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Progesterone reduces depressive behavior of young ovariectomized, aged progestin receptor knockout, and aged wild type mice in the tail suspension test

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Abstract

Progestins may have effects to reduce depressive behavior, in part through actions of its metabolite, 5 α -pregnan-3 α -ol-20-one (3 α ,5 α -THP) at GABA_A receptors, rather than through intracellular progestin receptors. In this study, we examined the effects of progesterone (10 mg/kg, subcutaneous injection) versus vehicle control (propylene glycol) on the depressive behavior of young and aged mice in the tail suspension test. In Experiment 1, we first characterized progesterone's anti-depressant effects by utilizing young (4–6-month-old) intact or ovariectomized female, and intact or gonadectomized male, C57BL/6 mice. Young female mice showed more depressive behavior than the young male mice. Compared with vehicle administration, progesterone reduced depressive behavior of ovariectomized female, but not male or intact female mice. In Experiment 2, mice were aged (20–24-month-old) intact wild type or progestin receptor knockout mice. Progestin receptor knockout mice showed less depressive behavior than wild type mice. Administration of progesterone to wild type and progestin receptor knockout mice reduced depressive behavior. Together, these data suggest that progesterone can decrease depressive behavior of young adult ovariectomized female, aged wild type and progestin receptor knockout mice. Thus, progesterone's effect to reduce depressive behavior of aged mice may not require actions at the intracellular progestin receptors.

Keywords

aging; allopregnanolone; depression; neurosteroids; non-genomic; senescent

Introduction

Depression is a serious and widespread mental disorder that may be influenced by many factors including steroid hormones. Findings have suggested that progestins may have effects upon depressive behaviors in both people and animals. Women, compared with men, who do not experience profound changes in progestins, are more susceptible to depression and/or anxiety disorders. Throughout the life-span, women experience varied, and occasionally dramatic, changes in their hormonal and reproductive cycles. 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

progesterone levels are changing (Angst et al., 2001; Backstrom et al., 2003; Endicott et al., 1999; Glick and Bennett, 1981; Markou et al., 2005; Pearlstein et al., 2005; Rapkin et al., 2002). Indeed, among some individuals, progesterone may exacerbate rather than mitigate, symptoms of PMDD, depression, mood or bipolar disorder (Freeman et al., 2002, 2009; Hardoy et al., 2006). However, among others, natural, age-related decline in steroid hormones may be associated with increased vulnerability to depression and/or suicidality (Lebowitz et al., 2006). Thus, progestins have been implicated in the pathophysiology of some depressive disorders.

Findings from animal models also support a role for progesterone in depressive behaviors. For example, when rodents are in the proestrous phase of the estrous cycle and have high levels of progestins, they show less depressive behavior compared with rodents that are in low progestin phases of their cycle (Barros and Ferigolo, 1998; Becker and Cha, 1989; Bitran et al., 1991; Frye et al., 2000; Gulinello et al., 2003; Marvan et al., 1997; Walf et al., 2006b). Pregnant rats, which have sustained, higher levels of progestins, show less depressive behavior in the forced swim test than do post-parturient rats, with lower levels of progestins (Frye and Walf, 2004). Ovariectomy (OVX), removal of the primary source of endogenous ovarian hormones, increases depressive behaviors of female rats in the forced swim test (Bekku and Yoshimura, 2005; Bekku et al., 2006; Frye and Walf, 2002; Frye and Wawrzycki, 2003; Walf et al., 2006b) and administration of progesterone can reverse these effects (Espallergues et al., 2009; Frye and Walf, 2004, 2009; Frye et al., 2004; Walf et al., 2006b). Thus, progesterone may reduce depressive behaviors of mice (albeit these effects of progesterone are associated with changes in estradiol as well).

Progesterone's actions may occur, in part, through its classic membrane receptors, progesterin receptors (PRs). Mifepristone (RU486), a dual PR and glucocorticoid receptor (GR) agonist, is being investigated clinically for its effects at reducing psychotic depressive symptoms (Blasey et al., 2009; Van Look and von Hertzen, 1995). Its antidepressant effects are reported within a week of its use in psychotic depression and it demonstrates efficacy in other mood and cognitive disorders through these mechanisms (DeBattista and Belanoff, 2006). Animal models confirm clinical studies, where RU486 has rapid antidepressant effects through synaptic alternation in the hippocampus (Murphy, 1997; Wu et al., 2007). However, whether these effects are via PRs or GRs cannot be determined. In fact, its antidepressant effects are often described as being mediated through GRs (Gallagher et al., 2008; Murphy, 1997; Nihalani and Schwartz, 2007), which implies there may be a PR-independent mechanism for some of progesterone's antidepressant effects.

Interestingly, recent clinical findings indicate that progesterone's antidepressant effects may involve actions of its metabolite, 5 α -pregnan-3 α -ol-20-one (3 α ,5 α -THP). Among some women at menopause, reduced levels of 3 α ,5 α -THP and other neurosteroids have been associated with depression and other mood disorders (Freeman et al., 2002; Girdler et al., 2001; Pearlstein, 1995). Some patients with depressive disorders have reduced plasma concentrations and/or cerebrospinal fluid (CSF) levels of 3 α ,5 α -THP (Romeo et al., 1998; Stahl, 1997; Uzunova et al., 1998). Administration of antidepressants, such as fluoxetine or fluvoxamine, normalize decreased 3 α ,5 α -THP concentrations concomitant with reducing depressive symptomology (Uzunova et al., 2004, 2006). However, recent findings also suggest that the increased CSF levels of 3 α ,5 α -THP may represent non-specific pharmacologic effects of antidepressants, rather than markers of therapeutic response (Schule et al., 2007). Thus, further investigation of 3 α ,5 α -THP's role in affective processes is needed.

Progesterone's antidepressant effects are related to actions of 3 α ,5 α -THP. First, progesterone and/or 3 α ,5 α -THP similarly decrease depressive behavior of rodents (Frye and

Walf, 2002; Hirani et al., 2002; Walf and Frye, 2007). Second, the antidepressant effects of progesterone are reduced when drugs that block conversion of progesterone to 3 α ,5 α -THP are co-administered (Hirani et al., 2002; Walf et al., 2006b). Third, the antidepressive effect of progesterone in the forced swim test are attenuated among 5 α -reductase knockout mice that cannot convert progesterone to 3 α ,5 α -THP (Frye et al., 2004). In other animal models of depression, socially isolating mice decreases 3 α ,5 α -THP levels, but can be reversed by progesterone or 3 α ,5 α -THP administration (Dong et al., 2001; Guidotti et al., 2001). 3 α ,5 α -THP has actions through gamma-aminobutyric acid (GABA_A)/benzodiazepine receptors complexes (GBRs) rather than via traditional actions at intracellular PRs (Bethea et al., 2002; Gulinello, et al., 2003; Lan and Gee, 1994; Lancel et al., 1996; Nicol et al., 1999). Thus, progesterone's actions on mood and/or anxiety-related behaviors may be dependent on conversion to 3 α ,5 α -THP and some of these actions may be mediated by GBRs rather than by classical actions at PRs.

It is important to understand the nature of progesterone's effects on depressive-like behaviors and possible underlying mechanism by which progesterone has antidepressive effects. In this experiment, we utilized young C57BL/6 and aged PR knockout (PRKO) and wild type mice to investigate whether progesterone's effects on depressive behavior in the tail suspension test require the PRs. We hypothesized that if progesterone has effects that reduce depressive behavior, then administration of progesterone should reduce mice immobility in the tail suspension task. Further, if progesterone's antidepressant effects occur independently of actions at the PRs, then administration of progesterone to wild type and PRKO mice should similarly reduce immobility.

Methods

Animals and housing

The paradigm was pre-approved by the Institutional Animal Care and Use Committee at the University at Albany – SUNY.

Mice were group-housed in a room with a reversed 12/12 hour light/dark cycle (lights on 08:00). Animals had free access to Purina rat chow (RHM #3000) and water in their home cages.

In Experiment 1, young C57BL/6 mice ($N = 56$), between 4 and 6 months old, were bred in the Life Science Laboratory Animal Care Facility at the University at Albany – SUNY. Mice were randomly assigned to gonadal status (intact or castrated). Female mice were intact ($n = 14$) or OVX ($n = 14$) mice. Male mice were intact ($n = 14$) or gonadectomized (GDX) ($n = 14$). Seven mice in each condition were randomly assigned to be administered progesterone and the remaining seven in each condition were administered vehicle.

In Experiment 2, wild type or PRKO mice ($N = 14$), between 20 and 24 months old, were bred in the Social Sciences Building Animal Care Facility at the University at Albany – SUNY. Wild type (female $n = 4$ and male $n = 3$) or PRKO mice (female $n = 3$ and male $n = 4$) remained intact due to their age, and the possibility of attrition associated with surgery. These mice were breeders that had been retired and were subsequently used in these experiments when our colonies had to be taken down because of a laboratory move. Regrettably, no younger counterparts were available for the PRKOs.

Genotype

Wild type and PRKO mice were genotyped by genomic DNA isolated from tails and subsequent analyses by polymerase chain reaction, according to methods previously described (Frye et al., 2006b). The following PR-specific primers were used: P1(5'-

TAGACAGTGTCTTAGACTCGTTGTTG-3'), P2 (5'-GATGGGCACATGGATGAAATC-3'), and a neo gene-specific primer, N2 (5'-GCATGCTCCAGACTGCCTTGGGAAA-3'). Bands of approximately 565 and 500 base pairs were amplified for wild type and PRKO mice.

Surgery

All young mice (Experiment 1) were operated on around 3–4 months of age. Briefly, mice were administered sodium pentobarbital anesthesia (70 mg/kg). Females were either OVX ($n = 14$) or sham-operated ($n = 14$), and males were either GDX ($n = 14$) or sham-operated ($n = 14$). As with previous methods, female mice require 1–2 weeks after OVX for physiological levels of estrogen (E_2) and progestins to be reduced (Frye and Walf, 2008; Walf et al., 2008a, b), while male mice require 4–6 weeks to clear endogenous androgens following GDX (Frye and Walf, 2009). After these time periods, mice were randomly assigned to progesterone or vehicle condition and were behaviorally tested (described below).

In Experiment 2, aged wild type or PRKO mice (between 20 and 24 months) remained intact for the following reasons. First, aged mice have significantly lower levels of sex hormones than younger mice (Nelson et al., 1992; Perrot-Sinal et al., 1998). Second, surgery may produce greater rates of attrition in aged mice compared with their younger counterparts. Thus, aged mice remained intact.

Hormone administration

All mice were randomly assigned to either progesterone (10 mg/kg) or vehicle (propylene glycol) condition. Progesterone was obtained from Sigma Chemical Co. (St Louis, MO, USA) and dissolved in propylene glycol to a concentration of 10 mg/ml. Mice received subcutaneous progesterone or vehicle injection 1 h prior to behavioral testing. This progesterone regimen produces levels of $3\alpha,5\alpha$ -THP around 35 pmol/g; it increases GABA-stimulated chloride influx in cortical synaptoneurosomes, and muscimol binding in the hippocampus among aged (20–24 months of age) wild type or PRKO mice (Frye et al., 2006a, b). We, and others, found that PRKO mice have decreased PR binding compared with their wild type counterparts (Frye et al., 2006a, b; Mani et al., 1997). Moreover, this progesterone regimen does not produce gross alterations in locomotion and/or coordination (Frye et al., 2006a). After mice were injected with progesterone (10 mg/kg) or vehicle, they were returned to their home cages for 1 h until behavioral testing.

Tail suspension

The tail suspension test is an animal model of depressive behavior, which was introduced as a screening test for antidepressant activity by Steru et al. (1985). There are several advantages of the tail suspension test for evaluating depressive behavior of rodents. First, the procedure is a very simple and objective test. Second, the results from this approach are in agreement with those from other validated animal models of depression, such as the Porsolt forced swim test (Steru et al., 1985). Moreover, a critical analysis by Porsolt (Porsolt et al., 1977), indicates that tail suspension and behavioral despair are the best animal model of depression, based on non-dependence on a mechanism, pharmacological validity, existence of genetic determinants, availability of a mouse version, procedural simplicity, and reproducibility. In this experiment, we utilized the procedures of Steru et al. (1985). We used a slightly modified version that was introduced by Steru. Briefly, mice were individually suspended 45 cm above an apparatus (50 cm high $\times$ 19 cm wide), (Stoelting Co., IL, USA) (Bilkei-Gorzo et al., 2002) by a gauze-covered binder clip affixed 1 cm from the tip of the tail (Kulkarni and Dhir, 2008; Zhang et al., 2008). For 6 min, the total duration of immobility (freezing time) was recorded each minute as an indicator of depressive

behavior. Immobility is a typical motionless position defined as the absence of active behaviors (i.e. searching behavior with intense movements, such as struggling). Following the test, mice were removed from the tail suspension apparatus and returned to their home cages.

In Experiment 2, limited numbers of aged wild type and PRKO mice were available. Given this, a two-week, repeated-measure design was utilized. Therefore, once mice were tested in either the progesterone or vehicle condition, they were re-tested in the opposite condition the following week. Whether progesterone or vehicle was received initially was counterbalanced across subjects (Frye et al., 2006b). There was no evidence for test decay between performances in the first and second week of testing.

Data analyses

For Experiment 1, a three-way analysis of variance (ANOVA) was utilized to evaluate the effects of sex (female, male), gonadal status (intact, OVX/GDX), and hormone condition (progesterone, vehicle). For Experiment 2, a two-between (sex; female, male; genotype; PRKO, wild type), one-within (condition; progesterone or vehicle), factor ANOVAs were used. The alpha level for statistical significance was $p < 0.05$. Where appropriate, ANOVAs were followed by Fisher's post-hoc tests to determine group differences.

Results

Experiment 1: young mice

There was a significant effect of sex ($F(1,48) = 17.26, p = 0.001$). Female mice showed more depressive behavior (mean immobility = 104 ± 7 s) than did male mice (69 ± 7 s). There was a significant interaction between sex, gonadal status, and progesterone ($F(1,48) = 10.59, p = 0.002$) that was due to progesterone significantly decreasing depressive behavior only among OVX female mice (Figure 1).

Experiment 2: aged PRKO mice

Progesterone ($F(1,10) = 6.43, p = 0.02$) and genotype ($F(1,10) = 5.30, p = 0.04$), but not sex, significantly influenced immobility time of aged wild type and PRKO mice. Progesterone (mean immobility = 93.6 ± 21.1 s), compared with vehicle (141.7 ± 26.9 s), decreased immobility in the tail suspension task. PRKOs showed less immobility (96.1 ± 30.8 s) than did wild type mice (138.8 ± 17.3 s). Aged female or male wild type and PRKO mice demonstrated less depressive behavior in response to progesterone, compared with vehicle, administration (Figure 2).

Discussion

The present results are consistent with the hypothesis that progesterone can decrease depressive behavior and that actions through the PRs may not be required for acute effects of progesterone in aged mice. In support, young female mice showed more depressive behavior than young male mice. Compared with vehicle administration, progesterone to young OVX mice, but neither intact female, nor male mice, significantly reduced freezing time. Administration of progesterone to aged intact female and male wild type and PRKO mice reduced freezing time. Together, these data suggest that progesterone may have effects that reduce depressive behavior in OVX females and that some of these effects of progesterone may be independent of actions at the PRs.

The results of this study confirmed previous findings that female rodents show more depressive behavior than male rodents. Here, we observed more depressive behavior among

young female mice than young male mice in the tail suspension test. These findings are analogous to those of others using different animal models. In the forced swim test, female rats, compared with males, have a longer duration of immobility (Frye and Walf, 2004; Paré and Redei, 1993; Walf et al., 2006b). Moreover, in the forced swim test, males show more recuperative behavior, such as head swinging, than do females (Drossopoulou et al., 2004). In a novel animal model of depression, young female Wistar rats showed more indications of vulnerability to depression induction than did males (Sun and Alkon, 2006). Thus, as seen in clinical studies and other animal models of depression, young female mice showed more depressive behavior than did young male mice.

Despite young female mice showing more depression behavior than young male mice, progesterone only had significant antidepressant effects among young OVX mice. One explanation for this may be that changes in the levels of ovarian hormones over the estrous and/or reproductive cycles may have influenced depressive behavior of intact female mice. For example, when rodents have high levels of ovarian hormones, such as occurs during proestrous or pregnancy, less depressive behavior is observed in the forced swim test compared with that of rats with low ovarian hormones (i.e. diestrous, post-parturient, or male rats) (Frye and Walf, 2004; Walf and Frye, 2007; Walf et al., 2006b). Rats that were three days post-partum displayed more depressive behavior than did cycling rats (Molina-Hernández et al., 2000). One drawback of the present experiment is that we neither controlled, nor evaluated, the phases of the estrous cycle in which young, intact female mice were tested. Despite this limitation, we did examine behavior of intact aged female mice that were between 20 and 24 months of age. Notably, about 80% of 17-month-old female C57BL/6NIA mice had irregular or absent cycles and 100% of their 25-month-old counterparts were acyclic (Frick et al., 2000). Based upon these findings, we expect that the majority of aged intact mice from Experiment 2 had very low levels of sex hormones, compared with young intact female mice. We observed that aged mice in Experiment 2 generally demonstrated more depressive behavior than did younger mice from Experiment 1. Although the aged female mice might be comparable to the OVX younger ones in terms of gonadal hormonal status, that does not explain the difference between the GDX young male mice and the aged intact males.

Just as endogenous decline in gonadal steroids with aging may precipitate vulnerability to increases in depressive behavior, extirpation of the gonads may also increase the likelihood of demonstrating depressive behavior. In this experiment, OVX increased depressive behavior over that of intact female mice. Progesterone administration to OVX, but not intact female and male mice, significantly reduced depressive behavior compared with vehicle administration. These findings are similar to those of previous reports that OVX increases depressive behaviors over that of intact and/or sham-operated rodents and administration of ovarian hormones can reverse these depressant effects (Bekku et al., 2006; Bernardi et al., 1989; Galea et al., 2001; Stoffel and Craft, 2004). Indeed, acute administration of progesterone to OVX rats increases antidepressive behavior in the forced swim test (Frye and Walf, 2002). Notably, the regimen of progesterone that has previously demonstrated antidepressant effects in the forced swim test when administered to young OVX mice, involves a higher concentration of progesterone (50, 1000, or 10,000 $\mu\text{g/kg}$) and chronic administration (subcutaneous injections four times daily) (Bernardi et al., 1989), compared with our dosing (10 mg/kg subcutaneous injection 1 h prior to testing). Previously, we observed that this same progesterone regimen increases anti-anxiety behavior of young and aged wild type/PRKO mice (Frye et al., 2006a). The pattern and magnitude of progesterone's effects are clearly consistent across our studies, which speaks to the veracity of the results, despite the small sample size and the large variability in the response to progesterone. In contrast, others have shown that acute administration of progesterone (10 mg/kg) to female intact albino mice (Laca strain) produced significant increases in

immobility in the forced swim test (Kaur and Kulkarni, 2002). Given that there are well-known differences between mouse strains in response to steroid administration and their behavioral effects (Svare, 1988), further investigations of dose-dependent effects of progesterone will be required to elucidate a clearer understanding of the nature of progesterone's antidepressant effects.

Progesterone's metabolite, 3 α ,5 α -THP, may underlie some of progesterone's antidepressant effects. Our work, and others, has elucidated progesterone, which binds to PRs, as having antidepressant effects (Espallergues et al., 2009; Frye and Walf, 2009). However, recent reports of progestins' effects on increasing anti-anxiety and antidepressive behavior suggest that these effects are mediated in part through actions at GBRs rather than via progesterone's traditional actions through PRs (Bethea et al., 2002; Gulinello et al., 2003; Lan and Gee, 1994; Lancel et al., 1999; Nicol et al., 1999). 3 α ,5 α -THP is one of the most potent positive allosteric modulators of GBRs (Compagnone and Mellon, 2000; Lambert et al., 1995; Paul and Purdy, 1992) and interacts with GBRs at low concentrations to increase the frequency and/or duration of openings of GABA-gated chloride channels (Lambert et al., 1995; Majewska et al., 1986; Paul and Purdy, 1992) or by changing specific GBR subunit gene expression (Guidotti et al., 2001). In Experiment 2, progesterone administration to aged wild type and PRKO mice reduced depressive behavior in the tail suspension test. In our previous investigation of anti-anxiety effects in aged wild type and PRKO mice, we (and previously others) found that PRKO mice are devoid of PRs (Frye et al., 2006b; Mani et al., 1997), but they readily convert progesterone to 3 α ,5 α -THP and have enhanced GABA-stimulated chloride influx (Frye et al., 2006a). 3 α ,5 α -THP's effects to reduce depressive behavior of rodents can be blocked with the co-administration of GBR antagonists in the forced swim test (Hirani et al., 2002; Rodríguez-Landa et al., 2007). Thus, progesterone's depression-reducing effects may not require actions at the PRs.

Other animal models and clinical studies indicate that 3 α ,5 α -THP has antidepressant effects. Administration of 3 α ,5 α -THP to OVX rats reduces duration of immobility in the forced swim test (Frye and Walf, 2004). Moreover, these effects of 3 α ,5 α -THP in the forced swim test are observed when it is administered intraperitoneally, intracerebroventricularly (Khisti and Chopde, 2000; Khisti et al., 2000), or directly to the nucleus accumbens (Molina-Hernandez et al., 2005). Further, high levels of 3 α ,5 α -THP are observed in the hippocampus of proestrous female rats, which show reduced immobility time in the forced swim test (Frye and Walf, 2002; Frye et al., 2000). 3 α ,5 α -THP has also been implicated in clinical depression. Some antidepressant medications enhance the production of 3 α ,5 α -THP (Frye and Seliga, 2003; Griffinn and Mellon, 1999; Marx et al., 2003). Patients with severe depression have decreased CSF levels of 3 α ,5 α -THP, which is normalized by treatment with a fluoxetine regimen that improves depressive symptomatology concomitant with increasing 3 α ,5 α -THP levels (Guidotti et al., 2001). Thus, progesterone's antidepressant effects may be due, in part, to 3 α ,5 α -THP's actions through the GBRs.

It is particularly important to investigate the effect of progestins on depressive behavior, and examine the ability of aged animals to respond to hormonal manipulations in order to understand fully the costs and benefits of the hormone's effects on depression. Together with data from animal models, levels of progesterone and depression-like behavior among some women need to be considered. Women experience changes in their levels of progestins through their life-span and reproductive cycle. For instance, levels of 3 α ,5 α -THP increase just before the onset of puberty (Fadalti et al., 1999). Across the menstrual cycle, the levels of 3 α ,5 α -THP remain low in the follicular phase and are elevated in the mid-luteal phase (Rapkin et al., 1997; Schmidt et al., 1994). The onset of premenstrual syndrome, which includes psychological symptoms such as anxiety, depression and irritability, is variable but most of these negative symptoms occur during the late luteal phase, when the levels of

progestins are low (Angst et al., 2001; Endicott et al., 1999; Hardoy et al., 2008; Pearlstein et al., 2005; Rapkin et al., 1997, 2002; Soares and Zitek, 2008). During pregnancy, levels of 3 α ,5 α -THP reach their highest, and this is in part due to increased progesterone production from the corpus luteum during the first 3 months, which is the trimester most often associated with increased anxiety and/or depression (Paoletti et al., 2006). Further, there are reports of non-significant findings in changes in estrogen and progesterone levels in women experiencing post-partum depression, albeit the authors did not analyze 3 α ,5 α -THP levels, which may have yielded different results (Klier et al., 2007). The levels of ovarian hormones start to change perimenopausally and circulating levels of ovarian hormones decline within a few years of menopause (Ballinger et al., 1987; Longcope, 1990; Markou et al., 2005). This menopausal transition is associated with increased incidence of affective and depressive symptoms (Markou et al., 2005). Some premenopausal and menopausal women experience negative physical and/or negative neuropsychological symptoms (Joffe et al., 2003; Pearlstein et al., 1997), which can be reversed by hormone therapy (Fitzpatrick et al., 2000; Sherwin, 1991; Sherwin and Gelfand, 1989). Among some women, anxiety or panic disorders emerge with increased emotional activities during the postmenopausal period (Claudia et al., 2004). Given that the population is aging and women are living longer in a state of ovarian hormone decline, it is essential to understand more about the effects and mechanisms by which hormones mediate depression.

In sum, our current experiment indicates that administration of progesterone to young mice and aged wild type and PRKO mice reduced depressive behavior in the tail suspension test. These findings imply that progesterone's effects may be in part independent of actions at the PRs and may involve 3 α ,5 α -THP's action through the GBRs. These findings are relevant in elucidating the role of progestins in the etiology, therapeutic treatment, and/or prognosis of depressive disorders. Information on the role and actions of progestins in menopause is lacking. As such, further research is required to understand fully the effect of progestins in reducing depressive behavior and/or depression-like symptoms. Although the present findings indicate actions at the PRs may not be required for antidepressant effects in mice, in humans the PR and GR agonist RU486 seems to have therapeutic efficacy. Indeed, a multisite trial indicated that patients with plasma levels of RU486 >1800 ng/ml were more likely to show improvements in their psychotic depression than did placebo controls (Blasey et al., 2009). However, the effects of RU486 on PRs versus GRs cannot be parsed out, and evidence remains strong and consistent for antidepressant effects of 3 α ,5 α -THP as the likely mediator behind progesterone's antidepressant effects.

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Figure 1.

Mean duration of freezing (s) in the tail suspension test of young adult (4–6 months of age) intact (white bars) or ovariectomized (black bars) female (left; $n = 7$ in each condition) and male young adult intact or gonadectomized (GDX) (right; $n = 7$ in each condition) C57/BL6 mice administered vehicle control (inset left) or progesterone (inset right). *Denotes a significant main effect for females and males to differ ($p < 0.05$), ^Indicates significant interaction wherein progesterone decreased depressive behaviors of female GDX mice but not other groups.

Figure 2.

Mean duration of freezing (s) in the tail suspension of aged adult (20–24 months of age) intact female (left panel; wild type $n = 4$, middle left; progesterin receptor knockout (PRKO) $n = 3$) and intact male (right panel; wild type $n = 3$, far right panel; PRKO $n = 4$) mice administered vehicle control (inset left) or progesterone (inset right). #Denotes a significant main effect for wild type and PRKO mice to differ ($p < 0.05$). *Denotes a significant main effect for vehicle and progesterone-administered mice to differ ($p < 0.05$).