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Review

Progestins influence motivation, reward, conditioning, stress, and/or response to drugs of abuse

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Abstract

Progesterone (pregn-4-ene-3,20-dione; P) and its metabolite 5α-pregnan-3α-ol-20-one (3α,5α-THP) are secreted by ovaries, adrenals, and glial cells. 3α,5α-THP in the midbrain ventral tegmental area mediates sexual receptivity of rodents through its actions at $GABA_A$, NMDA, and/or D_1 receptors. The extent to which 3α,5α-THP may influence anti-anxiety/anti-stress effects, conditioning and/or reward through these substrates and/or by altering hypothalamic pituitary adrenal axis function is discussed. Biosynthesis of 3α,5α-THP occurs in responses to mating and may underlie some of the rewarding aspects of sexual behavior. Recent findings from our laboratory which demonstrate that progestins can enhance approach to novel stimuli, conditioning, and reinforcement are reviewed. How progestins' effects on these processes may underlie response to drugs of abuse is considered and new findings which demonstrate interactions between progestins and cocaine are presented.

Keywords: Neurosteroid; Non-genomic; $GABA_A$; D_1 receptors; NMDA rececptor; Anxiety; Affect; Learning; Cocaine; Progesterone; 3α,5α-THP

Contents

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1. Introduction

Hormones are trophic factors that profoundly influence brain and behavior. In my laboratory, we are particularly interested in the steroid hormone progesterone (pregn-4-ene-3,20-dione; P), which is the primary progestin secreted by the ovaries, and to a lesser extent, the adrenals. In the brain, P is converted by the 5α-reductase enzyme to dihydroprogesterone (5β-Pregnan- 3,20-dione-DHP), which like P, binds with a high affinity for intracellular progestin receptors (PRs) that are located in the hypothalamus and other brain regions (reviewed in Blaustein et al., 1994; Iswari et al., 1986; Smith et al., 1974). DHP is subsequently converted in brain by the 3α-hydroxysteroid oxidoreductase enzyme to form 5α-pregnan-3α-ol-20-one (3α,5α-THP), which in physiological concentrations, does not bind readily to PRs (Rupprecht and Holsboer, 1999). 3α,5α-THP is secreted by the ovaries and adrenals and is formed centrally from metabolism of peripheral P and/or DHP. As well, 3α,5α-THP is synthesized centrally in the brain by glial cells in response to stress, independent of peripheral gland secretion. Centrally, 3α,5α-THP has actions via $GABA_A$, NMDA, and/or dopamine receptors, and downstream signal transduction pathways, rather than intracellular progestin receptors, which is a substrate for P's actions (Frye, 2001a,b; 2006a,b; Frye and DeBold, 1992; Frye and Vongher, 1999a,b; Frye et al., 1993, 1999, 2000, 2006a,b,c,d,e,f; Petralia and Frye, 2004). 3α,5α-THP can also have effects to dampen hypothalamic pituitary adrenal axis function (Patchev et al., 1994, 1996). Indeed, it has been hypothesized that 3α,5α-THP is a very important neuroendocrine regulator that may be involved in homeostatic responses, as demonstrated by its increase in response to stress and subsequent effects to enhance parasympathetic activity (Engel and Grant, 2001). Thus, this review paper discusses how variations in progestins may mediate behavioral processes, such as reward, conditioning, and/or stress, which may influence susceptibility and/or response to drugs of abuse.

2. Progestins and reproductive cycles

Progestins co-vary with estradiol (17β-estra-1,3,5(10)-triene-3,17 β-diol; E_2) across reproductive cycles. Throughout development, females have greater variations in, and higher levels of, P and 3α,5α-THP than do males. During the follicular phase of the menstrual cycle, progestin levels of women (P: 1–2 nmol/l; 3α,5α-THP 0.3 nmol/l) are low similar to that of men (P: 1–2 nmol/l; 3α,5α-THP 0.3 nmol/l). However, during the luteal phase (P: 25 nmol/l; 3α,5α-THP 2 nmol/l) and pregnancy (P: 650 nmol/l; 3α,5α-THP 14 nmol/l), progestin levels of women are much higher than are men's (Genazzani et al., 1998; Pearson Murphy and Allison, 2000). This same pattern occurs for rats and mice (Frye and Bayon, 1999; Frye and Vongher, 1999a,b,c,d,e, 2001; Holzbauer, 1975, 1976, 1985; Holzbauer et al., 1985). During the diestrous phase of the estrous cycle, progestin levels of female rats (P: 20-60 nmol/l; 3α,5α-THP 5–25 nmol/l) are low similar to that of males (P: 1–45 nmol/l; 3α,5α-THP 1–20 nmol/l). However, during the proestrous phase (P: 60–100 nmol/l; 3α,5α-THP 25–40 nmol/l) and pregnancy (P: 75–150 nmol/l; 3α,5α-THP 50–75 nmol/l), progestin levels of females are much higher than that of males.

Sex differences in progestin levels are mainly due to gonadal and adrenal sources; however, central biosynthesis of 3α,5α-THP may also be a source of differences in progestin concentrations. E_2 also varies with progestins over reproductive cycles and can enhance biosynthesis of progestins in brain and may influence processes related to effects of drugs of abuse (Carroll et al., 2004; Cheng and Karavolas, 1973; Frye and Rhodes, 2005a,b,c; Malendowicz, 1976; Resko et al., 1986; Vongher and Frye, 1999). However, effects of E_2 are not discussed further here, as this topic is addressed comprehensively in another contribution to this special issue.

3. Progestins and motivated behaviors

In animal models, progestins can influence the expression of motivated behaviors, such as feeding, fighting, fleeing, and mating. During reproductive cycles, when progestin levels are higher, the incidence of many motivated behaviors, including feeding, anti-conflict behavior, running wheel activity and lever presses, and sexual behavior, are greater than during the low-progestin phases of the cycle (Canonaco et al., 1990; Gerall and Dunlap, 1973; Gerall et al., 1973; Kanarek and Beck, 1980; Roberts et al., 1989a,b; Roth et al., 2005). Ovariectomy (ovx), removal of the ovaries which are the primary endogenous peripheral source of progestins, obviate cyclic increases in these motivated behaviors. Administration of P and/or its metabolites, but not vehicle, reinstates increases in food consumption, anti-aggressive behavior, running wheel activity and lever presses, and sexual behavior of ovx rats to levels which are comparable to that observed over the estrous cycle (Bless et al., 1997; Canonaco et al., 1990; Chen et al., 1996; Frye, 2001a,b; Marrone et al., 1975; Mascarenhas et al., 1992; Miczek et al., 2003; Pinna et al., 2005).

4. Progestins and lordosis

The lordosis reflex that sexually-receptive rodents display in response to mating-relevant stimulation is a motivated behavior that has been extensively utilized to ascertain effects and mechanisms of progestins. Using a standard laboratory mating paradigm, we have placed proestrous females with male rodents in a small arena, and the incidence and intensity of the female's lordosis response is assessed for a maximum of 10 min. Mice (c57s) that have higher incidence and intensity of lordosis on initial mating have greater central levels 3α,5α-THP than P in the hypothalamus and midbrain, brain areas that are required for P-facilitated mating (Frye and Vongher, 2001). As well, there are differences in lordosis and midbrain 3α,5α-THP levels of adult rats that were selectively bred for divergent anxiety responses to maternal separation as infants (Frye et al., 2006b,c,d). Adult rats that demonstrated higher infantile anxiety responses showed significantly greater incidence and intensity of lordosis, solicitation behavior, anti-aggressive behavior, and midbrain 3α,5α-THP than do their counterparts that were bred for low anxiety responses perinatally (Table 1). These findings suggest

Table 1
Reproductive and endocrine measures of adult, proestrous rats (n=8–16/grp) that were selectively bred for infantile vocalization responses to maternal separation

Measure	Rats selectively-bred for response to maternal separation as infants	
	High-anxiety	Low-anxiety
Incidence of lordosis (%)	80±6*	54±10
Intensity of lordosis	2.3±0.2*	1.4±0.3
Incidence of solicitation (%)	54±9#	33±10
Incidence of aggression (%)	17±5*	36±11
Plasma 3α,5α-THP levels (not-tested rats — nmol/l)	110±9#	84±10
Plasma 3α,5α-THP levels (tested rats — nmol/l)	168±21*	90±13
Midbrain 3α,5α-THP levels (not-tested rats — nmol/g)	27±5#	16±4
Midbrain 3α,5α-THP levels (tested rats — nmol/g)	18±2*	10±1

* Indicates analyses of variance or t-tests reveal a significant difference ($p<0.05$) between groups. # Indicates analyses of variance or t-tests reveal a tendency for differences ($p<0.10$) between groups.

that individual variability in reproductive behavior may be associated with endogenous differences in 3α,5α-THP.

Manipulating levels of progestins also alters reproductive behavior. Administering P or 3α,5α-THP systemically, to the hypothalamus, and/or midbrain, facilitates lordosis behavior of ovx, E_2-primed rodents (Frye, 2001a,b; Frye and Gardiner, 1996; Frye and Vongher, 1999c,d, 2001; Frye et al., 2004). Experimental manipulations that increase 3α,5α-THP, independent of P levels in midbrain, are sufficient to enhance lordosis (Frye, 2001a,b; Frye et al., 2003, 2004; Frye and Petralia, 2003a,b; Frye and Seliga, 2003). Inhibiting P's metabolism to 3α,5α-THP by systemic or intra-VTA infusions of metabolism inhibitors decreases lordosis commensurate with lowering 3α,5α-THP levels (Frye and Vongher, 2001; Frye et al., 1998; Petralia et al., 2001; Petralia and Frye, 2005). These findings demonstrate that there are causal effects of 3α,5α-THP in the midbrain VTA to facilitate lordosis.

Findings, such as these, have led us to consider the extent to which effects of 3α,5α-THP on lordosis are related to its effects on anxiety and/or changes in sensory processing. As such, we have begun to use another approach to examine this.

5. Progestins and paced mating

Although using lordosis as a bioassay has been advantageous to begin to elucidate progestins' actions in the VTA, there are serious limitations to this approach. First, lordosis may not be the most sensitive behavioral measure. It is a species-typical, stereotypic posture that female rodents assume to enable mating. Due to its reflexive nature, lordosis may be more impervious to manipulations, or subtle variations in response to manipulations, may not be evident. Second, the experimental paradigm of standard mating, which is typically employed when lordosis is used as a bioassay, is limited. In a standard mating paradigm, rats are typically placed in small arenas (aquaria) that may not enable the full complement of behaviors to be expressed and/or readily observed. Indeed, in a standard mating paradigm, male rats readily maneuver females into corners. Because females cannot escape in this situation, mating is very "efficient" and involves minimal social interaction, limiting the face validity and broader interpretations from this measure.

More naturalistic mating is characterized by exploration and affiliations, social behaviors that bring individuals together, as well as reproductive and aggressive behaviors (Carter et al., 1999). Reproduction requires that exploration occurs to find mates, that fearful responses to potential mates are suppressed, and that approaches are made to stimuli that previously elicited aggressive responses (Carter et al., 1999). Hence, exploration must be enhanced and aggressive behaviors inhibited for mating to occur. The prior section discussed evidence that 3α,5α-THP mediates lordosis. Notably, 3α,5α-THP may have a role in other mating-relevant behaviors (solicitation, aggression, anxiety), which suggest its functional role extends beyond the reflexive lordosis posture. The approaches and data in support of this are presented below.

One approach that we have used to address progestins' role and mechanisms in motivated behaviors beyond lordosis is to utilize a more ethologically-relevant mating paradigm. In semi-natural "paced" mating paradigms, female rats control sexual contacts from a male, the mating sequence takes longer to occur, and the resulting fertility and fecundity are greater than what occurs with standard mating (Coopersmith and Erskine, 1994; Frye and Erskine, 1990). Interestingly, female rats that can pace their reproductive contacts, but not those which are standard mated, demonstrate mating-induced conditioned place preference (CPP; Paredes and Alonso, 1997; Frye et al., 1998; Gonzalez-Flores et al., 2004). Notably, formation of 3α,5α-THP is necessary for paced mating to occur and paced mating (like standard mating—Table 1) also increases biosynthesis of 3α,5α-THP (Frye et al., 1996, 1998, 2000; Frye, 2002; Paredes and Alonso, 1997). Although these findings suggest that formation of 3α,5α-THP may underlie some of the uniquely rewarding aspects of paced mating, whether paced mating requires 3α,5α-THP stimulation of $GABA_A$ receptors, and/or can be mimicked by other $GABA_A$ agonists is not known but is the subject of future investigations in our laboratory.

6. Progestins and approach of novel stimuli

Because a defining aspect of paced mating is that female rats approach males, and progestins are integral for this, we have begun to investigate whether progestins enhance interaction with other novel stimuli. To address whether P would also influence approach of ovx rats towards a novel female, ovx rats were administered P (4 mg/kg, SC) or sesame oil vehicle and then placed in an open field with a novel conspecific. During a 5 min observation period, P administered rats (109±7 s) spent significantly longer in social interaction than did vehicle-administered rats (35±5 s). To ascertain whether these effects extended to novel stimuli, ovx rats were placed in an open field with two novel objects that were the same and the duration of time they spent investigating these objects was recorded for 3 min. Immediately after this training, rats were administered P

Table 2
Effects of P (4 mg/kg SC; $n=6$–8/grp) or vehicle (sesame oil, 0.2 cc, SC; $n=6$–8/grp) administration to ovariectomized rats on behavioral measures of approach in the social interaction, object recognition, and Y-maze tasks and endocrine measure (plasma and midbrain P and 3α,5α-THP levels)

Task/measure (units)	Compound administered	
	Progesterone	Vehicle
Social interaction/time with conspecific (% of total time)	37±7*	11±5
Object recognition/time with new object (% of total time)	76±7*	42±11
Y-maze/time in novel arm (% of total time)	62±6*	48±2
Plasma P levels (nmol/l)	96±15*	44±10
Plasma 3α,5α-THP levels (nmol/l)	48±21#	21±12
Midbrain P levels (nmol/g)	46±13*	16±4
Midbrain 3α,5α-THP levels (nmol/g)	23±7#	15±5

* Indicates analyses of variance or *t*-tests reveal a significant difference ($p<0.05$) between groups. # Indicates analyses of variance or *t*-tests reveal a tendency for differences ($p<0.10$) between groups.

(4 mg/kg, SC) or vehicle. Four hours later, rats returned to the open field and the duration of time spent exploring a novel and a familiar object was recorded. As data shown in Table 2 indicate, P administration increased the time spent investigating the novel object. Although there were no controls for habituation to the novel situation as opposed to the object in this paradigm, similar results were observed when effects of progestins on exploration of the novel arm in a Y-maze were investigated using a protocol previously described (Conrad et al., 2004). As Table 2 shows, P also increased the time spent in the novel arm over that observed with vehicle administration. As well, the P regimen used produced physiological levels of P and 3α,5α-THP in plasma and midbrain. Together, these findings suggest that progestins may enhance approach to novel stimuli; however, whether approach is facilitated due to increases in locomotion, effects on memory and/or anxiety were not revealed.

7. Progestins, estrogen and conditioning

Progestins, in conjunction with E_2, may influence discrimination and/or recall of familiar and/or novel factors in the environmental stimuli. Implicit memory involves associative learning, when two events occur together and one learns about the association between them. This kind of cognitive process relies upon the striatum and amygdala, for emotional associations. Effects of hormones on conditioning were originally proposed by one of the pioneering researchers in Behavioral Endocrinology, Frank Beach, when he was mentored by Karl Lashley, an eminent investigator in learning and memory (Beach, 1937). During behavioral estrus (proestrus), when rats are most receptive to mating, acquisition of conditioned avoidance responses is reduced compared to on diestrous (Diaz-Veliz et al., 2000), which may enable aversive aspects of mating to be tolerated. Environmental stimuli associated with mating, when E_2 and progestin levels are elevated, readily become conditioned stimuli (Domjan, 2005). For example, rats that have high E_2 and progestin levels readily learn to show preference for a setting associated with mating (Frye et al., 1998; Gonzalez-Flores et al., 2004; Oldenburger et al., 1992; Paredes and Alonso, 1997). Further, when there are endogenous or exogenous increases in E_2 and P, the rewarding value of brain stimulation is enhanced (Bless et al., 1997) and levels of dopamine in the VTA and nucleus accumbens are greater (Russo et al., 2003a,b). Together these findings suggest that progestins and/or E_2 may enhance conditioning for rewarding stimuli associated with mating.

As discussed above, female rats that are allowed to pace their contacts with males readily show a preference for the place associated with mating (Paredes and Alonso, 1997; Frye et al., 1998, 2000; Gonzalez-Flores et al., 2004). We have investigated this further to ascertain estrous cycle differences in pacing-enhanced conditioning. Experimental female rats were placed on one side of a conditioning chamber that allows them to "pace" and/or control their interactions with a male for 20 min. 6 h later, females' preference for the side associated with the male was assessed in a 30 min test. Our data (Fig. 1) shows that rats in the P-dominant cycle phase, behavioral estrus (proestrus), are more readily conditioned than diestrous or estrous rats, which have low P levels but discrepant estrogen levels. Proestrous spent more time on the side associated with the male (125±11 s) than did estrous (20±8 s) or diestrous (23±3 s) rats. These findings suggest that progestins, rather than E_2, may underlie the hormonal effects on conditioning observed. Furthermore, they are commensurate with the findings from other laboratories which demonstrate that conditioning to sexually-relevant stimuli can occur readily (Domjan, 2005; Paredes and Alonso, 1997) with even a one-trial conditioned place preference approach. As discussed below, typically 4 or 6 pairings is necessary when hormones are administered alone without being paired with sexually-relevant stimuli. Perhaps conditioning occurs so readily in response to sexually relevant because of enhanced neurosteroidogensis that mating can evoke (Frye, 2001a,b), which may

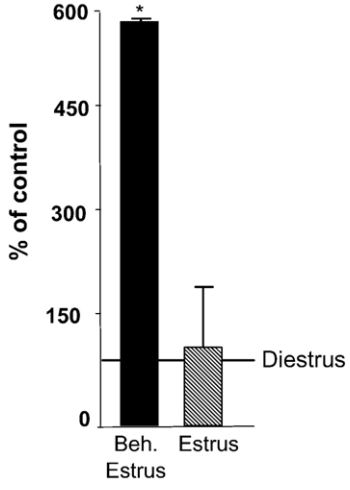

Fig. 1. The percentage difference in time spent on the male-associated side of the chamber for rats ($n=2$–4/grp) in proestrus (behavioral estrous; black bar) or estrous (diagonal striped bar) versus that of control diestrous rats for mating-induced conditioned place preference. Female rats in proestrus show a greater mating-induced conditioned place preference than do rats in estrus. * Indicates analyses of variance or *t*-tests reveal a significant difference ($p<0.05$) between groups.

serve to consolidate reproductively-relevant information and/or reduce anxiety to a novel context.

8. Progestins alone and conditioning

Evidence from the literature suggests that progestins can enhance conditioning in the absence of E_2. Administration of 3α,5α-THP to mice produces CPP (Finn et al., 1997) and state dependent reward (Romieu et al., 2005). Among rats, 3α,5α-THP administration can dose-dependently increase the release of dopamine in the nucleus accumbens (Rouge-Pont et al., 2002). However, a conditioned place aversion has been demonstrated among rats administered 3α,5α-THP (Beauchamp et al., 2000).

Progestins can act as a discriminative stimulus in rats perhaps related to their profound anesthetic effects (Selye, 1942). P (100 mg/kg, IP, 15–30 min before the test) and a synthetic hypnotic (viadril 25 mg/kg) exert similar discriminative stimulus effects in the T-maze (De Beun, 1999; Stewart et al., 1967). In other drug discrimination paradigms, P is discernable from vehicle, and generalizes to pentobarbital (Gorzalka et al., 1995; Heinsbroek et al., 1987a,b). In conditioned aversion tasks, P decreases avoidance behavior (Farr et al., 1995; Manshio and Gershbein, 1975). Findings from people are limited. Subjective memory complaints during pregnancy are associated with impairments in implicit memory (Buckwalter et al., 1998), which may be related to progestins having effects on optimal levels of arousal for performance. Because these findings suggest that progestins may have salient effects to enhance conditioning, we have begun to investigate this further using the CPP task.

9. Progestins and conditioned place preference

Conditioned place preference has been used to determine the rewarding effects of compounds by establishing the contingent associations between an agent administered and environmental stimuli paired with the agent (White and Carr, 1985). We have demonstrated that progestins can enhance CPP of rats (Frye, 2006a), which is mediated by the nucleus accumbens. In our CPP paradigm for rats, after 2 days of habituation to the CPP chamber, there is a baseline test day. Rats were then assigned to either receive vehicle or P (4 mg/kg) paired with the originally non-preferred side of the chamber on conditioning days (1–2 and 5–7). All rats receive vehicle paired with the originally preferred side of the chamber on control days (3–4 and 8–9). 24 h after the last pairing, rats are given a preference test. In OVX rats, pairing P with the originally non-preferred side of the chamber nearly doubled the time spent on the originally non-preferred side of the chamber on the test day. Notably this was not seen in vehicle-administered rats (Fig. 2). These data suggest that P can enhance CPP of rats.

To begin to address the putative mechanisms by which P may influence CPP, we have also investigated P's effects on CPP when administered to wildtype or progestin receptor knockout (PRKO) mice. A slightly different CPP paradigm is utilized for mice (Finn et al., 1997). Mice were habituated for 1 day to the conditioning apparatus. For the next 4 days, mice were administered P (10 mg/kg) or vehicle and placed in the conditioning chamber that had either a grid floor or a floor with holes in it. The following

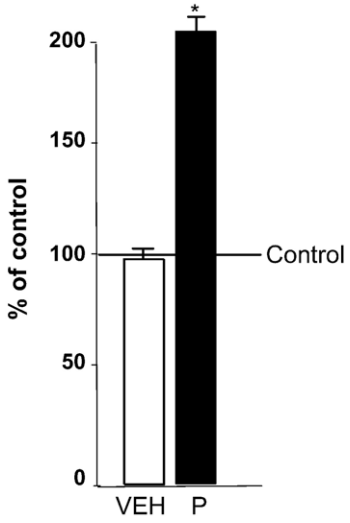

Fig. 2. The percentage difference in time spent on the originally non-preferred side of the chamber (control) when ovx rats (n=8–12/grp) that had been administered progesterone (4 mg/kg, SC; black bar) versus vehicle (open bar) on training days were subsequently tested for side preference. * Indicates analyses of variance revealed a significant increase ($p<0.05$) in conditioned place preference for P compared to vehicle administered ovx rats. *$p<0.05$.

4 days, mice were administered vehicle and placed in the chamber that had a floor type opposite to that they were exposed to previously. On test day, the floor of the conditioning chamber was equally divided so that half is a "grid" floor and half is a "hole" floor. The amount of time that mice spend on each floor type was recorded. P had similar effects to produce a place preference in wildtype and PR knockout (PRKO) mice compared to vehicle (Fig. 3). These data suggest that P can produce a CPP in mice and that these effects can occur independent of actions at nuclear PRs. Given that PRKO mice readily convert P to 3α,5α-THP (Frye et al., 2006d; Frye and Vongher, 1999a,b,c,d,e), 3α,5α-THP does not bind to PRs (Rupprecht and Holsboer, 1999), and 3α,5α-THP has been demonstrated to enhance CPP of mice in this paradigm (Finn et al., 1997), these findings are consistent with the notion that 3α,5α-THP may underlie effects of progestins to enhance conditioning. These findings that 3α,5α-THP may underlie such effects also provoke the question as to whether these data may not be explained by effects on conditioning and instead by simply a reduction in anxiety. Indeed, we have demonstrated that this P regimen can also reduce anxiety behavior, enhance 3α,5α-THP levels, and have agonist-like actions at $GABA_A$ receptors similarly among wildtype and PRKO mice (Frye et al., 2006b,c,d).

10. Progestins, stress, HPA function

It has been proposed that 3α,5α-THP may be an important neuroendocrine regulator that may mediate responses to stress and/or environmental stimuli (Engel and Grant, 2001). In support, previous studies show that both 3α,5α-THP antibody (Purdy et al., 1991) and THDOC administration (Owens et al., 1992) to rats reduce plasma corticosterone levels in response to stress, showing that neurosteroids attenuate HPA axis. These effects are likely due to inhibition of hypothalamic $GABA_A$ receptors that regulate CRH

transcription, peptide levels, secretion and subsequent activation of pituitary and adrenal responses. For example, administration of 3α,5α-THP to ovx rats decreases hypothalamic pituitary adrenal axis function. Acute administration of 3α,5α-THP counteracts the anxiogenic activity of CRH and interferes with corticosteroid mediated regulation of CRH release and gene transcription (Patchev et al., 1994). Acute administration of P can buffer glucocorticoid feedback on the gene expression of CRH in the hypothalamus and corticosteroid receptors in hippocampus (Patchev and Almeida, 1996). Based upon these findings, we investigated whether P administration to ovx rats alters plasma corticosterone levels. Ovx rats were administered 4 mg/kg of P or 3α,5α-THP 3 h before tested in the open field, plus maze, and social interaction tasks. Immediately following this test battery, serum was collected and corticosterone levels were measured by radioimmunoassay. As Fig. 4 illustrates, behavioral testing produced modest increases in plasma corticosterone secretion of ovx rats, but P or 3α,5α-THP administration attenuated this. These data, and the findings from the literature discussed above, suggest that P and 3α,5α-THP may enhance parasympathetic activity and thereby have effects to quiet stress-induced HPA (over)-activation.

The other main body of evidence that 3α,5α-THP may be an important neuroendocrine regulator that mediates stress responses is that 3α,5α-THP is increased rapidly in response to environmental stimuli. In support, a number of different types of acute stressors can alter 3α,5α-THP production. Elevations in plasma and central 3α,5α-THP levels occur rapidly (within 5 min) in response to ambient temperature swim stress (Purdy et al., 1991). Ether exposure can increase plasma levels of P (Erskine and Kornberg, 1992). Exposure to acute foot shock can increase levels of 3α,5α-THP in the cerebral cortex (Drugan et al., 1993). In addition to these life-threatening stimuli, other less aversive events can also alter 3α,5α-THP production. As previously indicated, mating produces rapid and robust increases in midbrain 3α,5α-THP levels in the absence of peripheral sources of steroid hormones from the ovaries and/or adrenals (Frye et al., 1996, 1998; Frye and Bayon, 1999; Frye, 2001a,b).

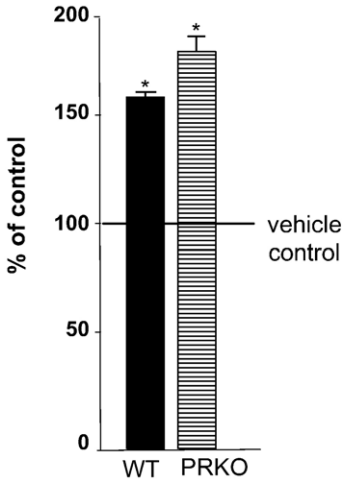

Fig. 3. The percentage difference in time spent on the conditioned floor of wildtype (WT; black bars) or PRKO (horizontal striped bars) mice (n=4–8/grp) that were administered P (10 mg/kg SC) paired with conditioning versus vehicle (sesame oil). P administration increases conditioned place preference in both WT and PRKO mice compared to vehicle control. * Indicates analyses of variance revealed a significant increase ($p<0.05$) in conditioned place preference at test time for P administered mice compared to vehicle controls. *$p<0.05$.

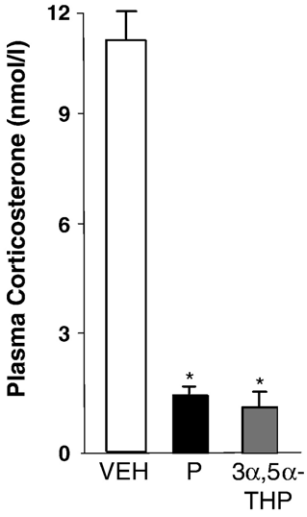

Fig. 4. Plasma levels of corticosterone following behavior testing for ovx rats (n=4–8/grp) administered P (4 mg/kg, SC; black bars), 3α,5α-THP (4 mg/kg, SC; grey bars) or vehicle (sesame oil 0.2 cc; open bars). * Indicates analyses of variance revealed a significant decrease ($p<0.05$) in corticosterone levels for P or 3α,5α-THP-administered mice.

In addition to behavioral experiences having salient effects to alter 3α,5α-THP production, evidence is emerging that some drugs of abuse may also alter neuroosteroidogenesis. Administration of various drugs of abuse has also been demonstrated to enhance production of 3α,5α-THP. For example, systemic administration of delta9-tetrahydrocannabinol can increase cortical levels of 3α,5α-THP (Grobin et al., 2005). High, but not lower, dosages of morphine also enhance cortical levels of 3α,5α-THP (Grobin et al., 2005) and 3α,5α-THP administration amplifies the release of dopamine in the nucleus accumbens in response to morphine (Rouge-Pont et al., 2002). Ethanol administration increases plasma and cortical concentrations of 3α,5α-THP (Barbaccia et al., 1999; Hirani et al., 2002; Janis et al., 1998; Morrow et al., 1999; VanDoren et al., 2000). The levels of 3α,5α-THP following these drug regimen are commensurate with those naturally produced by other rewarding behaviors, such as mating (Frye et al., 2001). P and 3α,5α-THP administration regimen that facilitate mating do so in part through their actions at $GABA_A$, NMDA and/or D_1 receptors in the midbrain. It is possible that drug-induced increases in 3α,5α-THP biosynthesis may have effects on anxiety/stress, conditioning, and/or rewarding effects through actions at these substrates. Given that: anxiety/stress responses, motivation, conditioning, and reward are processes that underlie drug effects, 3α,5α-THP can have a bearing upon these factors, and some drugs have been demonstrated to alter 3α,5α-THP levels, we have begun to investigate interactions between progestins and cocaine. Evidence is discussed below that suggest that gender and/or hormonal milieu, associated with differences in progestin concentrations, may mediate response to cocaine.

11. Gender/sex differences in response to drugs of abuse

Gender differences in drug addiction, relapse, craving, rate of drug use, and subjective effects of people suggest that women may be more sensitive to effects of drugs, such as cocaine (Chen and Kandel, 2002; Kosten et al., 1996; Robbins et al., 1999). Although men have more opportunities to try cocaine, women are as likely as men to use cocaine once exposure has occurred (Van Etten et al., 1999). Women are more likely to experience more nervousness after cocaine use, take longer to feel subjective effects of cocaine, report less euphoria and dysphoria, have more severe drug use, and have stronger cravings in response to cues, than do men (Kosten et al., 1996). Thus, women may experience greater physiological arousal in response to cocaine and the subjective effects may persist for longer, leading perhaps to more severe drug use and/or stronger cravings in response to cues.

There are also sex differences in response to cocaine in animal models. Female rats have greater locomotor and stereotypic behaviors than do male rats after acute and chronic cocaine administration (Festa et al., 2003, 2004; Van Etten and Anthony, 2001). Female rats require lower dosages of cocaine to achieve responses similar to those of male rats, and their behavioral responses persist longer than do male responses (Festa et al., 2004). Female rats self-administered cocaine faster and more often and develop faster contiguous associations between environmental context and cocaine's rewarding properties than do male rats (Lynch et al., 2000; Lynch and Carroll, 1999, 2000). Thus, female, as compared to male, rats may show greater sensitivity to the psychomotor effects of cocaine, and may more readily consume cocaine and condition to its effects.

12. Progestins and response to drugs of abuse

Women's hormonal milieu may influence their subjective response to cocaine. Women who use cocaine have attenuated subjective responses and less desire to smoke cocaine during the progestin-dominant luteal phase than during the follicular phase of the menstrual cycle (Evans et al., 2002; Sofuoglu et al., 2002). Oral administration of P may attenuate some of the subjective and/or the cardiovascular effects of cocaine self-administration in both men and women (Evans and Foltin, 2006; Sofuoglu et al., 2002; Sofuoglu et al., 2004). Thus, these findings suggest that progestins may dampen women's response to the effects of cocaine.

In animal models, progestins may also dampen effects of cocaine. In support, psychomotor effects of cocaine and self-administration are lower during the progestin-dominant phase of the estrous phase (Quinones-Jenab et al., 1999; Roberts et al., 1989a). Progesterone administration to rats attenuates CPP induced by cocaine and E_2-induced cocaine sensitivity/sensitization (Becker, 1999; Jackson et al., 2006; Niyomchai et al., 2005; Russo et al., 2003a,b; Sircar and Kim, 1999). Thus, these findings suggest that P may dampen rats' psychological and/or physiological response to the effects of cocaine.

To address this further, in collaboration with Dr. Quiñones-Jenab, we have investigated what the effects of cocaine are on HPA responses and de novo production of 3α,5α-THP and the extent to which P administration may alter these effects. Adult ovx female and gonadectomized male rodents were administered P (500 μg, SC) or sesame oil vehicle 3 to 4 h prior to cocaine (5 mg/kg IP for males or 20 mg/kg IP for females) or saline vehicle administration. As Table 3 indicates, P had modest effects in male and female rats to dampen plasma corticosterone secretion compared to vehicle administration. Cocaine had very dramatic effects to increase corticosterone secretion but co-administration of P dampened these responses. In the serum, striatum and hippocampus, cocaine also enhanced P and 3α,5α-THP levels, to concentrations which were comparable to that produced by P administration in the absence of cocaine, but co-administration of P and cocaine dampened down these stress-induced increases in neuroendocrine levels. Notably, the levels of progestins produced by cocaine or P alone were commensurate with circulating concentrations of P that we have previously demonstrated can produce mnemonic effects in learning tasks mediated by the striatum or hippocampus, whereas co-administration of P and cocaine produced lower levels of progestins and corticosterone, which may underlie the effects of P administration to obviate cocaine-induced CPP (Frye et al., 2006b,c,d; Frye and Rhodes, 2006; Niyomchai et al., 2005; Russo et al., 2003b; Walf et al., in press). Further, these findings suggest that physiological and/or interoceptive effects of cocaine may involve stress-induced increases in corticosteroids and progestins and that administration of P may dampen some of the psychotropic effects of cocaine by attenuating stress-induced activation of neuroendocrine responses. It is important to note that it has also been reported that cocaine has no effect on 3α,5α-THP levels (Grobin et al., 2005).

13. Progestins, sensory and/or attentional processing

It is also important to note that progestins can also influence sensory and/or attentional processes. There are menstrual cycle variations in sensitivity to tactile stimuli, olfaction and visual detection (Bereiter and Barker, 1980; DeMarchi and Tong, 1972; Diamond et al., 1972; Henkin, 1974; Kenshalo, 1996; Sommer, 1973; Zimmerman and Parlee, 1973). Among rodents, size of receptive fields for the whisker barrel, flank, or perineum is greater

Table 3
Effect of progesterone and/or cocaine administration on plasma corticosterone (B, nmol/l), circulating progesterone (P) and 3α,5α-THP levels (nmol/l) and P and 3α,5α-THP (nmol/g) levels in the striatum and hippocampus (n=6–8 observations/grp)

	Plasma			Striatum		Hippocampus	
	B	P	3α,5α-THP	P	3α,5α-THP	P	3α,5α-THP
♀, Vehicle, saline	4±1	55±9	30±3	18±6	12±4	46±10	37±15
♀, Vehicle, cocaine	42±12	95±15	52±8	29±10	20±6	75±10	64±16
♀, P, saline	2±1	92±28	54±4	21±8	20±6	58±15	52±7
♀, P, cocaine	32±6	36±5	36±6	16±9	13±5	48±14	32±9
♂, Vehicle, saline	2±1	41±3	20±3	15±4	10±3	35±9	26±9
♂, Vehicle, cocaine	27±8	73±12	45±9	22±5	18±6	49±15	36±10
♂, P, saline	1±1	82±20	39±10	19±6	14±5	42±14	30±10
♂, P, cocaine	21±5	60±19	29±9	18±6	12±5	37±11	33±9

when hormone levels are high (Frye and Rhodes, 2005a,b,c; Kow and Pfaff, 1983). Progestins can also enhance attentional processes. Rats in behavioral estrus show less distractability than do diestrous rats (Birke et al., 1979). Improved performance on perceptual restructuring tasks is seen during the progestin dominant luteal phase (Broverman et al., 1968; Klaiber et al., 1974). Thus, it will be important to evaluate how progestins' effects on these processes may also influence the outcomes discussed above.

14. Summary

Findings have been presented that demonstrated that: P and/or 3α,5α-THP can enhance, or be increased by rewarding behavior and that some of these effects occur independent of actions at intracellular PRs, implying actions of 3α,5α-THP via its substrates, which include $GABA_A$, NMDA, and/or D_1 receptors. Administration of P or 3α,5α-THP can enhance approach and dampen corticosterone secretion. 3α,5α-THP is increased in response to novel stressors, including cocaine administration. P administration can dampen stress hormone secretion in response to cocaine administration. These findings suggest that progestins may have effects on reward, conditioning and/or stress hormone secretion that may influence vulnerability to drug abuse.

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