a fundamental role in trophic actions that influence the development and function of the central nervous system (CNS) throughout the lifespan. In adult rodents, P facilitates social and sexual interactions. Progesterone influences the onset and duration of sexual behavior of rodents in part through its actions in the midbrain Ventral Tegmental Area (VTA). To elucidate functionally-relevant mechanisms of P, we have manipulated P's actions in the VTA of naturally, sexually-receptive or ovariectomized (OVX), estrogen (E)-primed rodents, and examined changes in social and sexual (socio-sexual) behavior. Progesterone's actions in the VTA occur independent of traditional actions at cognate intracellular progesterin receptors (PRs). Rather, P's actions in the VTA involve its conversion to 3 α -hydroxy-5 α -pregnan-20-one (3 α ,5 α -THP), which is devoid of affinity for intracellular PRs and has actions via neurotransmitter substrates (Frye 2001ab, 2007; Frye et al., 2006; Frye & Vongher, 1999). In addition to P and 3 α ,5 α -THP facilitating mating, sex further increases levels of neurosteroids.

Mating has dynamic effects upon levels of 3 α ,5 α -THP in the midbrain VTA. 3 α ,5 α -THP is readily formed in the midbrain from ovarian P, and is also a neurosteroid that is rapidly produced *de novo* in the midbrain following mating (Frye, 2007). Mating induces neurosteroidogenesis of 3 α ,5 α -THP in the midbrain, as well as the hippocampus, an important area of the brain for cognitive and emotional processes (Frye & Rhodes, 2006; Frye et al., 2006, 2007). We, and others, have demonstrated in separate lines of research that P and/or 3 α ,5 α -THP can influence social, cognitive, emotional and physical (SCEP) performance (Engel & Grant, 2001; Frye, 2007, 2008; Herbison, 2001; Miczek et al., 2002; Pinna et al., 2008; Sherwin, 1999).

In young adulthood and/or middle-age, alterations in 3 α ,5 α -THP may play a fundamental role to enhance reproduction and social bonds, thereby influencing SCEP. Social relationships have a substantial effect on health. Grief and bereavement increases morbidity and mortality. The loss of close relationships, especially among older persons, is one of the greatest risk factors for mental and physical decline. However, the neurobiological and behavioral mechanisms underlying these effects are not well understood. A greater understanding of the neurobiological and behavioral factors associated with social responding is essential in order to elucidate interventions that will promote health and/or prevent disease among individuals. The neurobiological and behavioral mechanisms that underlie mating-induced neurosteroidogenesis, and the subsequent impact on social, cognitive, emotional and physical (SCEP) function among young and/or mid-aged rats is the subject of this review.

2. Significance

The understanding of mental, cognitive, and/or physical decline with aging is becoming increasingly important as the world's population ages. There are individual differences in how people age. For example, about 60% of aging individuals will experience some cognitive decline. Among these, about half will experience benign senescent forgetfulness, or mild cognitive impairment (MCI) associated with cell loss in the subiculum region of the hippocampus. Others will experience Alzheimer's Disease (AD). In the early stages of AD, behavior impairments are virtually indistinguishable from those with MCI. However, the neural deficits associated with early AD are in the entorhinal cortex. With time, those with AD will experience profound cognitive and emotional impairment and neural deficits in the subiculum and entorhinal cortex. Indeed, some individuals will age well ("super" aging), others will experience normal aging, and many will experience cognitive decline. The neurobiological and/or behavioral underpinnings associated with these types of differences in aging between

individuals are not well understood. It is likely that life experience factors, such as those related to social factors, may have an effect, but this needs to be investigated.

One factor that may have a profound influence on the trajectory of age-related processes is social supports. Loss of a social relationship can contribute to decline in mental, cognitive, and/or physical functioning. The risk of bereavement (loss of a close personal relationship) increases from ~4% before adulthood (children losing parents) to ~15% and 45% among men and women, respectively, over 65 who are widowed (Stroebe et al., 2001, 2007). Those who are bereaved have an increased risk of mortality due to suicide and natural causes, independent of baseline health status, and other major risk factors (i.e. body-mass index, cardiovascular health, tobacco and/or alcohol use; Berkman, 2005; Murberg & Bru, 2001; Seeman et al., 1987). Bereaved persons have greater morbidity, as demonstrated by increases in new illnesses, exacerbation of existing conditions, greater use of medications, and poorer self-ratings of wellness (Thompson et al., 1984). Severe grief early in bereavement increases risk of heart attack and cancer (Chen et al., 1999). Dysregulation of autonomic, endocrine, and immune systems occur following loss of a loved one, or other forms of social isolation, which may contribute to heart disease and/or cancer (Berkman, 2000; Berkman et al., 2004; Cacioppo & Hawkley, 2003). Given that hormones are mediating factors between the central and peripheral nervous system, and can influence social, affective, and cognitive processes, their role underlying neurobiological and/or behavioral mechanisms that influence aging, are of interest.

It may be that quality social relationships improve health and/or well-being, but these effects can often be confounded with trophic actions of steroids. An example of this is parity, in which women experience robust fluctuations in hormones (progesterone, oxytocin, etc) and their trophic actions during pregnancy and post-parturition, and then intense social bonding with their offspring. Parity is typically associated with a reduction in breast cancer risk. In this example, and others, the extent to which these differences are due to hormonal experience or social factors is not clear. Oxytocin has clear effects to enhance affiliative behaviors, but its role for affective and cognitive responses is less clear than that observed with ovarian steroids and neurosteroids (Carter, 2007; Frye, 2008). A question is whether social and/or sexual experiences may have effects throughout the lifespan on social, affective, cognitive, and/or physical function. To address this, we have developed an animal model in which the neurosteroid, $3\alpha,5\alpha$ -THP's, trophic effects have been characterized. Background about this model follows.

3. Background

Hormones are pleiotropic and may have diverse actions that underlie their organizational and/or activational effects to influence normal cellular functions and/or behavioral processes. Emerging findings regarding the sources, mechanisms, and effects of steroids have challenged traditional dogma and revealed non-traditional actions of hormones to influence these processes. First, hormones are typically thought to be secreted from peripheral endocrine glands and get into circulation whereupon they can exert effects at distant target sites. The brain, like the gonads, adrenals, and placenta, is also an endocrine organ that requires coordinated actions of steroidogenic enzymes in neurons and glia in different parts of the CNS to metabolize peripheral steroids to neuroactive products (neuroactive steroids) or to produce steroids *de novo* independent of peripheral gland secretion (neurosteroids; Table 1). As such, hormones exert intracrine effects to mediate intracellular events, and paracrine, or neurotransmitter-like, effects to induce biological response in adjacent cells. Second, the classic mechanisms of steroids are considered to involve their binding to cognate, intracellular steroid receptors, which are present throughout the brain (Osterlund et al., 2000; Shughrue et al., 1997), and modulate transcription and translation (Pfaff et al., 1976). This process may take days, hours, or at least 10 minutes. Steroid hormones can also act in the CNS via membrane

receptors or rapid-signaling actions, which occur within seconds to minutes. Neuro(active) steroids produce rapid effects on neuronal excitability and synaptic function that involve direct or indirect modulation of neurotransmitter-gated ion channels, or other neurotransmitter receptors and transporters, rather than classic, nuclear hormone receptors (Baulieu, 1980; Gee et al., 1995; Herd et al., 2007; Rupprecht & Holsboer, 1999; Schlichter et al., 2006). Third, some of the most salient effects of hormones are to change the threshold for a biological or behavioral response to appropriate stimuli. We now know that hormone levels can change in response to extreme environmental and/or behavioral situations and, thereby, influence the likelihood of subsequent hormone-mediated processes (Barbaccia et al., 1996; Drugan et al., 1995; Patchev et al., 1994, 1996). There is now a greater understanding of more subtle and dynamic changes in hormones to mediate homeostatic processes, such as HPA function, which may exert proximate and discrete effects on physiological and/or behavioral processes. Details of the non-traditional sources, mechanisms, and effects of steroids relevant for SCEP are discussed below.

The brain as a source of 3 α ,5 α -THP

It is now generally understood that the brain, like peripheral glands (gonads, adrenals, placenta), is an endocrine organ (Diagram 1). The brain requires coordinated actions of steroidogenic enzymes in neurons and glia in different parts of the CNS to metabolize peripheral steroids to neuroactive products (neuroactive steroids) or to produce steroids *de novo* in the brain independent of peripheral gland secretion (neurosteroids). Baulieu and colleagues, discovered in the early eighties, that steroids could be synthesized within the brain and peripheral nerves and they termed these brain-derived steroids, neurosteroids (Baulieu, 1980, 1991). The initial discovery that steroids were synthesized in the brain came from observations that levels of steroids, such as pregnenolone, dehydroepiandrosterone, and their sulfate and lipoidal esters, were greater in the CNS and PNS, than in circulation. The same enzymes involved in steroidogenesis in peripheral glands were identified in the nervous system and found to be responsible for biosynthesis; albeit, they are typically expressed in brain at levels 2 to 5 orders of magnitude lower than in adrenal or gonadal tissues (Compagnone & Mellon, 2000; Furukawa et al., 1998). Central steroid concentrations also can be much *greater* than in the circulation and these levels can persist after extirpation of peripheral glands (gonadectomy-GDX, adrenalectomy-ADX). Together, these findings demonstrate that steroids are synthesized in the nervous system and their localization in the CNS/PNS was neither due to peripheral synthesis, nor sequestration and/or accumulation in neural tissues (Baulieu, 1980, 1991; Majewska, 1992; Mellon, 1994; Paul & Purdy, 1992). Summarized below is some of the key information regarding the production of neurosteroids.

Metabolic Pathways for Neurosteroidogenesis

The nervous system expresses all of the enzymes required for steroid biosynthesis to produce a variety of neurosteroids. However, it is beyond the scope of this review to address effects and mechanisms of all neurosteroids. Our focus is on 3 α ,5 α -THP.

The peripheral-type benzodiazepine receptor (PBR), which is essential for neurosteroidogenesis, binds cholesterol in nanomolar affinities (Diagram 2). The PBR helps import cholesterol into the mitochondria, where it can be oxidized to pregnenolone by two proteins that initiate steroidogenesis - the steroidogenic acute regulatory (StAR) protein and cytochrome P450-dependent C27 side chain cleavage enzymes (P450_{scc}), rate-limiting steps in steroid biosynthesis (King et al., 2004; Mellon & Deschepper, 1993; Papadopoulos et al., 2006). Once pregnenolone is synthesized from cholesterol by StAR and P450_{scc}, several 3 α -hydroxysteroid dehydrogenase (3 α -HSD) enzymes can convert the prohormones to neuroactive steroids. Key examples of neurosteroids/neuroactive steroids, which are derived from cholesterol and/or blood-borne precursors, respectively, are pregnenolone, which is

converted to P, and its product, 5 α -pregnane-3,20-dione-dihydroprogesterone, DHP), which can be converted to 3 α ,5 α -THP and its 5 β -stereoisomer (3 α ,5 β -THP).

Whether estrogens, androgens, and/or progesterone and its metabolites are synthesized in the CNS/PNS depends upon many factors including timing during development, expression of metabolism enzymes, and their substrates in particular tissues (brain regions), cell types (i.e. neurons vs. glia), and/or cellular regions (cell bodies, fibers etc). Neurosteroids are formed from biosynthesis of cholesterol by P450 and non-P450 enzymes (17 β -HSD, aromatase, 3 α -HSD, 5 α -reductase). Gene expression of P450c17, is developmentally regulated with early expression being different from that observed in the mature brain (Mellon, 2007). This implies that certain metabolites may play key roles that are relegated throughout development without continuous expression in adulthood. Further, there are developmental differences in the substrates that two 3 α -HSDs in human fetal brain utilize, with one using DHP and another using DHT (Reviewed in Frye 2008). Conservation in the localization of steroidogenic enzymes, which are involved in synthesizing neurosteroids, to specific brain regions within a variety of species, indicates that their function may be similar throughout evolution. Some investigations have attempted to colocalize steroidogenic enzymes in whole brain, neuronal, and/or glial cell cultures. Indeed, some steroidogenic enzymes are expressed only in neurons, or only in glia (type 1 astrocytes, Schwann cells), while other enzymes are expressed in both cell types (Martini et al., 2003; Mellon and Griffin, 2002). Investigations are still needed to elucidate how specific brain regions synthesize or metabolize steroids, which are essential to reveal the function of neurosteroids. Ascertaining the relative concentrations of peripheral versus central levels of 3 α ,5 α -THP is of great interest to understanding the functional significance of neurosteroids.

Non-classical actions of 3 α ,5 α -THP

Neurosteroids can have more immediate, rapid-signaling effects than steroids secreted by peripheral glands that act through classic nuclear steroid receptors. Neurosteroids can act through ion channel-associated membrane receptors to elicit rapid changes in signaling that can occur within milliseconds to seconds. The most extensively investigated actions of neurosteroids are those at synaptic and extrasynaptic γ -aminobutyric acid type A (GABA_A) receptors. In the presence of GABA, 3 α ,5 α -THP directly potentiates GABA_A receptors in nanomolar concentrations (Concas et al., 1998; Fodor et al., 2005; Puia et al., 1990; Schmid et al., 1998). 3 α ,5 α -THP increases chloride channel currents and lowers neuronal excitability with 20 and 200-fold higher efficacy than benzodiazepines or barbiturates, respectively (Belelli & Lambert, 2005; Brot et al., 1997; Gee et al., 1995; Lambert et al., 2003; Morrow et al., 1987; Reddy, 2004; Weir et al., 2004). Like other neurosteroids, 3 α ,5 α -THP can also have actions through other non-steroidal, ligand-gated, ion channel and/or G protein-coupled receptors and glutamate (among others; Rupprecht & Holsboer, 1999). P and/or 3 α ,5 α -THP have negative modulatory actions via norepinephrine, dopamine, serotonin, acetylcholine, oxytocin, and nicotinic/muscarinic receptors (Table 2) and may alter neuronal function through membrane E receptors (Chaban et al., 2004) and G protein-coupled membrane PRs (Zhu et al., 2003). Thus, 3 α ,5 α -THP has actions through non-traditional steroid targets that may play a role in SCEP.

Activational effects of progesterone and its metabolites

Activational effects are typically considered temporary changes in brain function and/or behavior that occur with the presence of hormones in the already developed CNS. In people, variations in P and 3 α ,5 α -THP levels have been examined. During the menstrual cycle, patterns in plasma levels of pregnenolone and 3 α ,5 α -THP are similar to that of P. During the luteal phase, circulating concentrations of pregnenolone and 3 α ,5 α -THP are 2 to 4 fold higher (2 - 4 nmol/L) than they are during the follicular phase (~1 nmol/L; Genazzani et al., 1998; Purdy et

al., 1990; Sundström and Bäckström, 1998ab; Wang et al., 1996; Table 3). Throughout pregnancy, serum levels of pregnenolone, P and 3 α ,5 α -THP increase with gestation (Luisi et al., 2000) and peak late in the 3rd trimester (50-100nmol/L; Herbison, 2001; Luisi et al., 2000). The levels achieved during late pregnancy are within the range that can produce sedation (80-160 nmol/L; Sundström et al., 1999). Notably, within 1 hour after delivery, maternal serum 3 α ,5 α -THP levels are decreased significantly, albeit pregnenolone levels in serum do not decline as substantially until 1 day later. There is evidence that P and 3 α ,5 α -THP bioaccumulate in brain. Investigation of levels of P and 3 α ,5 α -THP in the post-mortem brain of pre- and post-menopausal women show the expected patterns of menstrual variations and lower levels post-climacteric (Bixo et al., 1997; Purdy et al., 1991). Notably, 3 α ,5 α -THP levels varied by region with the highest concentrations being seen in the midbrain and hypothalamus (14-21ng/g; Bixo et al., 1997). These variations with reproductive experience imply that central neurosteroidogenesis may influence, or be influenced by, circulating steroid concentrations. Indeed, one of the rate-limiting factors in understanding more about the functional significance of neurosteroids lies in the challenge of being able to parse out the relative contributions of central versus peripheral endocrine glands. There is evidence that local biosynthesis and paracrine/autocrine effects of neurosteroids can precisely and rapidly alter neuronal function in a manner not achievable by neuroactive steroids derived from circulation. Some of these diverse activational effects are discussed below.

3 α ,5 α -THP & Sexual Behavior of Female Rodents

Given the potential involvement of neurosteroids in the etiology and/or therapeutic treatment of anxiety, stress and/or mood dysregulation, how neurosteroids influence sexual behavior, another robust sexually-dimorphic and hormonally-mediated function, has been investigated as a means to elucidate their physiological and ethological role. 3 α ,5 α -THP may be an important neuroendocrine factor that helps an organism respond to various environmental challenges, such as can occur with mating. In order for female rodents to be sexually receptive, actions of estradiol (E₂) and P are required. Notably, the effects and mechanisms of these steroids on sexual receptivity are diverse and site-specific. For example, in rodents, E and P initiate the facilitation of lordosis in part through actions to increase PR expression in the ventral portion of the ventromedial nucleus (VMN) (Schwartz-Giblin & Pfaff, 1986); however, in the midbrain VTA, which is devoid of PRs in adulthood (Blaustein, 2003; Frye & Vongher, 1999), 3 α ,5 α -THP mediates the duration and intensity of P-facilitated lordosis. In support, enhancing 3 α ,5 α -THP levels in the midbrain VTA facilitates sexual receptivity of rodents. 3 α ,5 α -THP levels in the midbrain are particularly dynamic and change in response to ovarian secretion of E₂ and P (and with mating, discussed below). In order for rodents to be sexually receptive, ovarian secretion or exogenous administration of E₂ is necessary. E₂ increases the formation of central 3 α ,5 α -THP, the activity of the 5 α -reductase enzyme (Cheng & Karavolas, 1973; Sinchak et al., 2003). Further increases in receptive behaviors are produced by ovarian secretion of, or exogenous administration of, progesterone and its metabolites, which increases midbrain levels of 3 α ,5 α -THP over that of diestrous, OVX, or OVX, E₂-primed rodents (reviewed in Frye, 2001ab). The frequency of lordosis displayed by proestrous rats, which have high endogenous 3 α ,5 α -THP in the midbrain VTA, are increased, compared to that of diestrous rats (Frye, 2001ab; Figure 1). These effects are reversed with OVX. Administration of E₂ and P or 3 α ,5 α -THP to the midbrain, but not co-administration of P and an inhibitor of 3 α ,5 α -THP formation, increases lordosis (Frye et al., 2006). These effects of 3 α ,5 α -THP in the midbrain VTA to enhance lordosis occur through 3 α ,5 α -THP's actions at GABA_A, D₁ receptors, and their downstream signal transduction targets, as blocking 3 α ,5 α -THP's actions at these substrates attenuate P- or 3 α ,5 α -THP-facilitated sexual receptivity (Frye & Walf, 2008b).

It is important to understand the role of 3 α ,5 α -THP because of its potential effects to mediate sexual and other, related behavioral processes and also because of its responsiveness to social

factors. For example, following mating, midbrain $3\alpha,5\alpha$ -THP levels are increased over those of non-mated naturally-receptive or hormone-primed rodents (Frye, 2001ab). The rapidity of the mating-induced increase in midbrain $3\alpha,5\alpha$ -THP, and independence of secretion from the ovaries and/or adrenals, suggest that biosynthesis and subsequent metabolism of central, rather than peripheral, progestogens underlie mating-induced increases in midbrain $3\alpha,5\alpha$ -THP that have been observed for rats, mice, and hamsters (reviewed in Frye, 2001ab; Frye & Rhodes, 2008a). The successive increases in midbrain $3\alpha,5\alpha$ -THP produced by E_2 and P-priming, and mating have led us to consider whether $3\alpha,5\alpha$ -THP in varying concentrations, or when derived from peripheral versus central precursors, may influence sexual behavior and/or related processes, such as affect, which may influence reproduction. Indeed, one well-recognized behavioral phenomenon about $3\alpha,5\alpha$ -THP is its bimodal effect on mood and aggression (Beauchamp et al., 2000; Fish et al., 2001; Miczek et al., 2003). Indeed, mating increases $3\alpha,5\alpha$ -THP levels in the midbrain and in the hippocampus, an important brain region that mediates affective and cognitive processes. We have found that mating increases anti-anxiety behaviors in the elevated plus maze, the open field and in social interactions tasks, concomitant with biosynthesis of $3\alpha,5\alpha$ -THP in the hippocampus and midbrain (Frye et al., 2007; Frye & Rhodes, 2008a). This has led us to consider whether $3\alpha,5\alpha$ -THP biosynthesis, due to social factors, may influence SCEP.

$3\alpha,5\alpha$ -THP & Homeostasis

One role of $3\alpha,5\alpha$ -THP may be to serve as a neuroendocrine factor that mediates parasympathetic tone and activity of the hypothalamic-pituitary-adrenal axis (HPA). $3\alpha,5\alpha$ -THP may be a homeostatic modulator that protects an animal from stressors and enables appropriate behavioral responses to occur (Engel & Grant, 2001). In support $3\alpha,5\alpha$ -THP is present during prenatal development and increases in response to stressors, such as maternal separation, as early as postnatal day 6 (Kellogg & Frye, 1999; Kehoe et al., 2000; McCormick et al., 2002). Stress manipulations during the critical time during hippocampal formation in the rodent brain (when there is much neuronal specification and cell body migration) can produce some deficits in long-term potentiation and long-term depression in hippocampus, spatial memory, increase anxiety and depressive behavior, and enhance susceptibility to addiction (Deminiere et al., 1992; Kippin et al., 2008; Walf & Frye, 2006ab; Weinstock, 2001, 2005, 2007). In adults, increases in $3\alpha,5\alpha$ -THP in response to acute cold-water swim, shock, and/or carbon dioxide exposure can be seen in intact, GDX, and/or ADX animals (Barbaccia et al., 1997; Paul & Purdy, 1992; Purdy et al., 1991; Valee et al., 2000), albeit, this is not always observed in ADX rats (Barbaccia et al., 1997). $3\alpha,5\alpha$ -THP has been demonstrated to attenuate enhancement of hypothalamic stress factor (corticotrophin-releasing hormone and vasopressin) mRNA expression in response to stress and its replacement to ADX rats attenuates anxiety associated with administration of corticotrophin-releasing hormone (Patchev et al., 1994, 1996). More subtle stimuli, such as social challenge and/or mating, also alter neurosteroidogenesis (Frye, 2001ab; Frye & Rhodes, 2008a; Miczek et al., 2003). Increases in $3\alpha,5\alpha$ -THP produced by such experiences are conserved across species, enhance GBR function, produce anxiolysis, and attenuate activation of sympathetic/HPA responses, which may help individuals return to a state of homeostasis following challenge (Barbaccia et al., 2001; Frye, 2001ab, 2008b; Patchev & Almeida, 1996; Paul & Purdy, 1992). As stress can alter neuroendocrine, cognitive and/or affective responding, we will investigate the role of $3\alpha,5\alpha$ -THP on SCEP of young adult and mid-aged rats.

Sex differences in $3\alpha,5\alpha$ -THP & stress responses

There are gender/sex differences in stress responding. Women have higher cortisol levels and respond with greater HPA reactivity to lower levels of stress stimuli than do men, particularly during perimenstrual or post-partum $3\alpha,5\alpha$ -THP withdrawal (Ellermeier & Westphal, 1995; Ferrini et al., 1997; Hinojosa-Laborde et al., 1999; Jezova et al., 1996; Rhodes & Rubin,

1999). Basal and stress-induced corticosterone levels are higher for female compared to male rats during $3\alpha,5\alpha$ -THP decline (Carey et al., 1995; Neumann, 2001; Oglivie & Rivier, 1997). Further, $3\alpha,5\alpha$ -THP administration to female or male rats attenuates the elevation of plasma ACTH and serum corticosterone secretion produced by emotional stress (Frye, 2007; Patchev et al., 1996). There are also gender differences in the social aspects of the response to stress. Males are thought to more likely respond to stress with agonistic/“fight-or-flight” approach, whereas females may use a more pro-social approach (i.e. “tend and befriend”; Taylor, 2008). The relative adaptive responses to stress, and the extent to which these differences in neurobiological and behavioral responses to stressors, are mediated by $3\alpha,5\alpha$ -THP, are of interest. Indeed, we have found that $3\alpha,5\alpha$ -THP levels among those with post-traumatic stress disorder are higher and negatively correlated with state anxiety following exposure to PTSD-relevant stimuli (Frye & Rhodes, 2008b). Throughout life, chronic stress can have neurodegenerative effects. $3\alpha,5\alpha$ -THP has been demonstrated to be neuroprotective, but this has mainly been investigated in *in vitro* models (Wang et al., 2007). However, we have data of the neuroprotective effects of $3\alpha,5\alpha$ -THP in *in vivo* systems, which are described in more detail below (Frye, 2008). Thus, we have investigated $3\alpha,5\alpha$ -THP’s role to promote and ameliorate stress- and age-induced decrements in socio-cognitive and/or stress responding among young adult and middle-aged rats.

$3\alpha,5\alpha$ -THP & affect of people

P and its metabolites may have effects upon depressive and anxiety behaviors in both humans and animals. Throughout the life-span, women experience varied and occasionally dramatic changes in their hormonal and reproductive cycles, and sensitivity in these periods of some women may contribute to greater incidence of anxiety and mood disorders of women compared to men. Among some women, hormonal and/or reproductive events may influence the onset or expression of depression and/or anxiety disorders, such as premenstrual syndrome, premenstrual dysphoric disorder (PMDD), and post-partum depression, syndromes which occur when endogenous levels of P and its metabolites are low (Backstrom et al., 2003; Endicott et al., 1999; Glick and Bennett, 1981; Markou et al., 2005; Pearlstein et al., 2005; Rapkin et al., 2002). For example, women with PMDD may be more sensitive to fluctuations in steroids, such that they report improved mood with ovarian suppression, but negative mood is increased by administration of E_2 and/or P (Schmidt et al., 1998). Furthermore, mood is more negative when hormone levels are higher during the luteal phase in PMDD patients (Hammarbäck et al., 1989; Seipel & Backstrom, 1998). Indeed, in collaboration with Dr. Ellen Freeman, we have also found that among some PMDD patients treated with selective serotonin reuptake inhibitors (SSRI), that had clinical improvement induced by placebo or SSRI, had lower levels of $3\alpha,5\alpha$ -THP (Freeman et al., 2002, 2004). Differences in affect are also observed with aging and the changes in steroid secretion at this time. Among some women at menopause, reduced levels of $3\alpha,5\alpha$ -THP and other neurosteroids has been associated with depression and other mood disorders (Barbaccia et al., 2000; Freeman et al., 2002; Girdler et al., 2001; Pearlstein, 1995). Moreover, changes in $3\alpha,5\alpha$ -THP levels are observed in people with affective disorders. For example, baseline plasma levels of $3\alpha,5\alpha$ -THP are normal in patients with generalized anxiety disorders and social phobia (Le Melledo & Baker, 2002). Moreover, levels are within normal limits following administration of pentagastrin, a panic-inducing agent (Tait et al., 2002). In people with panic disorder, $3\alpha,5\alpha$ -THP levels are higher than normal (Brambilla et al., 2003; Strohle et al., 2003), but were decreased by infusions of sodium lactate or cholecystokinintetrapeptide (CCK4) to induce panic attacks (Strohle et al., 2003). Notably, in people without a history of panic attacks, levels of neurosteroids are not affected or are increased following CCK4 treatment (Eser et al., 2005; Zwanzger et al., 2004). In women with panic disorder and agoraphobia, perimenstrual, but not midluteal, $3\alpha,5\alpha$ -THP levels, were significantly higher than among normal controls, and they correlated with their panic-phobic symptoms (Brambilla et al., 2003). Some of the most compelling evidence that neurosteroids

are involved in depression comes from clinical use of finasteride, a 5α -reductase inhibitor used for treatment of alopecia, which decreases production of $3\alpha,5\alpha$ -THP (Altomare & Capella, 2002; Townsend & Marlowe, 2004). As well, men with benign prostate hyperplasia are much more likely to develop depressive disorders when their treatment includes finasteride (Clifford and Farmer, 2002). That decreasing $3\alpha,5\alpha$ -THP production with finasteride can precipitate depressive symptoms in some individuals supports its role in the etiology of affective disorders.

The efficacy of some therapeutics to treat depressive and/or anxiety disorders are associated with their capacity to increase products of P metabolism (Griffin and Mellon, 1999; Uzunov et al., 1996; Uzunova et al., 1998). Interestingly, clinical findings indicate that P's anti-depressant effects may involve actions of $3\alpha,5\alpha$ -THP. Some patients who have depressive disorders have reduced plasma and/or cerebrospinal fluid levels of $3\alpha,5\alpha$ -THP (Romeo et al., 1998; Stahl, 1997; Uzunova et al., 1998). Administration of antidepressants, such as fluoxetine or fluvoxamine, normalize low $3\alpha,5\alpha$ -THP levels concomitant with reducing symptoms of depression (Uzunova et al., 2004, 2006). This implies that $3\alpha,5\alpha$ -THP may contribute to the antidepressant effects of some therapeutics.

$3\alpha,5\alpha$ -THP & Affective Behavior in Animal Models

Findings from animal models also support a role for P and its metabolites in depressive and anxiety behaviors. Figure 2 depicts a summary of depression behavior (as measured by time spent immobile in the forced swim test, a typical task utilized to measure depression-like behavior of rats) of rats across endogenous steroid milieu, in comparison to rats that have had their main endogenous source of circulating E_2 and P surgically removed (OVX) and were administered placebo vehicle. First, we have found little evidence for sex differences between male and female rats for depression behavior if they are tested as juveniles (i.e. before the pubertal onset in steroid secretion from the gonads in a sex-specific manner). Second, there are changes across the estrous cycle in depression behavior of rats. Rats during the late proestrous phase of the estrous cycle (i.e. behavioral estrus), when E_2 and P levels are higher than in other stages of the estrous cycle, have decreased depressive behavior in the forced swim test, compared to that observed in diestrous or male rats (Contreras et al., 2000; Frye & Walf, 2002; Frye & Wawrzycki, 2003; Marcondes et al., 2001; Marvan et al., 1996). Animal models also support a role of P and $3\alpha,5\alpha$ -THP in anxiety behavior, as measured by activity on the open arms of the elevated plus maze (Bitran et al., 2000; Guidotti & Costa, 1998; Jain et al., 2005). When P and $3\alpha,5\alpha$ -THP levels are high, such as during proestrus and pregnancy, anxiety behavior is reduced compared to when levels are declining or low (Becker & Cha, 1989; Bitran et al., 1991; Frye et al., 2000; Gulinello et al., 2003; Walf & Frye, 2006). OVX increases anxiety behavior (i.e. decreases open arm time) of female rodents and P or $3\alpha,5\alpha$ -THP reverses this (Frye & Walf, 2002; 2004; Frye et al., 2004ab; Walf et al., 2006b), unless $3\alpha,5\alpha$ -THP formation is compromised or withdrawal occurs (Frye & Walf, 2002; Frye & Walf, 2004b; Rhodes & Frye, 2001; Figure 3). Given that intractable depression is a significant problem among the elderly, we have examined, the role of P and $3\alpha,5\alpha$ -THP to alter anxiety behavior of young adult and middle-aged rodents.

$3\alpha,5\alpha$ -THP & Cognition

In addition to changes in mood, anxiety, and social functioning that characterize affective disorders of people, there are changes in cognitive function. Endogenous changes in progestins may influence cognitive performance mediated by the hippocampus. In young adult women, spatial performance either does not vary or is better among those tested in the menstrual and follicular, compared to the luteal (high P), phases (Maki et al, 2002; Rosenberg & Park, 2002). Among women, performance in the Wisconsin card sorting task and visual memory is better in the P-dominant luteal phase than during the ovulatory and/or menstrual phases (Berman et al, 1997; Hampson, 1990; Solis-Ortiz et al, 2004; Phillips & Sherwin, 1992). P

administration may have beneficial effects on PFC-mediated tasks. Transvaginal P (400 mg daily) to young women on lupron, a gonadotropin-releasing hormone agonist that suppresses endogenous gonadal steroid hormones, enhances cognition-related neural activity in the PFC (Berman et al, 1997). Furthermore, aging is associated with decline in cognitive performance of some women, and these changes occur at the same time that there are reductions in ovarian secretion of steroids. Thus, $3\alpha,5\alpha$ -THP may play a role in cognition of people.

$3\alpha,5\alpha$ -THP & Cognitive Behavior in Animal Models

There are activational effects of P and its metabolites for cognitive performance of rats. Young, rats, which have higher $3\alpha,5\alpha$, THP levels in the cortex (proestrus and late pregnancy), have better performance in the object recognition task than do diestrous rats or rats in early pregnancy (Figure 4). Among mid-aged rats, performance declines, particularly in reproductively-senescent rats compared to non-reproductively senescent rats. OVX impairs performance in this task and this can be reversed with administration of P or $3\alpha,5\alpha$ -THP; however, administration of P to OVX rats administered a 5α -reductase inhibitor produces similar effects as vehicle administration to OVX rats. Other studies have shown that administration of P, DHP, or $3\alpha,5\alpha$ -THP to ovx rats enhances performance in the object recognition and Y-maze tasks, both of which involve prefrontal and hippocampal processes, as well as conditioned and passive avoidance, tasks (Diaz-Veliz et al., 1994;Ebner et al., 1981;van Wimersma Greidanus, 1977,Walf et al., 2006a). Indeed, regression analyses revealed significant positive correlations between E_2 and $3\alpha,5\alpha$ -THP levels in the hippocampus and $3\alpha,5\alpha$ -THP levels in the prefrontal cortex for performance in the object recognition task (Walf et al., 2006a). It must be noted that there are reports of disorganizing effects of progestins that need to be taken into consideration. For example, among pregnant professional women, symptoms such as forgetfulness, disorientation, confusion, and reading difficulties are commonly reported (Poser et al, 1986). Studies in which ovx improved performance or progestin administration failed to enhance performance in ovx and/or aged rats may be due in part to disruptive effects of high progestin levels (Bimonte-Nelson et al, 2003;2004;Johansson et al, 2002;Zou et al, 2000), which can produce sedative/anesthetic effects (Holzbauer, 1975,1976; Selye, 1942) and decrease optimal levels of arousal for learning/memory performance. Thus, physiological levels of $3\alpha,5\alpha$ -THP may improve cognitive performance of rodents and decline in $3\alpha,5\alpha$ -THP with aging may contribute to cognitive decline.

Steroids & AD

Female-typical steroids may play a role in AD. Ovarian steroids, such as P and E decline with reproductive senescence and aging. Women are twice as likely as are men to develop AD (Gao et al., 1998; Payami et al., 1994). Potential beneficial effects of hormone therapy (HT) decline with delay in initiating HT (Resnick et al., 1997; Shumaker et al., 2003), age (Csizmadi et al., 2005), neurodegeneration (Henderson, 2000; Sherwin, 2006; Troncoso et al., 1996), and perhaps low levels of the P metabolite, and neurosteroid, $3\alpha,5\alpha$ -THP, are related to pathophysiology (Genazzani et al., 2001; Smith et al., 2006; Weill-Engerer et al., 2002). For example, we have shown that circulating $3\alpha,5\alpha$ -THP levels of those with AD or non-AD dementia are 33% lower than age-, gender-, and HT-matched, non-demented controls (Smith et al., 2006). We have recently investigated the role of P in a mouse model of AD, i.e. mice that overexpress the APP^{swe} and presenilin Δ exon 9 mutation (APP^{swe}+PSEN1 Δ e9 mice; obtained from Jackson Laboratory) (Frye & Walf, 2008a). Deficits in hippocampus-dependent tasks coincide with decrements in $3\alpha,5\alpha$ -THP in the hippocampus and P to ovx, wildtype (WT), but not APP^{swe}+PSEN1 Δ e9, mice improves performance in hippocampal tasks and reinstates hippocampal $3\alpha,5\alpha$ -THP levels (Frye & Walf, 2008a). P and/or $3\alpha,5\alpha$ -THP can have protective effects against seizures (Ciriza et al., 2006; Herzog & Frye, 2003; Reddy & Rogawski, 2001), glutamate toxicity in cultured hippocampal neurons (Nilsen & Brinton, 2002), and in animal models of neurodegeneration (Griffin et al., 2004; He et al., 2004a-c; Roof et al.,

1994; Vongher & Frye, 1999). It may be that $3\alpha,5\alpha$ -THP deficiencies, particularly in the hippocampus, may contribute, or be due, to age-related pathologies.

There is clear evidence that neurosteroids can play a role in hormonally- and developmentally-mediated behavioral processes, and that they may serve clinically-relevant functions across the lifespan. In order to further elucidate the role of neurosteroids, it may be necessary to think beyond heretofore defined clinical syndromes and consider common underlying symptoms that may be explained, or influenced in part by, neurosteroids. A truly productive translational approach will require careful elucidation and consideration of common features of neurosteroids' role in basic animal research and in clinical syndromes. As such, continued evaluation of the relationship between neurosteroidogenic capacity, neuroprotection, neurogenesis and therapeutic effects on basic biobehavioral processes across a number of paradigms may provide insight to their role in neurobiological and behavioral processes involved in SCEP.

4. Mating increases $3\alpha,5\alpha$ -THP in midbrain, cortex, hippocampus, and striatum

$3\alpha,5\alpha$ -THP levels in the midbrain are particularly dynamic and increase with mating. Notably, following standard mating (10 minutes or 10 sexual contacts with a male in an aquarium), midbrain $3\alpha,5\alpha$ -THP levels are increased over those of non-mated naturally-receptive or hormone-primed rodents (Frye, 2001ab; Fig. 5, top). In follow-up experiments, the effects of paced mating, in which proestrous rats are mated in a larger chamber wherein they can control the access to the male and thereby sexual contacts, rats were allowed to engage in an exploratory/anxiety tasks, social task, or no tasks, with or without paced mating. Irrespective of portion (Fig. 5, middle) or individual task engaged in (Fig. 5, bottom), paced mating was associated with $3\alpha,5\alpha$ -THP enhancement in brain but not serum (Frye et al., 2007). Engaging in paced mating uniquely increased biosynthesis of P metabolites, DHP and $3\alpha,5\alpha$ -THP, in midbrain > cortex > hippocampus > diencephalon (Frye & Rhodes, 2006). Thus, social interactions, such as paced mating, dynamically alter synthesis of P metabolites in brain areas involved in SCEP function. However, differences between standard and paced mating have not been compared and are of interest. As well, the acute and chronic consequences of such social interactions on SCEP will be investigated.

5. Mating increases gene expression in the midbrain

We examined differences in gene expression in the midbrain of naturally-receptive rats that underwent paced mating compared to naturally-receptive rats that did not mate. Midbrain tissues were sent to two core microarray facilities for Affymetrix GeneChip Rat 230 2.0 arrays per Affymetrix protocol. First, among mated rats, genes that were upregulated in the midbrain were primarily related to those substrates that our past studies have elucidated as targets for P and/or $3\alpha,5\alpha$ -THP actions to influence lordosis (i.e. GABA, glutamate, dopamine, signal transduction targets; Frye & Walf, 2008b). Second, mating induces $3\alpha,5\alpha$ -THP biosynthesis and many genes that were upregulated were those involved in steroid metabolism. Third, genes involved in cell proliferation and cell death were upregulated in the midbrain VTA of mated vs. non-mated rats. These data suggest that mating alters expression of genes associated with non-traditional steroid actions, steroid biosynthesis, and trophic actions in the midbrain of rats.

6. Parity enhances cognitive and anti-anxiety performance and $3\alpha,5\alpha$ -THP levels

One intriguing possibility that may underlie some of the common actions of $3\alpha,5\alpha$ -THP is its effects on neuroplasticity. For example, naked mole rats that are breeders have more favorable

neural morphology than do non-breeders (Holmes et al., 2007). Given that $3\alpha,5\alpha$ -THP is elevated in brain during pregnancy and that $3\alpha,5\alpha$ -THP has demonstrated trophic effects, the extent to which $3\alpha,5\alpha$ -THP may influence behavior associated with parity is of interest. Parity enhances cognitive function and affective behavior (Kinsley & Lambert, 2008; Paris & Frye, 2008; Pawluski et al., 2006; Walf & Frye, 2007). Furthermore, following mating and pregnancy, there is enhancement of neurogenesis in the hippocampus (Leuner et al., 2007; Pawluski & Galea, 2007). Indeed, rats with greater parity have more neurogenesis in the hippocampus. In our hands, we see that multiparous rats perform better on hippocampally-mediated tasks (elevated plus maze Figure 6, object recognition-Figure 7), than do nulliparous and/or primiparous rats and enhancements in cognitive performance occur concomitant with enhancements in circulating $3\alpha,5\alpha$ -THP among primiparous dams, albeit causal effects have not been established (Paris & Frye, 2008). For this reason, we will examine acute and long-lasting effects of mating and/or parity on social experience on SCEP.

7. Reproductive senescence influences social, cognitive, and affective performance

Social, cognitive and affective deficits can occur with aging in people and rodents. In females, these deficits may be initiated and/or coincide with the transition to reproductive senescence. Whether individual differences in the natural transition to reproductive senescence is associated with alterations in sexual, cognitive, and affective performance was investigated among age-matched, 12-month-old, Long-Evans female rats that were still reproductively-competent, transitioning to reproductive-senescence, or were reproductively-senescent based upon their estrous cyclicity, fertility, and fecundity. Rats were assessed for sexual behavior, object recognition and water maze performance, and behavior in the plus maze on separate testing days. Reproductively-competent rats had normal 4-5 day estrous cycles, were readily able to become pregnant, and had normal litter sizes. These rats performed significantly better than did reproductively-senescent rats (\downarrow cyclicity, fertility, fecundity) on sexual responding in the paced mating task (Figure 8), object recognition and water maze (Figure 9), and anti-anxiety behavior in the elevated plus maze (Figure 10). Rats that were transitioning to reproductive-senescence performed intermediate to other groups on these tasks. These data suggest that there are individual differences in sexual, cognition, and/or anti-anxiety behavior that coincide with changes in reproductive status in aging. However, these rats were all retired breeders and the nature of these effects in virgin rats needs to be assessed.

8. Conclusion

One factor that may have a profound influence on the trajectory of age-related processes are social supports. Loss of a social relationship can contribute to decline in mental, cognitive, and/or physical functioning. Given that hormones are mediating factors between the central and peripheral nervous system, and can influence social, affective, and cognitive processes, their role underlying neurobiological and/or behavioral mechanisms that influence aging, are of interest. The loss of close relationships, especially among older persons, is one of the greatest risk factors for mental and physical decline. However, the neurobiological and behavioral mechanisms underlying these effects are not well understood. The role of hormonal versus life experience factors, especially those related to social factors, have the potential to greatly alter social, affective, cognitive and physical functioning. How alterations in $3\alpha,5\alpha$ -THP may play a fundamental role to enhance reproduction and social bonds, and, thereby, influence SCEP is of interest throughout the lifespan. To summarize, our findings to date indicate the following. Mating increases levels of $3\alpha,5\alpha$ -THP in the midbrain, cortex, hippocampus and striatum. Mating increases expression in midbrain of genes involved in GABA, dopamine, and glutamate function, as well as steroid metabolism, neurogenesis, and apoptosis. Parity enhances levels of circulating $3\alpha,5\alpha$ -THP, cognitive, anti-anxiety, and sexual behavior. Reproductive

senescence is associated with decrements in paced mating, cognitive and anti-anxiety behavior. Questions to be addressed are whether: (1) There are specific types of sexual interactions that most readily evoke $3\alpha,5\alpha$ -THP biosynthesis in the midbrain and/or hippocampus. (2) There are causal effects of sexual experiences on SCEP (coincident with increases in $3\alpha,5\alpha$ -THP levels in the midbrain and/or hippocampus). (3) $3\alpha,5\alpha$ -THP biosynthesis or metabolism in the midbrain and/or hippocampus is necessary for sexual experience to alter SCEP. (4) Mating-induced $3\alpha,5\alpha$ -THP biosynthesis is due to neurogenesis/trophic factors in the midbrain and/or hippocampus.

9. Future Directions

The effects, sites of action, and neural mechanisms of mating-relevant interactions for social, cognitive, and affective behavior are of interest. Levels of P and its metabolites and effects on metabolism enzymes need to be examined in different regions of the brain. $3\alpha,5\alpha$ -THP can delay progression of neurodegenerative processes (Brinton & Wang, 2006; Langmade et al., 2006; Mellon et al., 2008) perhaps in part through activation of metabolism enzymes, including those involved in conversion of cholesterol to pregnenolone, the rate limiting step in neurosteroidogenesis. The neurotransmitter receptor targets are also of interest. $3\alpha,5\alpha$ -THP has agonist-like effects at GBRs and may have indirect antagonist-like effects via NMDARs (Frye et al., 2006; Leśkiewicz et al., 1998; Wang et al., 2007). Actions at these receptors, their downstream signal transduction pathways, and/or other substrates, such as membrane progesterin receptors, will be investigated in the future (Kirkness et al., 1989; Lin et al., 1996; Marshall, 1994; McDonald & Moss, 1994; Nilsen & Brinton, 2003; Singh, 2001; 2005; Singer et al., 1999). Whether manipulations of $3\alpha,5\alpha$ -THP or its targets directly in specific brain regions, such as the hippocampus, influence social, cognitive, and/or affective function will be elucidated.

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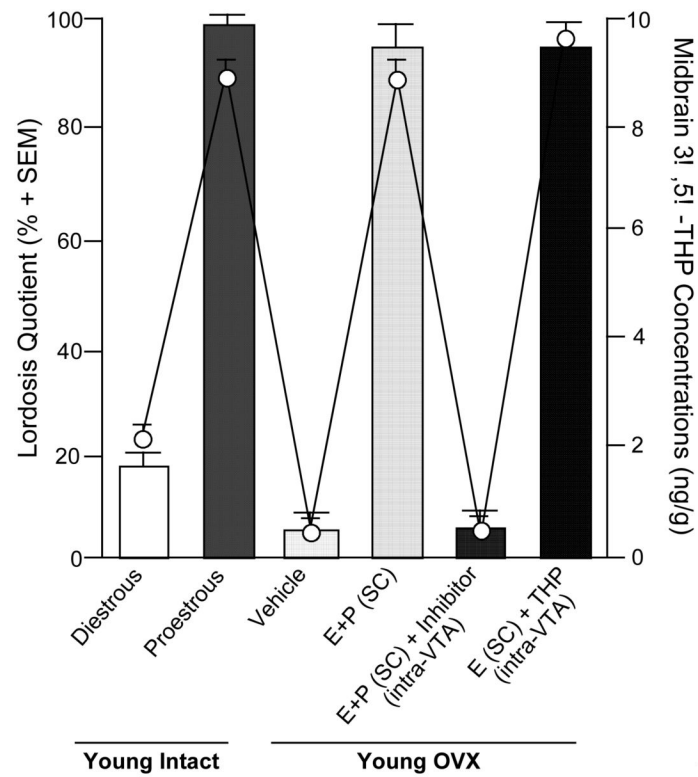


Figure 1. Sexual behavior correlates with $3\alpha,5\alpha$ -THP levels in the midbrain of young (diestrous or proestrous) or ovx (estradiol (E) and progesterone (P) with or without inhibition of $3\alpha,5\alpha$ -THP formation, or $3\alpha,5\alpha$ -THP rats. Bars represent lordosis quotients (mean \pm SEM) and dots represent $3\alpha,5\alpha$ -THP levels (ng/g \pm SEM) in midbrain.

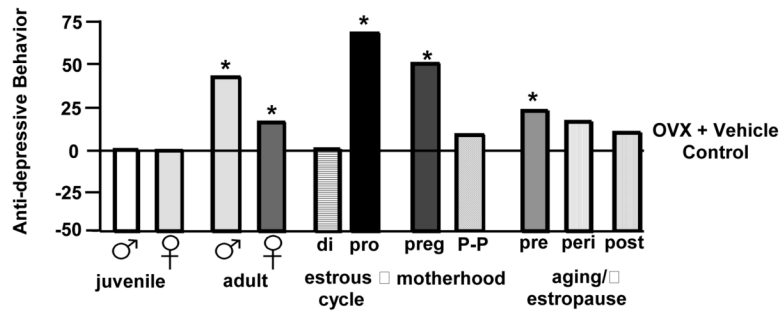


Figure 2.

Anti-depression behavior in the Porsolt forced swim task is greater among intact male and female adult rats compared to juvenile male and female rats. It is greater among proestrous or pregnant rats, compared to diestrous or post-partum rats. As well, it is greater among middle-aged reproductively competent rats compared to middle-aged rats that are reproductively senescent or transition to senescence. * indicates different from respective juvenile, diestrous, post-partum, or reproductively-senescent control, $p < 0.05$.

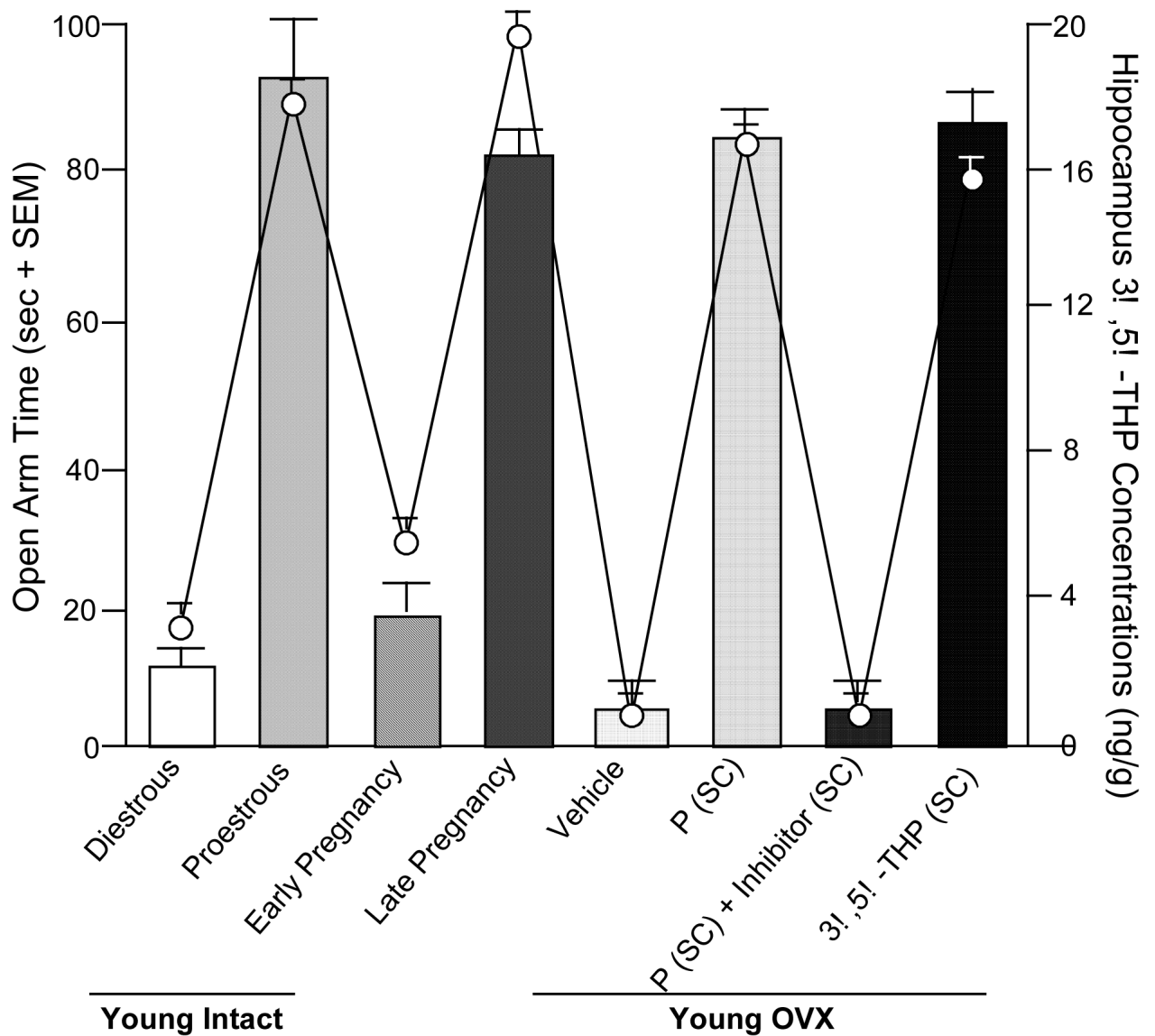


Figure 3.

Anti-anxiety behavior on the elevated plus maze correlates with $3\alpha,5\alpha$ -THP in hippocampus of young (diestrous or proestrous), mid-aged (reproductively-competent or reproductively-senescent), or OVX (progesterone (P) with/without $3\alpha,5\alpha$ -THP inhibition, or $3\alpha,5\alpha$ -THP administration) rats. Bars represent open arm time (seconds \pm SEM) and dots represent $3\alpha,5\alpha$ -THP levels (ng/g \pm SEM) in hippocampus.

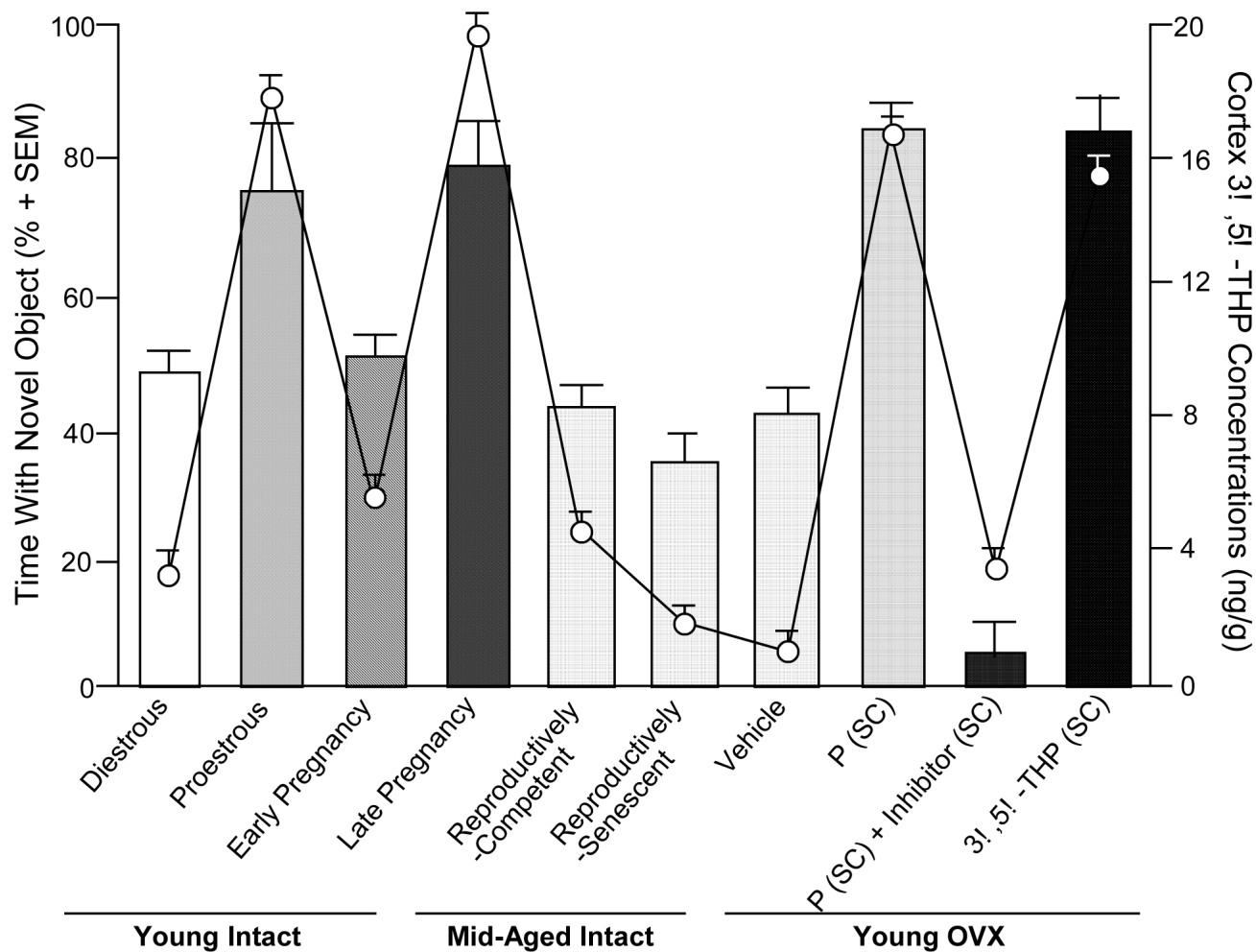


Figure 4.

Cognitive performance on the object recognition task correlates with $3\alpha,5\alpha$ -THP levels in the cortex of young (diestrous or proestrous), mid-aged (reproductively-competent or reproductively-senescent), or OVX (progesterone (P) with/without $3\alpha,5\alpha$ -THP inhibition, or $3\alpha,5\alpha$ -THP administration) rats. Bars represent time with the novel object (seconds \pm SEM) and dots represent $3\alpha,5\alpha$ -THP levels (ng/g \pm SEM) in cortex.

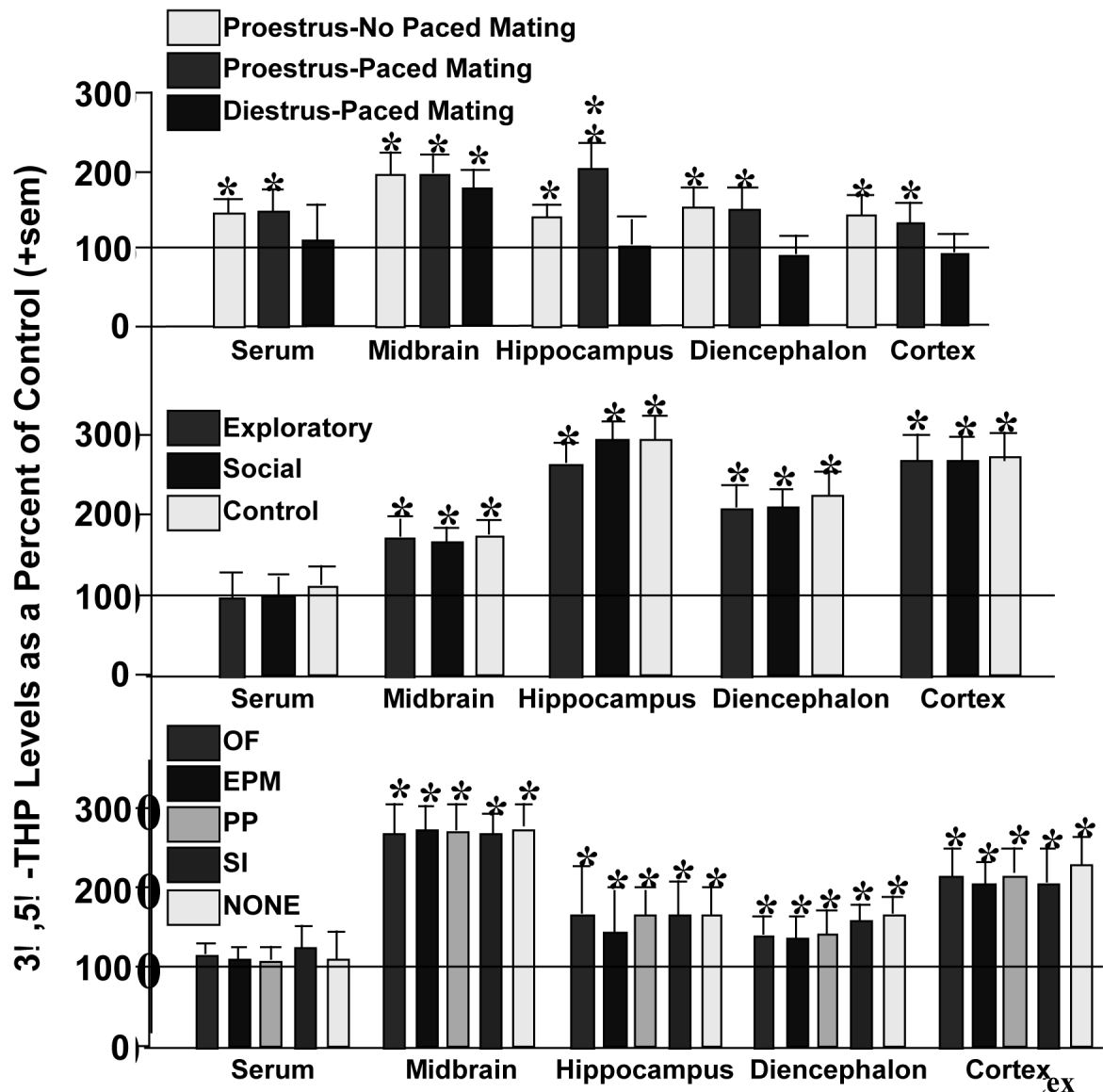


Figure 5. Depicts $3\alpha,5\alpha$ -THP levels in serum, midbrain, hippocampus, diencephalon, and cortex of proestrous or diestrous rats that engaged in paced mating or not (top), proestrous rats that engaged in exploratory (open field and elevated plus maze) or social (partner preference and social interaction) or no tasks with paced mating (middle), and proestrous rats that engage in only one task from above (open field, elevated plus maze, partner preference, social interaction, or no task) with paced mating (bottom). Line indicates performance of non-mated diestrous (top) or proestrous (middle, bottom) control. * indicates different from control, $p < 0.05$.

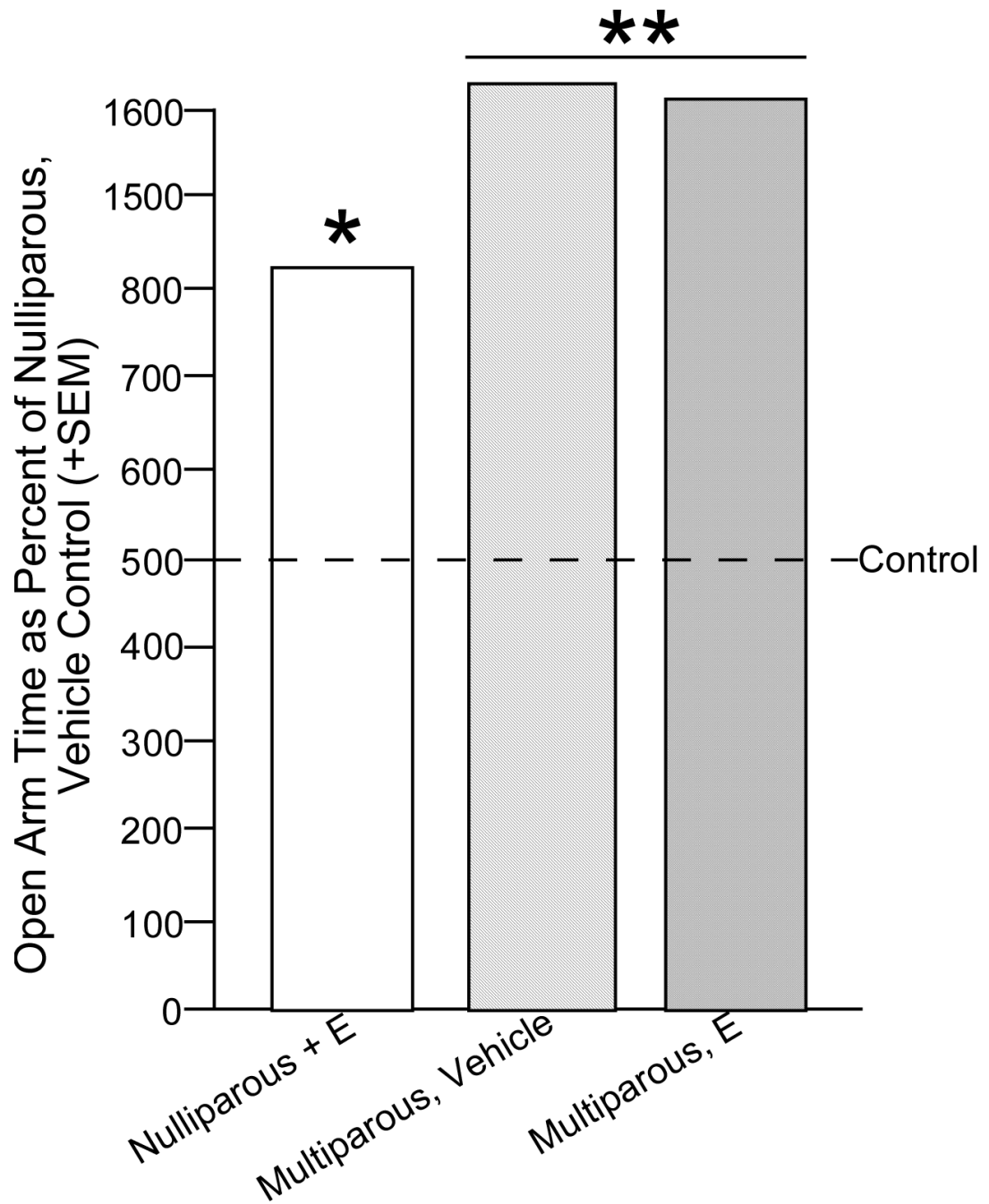


Figure 6. Ovariectomized, vehicle or estradiol (E)-primed multiparous rats have greater anti-anxiety behavior in the elevated plus maze than do nulliparous rats. Line indicates performance of nulliparous, vehicle-administered control. * indicates different from control, $p < 0.05$.

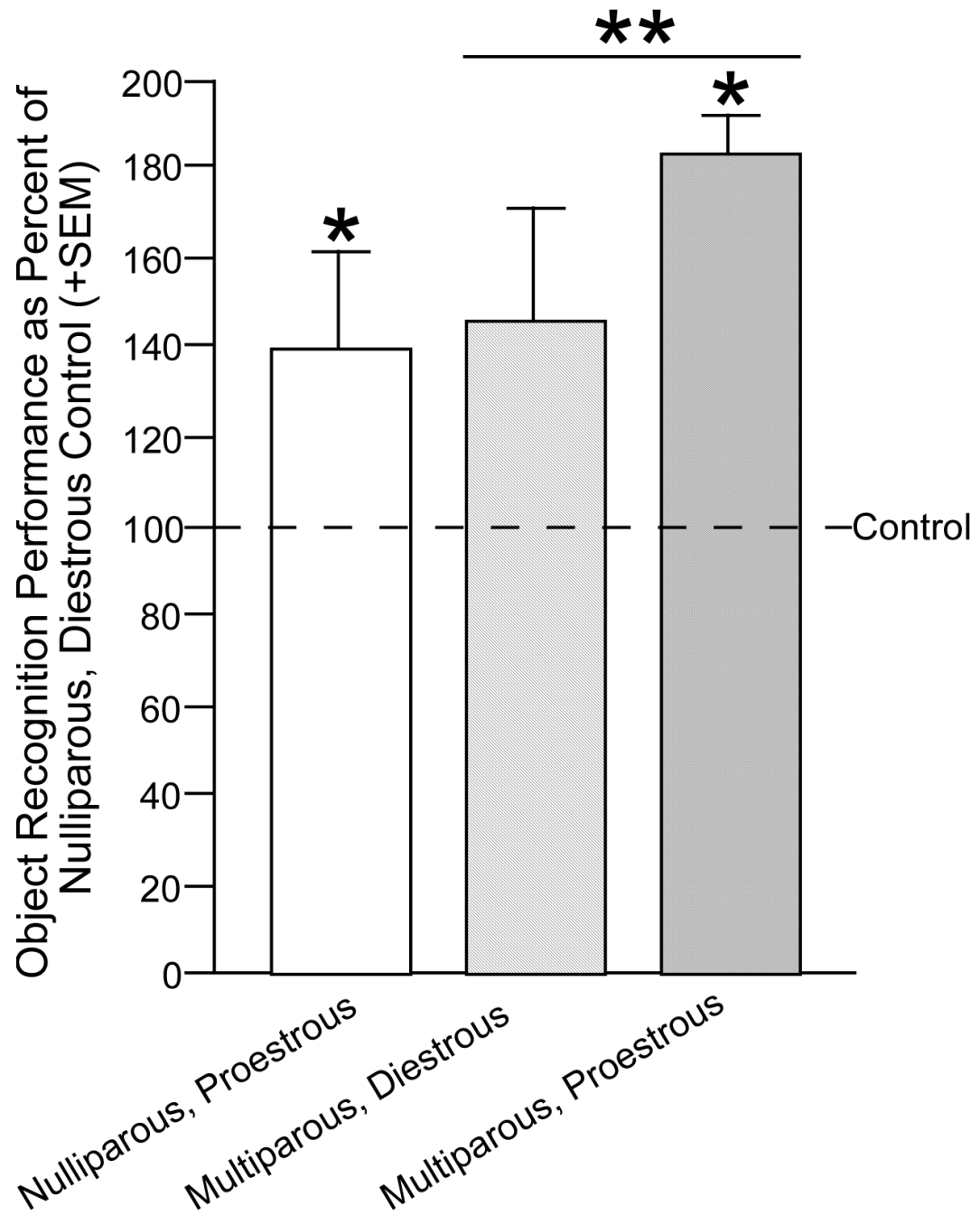


Figure 7.

Naturally-cycling, proestrous or multiparous rats outperform diestrous nulliparous rats in the object recognition task. Line indicates performance of diestrous, nulliparous control. * indicates different from control, $p < 0.05$.

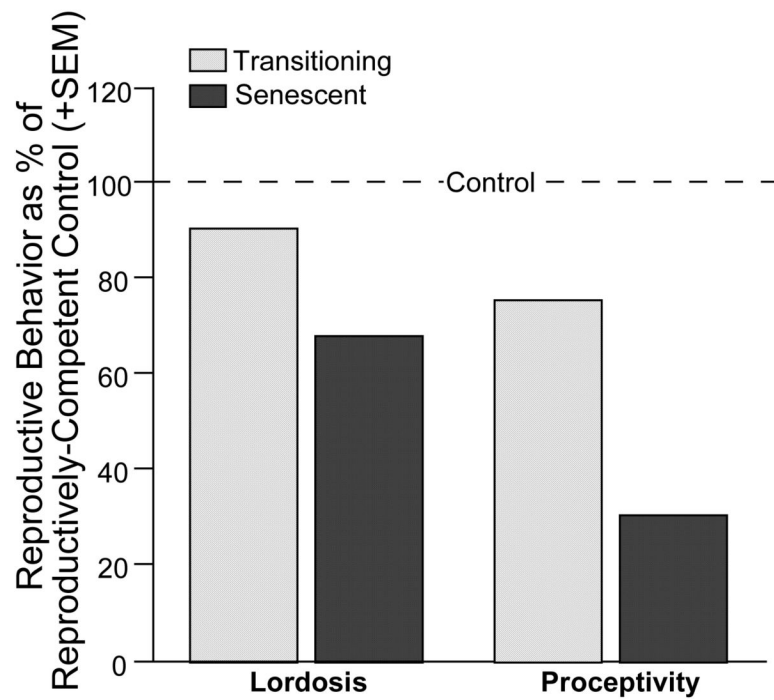


Figure 8. Among middle-aged rats, reproductively-competent rats had greater lordosis and proceptivity in a paced-mating task than did rats that were reproductively-senescent or transitioning to reproductive-senescence. Line indicates performance of reproductively-competent rats.

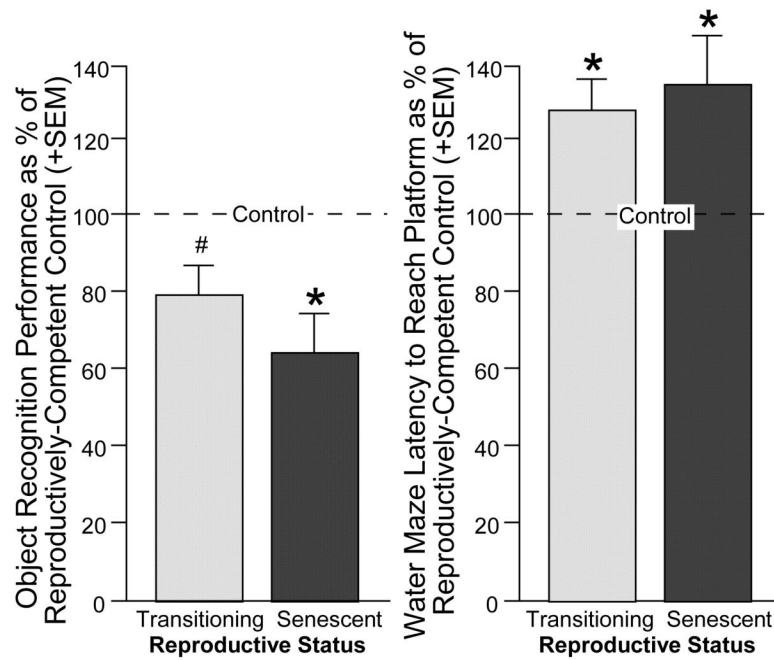


Figure 9.

Among middle-aged rats, reproductively-competent rats had greater cognitive performance in the object recognition task (left) and were faster to locate a hidden platform in the Morris water maze (right) compared to rats that were reproductively-senescent or transitioning to reproductive-senescence. Line indicates performance of reproductively-competent rats. * indicates different from control ($p < 0.05$). # indicates tendency to be different from control ($p < 0.10$).

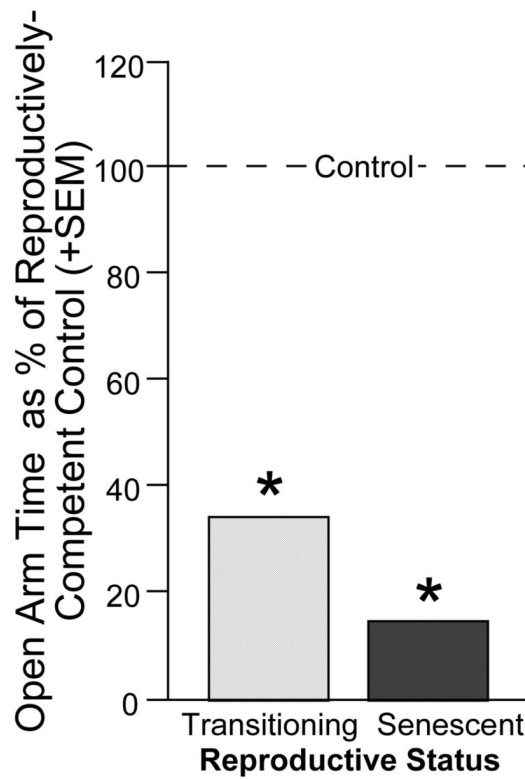


Figure 10.

Among middle-aged rats, reproductively-competent rats had greater anti-anxiety behavior in an elevated plus maze than did rats that were reproductively-senescent or transitioning to reproductive-senescence. Line indicates performance of reproductively-competent rats. * indicates different from control, $p < 0.05$.

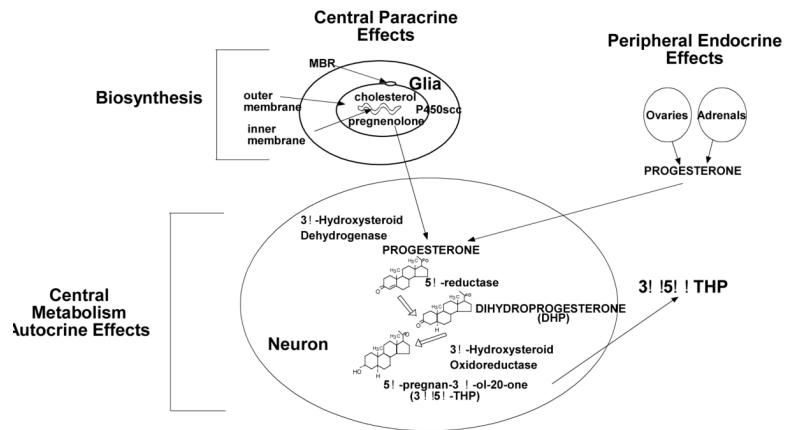


Diagram 1. Sources of 3α,5α-THP in the CNS include *de novo* biosynthesis in glial cells and metabolism of peripheral or central P.

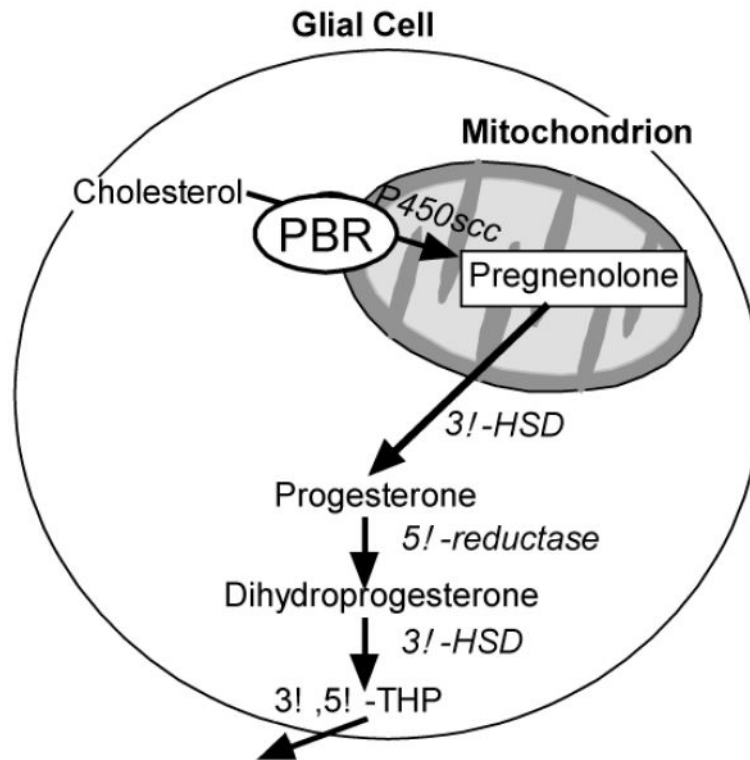


Diagram 2.

Depicts cholesterol transport into mitochondrion via PBR and enzymatic processes involved in neurosteroidogenesis.

Table 1

Provides a break down of the timing, ligands, sources, and targets of steroid actions

Parameter	Classic Steroid Action	Neurosteroid Action
Timing	Minutes, days, weeks	Seconds to minutes
Ligands	Progesterone (P), DHP	3 α ,5 α -THP
Sources	Ovaries, Adrenals	Brain
Targets	Intracellular PRs	NT receptors, HPA

Table 2

Provides the steroid sources and receptor targets of non-classical actions of neurosteroids

Receptor	Neurosteroid (Modulatory effect: + positive, - negative)
GABA _A	3 α ,5 α -THP (+), THDOC (+), 3 α -diol (+), pregnenolone sulfate (-), DHEA-S (-)
Glycine	P (-), 3 α ,5 α -THP (-), pregnanolone (-), Pregnenolone sulfate (-) DHEA-S (-)
Sigma type 1	DHEA (+), DHEA-S (+), pregnenolone sulfate (+), P (-)
NMDA	DHEA (+), pregnenolone sulfate (+), E ₂ (-)
AMPA	Pregnenolone sulfate (-)
Kainate	P (+), Pregnenolone sulfate (-)
Serotonin type 3	3 α ,5 α -THP (-), P (-), E ₂ (-), testosterone (-)
Neuronal nicotinic acetylcholine	3 α ,5 α -THP (-), P (-), pregnenolone sulfate (-)

Table 3

Plasma progestin measures in men and women in follicular or luteal phases of the menstrual cycle, or who are pregnant

Progestins (nmol/l)	Men	Women		
		Follicular	Luteal	Pregnant
Pregnenolone	2	2	4	60
Progesterone	1-2	1-2	25	650
3 α ,5 α -THP	0.3	0.3	2	14