

## Chapter 17

# The Role of 3 $\alpha$ -Hydroxy-5 $\alpha$ -Pregnan-20-One in Mediating the Development and/or Expression of Schizophrenia Spectrum Disorders: Findings in Rodents Models and Clinical Populations

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**Abstract** Neurosteroids, including 3 $\alpha$ -hydroxy-5 $\alpha$ -pregnan-20-one (3 $\alpha$ ,5 $\alpha$ -THP), mediate stress-responding, and the function and development of the central nervous system. 3 $\alpha$ ,5 $\alpha$ -THP can be produced in the brain or metabolized from peripheral sources, including the adrenals, gonads, and placenta. 3 $\alpha$ ,5 $\alpha$ -THP has actions to dampen stress-responding and reinstate parasympathetic tone. There are sex differences in stress-responding, such that women are more stress-responsive than men. Further, there are sex differences in 3 $\alpha$ ,5 $\alpha$ -THP, such that women have greater variations across the menstrual cycle and across the lifespan compared to men. Similar differences and variations in 3 $\alpha$ ,5 $\alpha$ -THP are observed among rodent species, and elevated levels of 3 $\alpha$ ,5 $\alpha$ -THP are associated with dampened stress-responding. These sex differences in stress-responding and neurosteroids may be related to sex differences in the incidence and/or expression of schizo-affective disorders. This chapter reviews findings in support of the hypothesis that 3 $\alpha$ ,5 $\alpha$ -THP has a role in schizophrenia and/or affective disorders.

**Keywords** Neurosteroids · 3 $\alpha$ ,5 $\alpha$ -THP · Allopregnanolone · Schizophrenia · Affective disorders · Cognition · Stress

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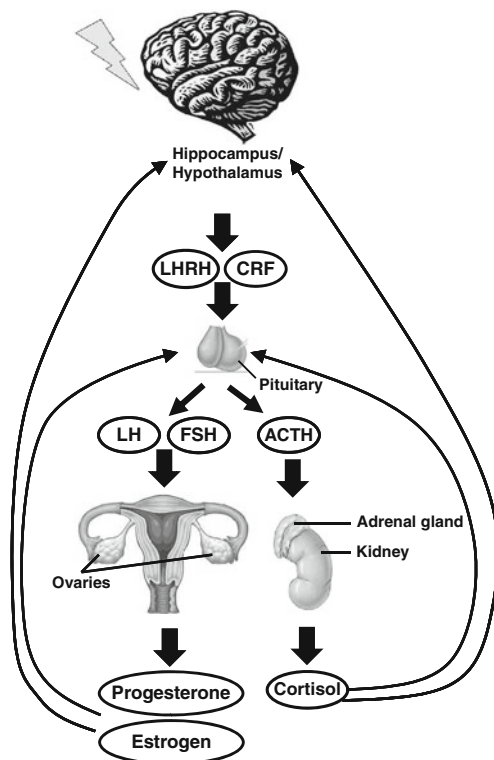
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## Abbreviations

MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
3 $\alpha$ ,5 $\alpha$ -THP	3 $\alpha$ -hydroxy-5 $\alpha$ -pregnan-20-one
3 $\alpha$ -HSOR	3 $\alpha$ -hydroxysteroid oxidoreductase
3 $\beta$ -HSD	3 $\beta$ -hydroxysteroid dehydrogenase
5 $\alpha$ -R	5 $\alpha$ -reductase
5 $\alpha$ -RKO	5 $\alpha$ -R knockout mice
ADX	Adrenalectomized
ACTH	Adrenocorticotropin
apoER2	Apolipoprotein E2 receptor
ADHD	Attention deficit hyperactivity disorder
CNS	Central nervous system
B	Corticosterone
CRH	Cortico-tropin-releasing hormone
P450 <sub>scc</sub>	Cytochrome P450-dependent C27 side chain cleavage enzymes
DHP	Dihydroprogesterone
DA	Dopamine
D <sub>1</sub>	DA-like type 1 receptors
DAT	DA transporters
DATKO	DA transporter knockout mice
ER	Endoplasmic reticulum
E	Estrogen
FST	Forced swim task
GBRs	GABA <sub>A</sub> /benzodiazepine receptor complexes
GD	Gestational day
GAD	Glutamic acid decarboxylase
HPA	Hypothalamic pituitary adrenal
IL-1 $\beta$	Interleukin-1 $\beta$
METH	Methamphetamine
NMDARs	N-methyl-D-aspartate receptors
OVX	Ovariectomized
PFC	Prefrontal cortex
PMDD	Premenstrual dysphoric disorder
PNS	Prenatal stress
PPI	Prepulse inhibition
P	Progesterone
PR	Progesterin receptor
PND	Post-natal days
RED	Reproductive Endocrine Dysfunction
StAR	Steroidogenic acute regulatory protein
TSPOs	Translocator proteins
USV	Ultrasonic vocalization
VTA	Ventral tegmental area
VLDLR	Very low-density lipoprotein receptor

## Introduction

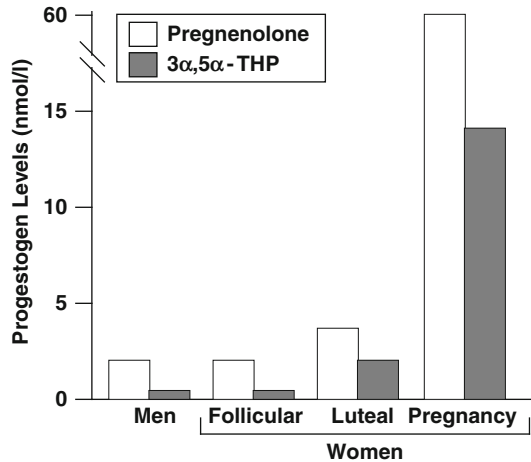
Neurosteroids, steroid hormones produced in the brain, such as 3 $\alpha$ -hydroxy-5 $\alpha$ -pregnan-20-one (3 $\alpha$ ,5 $\alpha$ -THP), are important endogenous modulators of the hypothalamic pituitary adrenal (HPA) axis, and the function and/or development of the central nervous system (CNS). 3 $\alpha$ ,5 $\alpha$ -THP can be produced in the brain in response to stress to dampen HPA-responding and reinstate parasympathetic tone (Diagram 17.1) [1, 2]. 3 $\alpha$ ,5 $\alpha$ -THP can also be metabolized from progesterone (P) secreted by the adrenals, ovaries and/or placenta [3], where actions in the brain can also mitigate stress-responding. Thus, production of 3 $\alpha$ ,5 $\alpha$ -THP mediates stress-responding.



**Diagram 17.1** The influence of endogenous hormones on the hypothalamic-pituitary-adrenal and the hypothalamic-pituitary-gonadal axes are depicted in this diagram

There are sex differences in stress-responding, such that women respond with greater HPA-reactivity and have higher cortisol (stress hormone) levels when presented with stressful stimuli, compared to men [4–6]. There are also sex differences in basal levels of 3 $\alpha$ ,5 $\alpha$ -THP, such that women in the luteal phase and pregnancy have higher levels of 3 $\alpha$ ,5 $\alpha$ -THP in plasma and hippocampus

**Fig. 17.1** There are sex differences in basal levels of  $3\alpha,5\alpha$ -THP, such that women in the luteal phase and pregnancy have higher levels of  $3\alpha,5\alpha$ -THP in plasma compared to men and women in the follicular phase



compared to men and women in the follicular phase (Fig. 17.1) [7, 8]. Sex differences in  $3\alpha,5\alpha$ -THP coincide with sex differences in stress-responding, particularly during perimenstrual or post-partum  $3\alpha,5\alpha$ -THP withdrawal [9, 10]. Thus, sex differences in stress-responding may be mediated by sex differences in  $3\alpha,5\alpha$ -THP.

Similar patterns of stress-responding and differences in  $3\alpha,5\alpha$ -THP are observed among female and male rodents. Basal and stress-induced corticosterone (B) levels are higher among females during  $3\alpha,5\alpha$ -THP decline compared to males [11–13]. Further, stress-induced elevations in  $3\alpha,5\alpha$ -THP are greater and occur more rapidly among female rats, particularly when gonadal sources of  $3\alpha,5\alpha$ -THP are low [14, 15]. Administration of  $3\alpha,5\alpha$ -THP to females and males attenuates the elevation of plasma adrenocorticotropin (ACTH) or serum B secretion produced by emotional and/or physical stress [2, 16]. Thus, enhanced levels of  $3\alpha,5\alpha$ -THP dampens stress-responding in female and male rodents.

Sex differences in stress-responding and  $3\alpha,5\alpha$ -THP may be related to sex differences in the incidence and/or expression of schizo-affective disorders among women and men. Women suffer from mood disorders and are uniquely at risk for affective disorders that are linked to hormonal status compared to men. Affective disorders that are typically diagnosed in women and are associated with precipitous decreases in  $3\alpha,5\alpha$ -THP levels include premenstrual syndrome, post-partum depression, and associated psychoses [17–19]. This chapter reviews findings in support of the hypothesis that  $3\alpha,5\alpha$ -THP has a role in schizophrenia and/or affective disorders. Basic research from our laboratory using various animal models of schizo-affective disorders (prenatal stress, social isolation, perinatal hippocampal lesion, dopamine transporter knockout mice, psychostimulants) will also be discussed to support the potential role of  $3\alpha,5\alpha$ -THP in the development, etiology, and/or treatment of schizo-affective disorders.

## Biosynthesis and Metabolism of 3 $\alpha$ ,5 $\alpha$ -THP

The source of 3 $\alpha$ ,5 $\alpha$ -THP can be central and/or peripheral. Central production is from biosynthesis, while peripheral production is from metabolism of hormones released from the adrenals, gonads and/or placenta. The enzymes necessary for neurosteroid biosynthesis and metabolism are expressed by the CNS, and are highest in the midbrain, limbic regions, cerebellum, tectum, pons, medulla, spinal cord, and pituitary. Further, this pattern of localization of these enzymes is conserved across species [20]. Biosynthesis of 3 $\alpha$ ,5 $\alpha$ -THP starts with the expression of translocator proteins (TSPOs), which are high affinity cholesterol binding proteins that import cholesterol into the mitochondria and are highly expressed in steroidogenic tissues. The steroidogenic acute regulatory protein (StAR) and cytochrome P450-dependent C27 side chain cleavage enzymes (P450<sub>scc</sub>) are proteins that initiate steroidogenesis by oxidizing cholesterol to pregnenolone [21–23]. Following formation of pregnenolone, it is converted to P by 3 $\beta$ -hydroxysteroid dehydrogenase (3 $\beta$ -HSD). P, that is from biosynthesis previously described, or has been released from a peripheral source, is metabolized to dihydroprogesterone (DHP) by 5 $\alpha$ -reductase (5 $\alpha$ -R) and to 3 $\alpha$ ,5 $\alpha$ -THP by 3 $\alpha$ -hydroxysteroid oxidoreductase (3 $\alpha$ -HSOR). Thus, biosynthesis and/or metabolism leads to the formation and potential actions of 3 $\alpha$ ,5 $\alpha$ -THP.

### *Genes Implicated in 3 $\alpha$ ,5 $\alpha$ -THP Dysregulation*

A null mutation in a candidate gene that regulates biosynthesis of 3 $\alpha$ ,5 $\alpha$ -THP and has been implicated in schizo-affective disorders disrupts the function of TSPO. This is found to be higher among schizophrenics, than in a control population [24]. As well, there is evidence for deficits in metabolic signaling in those diagnosed with schizo-affective disorders, mental retardation, Parkinson's Disease, Alzheimer's Disease, depression, brain development and ischemic stroke [25]. Thus, genes which regulate 3 $\alpha$ ,5 $\alpha$ -THP biosynthesis may be important markers in the development, etiology, pathophysiology and vulnerability to dysregulation in stress-responding among schizo-affective patients.

### **Mechanisms of Action of 3 $\alpha$ ,5 $\alpha$ -THP**

3 $\alpha$ ,5 $\alpha$ -THP has actions at several non-traditional steroid targets, including glutamate, norepinephrine, dopamine, serotonin, acetylcholine, and oxytocin receptors [26]. We will focus on actions of 3 $\alpha$ ,5 $\alpha$ -THP through GABA<sub>A</sub>, dopamine (DA), and N-methyl-D-aspartate receptors (NMDARs).

Actions of 3 $\alpha$ ,5 $\alpha$ -THP at GABA<sub>A</sub>/benzodiazepine receptor complexes (GBRs) have been investigated the most. At low concentrations, 3 $\alpha$ ,5 $\alpha$ -THP alters the duration of GABA current by enhancing GABA influx [27–32]. This can occur through 3 $\alpha$ ,5 $\alpha$ -THP enhancing GBR binding site number and/or affinity, and/or

increasing GABA synthesis, in neurons through glutamic acid decarboxylase [33]. However, at high concentrations,  $3\alpha,5\alpha$ -THP exerts an intrinsic agonistic activity at GBRs in the absence of GABA [31]. In fact,  $3\alpha,5\alpha$ -THP is the most potent naturally occurring ligand for GBRs such that its effects are  $\sim 600$  times more potent than the most effective barbiturate, and  $\sim 60$  times more potent than P itself [30]. Thus,  $3\alpha,5\alpha$ -THP has actions involving GABA<sub>A</sub>.

Actions of  $3\alpha,5\alpha$ -THP at DA-like type 1 receptors (D<sub>1</sub>) may be downstream of GBRs [34–36]. GABA neuron migration to the cerebral cortex is promoted by actions at D<sub>1</sub> during development. GABA neuron migration from the basal forebrain to the cerebral cortex can be altered by impairment of D<sub>1</sub> [37]. Thus,  $3\alpha,5\alpha$ -THP can have actions at D<sub>1</sub> and/or GBRs to influence brain development.

Actions of  $3\alpha,5\alpha$ -THP at NMDARs can enhance glutamate and cognitive performance in cortical tasks [33, 38, 39]. Enhancement in learning and memory is associated with actions at glutamatergic substrates, particularly in limbic regions [40, 41]. However, aberrant neural development can occur if there is glutamate overactivity and subsequent excitotoxicity [42]. Thus, GABAergic, DA-like, or glutamatergic targets that can be altered by  $3\alpha,5\alpha$ -THP may influence the development and/or expression of aberrant behaviors, such as those observed in schizo-affective disorders.

## **Animal Models of Schizo-Affective Disorders and Alterations in $3\alpha,5\alpha$ -THP**

Animal models are important in the investigation of the mechanisms underlying human disease and in designing new therapies. For example, these models may be used to test the plausibility of theories about the origin of schizophrenia; explore the mechanisms of schizophrenia-like phenomena; test the effects of confounding factors, such as medication and postmortem interval, or time since death; investigate therapeutic and adverse effects of the drugs used for the treatment of schizophrenia and develop potential new treatments [43]. It is important to reveal  $3\alpha,5\alpha$ -THP's effects and mechanisms due to its potential role in the etiology and/or treatment of schizo-affective disorders and HPA responses. Few investigations to date have examined  $3\alpha,5\alpha$ -THP's functional role; yet, those involving  $3\alpha,5\alpha$ -THP and schizo-affective disorders, have primarily utilized men, despite more women being affected. Thus, understanding the role, source, and mechanisms of  $3\alpha,5\alpha$ -THP in females is required to fill gaps in the current knowledge.

## **Stress-Responding and $3\alpha,5\alpha$ -THP**

$3\alpha,5\alpha$ -THP modulates the HPA axis and may serve to buffer stress-responding. P and  $3\alpha,5\alpha$ -THP reduce levels of cortico-tropin-releasing hormone (CRH) in response to an acute stressor [44]. Acute increases in  $3\alpha,5\alpha$ -THP, due to stress, enhances GABA<sub>A</sub> receptor function, and attenuates activation of HPA-responding,

which may help individuals return to a state of homeostasis following challenge [2, 16, 45–47]. Blocking  $3\alpha,5\alpha$ -THP's actions at  $GABA_A$  receptors prevents stress-induced glucocorticoid secretion and anti-anxiety behavior.

$3\alpha,5\alpha$ -THP is present early in prenatal development at embryonic day 17 [48, 49]. As early as post-natal day 6, brain  $3\alpha,5\alpha$ -THP concentrations increase in response to stressors, such as isolation from the nest, dam, and siblings [50, 51]. Neonatal stress also has more pervasive effects on females than males, such as greater weight loss in neonatally-stressed females compared to males in response to chronic restraint in adulthood [52]. Cold water-swim, and other stressors, increase brain  $3\alpha,5\alpha$ -THP levels of female, more so than male, gonadectomized (GDX) and adrenalectomized (ADX) rats [3, 53, 54]. Increases in  $3\alpha,5\alpha$ -THP produced by such acute stress experiences are conserved across species, and produce anxiolysis among avian, amphibian, and mammalian species in response to “fight-or-flight” stimuli [33, 55]. Thus, actions of  $3\alpha,5\alpha$ -THP mediates stress-responding early in development.

### ***Schizo-Affective Disorders and Stress-Responding***

Diagnosis of schizophrenia is based upon both positive (hallucinations, delusions) and negative symptoms (avolition, alogia) [56]. There has been a recent emphasis on negative symptoms, which correlate with loss of social function [57] and plasma levels of stress hormones [58–60]. Notably, there is dysregulation of the HPA axis among people with schizophrenia or affective disorders [61–66]. Plasma levels of cortisol and/or ACTH of schizophrenics are higher than controls and correlate with their negative symptoms [59, 67–71]. How dysfunction of the HPA axis contributes to the pathophysiology of schizophrenia needs to be better-understood [72, 73]. Thus, the pathophysiology of stress-responding and other affective and cognitive disruptions associated with schizo-affective disorders may be related to actions of  $3\alpha,5\alpha$ -THP.

### ***Prenatal Stress and $3\alpha,5\alpha$ -THP***

Stress during critical periods in development may influence stress responding in adulthood and vulnerability to psychiatric disorders. Women whose children were exposed to inordinate stress during pregnancy have an increased incidence of schizo-affective disorders [74–76]. Gestational stress activates the maternal HPA axis and can cause increases in placental CRH [77] and fetal hypoxia [78]. CRH secretion, as a result of prenatal and early life stress, may contribute to the development of stress-related mood and anxiety disorders in adulthood. An animal model of prenatal stress (PNS) has been used by our lab and others as a model of schizo-affective disorders. Methods of producing such a model using PNS vary, but common characteristics result from most models, including neuroendocrine, neuroanatomical, and behavioral sequelae similar to those observed in schizo-affective disorders. In

support, people or rodents respond to stressful stimuli in adulthood with higher and/or more prolonged elevation of ACTH and/or corticosteroids if exposed to PNS during development [79–83]. As well, rats exposed to PNS had adrenal hypertrophy, which may have resulted from chronic over-stimulation of the adrenal gland by ACTH [84]. Further, PNS exposure is associated with abnormal development of the hippocampus and the prefrontal cortex (PFC) in people and rodents [85–90]. Behavioral inhibitions, demonstrated by timidity and shyness in people [91], and reduced exploration in social and novel situations in animal models [92–96], are produced by PNS. Thus, PNS may be a useful model to examine the link between developmental exposure to stress and the expression of characteristics relevant for schizo-affective disorders.

Our laboratory has used several different models of PNS in rodents. The most simplistic model involved restraining dams under bright lights for 20 min on gestational day (GD) 18, when the hippocampus, PFC, and midbrain are developing [97]. Offspring of these dams had lower levels of  $3\alpha,5\alpha$ -THP in hippocampus, but not plasma, when examined during adulthood [34]. Plasma B levels were significantly higher among PNS rats exposed to an acute stressor during adulthood, compared to basal levels of B and non-PNS controls [34]. The hippocampus of PNS rats had significantly fewer granule cells compared to non-PNS controls [98]. Behavioral inhibition was observed wherein PNS rats demonstrated more anxiety-like behavior and less sociability compared to controls. Thus, this model of PNS is related to changes in  $3\alpha,5\alpha$ -THP and stress hormone levels, hippocampal integrity, and behavioral inhibition.

PNS alters behaviors related to inhibition, including affect, depression and stress-responding, suggesting that PNS may alter responses to gonadal hormones. For example, estrogen (E) is a gonadal hormone that mediates expression of depressive behavior in the forced swim task (FST) and enhances P metabolism to  $3\alpha,5\alpha$ -THP [99, 100]. Data indicate that non-PNS and PNS rats administered E show less depressive behavior compared to non-PNS and PNS rats administered vehicle, respectively [101]. Response to an acute stressor is also altered in PNS rats and may be related to aberrant responding to gonadal hormones, such as E. Ovariectomized (OVX), E-administered, PNS rats exposed to 20 min of restraint stress immediately prior to exposure to a novel environment demonstrate more anxiety-like behavior compared to OVX, E-administered, non-PNS and OVX, vehicle-administered, PNS rats also given 20 min of restraint stress [102]. Together these data suggest that PNS can induce behavioral changes and that an acute stressor can amplify these effects on behavior and responsiveness to gonadal hormones. Thus, the effects of PNS on behavioral and neuroendocrine outcomes are of interest, particularly when examined across development and adulthood.

### ***Effects of Prenatal Stress on Offspring Before Puberty***

The effects of PNS on offspring before puberty is of interest, as this represents critical time points in development, and may provide insight of how alterations of



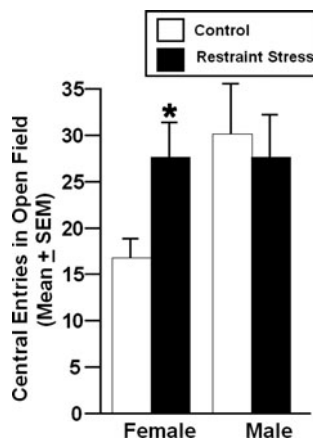
behavioral and neuroendocrine responses manifest in adulthood as a result of early developmental stress and challenge. As well, these changes that occur across development and into adulthood may predict vulnerability to etiology, expression and/or prognosis of schizo-affective disorders.

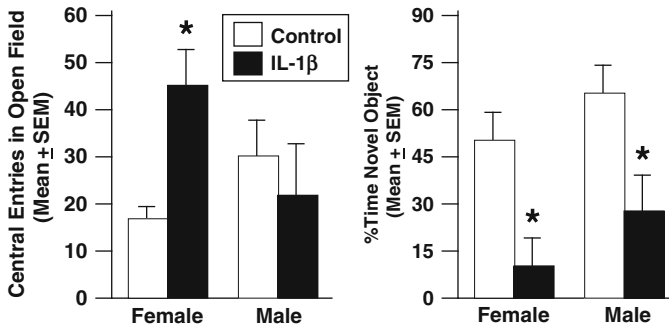
One model involved dams that were chronically-exposed to restraint stress for 45 min under a bright light, three times a day, on GDs 17–21, or not. PNS and control offspring were cross-fostered to non-manipulated dams in our colony and weaned at post-natal days (PND) 20–21. Offspring were tested for cognitive performance as juveniles at PND 28–30. Results indicate that PNS offspring showed reduced 5 $\alpha$ -R of P and show decreased cognitive performance [103]. Further, although sex differences in cognitive performance were not observed, there were sex differences in anxiety-like responding such that PNS females demonstrated less anxiety-like behavior compared to controls, and no differences were observed among males (Fig. 17.2). Thus, sex differences in affective behavior are altered following chronic restraint stress during gestation.

Another model our lab used was immune challenge during gestational development by exposing dams to the cytokine interleukin-1 $\beta$  (IL-1 $\beta$ , 1  $\mu$ g, IP) on GDs 17–20, and offspring were assessed for cognitive performance and affective behavior. Juvenile rats exposed to IL-1 $\beta$  demonstrate decreased cognitive performance compared to controls (Fig. 17.3). Further, anxiety-like behaviors of rats exposed to IL-1 $\beta$  are similar to rats exposed to PNS in that females demonstrate less anxiety-like behavior following gestational exposure to IL-1 $\beta$  (Fig. 17.3). These data imply the important role that physiological immune response of the dam may play on fetal development. However, the stress response to psychological aspects of these may encompass only one aspect of these effects.

The stress response of the dam may also account for much of these effects on offspring. When stressors are unpredictable, they can have even more salient effects on HPA function. We investigated the effects chronic unpredictable stressors (combinations of forced swim for 15 min, restraint for 60 min, cold exposure for 6 h, overnight fasting, lights on during the dark phase of the circadian light-cycle, social

**Fig. 17.2** PNS females demonstrate less anxiety-like behavior in the open field compared to controls, and no differences were observed among males

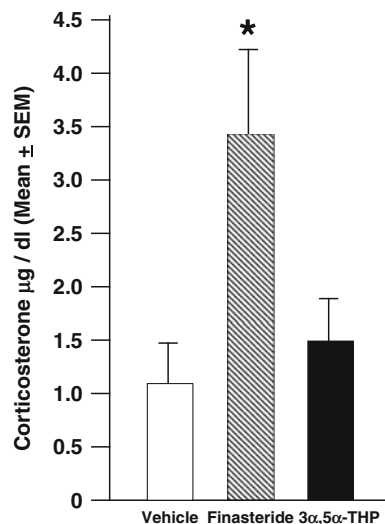




**Fig. 17.3** Juvenile offspring of dams exposed to IL-1β during gestation demonstrate decreased cognitive performance in the object recognition task compared to controls. Offspring are similar to those exposed to PNS in that females exposed to IL-1β demonstrate less anxiety-like behavior in the open field

crowding) thrice daily to dams from GDs 17–21. Results indicate that variable stress-exposure reduces cognitive performance among juvenile rats compared to rats that were minimally handled [104]. Notably, females appeared more affected; however, significant sex differences were not observed as neither males, nor females, that were stressed demonstrated significantly different affective behavior. Thus, sex differences in behaviors are not observed among animals that experience variable stress, such that females may become more male-like in their behavioral phenotype.

To begin to assess mechanisms that may underlie offspring performance, HPA response to handling was examined in 28–30-day-old juvenile rats that were prenatally exposed to maternal injections of vehicle oil, finasteride (50 mg/kg, SC), or 3α,5α-THP (8 mg/kg, SC) on GDs 16–20. Plasma B levels in response to handling was significantly elevated in the finasteride-exposed group compared to vehicle- or



**Fig. 17.4** Plasma B levels in response to handling was significantly elevated in the finasteride-exposed group compared to vehicle- or 3α,5α-THP-administered offspring

3 $\alpha$ ,5 $\alpha$ -THP-administered offspring (Fig. 17.4). These data support the notion that developmental changes in HPA-responding of offspring can result when maternal 3 $\alpha$ ,5 $\alpha$ -THP is perturbed during late pregnancy. These data provide proof-of-concept that exposure to psychological, physical, or immune stressors during late pregnancy can reduce cognitive performance among offspring. Further, disruption of maternal 3 $\alpha$ ,5 $\alpha$ -THP alone can have commensurate negative impact of gestation and offspring cognitive development. These observations may be related to HPA dysfunction that results in prenatally-stressed offspring as data show that perturbing maternal 3 $\alpha$ ,5 $\alpha$ -THP in late gestation can alter later neuroendocrine response to a mild stressor.

### **Sex Differences in 3 $\alpha$ ,5 $\alpha$ -THP and Incidence and Symptom Manifestation of Schizophrenia**

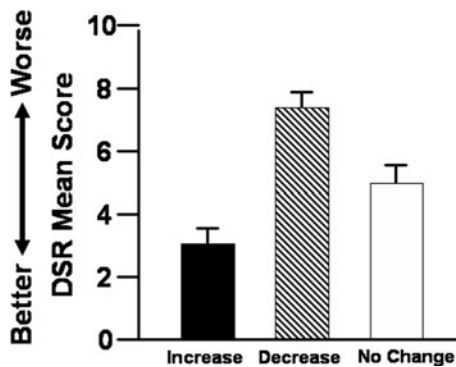
The incidence and/or expression of schizophrenia may be mediated by sex differences in biosynthesis and/or metabolism of 3 $\alpha$ ,5 $\alpha$ -THP. Women, compared to men, typically have higher levels of 3 $\alpha$ ,5 $\alpha$ -THP, are more likely to have schizophrenia with later onset, better prognosis, and therapeutic response to lower dosages of antipsychotics [105, 106]. More women than men suffer from mood disorders [107]. Women are uniquely at risk for affective disorders that are linked to hormonal status. First onset, or recurrence of psychotic episodes, are more likely and more negative symptoms are reported when 3 $\alpha$ ,5 $\alpha$ -THP levels among women are low perimenstrually or post-menopausally [108–111]. Sex differences that favor women suggest that 3 $\alpha$ ,5 $\alpha$ -THP may have a protective role in schizophrenia. Women with schizophrenia experience later age of onset, less debilitating psychiatric symptoms, fewer psychiatric hospitalizations, better pre- and post-functioning, and a more rapid and greater response to drug treatments than do men [112, 113]. Women who were diagnosed with schizo-affective disorder and were currently on a second-generation anti-psychotic medication received adjunctive pregnenolone treatment. These women had higher 3 $\alpha$ ,5 $\alpha$ -THP levels and demonstrated improved performance in cognitive tasks than those who were on adjunctive placebo [114]. It should be noted that there is little evidence to suggest that women with psychopathologies, such as schizo-affective disorders, have different absolute levels of 3 $\alpha$ ,5 $\alpha$ -THP, rather they may be more sensitive to changes in 3 $\alpha$ ,5 $\alpha$ -THP [105] or more vulnerable to stress when levels change. Thus, 3 $\alpha$ ,5 $\alpha$ -THP may play an important role in schizo-affective disorders.

### **Interactions of Therapeutics and Neurosteroids in Schizophrenia**

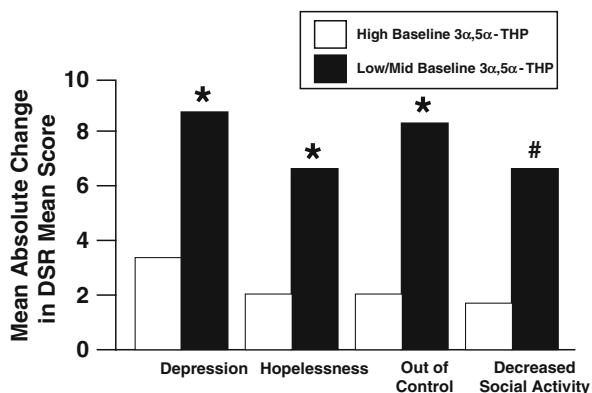
Affective disorders associated with the onset of psychiatric disturbances with menstruation or parturition, when there are precipitous decreases in 3 $\alpha$ ,5 $\alpha$ -THP, include premenstrual syndrome, postpartum depression, and associated psychoses [17, 107, 115]. 3 $\alpha$ ,5 $\alpha$ -THP may underlie the pathophysiology and/or treatment of

schizo-affective disorders, as some anti-depressant and anti-psychotic treatments can increase  $3\alpha,5\alpha$ -THP levels. Women who were diagnosed with severe premenstrual syndrome, also known as premenstrual dysphoric disorder (PMDD), were examined during the luteal phase for changes in severity of symptoms and changes in levels of  $3\alpha,5\alpha$ -THP while on an anti-depressant (sertraline, desipramine, or placebo) for at least 2 months. Results indicate that women who demonstrated an increase in  $3\alpha,5\alpha$ -THP levels reported improvements in symptom severity. Other women who had a decrease in serum  $3\alpha,5\alpha$ -THP reported worsening of symptoms, compared to those that did not show changes in  $3\alpha,5\alpha$ -THP (Fig. 17.5) [17]. Further, SSRI treatment with sertraline may be influenced by baseline levels of  $3\alpha,5\alpha$ -THP in that women who demonstrated low levels of  $3\alpha,5\alpha$ -THP had a significant increase in levels of  $3\alpha,5\alpha$ -THP following SSRI treatment, while women with high baseline levels demonstrated a decrease following SSRI treatment. Those with low and mid baseline levels of  $3\alpha,5\alpha$ -THP showed at least a 50% improvement in PMDD symptoms, while those with high baseline levels showed no change in symptoms (Fig. 17.6) [116]. Thus, changes in  $3\alpha,5\alpha$ -THP levels following anti-depressant treatment may mediate symptoms associated with PMDD such that a greater change in levels are associated with a reduction in PMDD symptoms.

Men can also experience symptom improvement with changes in levels of  $3\alpha,5\alpha$ -THP following treatment. Depressed men treated with an SSRI, fluoxetine, had increased  $3\alpha,5\alpha$ -THP levels, but not P or DHP, similar to non-depressed controls in their cerebral spinal fluid, and concomitant with alleviation of their depressive symptomology [117, 118]. Due to this evidence that  $3\alpha,5\alpha$ -THP may have a role in schizo-affective disorders, its effects in multiple animal models has been investigated. Findings from animal models suggest that  $3\alpha,5\alpha$ -THP has anti-depressant effects [119, 120]. Male mice administered fluoxetine,  $3\alpha,5\alpha$ -THP, or a drug that increases biosynthesis of  $3\alpha,5\alpha$ -THP, show less depressive behavior



**Fig. 17.5** Women diagnosed with PMDD were examined during the luteal phase for changes in severity of symptoms and changes in levels of  $3\alpha,5\alpha$ -THP while being treated with an anti-depressant. Women that demonstrate an increase in  $3\alpha,5\alpha$ -THP levels reported improvements in symptom severity. Women that demonstrate a decrease in  $3\alpha,5\alpha$ -THP levels reported worsening of symptoms, compared to those that do not show changes in levels of  $3\alpha,5\alpha$ -THP

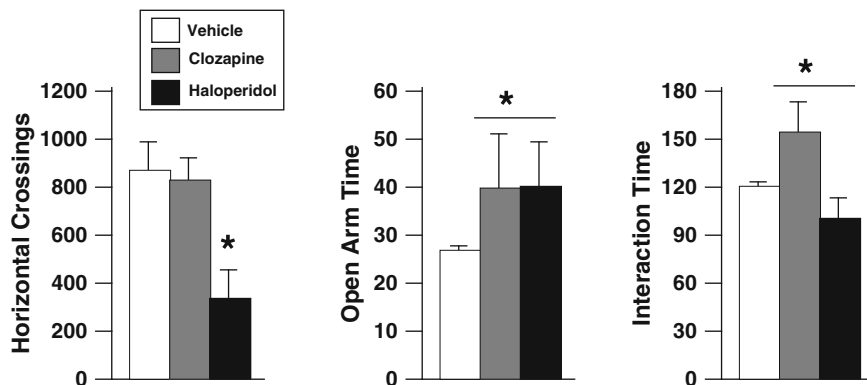


**Fig. 17.6** Women diagnosed with PMDD treated with sertraline demonstrated an increase in  $3\alpha,5\alpha$ -THP levels when levels prior to treatment were low, while women that had high baseline  $3\alpha,5\alpha$ -THP demonstrated a decrease in  $3\alpha,5\alpha$ -THP levels following treatment. Women with low and mid baseline levels of  $3\alpha,5\alpha$ -THP showed at least a 50% improvement in symptoms, while those with high baseline levels of  $3\alpha,5\alpha$ -THP showed no change in symptoms, following treatment

than vehicle-administered mice [121]. Thus,  $3\alpha,5\alpha$ -THP may be involved in the pathophysiology and/or treatment of depression associated with schizo-affective disorders.

### ***Anti-psychotics, Anti-depressants and $3\alpha,5\alpha$ -THP***

Data from clinical reports suggest that olanzapine, a novel atypical anti-psychotic, may be as efficacious as traditional anti-psychotics at treating schizo-affective symptoms. Olanzapine reduces negative and positive symptoms, disorganized thoughts, impulsivity/hostility, and anxiety/depression [122, 123]. Notably, in contrast to traditional anti-psychotics, such as haloperidol, olanzapine's therapeutic effects occur with negligible extrapyramidal side effects or akathisia. Olanzapine can improve affect, cognition, interpersonal relationships, impulsivity, and agitation [124, 125]. Olanzapine can also reduce behavioral inhibition in animal models by attenuating fear and anxiety [126, 127]. As well, it increases positive affect and social interactions [128]. Although the mechanisms by which olanzapine may have its therapeutic effects are not known, administration of olanzapine to male or female rats increases central  $3\alpha,5\alpha$ -THP levels compared to vehicle [129, 130]. Further, haloperidol, and the atypical anti-psychotic, clozapine (which alters biosynthesis of  $3\alpha,5\alpha$ -THP), were administered to OVX, E-primed female rats. Haloperidol reduced motor behavior and did not improve sociability. However, clozapine or haloperidol enhanced affective behaviors (Fig. 17.7). Together, these data suggest that schizo-affective disorders may involve a reduced capacity to synthesize  $3\alpha,5\alpha$ -THP in the brain, which may increase sensitivity to stress and expression of anxiety-like behaviors.

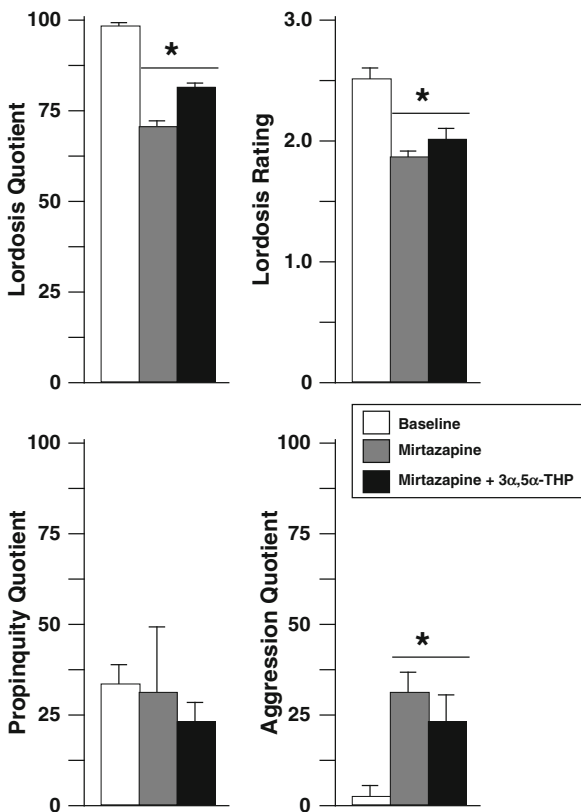


**Fig. 17.7** OVX, E-primed female rats administered haloperidol demonstrated reduced motor behavior in the open field and no change in sociability in the social interaction task. Rats administered clozapine or haloperidol demonstrated enhanced affective behavior in the elevated plus maze

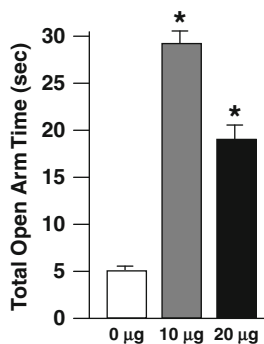
Another anti-depressant, mirtazapine, is an atypical anti-depressant that is a 5-HT<sub>2</sub>/alpha<sub>2</sub>-adrenoceptor antagonist devoid of affinity for 5-HT and NA reuptake sites [131]. Acute administration of mirtazapine enhances copulatory performance of male rats and strongly stimulates sexual motivation [132]. Chronic treatment with mirtazapine increases 3 $\alpha$ -reduced neuroactive steroids by influencing 3 $\alpha$ -HSD enzyme activity [133]. We investigated the effects mirtazapine may have on sexual receptivity in OVX, E- and P-primed female rats when administered with vehicle or 3 $\alpha$ ,5 $\alpha$ -THP. Rats were tested for baseline sexual receptivity, and immediately following baseline assessment, rats were administered mirtazapine and assessed for sexual receptivity 20 min later. Results indicate that rats administered mirtazapine demonstrated a significant decrease in lordosis and a significant increase in aggression compared to baseline assessment (Fig. 17.8). Following the second assessment, rats were administered 3 $\alpha$ ,5 $\alpha$ -THP or vehicle and tested for sexual behavior 20 min later. At 40 min following mirtazapine administration, rats continued to demonstrate a significant decrease in lordosis, propinquity and an increase in aggression compared to baseline assessment (Fig. 17.8). Administration of 3 $\alpha$ ,5 $\alpha$ -THP attenuated the sexual side effects of mirtazapine, but this did not reach statistical significance (Fig. 17.8). These data from suggest that further investigation of 3 $\alpha$ ,5 $\alpha$ -THP's involvement in the therapeutic action of anti-psychotic and anti-depressant drugs is warranted.

To begin to examine the mechanisms by which some anti-psychotic and anti-depressant drugs may have their therapeutic actions, olanzapine and fluoxetine were administered to the hippocampus of rats. Olanzapine administration to the hippocampus of OVX, E-primed rats increases affective behaviors compared to OVX, E-primed rats administered vehicle to the hippocampus (Fig. 17.9). Administration of fluoxetine to the ventral tegmental area (VTA) of OVX, E-primed rats enhances 3 $\alpha$ ,5 $\alpha$ -THP-dependent sex behavior and increases central 3 $\alpha$ ,5 $\alpha$ -THP [134]. Thus,

**Fig. 17.8** OVX, E- and P-primed rats administered mirtazapine 20-min prior demonstrate a significant decrease in lordosis and a significant increase in aggression compared to baseline assessment. Rats administered 3 $\alpha$ ,5 $\alpha$ -THP following mirtazapine assessment demonstrated attenuated sexual side effects



**Fig. 17.9** OVX, E-primed rats administered olanzapine to the hippocampus demonstrate increases in affective behaviors in the elevated plus maze, compared to vehicle administered rats



administration of anti-psychotics and/or anti-depressants that increase levels of 3 $\alpha$ ,5 $\alpha$ -THP, or co-administration of 3 $\alpha$ ,5 $\alpha$ -THP, may mediate anxiety-like, reproductive, and social approach behaviors that may or may not be associated with side effects of treatment.

### ***3 $\alpha$ ,5 $\alpha$ -THP Actions in the PFC, Hippocampus, and/or VTA to Mediate Behaviors***

In adulthood, 3 $\alpha$ ,5 $\alpha$ -THP may influence the function of the PFC to mitigate negative symptoms of schizo-affective disorders. Schizo-affective disorders involve PFC hypofunction, poor social function, and disrupted working memory, and the PFC is integral to decisions made regarding social and cognitive function [135–137]. Notably, the PFC is sensitive to progestins such that systemic administration of precursors of 3 $\alpha$ ,5 $\alpha$ -THP enhance working memory [138] and 3 $\alpha$ ,5 $\alpha$ -THP enhances DA secretion in the PFC in response to stress [139]. Whether these effects are due to direct actions of progestins on the PFC or indirect actions of progestins on the hippocampus and/or VTA, which project to the PFC, has not been established. Progestins mediate social behavior, in part, through actions in the VTA. Administration of 3 $\alpha$ ,5 $\alpha$ -THP to the VTA of rats increases sociability and blocking 3 $\alpha$ ,5 $\alpha$ -THP formation in the VTA attenuates social behavior [140]. Progestins can also influence affective and cognitive processes through actions in the hippocampus. 3 $\alpha$ ,5 $\alpha$ -THP is increased in the hippocampus concomitant with reduced anxiety-like behavior and enhanced cognitive performance [141, 142]. Blocking the formation of 3 $\alpha$ ,5 $\alpha$ -THP in the hippocampus increases anxiety behaviors and impairs cognitive performance [142, 143]. Thus, 3 $\alpha$ ,5 $\alpha$ -THP-enhanced social interactions and cognitive performance may be initiated in the VTA and/or hippocampus and involve projections to the PFC.

### **3 $\alpha$ ,5 $\alpha$ -THP's Biosynthesis and Social Approach**

A hallmark of schizo-affective disorders is Reproductive Endocrine Dysfunction (RED). In women with RED, differences in levels of progestogens may be absent, but there is evidence for HPA axis and/or response dysfunction. There are normal changes in progestogens, and people diagnosed with schizo-affective disorders experience these same changes, but they are different in their receptor mediated responses to fluctuations, such that they exhibit a dysregulatory response. Reproductive behaviors are linked to RED, as dysregulation in progestogens influences reproductive function and behaviors associated with reproductive success. The behaviors that are implicated in predicting reproductive success are also implicated in schizo-affective disorders, including stress responding, anxiety, depression, and social approach.

Environmental/behavioral stimuli may include social interactions with stimulus males and/or conspecifics, which may be particularly expressed during reproductive ventures when females are in proestrous. In the lab, we have used semi-natural mating situations, including larger mating arenas and/or enabling females to pace their sexual contacts with the male by escaping to a side of the chamber where the male is unable to follow (“pacing” chamber). In natural or semi-natural laboratory mating situations, female rats spontaneously exhibit social approach and avoidance behaviors (pacing behaviors), and other social solicitation behaviors (e.g. hopping,



darting, and ear-wiggling) toward males, which enable them to control the temporal pattern of mating and optimize their fertility and fecundity. These social approach and avoidance behaviors are readily observed and quantified in the lab using the pacing paradigm. Thus the pacing paradigm is a useful laboratory tool in assessment of the role of 3 $\alpha$ ,5 $\alpha$ -THP in social approach and avoidance behaviors in a reproductive context.

3 $\alpha$ ,5 $\alpha$ -THP has been demonstrated to mediate feedback of female sexual behaviors, including lordosis, social approach/avoidance, cognition, and reward, through actions in the VTA. The biosynthesis of, and metabolism to, 3 $\alpha$ ,5 $\alpha$ -THP in the VTA is important for mediating lordosis, sociability and cognition. In our model, we have investigated how 3 $\alpha$ ,5 $\alpha$ -THP mediates reproductive behaviors, social approach, and how actions in the VTA are linked to the hippocampus and PFC. Systemic administration of P or 3 $\alpha$ ,5 $\alpha$ -THP to OVX E-primed rats similarly increases social solicitation behaviors [99, 140]. Co-administration of biosynthesis or metabolism inhibitors with P decreases P-facilitated solicitation behaviors and completely eliminates pacing behavior. Biosynthesis of 3 $\alpha$ ,5 $\alpha$ -THP is enhanced by paced mating. Female rats that pace their sexual contacts have significantly higher whole brain and midbrain 3 $\alpha$ ,5 $\alpha$ -THP levels than do females mated in standard arenas that cannot pace their sexual contacts or rats that are not mated. Solicitation and approach behaviors are attenuated in both standard and paced mating paradigms when biosynthesis or metabolism of 3 $\alpha$ ,5 $\alpha$ -THP is blocked [33, 144, 145]. Thus, 3 $\alpha$ ,5 $\alpha$ -THP may have an important role in mediating mating and solicitation behaviors.

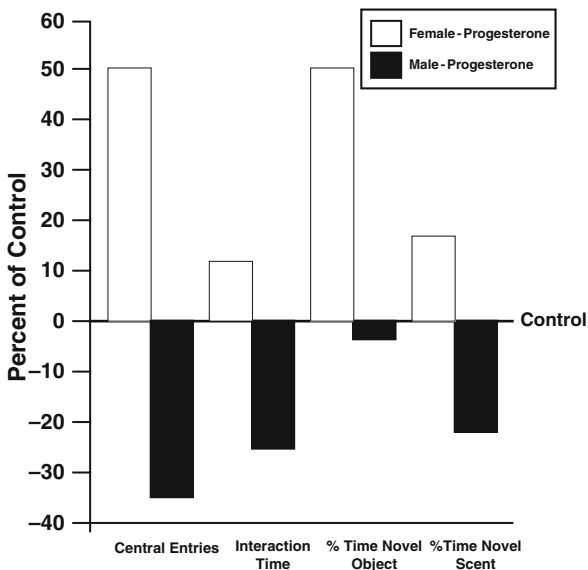
Levels of P and 3 $\alpha$ ,5 $\alpha$ -THP are increased coincidentally with lordosis, and expression of lordosis is mediated by metabolism to 3 $\alpha$ ,5 $\alpha$ -THP. Elucidating the source of 3 $\alpha$ ,5 $\alpha$ -THP in the VTA for its behavioral effects is necessary to distinguish if such effects are via traditional endocrine/autocrine mechanisms (metabolism from P) and/or via paracrine effects (biosynthesis in glial cells). 3 $\alpha$ ,5 $\alpha$ -THP biosynthesis occurs within seconds of environmental/behavioral events, whereas peripheral progestins are not as rapidly induced. Thus, dissociating the sources of 3 $\alpha$ ,5 $\alpha$ -THP is important because central biosynthesis, and paracrine effects, may be an adaptive mechanism for mediating reproductive behaviors and social approach.

### ***P, 3 $\alpha$ ,5 $\alpha$ -THP and Social Approach/Avoidance Behaviors***

P and/or 3 $\alpha$ ,5 $\alpha$ -THP have been demonstrated to influence social approach/avoidance behaviors. Approach/avoidance behaviors are increased between sexual contacts in the paced mating paradigm when P or 3 $\alpha$ ,5 $\alpha$ -THP are administered [144–146]. The social behaviors observed may be primarily mediated by 3 $\alpha$ ,5 $\alpha$ -THP actions at GABA<sub>A</sub> and/or D<sub>1</sub> receptors in the VTA. Solicitation and approach behaviors of female rodents are significantly reduced when actions of progestins at GABA<sub>A</sub> or D<sub>1</sub> receptors in the VTA are blocked [33, 99, 145, 147, 148]. Thus, these behavioral effects on social approach/avoidance involved in reproductive behaviors are likely due to 3 $\alpha$ ,5 $\alpha$ -THP's actions at GABA<sub>A</sub> and/or D<sub>1</sub> receptors in the VTA.

3 $\alpha$ ,5 $\alpha$ -THP may also mediate social interactions in non-mating paradigms and is also of interest for schizo-affective disorders given that a hallmark of schizophrenia is that engaging in social interactions is less rewarding and willingness to approach novel conspecific stimuli may be attenuated. Two behavioral paradigms which assess this type of approach behavior, independent of mating, are the open field and elevated plus maze. Approach responses of female rodents in the open field are significantly decreased when formation of 3 $\alpha$ ,5 $\alpha$ -THP is blocked systemically or in the hippocampus or amygdala [119, 120, 142]. Further, approach behaviors of 5 $\alpha$ -R knockout mice (5 $\alpha$ -RKO) are not increased following P administration compared to their wildtype counterparts [149]. Progesterin receptor (PR) knockout mice administered P demonstrate increased approach behaviors in the open field similar to controls, which may be indicative of 3 $\alpha$ ,5 $\alpha$ -THP's actions independent of intracellular PRs [147]. Our lab has also examined sex differences in rats in response to P in the open field, and results show that vehicle males demonstrate more approach behaviors than females. However, this is attenuated when males are administered P compared to males administered vehicle (Fig. 17.10). Thus, P and/or 3 $\alpha$ ,5 $\alpha$ -THP's actions may mediate approach behaviors of rodents in an open arena.

The elevated plus maze consists of a dichotomous choice to approach, as indicated by increased open arm time, or avoid, as indicated by decreased open arm time. Results are similar to those of open field in that OVX decreases approach behaviors, but administration of P or 3 $\alpha$ ,5 $\alpha$ -THP systemically or to the hippocampus or amygdala of rodents increases approach behaviors, independent of motor behavior [120, 145]. Approach behaviors are attenuated when metabolism of 3 $\alpha$ ,5 $\alpha$ -THP is blocked pharmacologically or genetically [45, 149, 150]. As well, PR knockout



**Fig. 17.10** Male rats administered vehicle show more approach behaviors compared to females, while males administered P show attenuated approach behaviors, in the open field, social interaction, object recognition, and social cognition tasks

mice administered P demonstrate approach behaviors similar to controls with PRs [151]. Thus, P or  $3\alpha,5\alpha$ -THP may mediate approach behaviors of female rodents in the elevated plus maze task such that approach is more likely to be demonstrated when  $3\alpha,5\alpha$ -THP can metabolize and have actions.

Social interactions also require approach behaviors to be expressed, and  $3\alpha,5\alpha$ -THP may mediate social behaviors that involve conspecifics. When P and  $3\alpha,5\alpha$ -THP levels are elevated, female rodents demonstrate more sociability with a conspecific, including sniffing, grooming, crawling over or under, and following. If metabolism of  $3\alpha,5\alpha$ -THP is blocked, social approach and interaction is attenuated. There is a sex difference in sociability such that females typically demonstrate more pro-social behaviors, while males typically demonstrate more aggressive behaviors. Female mice administered P show decreased aggressive acts towards an intruder, but these behaviors are not altered by P administration in  $5\alpha$ -RKO mice. As well, administration of  $3\alpha,5\alpha$ -THP to the VTA decreases aggressive behaviors of male hamsters in response to intruders [152]. Males administered P show less pro-social behaviors than males administered vehicle. As well, increased levels of P and  $3\alpha,5\alpha$ -THP in plasma and hippocampus are associated with decreased sociability in male rats (Fig. 17.10). Thus, actions of P and/or  $3\alpha,5\alpha$ -THP may play a role in mediating social interaction behaviors of female and male rodents.

### ***P, $3\alpha,5\alpha$ -THP and Socially-Relevant Cognitive Performance***

Social experiences may influence biosynthesis of  $3\alpha,5\alpha$ -THP and, in turn, mediate cognitive processing. Biosynthesis of  $3\alpha,5\alpha$ -THP is enhanced in response to social experience in the hippocampus and PFC. Cognitive processing is an important factor in socialization, and deficits in cognition may be related to deficits in sociability. In support, administration of P or  $3\alpha,5\alpha$ -THP to OVX rodents increases cognitive processing and performance, similar to increases in sociability associated with P and  $3\alpha,5\alpha$ -THP. Blocking metabolism of  $3\alpha,5\alpha$ -THP attenuates these effects, also similar to changes in sociability. There are also sex differences in cognitive processing, such that women perform better in verbal tasks and men perform better in spatial tasks. Our lab has examined sex differences in response to P in cognitive processing, and there is a clear sex difference at baseline performance such that intact male rats outperform intact female rats. However, the performance of males is significantly decreased, while the performance of females is increased, following P administration. Further, increased hippocampal P and  $3\alpha,5\alpha$ -THP levels are associated with increased cognitive performance of females, and decreased cognitive performance of males (Fig. 17.10). In another cognitive task wherein rodents must differentiate between a familiar and a novel scent, males outperform females at baseline, but P administration attenuates this effect in males (Fig. 17.10). Thus, actions of P and  $3\alpha,5\alpha$ -THP may mediate sex differences in cognitive performance such that females outperform males when progestogen levels are elevated in both females and males.

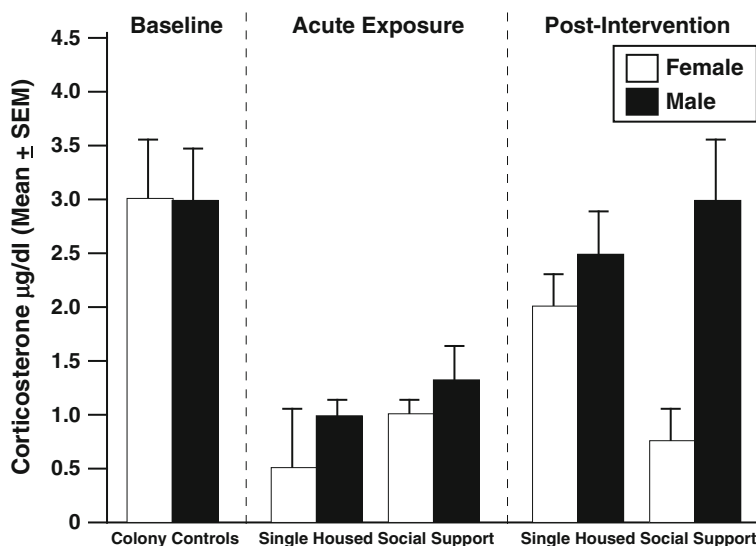
## **Social Isolation and 3 $\alpha$ ,5 $\alpha$ -THP**

Separate reports indicate that social isolation, another animal model of schizo-affective disorders, produces differences in 3 $\alpha$ ,5 $\alpha$ -THP concentrations, B levels, and behavioral inhibition. Social support minimizes stress and improves social functioning [153] and is used to manage schizo-affective disorders. Male mice that are socially-isolated have less 3 $\alpha$ ,5 $\alpha$ -THP biosynthesis in the PFC and higher plasma B levels compared to group-housed control mice [154]. Social isolation is detrimental to social functioning in adult rats [155] and lack of social support can lead to marked behavioral changes, such as an increase in locomotor activity, anxiety, depression, and aggression, suggesting that lack of social support may be a stressor and these behaviors manifest as a result when it becomes chronic. As well, social isolation of male rats at weaning is associated with decreased levels of 3 $\alpha$ ,5 $\alpha$ -THP in brain and increased anxiety-like behaviors during adulthood [156]. Social isolation can lead to reduced investigation of social odors when compared to group housed animals [157]. Together these data suggest that 3 $\alpha$ ,5 $\alpha$ -THP may have an important role in schizo-affective disorders.

Data from our laboratory indicates that the presence of social isolation versus social support influences neuroendocrine responding, but not affective behaviors, following exposure to an unpredictable auditory stressor and environmental enrichment. These animals were exposed to an unpredictable stressor over 20 generations intermittently and were acutely exposed in either single- or group-housed conditions for the experiment conducted. During exposure to stressor, there were no significant sex differences or single- versus group-housed differences in corticosterone levels among rats. However, post-environmental enrichment results indicate that corticosterone levels were lower among female rats that were group-housed in comparison to male group-housed and female and male single-housed rats (Fig. 17.11). This may indicate that females may be more reliant on social support when experiencing an acute stressor, compared to males. Thus, these data suggest that social support in females can have beneficial effects on HPA responding, but males may not benefit from social support.

## ***Maternal Separation Stress and 3 $\alpha$ ,5 $\alpha$ -THP***

Maternal separation is considered the ultimate social isolation as it occurs during a time when offspring are most dependent and can alter progesterone production. Perturbations during early post-natal development can have long last effects on offspring. In fact, those who are diagnosed with schizo-affective disorders commonly have a history of physical or psychological abuse beginning from an early age. Among offspring, stress-induced perturbations in progesterone-HPA homeostasis can be pervasive and persist throughout life [158]. In support, we have observed that acute perinatal stress via maternal separation and lithium chloride injection can alter 3 $\alpha$ ,5 $\alpha$ -THP formation in circulation, whole brain and/or hippocampus, an important brain region for normative affective, cognitive, and ictal behavior, immediately



**Fig. 17.11** Rats exposed to unpredictable stress over 20 generations intermittently, and acutely exposed to a stressor while single- or group-housed, did not demonstrate sex differences or plasma B levels. Post-environmental enrichment improved plasma B levels among females that were group-housed, compared to male group-housed and female and male single-housed rats

following isolation [50] and well into adulthood [47]. Neurodevelopmental and seizure disorders are commonly noted among premature children. Further, studies conducted in rhesus monkeys have demonstrated that infants who are subjected to maternal separation and social isolation develop behavioral and neurobiological profiles in which they are more likely to engage in drug and alcohol abuse [159]. Anxiety behaviors are altered in female and male rodents in adolescence after exposure to postnatal maternal separation, such that anxiety behavior is increased in the elevated plus maze in females and males, and in approach to a novel object latency is increased in females [160]. As well, female and male rats that were selectively bred to be low or high rates of ultrasonic vocalization (USV) following maternal separation were behaviorally tested. Results indicate that low responders show lower anxiety and depression behaviors compared to high responders. Further, levels of  $3\alpha,5\alpha$ -THP were elevated among high responders compared to low responders (Table 17.1). Thus, early stress-exposure may underlie neurodevelopmental aberrations that persist throughout life and dysregulation in  $3\alpha,5\alpha$ -THP formation may influence some of these observations.

## Hippocampal Lesions and Schizo-Affective Behaviors

The hippocampus influences downstream HPA and HPG responding. Progesterin receptors have been localized to the hippocampus [161, 162]. Excitability of hippocampal neurons is altered by P [161], and learning tasks involving the

hippocampus can be mediated by P [142, 163, 164]. The hippocampus is also vulnerable to stress [165, 166]. Glucocorticoid receptors have been localized to the hippocampus [167, 168] and neuronal firing in the hippocampus is altered by B, as is learning [169, 170]. Thus, the hippocampus may be altered following prolonged periods of stress, and this may be mediated by P.

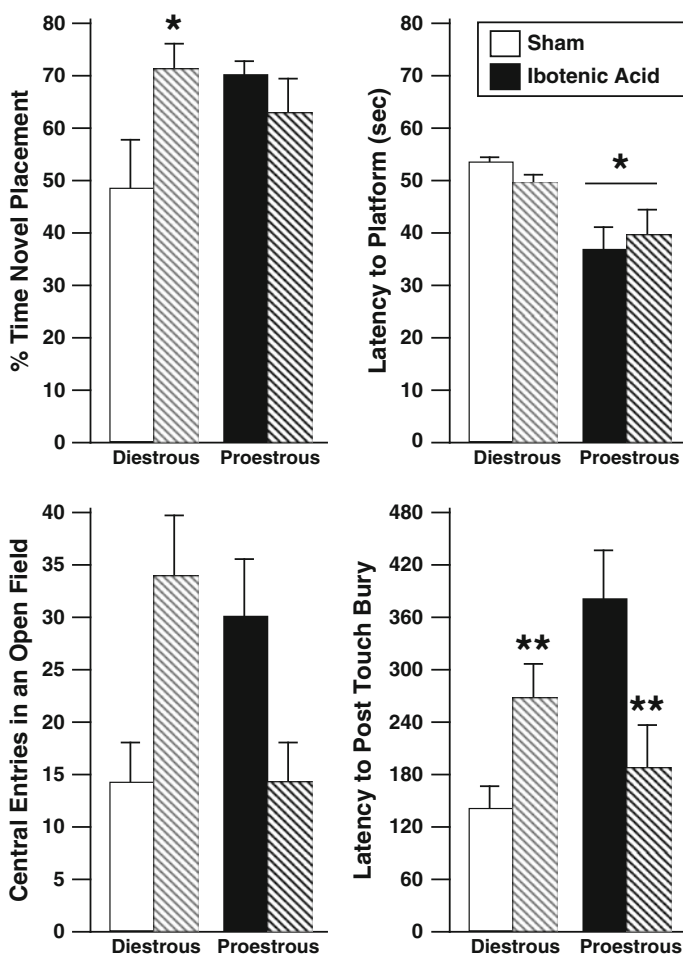
There is evidence for an interaction between adrenal and gonadal hormones to influence hippocampal morphology. Extreme (low or high) levels of adrenal hormones produce cell death in the hippocampus [98, 171]. We examined if there are interactions between gonadal and stress hormones in the hippocampus to examine how  $3\alpha,5\alpha$ -THP production mediates effects on behaviors. Previous data from our lab indicate that increasing biosynthesis of  $3\alpha,5\alpha$ -THP in the hippocampus of male rats increases  $3\alpha,5\alpha$ -THP levels in the hippocampus and concomitantly enhances affective behaviors [172]. Pre-treatment with PK 11195 to the hippocampus attenuated the effects of enhancement of  $3\alpha,5\alpha$ -THP biosynthesis on behavioral inhibition and neurosteroidogenesis [172]. Although these data suggest that manipulating  $3\alpha,5\alpha$ -THP production in the hippocampus of males can have salient effects on behavior, there has not yet been a systematic investigation of manipulating neurosteroidogenesis in the hippocampus of females to mediate behaviors related to schizo-affective disorders. Thus, gonadal hormones in the hippocampus may influence stress responding and expression of schizo-affective behaviors.

An animal model of schizo-affective disorders can be produced to examine the role of  $3\alpha,5\alpha$ -THP in expression of symptoms associated with hippocampal function. A neonatal excitotoxic lesion of the ventral hippocampus during early development produces symptoms that parallel schizo-affective disorders, and indicate that early damage to the hippocampus may contribute to the prevalence [173]. Symptoms that indicate schizophrenic-like behaviors include: cognitive and

**Table 17.1** Activity and  $3\alpha,5\alpha$ -THP levels in Low versus High responding ultra-sonic vocalization rats

Activity	Low responders	High responders
Saline	3,000	3,000
Cocaine	8,000	6,000
Hippocampus levels of $3\alpha,5\alpha$ -THP	Low Responders	High Responders
Saline	6.5	4
Cocaine	2.5	7
Midbrain levels of $3\alpha,5\alpha$ -THP	Low Responders	High Responders
Saline	4.5	2.7
Cocaine	2.5	3.7
Cortex levels of $3\alpha,5\alpha$ -THP	Low Responders	High Responders
Saline	6	3.7
Cocaine	7	9.8
Amygdala levels of $3\alpha,5\alpha$ -THP	Low Responders	High Responders
Saline	4.7	3.5
Cocaine	3.7	6

social deficits, hyper-locomotion, enhanced sensitization to psycho-stimulants, and increased aggression [174]. Our lab conducted a study to determine the effects that neonatal ibotenic acid lesions to the ventral hippocampus of female rats on PND 7 would have on behavior and levels of 3 $\alpha$ ,5 $\alpha$ -THP in adulthood. Results indicate that 40% of rats in the ibotenic acid group demonstrated abnormal cyclicity and proestrous rats showed decreased reproductive behaviors and increased aggressive behaviors compared to controls. Anxiety-like behavior of lesioned proestrous and diestrous animals was similar. However, there were differences in some cognitive performance due to cycle condition, but no differences due to cycle or lesion in working memory, spatial memory, or depressive tasks (Fig. 17.12). Thus,



**Fig. 17.12** Forty percent of female rats exposed to ibotenic acid demonstrated abnormal cyclicity and proestrous rats demonstrated decreased reproductive behaviors and increased aggressive behaviors compared to controls. Proestrous and diestrous females exposed to ibotenic acid did not demonstrate differences in anxiety-like behavior. There were no differences due to cycle or lesion in working memory, spatial memory, or depressive behavior

neonatal manipulations of the hippocampus can produce behavioral effects that persist into adulthood, and produce abnormal behaviors that appear to be related to changes in  $3\alpha,5\alpha$ -THP due to abnormal cyclicity and changes in reproductive behaviors.

Another point of interest is whether insults in adulthood may produce similar long term effects in rodent models. Rats administered P then administered kainic acid or vehicle indicates that rats administered kainic acid show mild behavioral symptoms, such as low activity followed by periods of hyperactivity, head nodding, myoclonic jerks of forelimbs and jaws, wet dog shaking, and/or modest salivation [175]. Kainic acid administration produces neural insult in the hippocampus, increases plasma B levels, and decreases cognitive performance [175, 176]. Administration of P prior to kainic acid enhances cognitive performance in comparison to rats that were administered P following kainic acid [7]. Thus, these data suggest that P and/or  $3\alpha,5\alpha$ -THP may be protective against a kainic acid-induced seizure model behavioral effects.

## **Dopamine in Schizo-Affective Disorders**

Motivation and executive function can be mediated not only by  $3\alpha,5\alpha$ -THP's actions, as evidence by its role in reward associated with social approach and reproduction. The DA and serotonin systems have been implicated in striatal dysfunction associated with schizophrenia and may also play a role in drug reward and abuse [177, 178]. As well,  $3\alpha,5\alpha$ -THP has actions at  $D_2$  receptors, in addition to actions at  $GABA_A$  and NMDARs. DA initiates and maintains responses to salient stimuli such as drugs [179]. Changes in DA levels are of interest given how it may influence short- or long-term behavioral outcomes. Blockade of glucocorticoids reduces release of DA. As we grow older we lose DA transporters (DAT) in our brain. As well, persons with attention deficit hyperactivity disorder (ADHD) have lower  $D_2$  and  $D_3$  receptors in the hypothalamus, ventral striatum, and mesencephalon. DA also regulates serotonin release in the forebrain, and there is a sex difference in DAT such that females have more than males. Social isolation just after birth alters levels of DA, B and  $3\alpha,5\alpha$ -THP when examined during adolescence under stressful conditions [51]. Thus, DA and actions at  $D_2$  receptors play a role in reward, motivation and executive functions, and this may be related to levels and/or actions of  $3\alpha,5\alpha$ -THP in behaviors relevant for schizo-affective disorders.

### ***Dopamine Transporter Knock-Out Mouse Model***

Evidence that P may influence mood and/or arousal among some people with schizo-affective disorders led us to examine the effects of P on DA transporter knockout mice (DATKO), an animal model of schizo-affective disorders. The DAT



is a plasma membrane transport protein thought to control extracellular DA concentrations and is an important target for a variety of therapeutic agents [180]. DATKO mice exhibit elevated interstitial levels of dopamine or serotonin and a range of behavioral alterations, including poor cognitive function [181], hyperactivity, and some stereotyped and/or preservative behavior [182] in the cliff avoidance reaction task. DATKO mice also have impaired prepulse inhibition (PPI), a model of sensorimotor gating in schizo-affective disorders [183]. As such, DATKO mice are known to be one of the animal models of schizo-affective disorders.

Our lab examined behavioral effects of P administration in DATKO mice and wildtype counterparts. Young adult, male and female DATKO and wildtype mice were subcutaneously administered P or vehicle 1 h prior to testing in the PPI, activity monitor, or open field. DATKO mice had impaired PPI compared to wildtype, but there was no effect of P. In the activity monitor, DATKO mice showed significantly greater distance traveled during the 60 min test compared to wildtype, and P decreased activity of DATKO mice. In the open field, DATKO mice made a significantly greater number of total, but fewer central, entries than did wildtype mice, and P decreased total entries of DATKO mice. P increased the number of central entries made by DATKO and wildtype mice [184]. Thus, P partially attenuated the hyper-active phenotype of DATKO mice, indicating that P and/or 3 $\alpha$ ,5 $\alpha$ -THP may play a role in the behavioral phenotype of an animal model of schizophrenia.

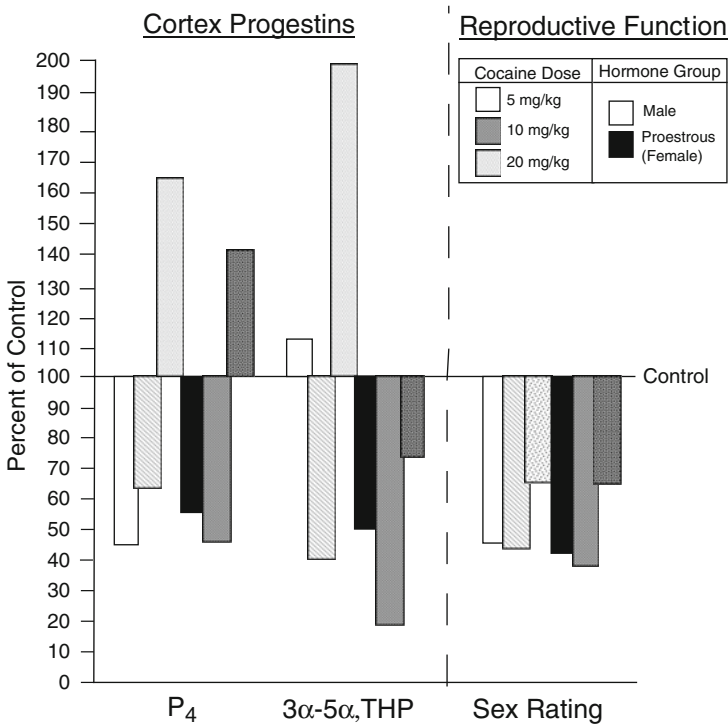
### ***Cocaine, Schizo-Affective Disorders and 3 $\alpha$ ,5 $\alpha$ -THP***

One drug of abuse that has been implicated for behaviors similar to schizo-affective disorders is cocaine, as it involves the DA reward system and influences levels of 3 $\alpha$ ,5 $\alpha$ -THP. Cocaine can have developmental effects and activational effects when administered in adulthood. Rat strains have been bred to emit low versus high rates of USVs in response to maternal separation at 10 days of age. The High line demonstrates an “anxiety-like and depressive” behavioral phenotype. Notably, 3 $\alpha$ ,5 $\alpha$ -THP levels in midbrain and plasma were significantly greater in High line compared to Low line rats. Further, these levels of 3 $\alpha$ ,5 $\alpha$ -THP in the midbrain were found to correspond with differences in reproductive behaviors between the High and Low line females. Male High line rats had shorter latencies to initial intromission and shorter intervals between intromissions, but longer latencies to ejaculation and longer post-ejaculatory intervals than Low line rats. Female High line rats had higher lordosis quotients and lordosis ratings, were more likely to pace their sexual contacts, and typically stayed away from the male-associated side of the mating chamber longer than Low line rats. These data indicate that endogenous levels of 3 $\alpha$ ,5 $\alpha$ -THP in the midbrain may be associated with individual differences in sexual behavior of rodents.

Low line and High line rats may demonstrate differences in activity when administered cocaine versus saline in adulthood, and this may be related to differences in levels of 3 $\alpha$ ,5 $\alpha$ -THP. Activity levels differ such that Low line rats are more active

following saline administration and less active following cocaine administration, compared to High line rats (Table 17.1). A similar pattern is observed for levels of  $3\alpha,5\alpha$ -THP in hippocampus, cortex, midbrain, and amygdala, such that Low line rats have higher  $3\alpha,5\alpha$ -THP levels compared to High line rats when administered saline. As well, cocaine increases levels of  $3\alpha,5\alpha$ -THP in High line rats, but not in Low line rats (Table 17.1). These data demonstrate that levels of  $3\alpha,5\alpha$ -THP at baseline may predict activity and/or stress reactivity in response to cocaine administration. Thus,  $3\alpha,5\alpha$ -THP levels may influence HPA-responding dependent on vulnerability to expression of stress responses.

Cocaine disrupts not only activity, but also normative reproductive function among all rats. This effect is such that reproductively active (proestrous) rats, exhibit significant decreases in reproductive function, concomitant with brain progesterin levels. Of interest, males administered a high dose of cocaine (the dose at which we observed a motor response), show significant increases in brain progestogens (Fig. 17.13). These data indicate that levels of  $3\alpha,5\alpha$ -THP and reproductive behaviors of female and male rats may be influenced by administration of cocaine, such that higher doses of cocaine negatively influence reproductive function. Thus,



**Fig. 17.13** Proestrous female rats administered cocaine demonstrate significant decreases in reproductive function, concomitant with brain progesterin levels. Males administered a high dose of cocaine demonstrate significant increases in brain progestins

cocaine can impact reproductive behaviors through altering levels of 3 $\alpha$ ,5 $\alpha$ -THP biosynthesis in females and males.

## **Methamphetamine, Endoplasmic Reticulum, and Schizo-Affective Disorders**

Methamphetamine (METH), another drug of abuse, may be related to schizo-affective disorders, as it can negatively impact the endoplasmic reticulum (ER). The ER is an intracellular organelle which is involved in diverse arrays of cellular functions, is mediated by cholesterol signaling, and is affected by METH. The ER is very densely packed with enzymes that are involved in quality control of protein synthesis and post-translational modification including folding of proteins. Malfunctions in these processes result in misfolded and/or unfolded proteins that can accumulate in the ER, with consequent activation of compensatory reactions such as the unfolded protein response. If these compensatory mechanisms fail to restore cellular homeostasis, cell death ensues via activation of ER-dependent apoptosis [185]. The accumulated evidence supports the involvement of ER stress and related molecular events in neurodegenerative events including METH-induced neuronal apoptosis. METH addicts often use large quantities of the drug and can suffer from drug-induced psychosis similar to symptoms of schizo-affective disorders. Neuroimaging studies have also revealed a number of abnormalities in the brains of these patients, including loss of striatal DAT and of serotonin transporters and evidence of reactive microgliosis. Previous postmortem studies are in agreement with some of those results. Moreover, METH can cause degeneration of monoaminergic systems and neuronal apoptosis in various brain regions including the rodent striatum. METH-induced cell death is dependent, in part, on activation of ER-dependent death pathways. With protracted absence of METH, there can be partial recovery of brain DAT. Thus, ER activation is important for cellular functions that may be disrupted in schizo-affective disorders and/or as a result of drugs that induce schizo-affective-like behaviors.

There exists a clear sex difference in E, which clearly plays an important role in modulating the nigrostriatal dopaminergic system in response to neurotoxins. For example, male mice display greater function in response to neurotoxins. Moreover, administration of high doses of METH produces more severe striatal DA depletions in male compared to female Swiss-Webster mice without E treatment following 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration. In adolescence, socially stressed females show greater stereotypy to amphetamines than do males. Amphetamine has been demonstrated to be rewarding in that socially stressed females show greater conditioned place preference compared to males. Socially stressed females and males demonstrate long lasting deficits in object spatial location, but not object memory compared to controls. Socially stressed males show long lasting deficits in contextual, conditioned, and generalized fear compared to controls. Females demonstrate long lasting deficits in neurogenesis, and these deficits take a long period of time to emerge and lead to hippocampal deficits. Socially

stressed males demonstrate increased neurogenesis compared to controls. Thus, amphetamines can influence expression of psychosis-like phenotype as indicated by changes in stress reactivity, cognition, fear behaviors and levels of progesterones, and these changes may be related to differences in resilience, relationships and resources that mediate manifestation of this phenotype.

## Other Genetic Mutations in Schizo-Affective Disorders

There are several candidate genes which have been implicated in schizo-affective disorders, including those which regulate  $3\alpha,5\alpha$ -THP biosynthesis, neuronal migration in development, and influence plasticity. Mutations that have been identified are in RELN and DISC1 genes. RELN encodes reelin, which is an evolutionarily-conserved nonabundant extracellular glycoprotein that can exist in multiple isoforms. Reelin is important in the organization of the developing fetal brain and neuroplasticity in the adult brain [186]. If there are disruptions in reelin-signal transduction, this can lead to disruption of the cytoskeletal structure of neurons [187]. In relation to reelin-signaling is the very low-density lipoprotein receptor (VLDLR), and reelin-signal transduction is interfered with in a VLDLR-deficient knockout mouse [188]. There are functional impairments of reelin signaling as indicated by attenuated levels of VLDLR mRNA in those diagnosed with schizophrenia [189]. Further, expression of the apolipoprotein E2 receptor (apoER2) is important for reelin binding. Mice with mutations of both VLDLR and apoER2 demonstrate a phenotype similar to the reelin phenotype, with disruptions in reelin protein [188]. Thus, mutations which alter receptor expression may disrupt reelin-signal transduction, an important mediator of neuronal migration and subsequent brain structure.

DISC1 has also been implicated in schizophrenia, as it is related to functional anatomic and cognitive consequences due to alterations in the cortex and hippocampus of those diagnosed with schizophrenia [190]. Several genetic studies have found that the DISC locus is related to many psychiatric disorders and cognitive disruptions [191, 192]. Further, mouse models of mutations in DISC1 demonstrate impairments in neurite outgrowth in vitro, and disrupted development of the cerebral cortex and behavioral impairments in vivo [193–198]. As a result, DISC1 may be important for effects on the organization of brain structures which may lead to vulnerability to the development of schizophrenia. Further, DISC1 is implicated in neurogenesis, neural migration, and synaptogenesis, which may be related to early development of schizophrenia [199]. Thus, there are genetic implications for schizo-affective disorders, some of which may be involved in development and/or  $3\alpha,5\alpha$ -THP biosynthesis.

## Conclusions and Future Directions

The neurobiology and pathology of schizoaffective disorders will not be understood by considering these disorders as they are defined in the DSM-IV-TR. Many

of the disorders classified as “schizo-affective” overlap with neurodevelopmental disorders such as autism, and this review will not be constrained to the DSM criteria because this is not a useful approach to understanding the mechanisms that may drive disorders with similarities. There are slightly different manifestations of common neurobiological factors that manifest in schizoaffective, as well as neurodevelopmental disorders. Due to the prevalence of schizophrenia and affective disorders in the population today and the aging population that may be more vulnerable to schizo-affective disorders due to hormonal changes, it is critical that all avenues of treatment, particularly hormones, are considered. While there has been interest in the ability of steroid hormones to mediate affective and depressive disorders, there has been little basic research done to characterize these effects and determine the mechanisms by which hormones may act to mediate these behaviors. Further understanding of neurosteroids is relevant for etiology, manifestation, and treatment options for people with affective and depressive disorders.

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