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The Role of Progestins in the Behavioral Effects of Cocaine and Other Drugs of Abuse: Human and Animal Research

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Abstract

This review summarizes findings from human and animal research investigating the influence of progesterone and its metabolites allopregnanolone and pregnanolone (progestins) on the effects of cocaine and other drugs of abuse. Since a majority of these studies have used cocaine, this will be the primary focus; however, the influence of progestins on other drugs of abuse will also be discussed. Collectively, findings from these studies support a role for progestins in: 1) attenuating the subjective and physiological effects of cocaine in humans, 2) blocking the reinforcing and other behavioral effects of cocaine in animal models of drug abuse, and 3) influencing behavioral responses to other drugs of abuse such as alcohol and nicotine in animals. Administration of several drugs of abuse in both human and nonhuman animals significantly increased progestin levels, and this is explained in terms of progestins acting as homeostatic regulators that decrease and normalize heightened stress and reward responses which lead to increased drug craving and relapse. The findings discussed here highlight the complexity of progestin-drug interactions, and they suggest a possible use for these agents in understanding the etiology and developing treatments for drug abuse.

Keywords

Progesterone; Allopregnanolone; Drug dependence; Cocaine; Animal models; Sex differences

Introduction

Research with humans indicates that females, compared to males, exhibit greater vulnerability to several drugs of abuse at stages of the addiction process that mark transitions in drug use such as initiation, bingeing, withdrawal, and relapse. Women are more likely to initiate cocaine use at an earlier age than men (Chen and Kandel, 2002) and they are more vulnerable to binge-like patterns of alcohol intake (Mann et al., 2005; Randall et al., 1999). Women also report greater difficulty in quitting cigarette smoking (Carpenter et al., 2006) and report greater craving after quitting cocaine (Robbins et al., 1999) than men. They are more sensitive to stress-induced craving of cocaine (Fox and Sinha, 2009), are more likely to relapse (Ignjatova and Raleva, 2009), and also take more cocaine following relapse (Gallop et al., 2007).

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Animal models of drug abuse add further support to enhanced female vulnerability across these stages of the addiction process by indicating that female rats acquire drug self-administration at a faster rate (Chaudhri et al., 2005; Fattore et al., 2007; Jackson et al., 2006; Lynch 2008; Lynch and Carroll, 1999), exhibit greater binge-like patterns of drug intake (Roth and Carroll, 2004), and are more vulnerable to relapse of drug-seeking behavior (Anker and Carroll, 2010; Kerstetter et al., 2008; Kippin et al., 2005; Lynch and Carroll, 2000). The animal literature suggests that females are more vulnerable to several aspects of drug abuse than males, possibly due to an underlying biological predisposition. Thus, it is important to not only identify biological vulnerability factors that could contribute to the onset and progression of drug abuse in women but to consider possible sex-specific treatments as well.

An increasing number of findings indicate that these sex differences are influenced by female gonadal hormones. Specifically, increases in drug-related responses in humans are associated with higher levels of endogenous estrogen (EST) (Evans et al., 2002; Sofuoglu et al., 1999). Systemic administration of EST also increases measures of drug-seeking behavior in animal models of drug abuse (Anker et al., 2007, 2009; Becker, 1990b; Jackson et al., 2006; Larson and Carroll, 2007; Larson et al., 2005, 2007). Thus, EST has emerged as a major facilitator of drug effects in females. Progesterone (PROG) has received less attention than EST, but recent findings indicate that PROG, and its metabolites allopregnanolone (ALLO) and pregnanolone, collectively termed progestins (see Frye, 2007), may also be important in altering drug effects during critical stages of the drug abuse process. Of the abused drugs that have been studied, results with cocaine have been the most consistent (Turner and de Wit, 2006); however, other drugs such as alcohol and nicotine have also been examined.

Evidence suggests that hormones may interact with stress and reward systems to affect drug-taking/-seeking behavior. Stress is a major vulnerability factor in drug addiction and it is regulated by several neurobiological systems including the hypothalamic-pituitary-adrenal (HPA) axis (Sinha, 2008). The reward system, which includes dopamine circuitry in the nucleus accumbens (NAc) and ventral tegmental areas of the brain, is also integral to the formation and persistence of addictive behaviors associated with drug abuse (Brieter et al., 1997; Spangel and Wiess, 1999; Volkow et al., 1999).

The purpose of this review is to discuss human and animal research examining the influence of progestins on behavior maintained by cocaine and other drugs of abuse. The paper begins with a small section describing the biosynthesis of progestins and follows with sections devoted to research on the influence of endogenous and exogenously-administered progestins on cocaine-induced subjective and physiological effects in humans. These sections are followed by a discussion of findings from animal research examining cocaine self-administration during critical phases of the animal model of drug abuse under different hormonal conditions, either during the rat or monkey hormone cycle or following systemic progestin administration. Human and animal research examining the interaction between progestin's and other drugs of abuse such as alcohol and nicotine will then be considered. Finally, mechanisms that may underlie the influence of progestins on behaviors induced by drugs of abuse are described in the final section of the paper. Particular attention is given to the effects of progestins on systems that are thought to underlie drug abuse, such as the stress and reward systems.

Biosynthesis of progestins

In the female mammalian body, the primary source of EST is secretion by the ovaries (Frye, 2007), while the ovaries and the adrenal glands synthesize PROG. ALLO is also secreted by

the ovaries as well as the adrenal glands, and it is manufactured in glial cells (Kabbadj et al., 1993). However, the primary source of ALLO and pregnanolone is through metabolism of peripheral sources of PROG (Frye, 2007). The conversion of PROG into its metabolites occurs in a series of metabolic steps. Pregnenolone is converted to PROG which is then reduced to 5-alpha-dihydroprogesterone (DHP) and 5-beta-DHP by 5-alpha- and -beta-reductase, respectively. ALLO and pregnanolone are subsequently synthesized from the 5-alpha and 5-beta forms of DHP by 3-alpha-hydroxysteroid oxidoreductase (Mellon, 2004). For clarification, pregnenolone with an e is the precursor to PROG and pregnanolone with an a is a metabolite of PROG.

Progestin effects on cocaine-induced behavior: human research

Two methods are primarily used in human research to investigate the effects of progestins and other female hormones on drug-related behaviors. The first compares drug-elicited responses across different phases of the female hormone cycle, while the second involves direct manipulation of hormone levels by their systemic administration. Most studies have employed the former method and have focused on menstrual cycle interactions with stimulant-elicited subjective and physiological responses. The 28-day human menstrual cycle is composed of two main phases: follicular and luteal, each characterized by differing levels of the female hormones, EST and PROG (see Figure 1). During the follicular phase (~14 days) PROG levels remain low (10 ng/ml), similar those of men (10 ng/ml), and EST levels increase until they peak just prior to ovulation (210 pg/ml). Ovulation occurs right after the follicular phase and is characterized by declining levels of EST, low levels of PROG, and a surge of luteinizing hormone and follicle stimulating hormone (not shown). After ovulation, during the luteal phase (~7 days), EST levels continue to decline (50 pg/ml) and remain relatively low while PROG levels continue to increase (200 ng/ml), surpassing levels in men (Carter, 1994; Genazzani et al., 1998; Pearson Murphy and Allison, 2000; Redei and Freeman, 1995). The luteal phase also marks the period of largest increases of the PROG metabolites, ALLO and pregnanolone (Bixo et al., 1997).

Progesterone effects on cocaine across the menstrual cycle

In human research, fluctuations of PROG during the menstrual cycle correspond to differences in the physiological and subjective effects of cocaine. Cardiovascular and/or positive subjective responses to cocaine (Evans and Foltin, 2006; Evans et al., 2002; Sofuoglu et al., 1999) were reduced during the luteal phase of the menstrual cycle (when PROG levels are high) compared to the follicular phase in women.

These results have also been extended to measures of stress reactivity and craving elicited by cocaine-related stimuli in cocaine-dependent women (Sinha et al., 2007). In this study, participants were separated into three groups that had high, medium, or low levels of circulating PROG, corresponding to their midluteal, early luteal, and follicular phases of their menstrual cycles. Groups were then exposed to imagery related to a personally stressful event, or to cocaine-related cues, and compared on measures of cocaine craving, subjective anxiety, and diastolic and systolic blood pressure. Following the drug-cue exposure, women with high levels of PROG showed lower diastolic and systolic blood pressure responses and scored lower on self-reported measures of anxiety and drug craving than women with low levels of PROG. Heightened plasma PROG levels were also associated with less severe stress-induced craving for cocaine (Sinha et al., 2007). This result is particularly important, as stress has long been considered a primary vulnerability factor in addiction: drug abusers often report taking drugs in order to cope with stressful situations and to protect against potentially distressing withdrawal effects (Baker et al., 2004; Khantzian, 1985). Together these results indicate that the phase of the menstrual cycle in which PROG levels are at the

highest was associated with low positive affective responses to cocaine and diminished cue- and stress-induced cocaine craving.

In contrast, others have found no differences in the physiological and subjective responses to cocaine during the menstrual cycle (Lukas et al., 1996; Mendelson et al., 1999). However, methodological differences related to the route of cocaine administration may account for these discrepancies. Unlike findings with smoked cocaine (Evans et al., 2002; Sofuoglu et al., 1999), menstrual cycle phase failed to alter subjective or physiological measures following intranasal cocaine administration in women (Collins et al., 2007; Lukas et al., 1996). This lack of an effect may be related to menstrual cycle-dependent changes in nasal secretion. For example, high levels of EST are associated with nasal secretion (Philpott et al., 2004), which may decrease the absorption of cocaine into the nasal mucosa and lower the effects of intranasal cocaine during the EST-dominant follicular phase.

Systemic progesterone administration

The influence of systemic PROG administration on the subjective and physiological effects of cocaine has been examined in several studies using humans. In these experiments, PROG was administered in the micronized (extended release) form at a concentration that produces a physiological level comparable to the midluteal phase of the menstrual cycle.

Micronization of PROG results in a decrease in the size of PROG particles and substantially increases the bioavailability of the hormone (Morville et al., 1982). Results from a study conducted by Sofuoglu et al. (2002) indicated that women treated with PROG showed a decrease in the positive subjective effects of smoked cocaine compared with placebo-treated controls (Sofuoglu et al., 2002). This study was subsequently extended to examine PROG's effects on iv cocaine self-administration in female and male participants (Sofuoglu et al., 2004), and PROG failed to alter iv cocaine self-administration in both groups. This lack of a difference may have been due to a ceiling effect, as both groups self-administered their total allotment of cocaine infusions. However, physiological measures such as cocaine-induced increases in diastolic blood pressure and subjective ratings of "feeling high" and "feeling the effects of the last administered dose" were diminished in PROG-treated vs placebo-treated participants (Sofuoglu et al., 2004).

Similar results were also found in a study conducted by Evans and Foltin (2006). However, the inhibitory effects of PROG were variable and dependent on the cocaine dose as well as the sex of the participant. For example, PROG attenuated cocaine-induced increases in heart rate in women across all of the cocaine doses, but this effect was dose-specific in males. Subjective ratings of "feeling high," "overall drug quality," and "willingness to pay for an experimenter-administered dose of cocaine" were also decreased following PROG treatment in females, while PROG had little or no effect on these measures in male patients (Evans and Foltin, 2006). The lack of an effect in males was further supported by research in which PROG failed to decrease outpatient cocaine use in male cocaine users (Sofuoglu et al., 2007). Overall, results from human research indicated that endogenous and exogenous (i.e., systemically administered) PROG decreased certain cocaine-induced subjective and physiological responses, and this effect was generally specific to women.

Few studies using humans as subjects have examined the influence of PROG on motivational aspects of cocaine abuse (cf. Sofuoglu et al., 2004), and none have examined the influence of PROG's metabolites (ALLO or pregnanolone) on these measures. This would be of interest given that levels of these metabolites show significant increases during the luteal phase of the menstrual cycle when PROG levels are high (Bixo et al., 1997) or following systemic PROG injections (Soderpalm et al., 2004). Table 1 summarizes results across the menstrual cycle and PROG's effects on amphetamine- and cocaine-induced subjective measures in women.

Progestin effects on cocaine-induced behavior during different phases of drug abuse: animal models

There is typically close agreement between results from animal and human research in the screening, prevention, and treatment of drug abuse; thus, animal models of drug self-administration have translational value for the treatment of many aspects of this disorder (Carroll et al., 2009). Studies using animal models of drug self-administration have extended findings from human research and have examined PROG and its metabolite ALLO across critical phases of the drug abuse process that are unable to be studied in humans. As previously mentioned, these stages of drug abuse include initiation, bingeing, withdrawal, and relapse, and they are modeled in animals using acquisition, escalation, withdrawal/extinction, and relapse procedures (Carroll et al., 2009). The following section highlights major findings from animal research examining the effects of PROG and its metabolite ALLO on these important phases of cocaine abuse in addition to progestin effects on other cocaine-induced behavior.

Maintenance of cocaine-seeking behavior across the nonhuman primate menstrual cycle

In animal research, the use of monkeys provides an invaluable model for the human menstrual cycle due to the similarity in its duration and hormonal changes. Similar to findings from human research, research with nonhuman primates indicates hormone cycle-dependent alterations of stimulant-related behaviors. For example, during the maintenance of cocaine self-administration under a progressive-ratio (PR) schedule, cynomolgus female monkeys reached significantly lower breakpoints (i.e., decreased motivation) for a low dose of cocaine (0.0032 mg/kg/iv injection) during the luteal phase of the menstrual cycle, when PROG levels are high compared with the follicular phase when PROG levels are low (Mello et al., 2007).

Cocaine-seeking behavior across the rodent estrous cycle

While the rodent estrous cycle is much shorter than the primate menstrual cycle (approximately 4–5 days vs 28 days), changes in cocaine self-administration have been noted across estrous phases. The rodent cycle consists of four distinct phases (metestrus, diestrus, proestrus, and estrus), each characterized by varying levels of EST and PROG (Figure 2). During early metestrus, EST (10 pg/ml) and PROG (20 ng/ml) levels remain relatively low until late metestrus when PROG levels rise (28 ng/ml) until they decrease again during early diestrus (8 ng/ml). EST levels slowly increase during both metestrus and diestrus until mid proestrus when they increase dramatically and peak (35 pg/ml). Shortly thereafter, PROG levels reach their highest level in mid proestrus (50 ng/ml). Both hormones reach their lowest levels during the estrus phase of the female rat cycle (EST: 5 pg/ml; PROG: 5 ng/ml) (Brown-Grant et al., 1970; Feltenstein and See, 2006; Naftolin et al., 1972; Roth et al., 2002; Shaikh, 1971). Despite challenges associated with rapid estrous phase transitions, animal research supports human and nonhuman primate work suggesting a role for endogenously circulating PROG in the attenuation of cocaine-related responses during several phases of the drug abuse process.

Maintenance—Similar to findings with nonhuman primates (Mello et al., 2007), research with rodents indicates hormonal cycle effects in the maintenance of cocaine self-administration under a PR schedule. Breakpoints under a PR schedule were higher (increased motivation) for iv cocaine in female (vs male) rats (Hecht et al., 1999; Roberts et al., 1989), and in other studies rats consumed more drug (Feltenstein and See, 2006; Lynch, 2008) during the estrus phase, when both EST and PROG levels were at their lowest, than at all other phases of the estrous cycle. These results suggested that phases of the female

hormone cycle associated with lower PROG levels corresponded with higher motivation to self-administer cocaine.

Extinction/reinstatement—The extinction and reinstatement (relapse) phases of drug abuse have been modeled in rats, and they are considered to be representative and predictive of abstinence and relapse in humans. Female rats in the estrus phase (low PROG) were more resistant to extinction of lever responding that was previously reinforced with iv cocaine than rats in other estrous phases (Feltenstein and See, 2007; Kerstetter et al., 2008). During reinstatement, females in estrus also exhibited higher levels of cocaine-primed responding on a lever previously associated with cocaine delivery compared to rats in other phases of the estrous cycle (Feltenstein and See, 2007; Kerstetter et al., 2008; Kippin et al., 2005). Moreover, plasma PROG levels in free-cycling female rats were negatively correlated with cocaine seeking during extinction and cocaine-primed reinstatement (Feltenstein and See, 2007). These results did not extend to cue-induced reinstatement, as female rats responded similarly following a cue previously paired with cocaine self-administration during all phases of the estrous cycle (Fuchs et al., 2005).

Systemic progestin administration

Due to the relatively short duration of the rodent estrous cycle and the rapid shifts of EST and PROG across cycle phases, it can be difficult to adequately differentiate the relative contributions of individual female gonadal hormones on cocaine-related effects. An added difficulty is interpreting contributions of hormone metabolites to these effects. As a consequence, direct manipulation of hormone and metabolite levels can be employed to examine dose-dependent effects of individual hormones and/or their metabolites. In animal research, this generally involves depleting hormone levels by ovariectomy (OVX), waiting for the endogenous hormones to deplete (e.g., 5 days), and then administering the hormone or metabolite of interest. The following sections describe recent findings from animal research using surgical methods and/or pharmacological manipulation to examine progestins' effects on cocaine-maintained behavior during the acquisition, escalation, and reinstatement phases of the drug abuse process.

Acquisition—In a study conducted by Jackson et al. (2006), OVX female rats treated with vehicle (VEH), EST, or EST+PROG were compared during the acquisition of cocaine self-administration. Results indicated that EST treatment facilitated the acquisition of cocaine self-administration in OVX female rats (but not castrated male rats) relative to VEH-treated controls, as previously reported (Lynch et al., 2001), and PROG attenuated this EST-induced facilitation. Cocaine intake was also reduced in female rats treated with EST +PROG relative to OVX rats treated with EST alone (Jackson et al., 2006). These results suggested an important role for PROG in limiting the initiation of cocaine-seeking behavior.

Escalation—In humans, bingeing on drugs is a sign of out-of-control, compulsive, dysregulated behavior that is a hallmark of the progression from drug use to dependence (Koob and Le Moal, 2008). Bingeing on a drug is modeled in animals by increasing access to the self-administered drug (e.g., increasing session length from 2 h to 6 h) for an extended period of time (e.g., 21 days) and then measuring the subsequent escalation of drug intake in the long access vs short access groups (Ahmed and Koob, 1998). Animal research indicates that the development of escalation of cocaine self-administration in rats is influenced by female sex hormones (Larson et al., 2007). In one study rats that were OVX or sham-operated and treated with VEH, EST, PROG, or EST + PROG were compared on the escalation of their cocaine intake over 21 days. Groups did not differ in cocaine self-administration when access was restricted to 2 h (short access); however, when access was increased to 6 h (long access), intact rats, or those treated with EST, progressively increased

cocaine intake across the 21-day period, while OVX or PROG-treated sham-operated rats' intake did not increase (see Figure 3A). Additionally, short-access (2 h) cocaine intake that followed long access (6 h) was higher than the initial short-access intake, except in the PROG-treated rats and VEH-treated sham-operated rats (data not shown).

Recently, these findings were extended to ALLO. In this study, rats were administered ALLO (15 mg/kg) or VEH and allowed to self-administer cocaine under the same experimental conditions described above (6 h/day, 21 days) (Anker and Carroll, unpublished data). Similar to the findings with PROG, ALLO-treated rats did not show escalation of cocaine self-administration during the 21 days, and they earned fewer infusions than VEH-treated controls (see Figure 3B). Additionally, ALLO-treated rats did not show an increase in short-access cocaine self-administration after the long-access period (Anker and Carroll, unpublished data). Relatively few studies have examined pharmacological interventions in the escalation of drugs of abuse using animal models (Hansen and Mark, 2007; Morgan et al., 2002; Specio et al., 2008). However, findings from the studies described above suggest that PROG, and/or its metabolite ALLO, may be important inhibitory agents in the escalation of cocaine use in females.

The rewarding effects of cocaine that lead to excessive or binge-like patterns of cocaine intake during long access (escalation) can result in aversive and potentially lethal consequences. Individuals that consume excessive amounts of cocaine run the risk of overdose, which can take the form seizures, hyperthermia, coma, headache, intracranial hemorrhage and ultimately death (Brody et al., 1990; Lange 2001; Pozzi et al., 2008; Rothman et al., 2001). Kaminski et al. (2003) examined the protective effect of PROG's metabolites ALLO and pregnanolone against cocaine-kindled seizures in mice. Both treatments attenuated the occurrence of cocaine-precipitated seizures, while ALLO prevented the development of kindling, as reflected by the number of mice exhibiting seizures following repeated cocaine administration (Kaminski et al., 2003; also see Leskiewicz et al., 2003). These results further emphasize the potential value of progestins not only for preventing the escalation of cocaine use but for protection from the negative consequences of cocaine administration.

Reinstatement—Systemic administration of PROG or ALLO has also been implicated in the attenuation of cocaine- and stress-induced reinstatement of drug seeking in female rats. In one study, PROG treatment in sham-operated (i.e., gonadally intact) female rats decreased reinstatement responding following an injection of cocaine relative to sham-operated rats treated with VEH (Figure 4A). In contrast, EST treatment in OVX female rats potentiated cocaine-primed reinstatement responding relative to OVX rats treated with VEH (Figure 4B), and PROG counteracted the potentiating effects of EST in a separate group (Figure 4B). In a similar study, PROG administration during the estrus phase of freely cycling female rats also decreased reinstatement responding following a cocaine priming injection relative to VEH-treated rats (Feltenstein et al., 2009).

In a separate study, the effects of ALLO were examined in gonadally intact female and male rats. Finasterdie (FIN), a compound that blocks the conversion of PROG into ALLO, was administered with PROG in female rats to determine if PROG's attenuating effects on cocaine-primed reinstatement were due to its metabolism into ALLO. Hormone treatments were given to intact rats; 2 male groups: 1) VEH and 2) ALLO (30 mg/kg) and 5 groups of females: 1) VEH, 2) ALLO (15 mg/kg), 3) ALLO (30 mg/kg), 4) PROG, and 5) PROG + FIN. Compared to VEH, ALLO (30 mg/kg) decreased responding on a previously active lever in gonadally intact female rats (Figure 4C) at doses that do not interfere with locomotor activity or food maintained responding (Anker et al., 2009). However, ALLO (30 mg/kg) had no effect on cocaine-primed reinstatement in gonadally intact male rats (Figure

4D) in the same study (Anker et al., 2009, Figure 4D). As previously shown (Anker et al., 2007, Figure 4A), PROG also reduced reinstatement in female rats, and this effect was reversed by FIN, suggesting that PROG may act through ALLO to attenuate cocaine-primed reinstatement (Anker et al., 2009, see Figure 4C). These data suggest that the suppressant effects of PROG on cocaine-seeking behavior are specific to females and could be attributed in part to the PROG metabolite ALLO (Anker et al., 2009).

While many of the reinstatement studies have been conducted with ip priming injections of cocaine, other events such as drug-associated exteroceptive cues or stress-evoking stimuli have been used in animal models of relapse. Stress has emerged as a major factor that predicts cocaine craving (Sinha et al., 2003) and relapse to cocaine abuse (Sinha, 2008; Stewart, 2000) in humans as well as the reinstatement of cocaine seeking in rats (Brown and Erb, 2007; Boutrel et al., 2005; Feltenstein and See, 2006; Shalev et al., 2003).

Since previous findings with humans showed attenuated stress-induced craving during the progestin-dominant luteal phase (Sinha et al., 2007), ALLO was tested in gonadally intact female and male rats for its ability to suppress the reinstatement of cocaine seeking precipitated by the anxiogenic drug yohimbine. In this study yohimbine reliably reinstated cocaine-seeking behavior as previously reported (Feltenstein and See, 2006); however, ALLO decreased the yohimbine-induced reinstatement in female rats (Figure 5A). Similar to findings with cocaine-primed reinstatement (Anker et al., 2009), ALLO did not attenuate yohimbine-induced reinstatement in male rats (Anker and Carroll, 2010, see Figure 5B). That ALLO mediates stress-induced reinstatement of cocaine seeking suggests that PROG's inhibitory effects on stress-elicited craving in female cocaine addicts may be related to the PROG metabolite ALLO (Sinha et al., 2007). Table 2 summarizes findings from animal research examining the effects of endogenous and exogenous progestins on cocaine-seeking behavior across several phases of the drug abuse process.

Effects of progestins on other cocaine-induced behaviors related to drug seeking

PROG and ALLO have been implicated in other behavioral responses to cocaine, such as cocaine-induced conditioned place preference (CPP), locomotor activity, and cocaine discrimination (see Table 3). These behaviors are thought to measure different effects of drugs of abuse associated with their conditioned rewarding effects (CPP), behavioral-activating effects (locomotor activity), and their discriminative-stimulus effects (drug discrimination).

Similar to its effects on cocaine self-administration (Jackson et al., 2006), PROG attenuated cocaine-induced CPP in female rats (Russo et al., 2003, 2008) and in male mice (Romieu et al., 2003) at doses that did not affect ambulatory or rearing behaviors. However, despite the relatively consistent findings concerning PROG's influence on other cocaine-related behaviors, the effects of PROG on cocaine-induced locomotor activity have been mixed. PROG increased (Niyomchai et al., 2008; Perrotti et al., 2001; Quinones-Jenab et al., 2000b; Sircar and Kim, 1999), decreased (Niyomchai et al., 2008; Sell et al., 2000; Yang et al., 2007), or had no effect (Perrotti et al., 2001; Quinones-Jenab et al., 2000b; Sircar and Kim, 1999; Yang et al., 2007) on locomotor activity in OVX female rats following cocaine administration. Discrepancies in these results may be explained by the timing, dose, and/or route of administration of PROG and the presence or absence of EST. Thus, results from locomotor activity studies failed to support previous work showing an attenuating effect of progestins on the conditioned rewarding effects of cocaine, suggesting that progestins may specifically inhibit the direct rewarding effects of cocaine.

Drugs of abuse serve as powerful discriminative stimuli, and the translational value of the drug discrimination paradigm is high, as drug discrimination in rodents and nonhuman

primates has closely agreed with self-reported subjective effects in humans (Dykstra et al., 1997; Kamien et al., 1993; Schuster and Johanson, 1988). Pharmacological agents that block drug discrimination may also decrease the drug's reinforcing effects; thus, drug discrimination has been useful for screening possible treatments of drug abuse (Solinas et al., 2006). There has been only one study examining the effects of a progestin on the discrimination of cocaine. Quinton et al. (2006) trained rats to discriminate between saline or two doses of cocaine (5.6 or 10 mg/kg) for food presentation under an operant schedule. Pregnanolone failed to substitute for cocaine in the task, but when it was administered prior to cocaine, the discriminative stimulus effects of cocaine were attenuated. One explanation of this finding may be related to state-dependent learning and a stimulus-generalization decrement. For example, stimulant discrimination is dependent on behavioral and neurochemical responses to stress (Kamien and Woolverton, 1989; Johanson and Barrett, 1993; Spealman, 1995; Mantsch and Goeders, 1998), while the anxiolytic pregnanolone exerts a mitigating effect on stress-related responses (Bitran et al., 1991). Thus, discrimination may have been attenuated when tested in a "nonstressed" state because it was learned in a cocaine-induced "stressed" state.

Effects of progestins on behavior maintained by other drugs of abuse

An additional question to be considered is whether PROG's effects on cocaine-reinforced behaviors are specific to cocaine or if they occur with other drugs of abuse. Research indicates that progestins mediate responses to other abused drugs; however, the available literature is not as extensive as for cocaine, and there is relatively little data on progestins' effects during different phases of the drug abuse process. The reported effects also vary depending on the subjects (human or animal), drug, and/or methodology (hormone cycle monitoring or systemic administration) used in the studies. The following section discusses findings from human and animal research on the effects of progestins on behavioral responses to other drugs of abuse. Particular attention is given to alcohol, as it has been one of the most widely studied drugs.

Progestins, other drugs, and the human menstrual cycle

Compared to results with stimulants, behavioral/subjective responses to other drugs of abuse do not consistently vary with phase of the menstrual cycle in humans (see Table 4). During the luteal phase in women, it was reported that alcohol (Garcia-Closas et al., 2002; Harvey and Beckman, 1985) and nicotine (DeBon et al., 1995; Mello et al., 1987; Snively et al., 2000) intake increased (compared to the follicular phase), while in other studies there was either a decrease or no menstrual cycle effect on alcohol (Holdstock and de Wit, 2000; Pomerleau et al., 1994), nicotine (Allen et al., 1996, 1999; Allen et al., 2009a, b; Marks et al., 1999; Pomerleau et al., 1994) marijuana (Griffin et al., 1986), and opioid (Sener et al., 2005) consumption.

These findings also extend to other drug-related measures. For example, similar to drug intake, research has been unable to establish a connection between menstrual cycle and self-reported measures of positive affect, intoxication, and craving. Subjective measures were insensitive to menstrual cycle effects following alcohol (Freitag and Adesso, 1993; Hay et al., 1984; Holdstock and de Wit, 2000; Nyberg et al., 2004; Sutker et al., 1987), nicotine (Allen et al., 1999, 2004; Pomerleau et al., 1992, 2000; Snively et al., 2000), marijuana (Lex et al., 1984), and opioid (Gear et al., 1996) administration in women; however, similar to results with cocaine (Evans and Foltin, 2006; Evans et al., 2002; Sofuoglu et al., 1999), women reported decreased positive subjective effects following amphetamine administration during the luteal phase compared to follicular phase of the menstrual cycle (Justice and de Wit, 1999, 2000; White et al., 2002). Overall, these findings indicate a lack of an effect of

menstrual cycle phase on behavioral/physiological and subjective measures of alcohol, nicotine, marijuana, and opioid use in humans.

Despite the lack of a consistent effect on these measures, recent work with nicotine indicates that menstrual cycle phase plays an important role in the likelihood of abstaining from smoking in women. In a study by Carpenter et al. (2008), women reported their menstrual cycle phase and were randomly placed into groups that had quit dates assigned to either the luteal or follicular phase. This study found that abstinence was higher in the group that quit during the follicular phase; however, this group also experienced more withdrawal symptoms and cravings suggesting multiple determinants of drug use cessation. In a similar study in which menstrual cycle phase was self-reported, Franklin et al. (2008) found that the success rates of females in the follicular phase of their menstrual cycle was significantly higher than that of females in the luteal group, and these differences lasted for up to nine weeks following the study even as women progressed through other phases of their menstrual cycle (Franklin et al., 2008). Opposite results were reported by Allen and colleagues (2009a). In this study, menstrual cycle phase was biochemically verified, and the results indicated that women were more likely to successfully quit smoking during the luteal phase of the menstrual cycle. Regardless of the inconsistent results, these studies demonstrated that timing quit attempts around periods of the menstrual cycle might improve abstinence from drug abuse.

Systemic progesterone administration: human research

In contrast to research with cocaine, relatively few studies using humans have assessed the effects of PROG administration on responses to other drugs of abuse. In one study, Sofuoglu and colleagues (2001) administered PROG or a placebo to women during the early follicular phase and measured behavioral and subjective responses to cigarettes. Women treated with PROG (vs placebo-treated controls) showed a marked decrease in craving before smoking, and after having two puffs they reported an additional decrease in cigarette-induced positive affect. However, there were no reported effects of PROG on the number of cigarettes smoked. In a follow-up study, Sofuoglu et al. (2009) reported that PROG treatment decreased self-reported measures of “drug liking” following iv nicotine administration in female smokers. Results from these studies indicated differential effects of PROG on measures of subjective responses vs reinforcing effects of smoking, and they support previously mentioned findings showing a similar dissociation of subjective effects with iv cocaine self-administration (Sofuoglu et al., 2004). Table 4 summarizes findings from human research examining menstrual cycle effects and the effects of systemically-administered PROG on drug intake and subjective responses following amphetamine, nicotine, alcohol, marijuana, and opioid administration in human studies.

Effects of estrous cycle on behavior maintained by other drugs of abuse

Similar to findings with humans, in rodents there does not appear to be a consistent effect of circulating PROG on the behavioral effects of drugs of abuse other than cocaine (see Table 5). However, when noted, these effects are specific to the drug, behavioral measures, and phases of the hormone cycle. For example, during the diestrus phase of the estrous cycle (associated with low progesterone levels), female rats were more sensitive to the reinforcing effects of ethanol under an operant self-administration procedure than during the estrus and proestrus phases (higher levels of progesterone) (Roberts et al., 1998), a finding similar to that reported by Forger and Morin (1982). However, in another study ethanol intake by rats was unaffected by estrous cycle, but the duration of self-administration bouts was longer during proestrus compared to all other phases (Ford et al., 2002).

In research with female rhesus monkeys, menstrual cycle phase was not related to ethanol intake under a second order schedule of reinforcement except during menstruation (low PROG and EST) when alcohol intake was significantly lower than all other phases of the cycle (Mello et al., 1986). These results are opposite to those found with rhesus monkeys when orally self-administered PCP was the reinforcer. In this study PCP intake increased during the luteal vs the follicular phase (Newman et al., 2006), a result that agrees with human studies showing increased alcohol (Garcia-Closas et al., 2002; Harvey and Beckman, 1985) and nicotine (DeBon et al., 1995; Mello et al., 1987; Snively et al., 2000) intake during the luteal phase.

Results from animal studies using nicotine as a reinforcer are inconclusive. For example, Donny and colleagues (2000) reported that nicotine self-administration was insensitive to estrous cycle changes at various response requirements under a FR and PR schedule for a range of nicotine doses, and others found no effect of the rodent estrous cycle on behaviors related to nicotine withdrawal (e.g., whole-body shakes, diarrhea, and empty-mouth chewing) (Hamilton et al., 2009). In contrast, Lynch (2009) demonstrated that nicotine infusions, earned under a PR schedule, were negatively correlated with plasma PROG levels in female rats. Together, these results provide little support that nicotine reinforcement and withdrawal are affected by hormone cycle phase in animals.

Systemic progestin administration: animal research

The following section discusses further research on the effects of PROG and its metabolites on drug-induced behaviors in animals. There have been many studies on this topic; however, only research investigating behaviors related to drug reinforcement (drug seeking), withdrawal, and overdose will be discussed, as they are the most representative of drug abuse (see Table 6).

Alcohol

Drug seeking: Despite a lack of evidence indicating hormone cycle effects on alcohol reinforcement, a host of studies using controlled progestin manipulation techniques suggest a strong relationship between alcohol and progestins, particularly ALLO. In these studies, the influence of systemic progestin administration on alcohol reinforcement is dependent on the history of alcohol intake (Morrow et al., 2001). Rodents with a brief history of ethanol exposure show an increase (Janak et al., 1998; Morrow et al., 2001; VanDoren et al., 2000) or no change (Martin-Garcia et al., 2007) in ethanol self-administration following treatment with a low dose of ALLO; whereas, rats and mice with an extensive history of ethanol exposure show a decrease in ethanol self-administration (Ford et al., 2005; Martin-Garcia et al., 2007; Morrow et al., 2001). Differences in the effects of ALLO on these measures may be related to the differential effects of chronic vs acute ethanol exposure on GABA_A receptor subunit expression and their subsequent function in mesolimbic areas of the brain that underlie the rewarding effects of ethanol (Papadeas et al., 2001).

Blocking ALLO biosynthesis, through the administration of finasteride, forestalls the acquisition and decreases the maintenance (Ford et al., 2008) of ethanol-seeking behavior in rodents. However, the administration of a priming injection of ALLO reinstates ethanol seeking following a period without alcohol (Finn et al., 2008). These results indicate a role of ALLO in the discrimination of alcohol and they support previous human research showing a correlation between progestin increases and alcohol-induced intoxication and positive subjective effects (Torres and Oretag, 2003, 2004; Pierucci-Lagha et al., 2005). Results with cocaine are different, and this illustrates the pharmacological specificity of ALLO's effects on drug seeking. Like alcohol, cocaine increases plasma levels of ALLO (Quinones-Jenab et al., 2008); however, ALLO did not reinstate cocaine-seeking behavior

when injected alone but rather decreased this behavior (Anker et al., 2009). This indicates that ALLO's effects on drug seeking may be dependent on the pharmacological class of the self-administered drug.

Withdrawal: ALLO and pregnanolone have also been studied for their potential in treating symptoms associated with alcohol withdrawal. In animal research, decreases in PROG and ALLO (Finn et al., 2000) levels were found during ethanol withdrawal, and further decreasing ALLO levels by administering finasteride (Gorin-Meyer et al., 2007) or by performing an adrenalectomy (Strong et al., 2009) potentiated the severity of these withdrawal effects. Interestingly, increasing ALLO levels alleviated ethanol-induced withdrawal effects in rats (Hirani et al., 2002; Martin-Garcia and Pallares, 2005; Uzbay et al., 2004). These findings are supported by human research indicating that decreased biosynthesis of ALLO contributed to the severity of withdrawal symptoms in alcoholics (Hill et al., 2005; Romeo et al., 1996), while the reinstatement of baseline levels of PROG and ALLO produced psychosomatic stability in patients receiving alcohol detoxification therapy (Hill et al., 2005). These findings suggest a possible role for progestins in the alleviation of alcohol withdrawal symptoms in alcoholics.

Progestin-alcohol interactions may be related to their similar neurobiological and behavioral profiles during tolerance and withdrawal states (Deitrich et al., 1989; Frye et al., 1981). Exposure to ethanol resulted in a decrease in receptor sensitivity to GABA (Chandler et al., 1998; Faingold et al., 1998; Grobin et al., 1998) and behavioral tolerance (Allan and Harris, 1987). In addition, following discontinuation of ethanol use, a withdrawal state characterized by depression (McKeon et al., 2008), anxiety, and seizure susceptibility occurred (McKeon et al., 2008; Ueno et al., 2001). Similarly, prolonged exposure to progestins reduced the efficacy of GABA_A in neuronal cultures (Friedman et al., 1993, 1996; Yu and Ticku, 1995; Yu et al., 1996), precipitated tolerance to their anticonvulsant effects (Czlonkowska et al., 2001), and like alcohol, produced a withdrawal state characterized by depression (as measured by the forced swim test) (Beckley and Finn, 2007), anxiety (Smith et al., 1998), and susceptibility to seizures (Frye and Bayon, 1998). These results highlight the close relationship between the neurobiological and behavioral effects of progestins and alcohol. It is possible that in the aforementioned studies ALLO contributed to the behavioral and neurobiological effects of alcohol, as ALLO levels dramatically increased following alcohol administration (Torres and Oretag, 2003, 2004; Pierucci-Lagha et al., 2005).

Overall, research suggests that PROG and its metabolite ALLO are important determinants of behaviors associated with alcohol abuse and withdrawal. The effects of progestins on alcohol administration differ depending on the history of alcohol exposure and the neurobiological and behavioral profiles of progestins and alcohol are similar. Results from these studies indicate a possible etiological relationship between progestins and alcohol abuse, and they suggest that knowledge of the progestin-alcohol relationship may lead to novel methods for the treatment of alcohol dependence.

Other drugs of abuse—Progestins are also involved in the attenuation of behavioral responses to nicotine, benzodiazepines, and morphine; however, relatively few studies have examined the effects of progestins on these drugs of abuse across different phases of the drug abuse process. Studies examining these effects indicate that treatment with PROG's precursor (pregnenolone), its metabolite (ALLO), or PROG itself, blocked the development of tolerance and the expression of withdrawal signs following benzodiazepine (Reddy and Kulkarni, 1997a) and morphine administration (Reddy and Kulkarni, 1997b) in mice. In addition, similar to its effects on cocaine-induced seizures (Kaminski et al., 2003; Leskiewicz et al., 2003), systemic (Luntz-Leymann et al., 1990) or intrahippocampal

(Martin-Garcia and Pallares, 2005) administration of ALLO resulted in an attenuation of seizures precipitated by large doses of nicotine, purportedly through its mediation of the GABAergic neurotransmitter system (Frye, 1995; Frye et al., 2000).

This section expanded the results with cocaine and discussed human and animal research examining the interaction between other drugs of abuse and progestins. One conclusion is that there are relatively few consistent reports in humans and/or animals concerning the influence of progestins on the positive subjective and reinforcing effects of drugs of abuse other than those reported with cocaine. However, variations in the methodology employed in studies examining drugs other than the stimulants may preclude an accurate comparison of their findings.

Mechanisms of progestins' effects on drug-mediated behavior

Progestins influence a range of neurobiological mechanisms that are related to drug abuse. In addition, the effects of progestins on drug-related behaviors might be dependent on EST levels and/or their influence on the pharmacokinetics of drugs of abuse. The following section attempts to improve our understanding of the effects of drugs of abuse on progestin levels, as that may clarify the mechanisms by which progestins interact with drug-induced behaviors. Particular attention is given to the progestin interaction with neurobiological systems that regulate cocaine abuse, as research on this topic is the most abundant.

Neurobiological mechanisms of progestins on drug seeking

Progestins influence several stress- and reward-related neurobiological substrates that underlie drug abuse such as GABA_A (Schumacher and McEwen, 1989; Schumacher et al., 1989; for reviews, see Lambert et al., 1995; Gasior et al., 1999), 5-HT₃ (Wetzel et al., 1998), and nicotinic acetylcholine (Bullock et al., 1997) receptors in addition to HPA activation (Drugan et al., 1993; Owens et al., 1992; Patchev et al., 1994; Purdy et al., 1991) and dopamine signaling (Barrot et al., 1999; Jaworska-Feil et al., 1998; Laconi et al., 2007; Rouge-Pont et al., 2002). The following section discusses the more commonly accepted neurobiological mechanisms that are thought to underlie the effects of progestins on drug-related behaviors. These mechanisms most likely do not operate independently but in concert to influence drug abuse. Their interactions are assumed to be complex and have not been extensively studied. Thus, the following sections will focus primarily on how progestins mediate each mechanism related to drug abuse, and neurobiological interactions (e.g., GABA's effects on dopamine transmission) will be discussed when supported by relevant research.

HPA axis—As suggested by Koob and Volkow (2009), drug taking is initially regulated by positive reinforcement through interaction with the mesolimbic dopamine system. However, over time and with repeated binge and withdrawal cycles, this behavior is increasingly regulated by negative reinforcement through heightened withdrawal, craving, and increased sensitivity to stress that may further enhance vulnerability to drug bingeing and/or relapse. In both humans and animals the administration and subsequent withdrawal from several drugs of abuse (e.g., cocaine, nicotine, alcohol, cannabinoids, opiates) increases extracellular CRF, enhances HPA activation, and produces anxiogenic-like behavior (Fox and Sinha, 2009; George et al., 2007; Knapp et al., 2004; Overstreet et al., 2004; Rodriguez de Fonseca et al., 1997; Sarnyai et al., 1995). Furthermore, stress and HPA activity disruption are predictors of craving (Piasecki et al., 2003; Stine et al., 2002), treatment outcomes, and relapse (Sinha and Fox, 2008) in humans (Fox and Sinha, 2009) and are associated with drug bingeing and relapse in animal models of drug abuse (Harris and Aston-Jones, 2003; Hutcheson et al., 2001; Shaham et al., 1996; Valdez et al., 2002). Therefore, agents that

normalize drug-induced disruption in the stress system may be useful treatments for drug abuse.

Interestingly, PROG and/or ALLO alleviate anxiogenic-like behaviors (Bitran et al., 1995; Brot et al., 1997; Laconi et al., 2001), normalize overactive HPA activity by attenuating the release of CRF following exposure to stress (Drugan et al., 1993; Frye et al., 2006; Owens et al., 1992; Patchev et al., 1994; Purdy et al., 1991), and as previously mentioned, inhibit the potentiating effects of stress on cocaine-related responses. For example, increases in PROG were associated with decreased stress-induced craving in women addicted to cocaine (Sinha et al., 2007). Furthermore, reinstatement of cocaine-seeking behavior induced by a stressful stimulus (yohimbine) was significantly attenuated by ALLO in female rats (Anker and Carroll, 2010). Thus, one mechanism that may explain the effects of PROG and ALLO on cocaine-elicited behavior involves their attenuation of stress- and cocaine-induced HPA activation.

The effects of EST on HPA activation and HPA-mediated behaviors are opposite to those of PROG and its metabolite, ALLO. In rats, EST potentiated the release of CRF (Patchev et al., 1995; Swanson and Simmons, 1989) and increased adrenocorticotrophic hormone (ACTH) and corticosterone (Burgess and Handa, 1992), leading to increased HPA activity (Dallman et al., 2004). These effects also extended to cocaine-induced HPA activation. In a study by Niyomchai and colleagues (2005), EST increased cocaine-induced corticosterone levels relative to VEH-treated controls. Behavioral studies provided further support for the opposing effects of PROG and EST. Estrogen facilitated fear-potentiated startle in OVX female rats relative to OVX rats treated with VEH, while the administration of PROG attenuated this facilitation (Hiroi and Neumaier, 2006; Toufexis et al., 2004). Further work is needed to examine the interaction between EST and progestins in relation to their effects on stress-related drug abuse. One question for further research is whether PROG or ALLO can block EST's potentiating effect on cocaine-induced corticosterone release and whether this effect is related to cocaine seeking.

Dopamine—Dopamine mediates stress (Deutch and Roth, 1990; Imperato et al., 1991; Inglis and Moghaddam, 1999; Koob, 2009; Koob and Le Moal, 2005, 2008) in addition to the rewarding effects associated with cocaine (Koob and Kreek, 2007; Pierce and Kumaresan, 2006; Spanagel and Weiss, 1999). These effects occur in the NAc and ventral tegmental areas of the brain (Spangel and Wiess, 1999) that are thought to play a crucial role in cocaine craving in humans (Brieter et al., 1997; Volkow et al., 1999). These regions are also implicated in drug self-administration (Carelli, 2002; Kiyatkin and Stein, 1995) and in the reinstatement of drug seeking in rats (Anderson et al., 2003, 2006; Schmidt et al., 2006). Research with rodents indicated that progestins modulated dopamine in these brain areas. For example, ALLO attenuated stress-induced increases in dopamine (Dazzi et al., 2002) and altered dopamine release in the striatum and NAc (Barrott et al., 1999; Jaworska-Feil et al., 1998; Laconi et al., 2007; Rouge-Pont et al., 2002). PROG also modulated dopamine levels in the striatum; however, results from these studies were equivocal and dependent on the time of testing, manner of administration, and presence or absence of EST (Dluzen and Ramirez, 1984; Fernandez-Ruiz et al., 1989). Nevertheless, evidence suggests that PROG and ALLO may interact with dopamine to produce attenuating effects on drug-seeking behavior.

GABA—Progestins' effects on GABA neurotransmission may be an additional mechanism influencing drug-induced responses. Pharmacological agents that enhance GABA neurotransmission (e.g., topiramate, tiagabine, and baclofen) decrease dopamine transmission in areas of the brain that support the rewarding effects of drugs of abuse and have shown promise in treating drug dependence in humans (Kalivas, 2007; Karila et al.,

2008). Furthermore, there is reduced craving in humans and/or cocaine seeking in animals following treatment with the GABA_B agonist baclofen (Brebner et al., 2002; Campbell et al., 1999, 2002; Ling et al., 1998; Shoptaw et al., 2003), the GABA upregulator topiramate (Reis et al., 2008), and the irreversible GABA transaminase inhibitor vigabatrin (Fechtner et al., 2006; Kushner et al., 1999; Peng et al., 2008). Given that ALLO and pregnanolone are potent positive allosteric modulators of GABA_A receptors (Gasior et al., 1999; Schumacher and McEwen, 1989; Schumacher et al., 1989; for a review see Lambert et al., 1995), their actions on the GABA receptor system may partially explain their attenuating effects on drug seeking.

Progesterone receptors and sigma receptors

PROG receptors are present in areas of the brain implicated in behavioral responses to drugs of abuse such as prefrontal cortex, ventral tegmental area, and hippocampus (Parsons et al., 1982; Guerra-Araiza, 2000; Frye, 2001). In one study, Wu et al., (2006) demonstrated that PROG receptor protein levels and DNA binding complexes in rats were significantly increased in the NAc following increases in PROG serum levels.

PROG is an antagonist of sigma1 (σ 1) receptors that are important neurosubstrates of learning and memory processes (Maurice et al., 2002). σ 1 receptors are also thought to regulate drug-seeking behaviors such as withdrawal and relapse (Romieu et al., 2004). For example, the administration of σ 1 antagonists blocked the formation and reinstatement of cocaine-induced conditioned place preference in mice (Romieu et al., 2002, 2004). Thus, PROG receptors and σ 1 receptors may be implicated in the effect of PROG on drug-seeking behavior.

Progestins' dependence on estrogen—Findings suggest that the attenuating effects of progestins on cocaine reinforcement may be dependent on the interaction of the progestin with EST. For example, PROG, when coadministered with EST, blocked EST-induced enhancement of cocaine-seeking behavior in OVX female rats (Anker et al., 2007, 2009; Jackson et al., 2006; Larson et al., 2007), but it failed to alter cocaine-induced reinstatement in OVX female rats in the absence of EST (Anker and Carroll, unpublished data). These findings suggest that PROG decreased cocaine-induced responses to the levels of those found in OVX rats, without decreasing them below response levels seen under conditions where EST is low (e.g., following OVX).

Results with cocaine-elicited CPP in OVX female rats are opposite to those reported for cocaine-seeking behavior (Anker and Carroll, unpublished data; Anker et al., 2007, 2009; Jackson et al., 2006; Larson et al., 2007). For example, cocaine-induced CPP was potentiated when PROG was coadministered with EST (Russo et al., 2003) but was blocked when PROG was administered alone. One explanation for these divergent findings may be related to the different learning mechanisms that mediate CPP and drug seeking. For example, drug seeking is guided by response-outcome contingencies (operant conditioning), but it is unknown whether the expression of CPP is mediated by operant and/or stimulus-outcome contingencies (classical conditioning) (Bardo and Bevins, 2000). A comparison of CPP and drug self-administration studies draws further distinction and indicates dissociation between the neurobiological mechanisms that mediate both behaviors (for review see Bardo and Bevins, 2000). Indeed, endogenous levels of PROG and EST, or their systemic injection following OVX in female rats, enhanced performance on learning and memory tasks such as the object recognition and object placement tasks (Frye, 2007; Paris and Frye, 2008), while the administration of both hormones decreased operant behavior maintained by a nondrug food reinforcer (Rodriguez-Sierra et al., 1984). Thus, EST and PROG may facilitate the recall of stimulus-outcome contingencies that guide cocaine-induced CPP (Russo et al.,

2003) while they attenuate response-outcome contingencies underlying operant responding and cocaine seeking (Anker et al., 2007; Jackson et al., 2006; Larson et al., 2005, 2007).

In contrast to results with CPP and cocaine seeking, findings concerning EST-dependent effects of progestins on cocaine-induced locomotor activity are equivocal. For example, locomotor activity following cocaine administration increased (Sircar and Kim, 1999; Perrotti et al., 2001), decreased (Sell et al., 2000), or was not affected (Peris et al., 1991; Perrotti et al., 2001) by coadministration of PROG and EST in OVX female rats relative to OVX VEH-treated controls. Furthermore, administration of PROG alone in OVX females decreased cocaine-induced stereotypy (Niyomchai et al., 2005), but it had no effect on cocaine-induced locomotor activity (Quinones-Jenab et al., 2000b; Perrotti et al., 2001; Sell et al., 2000). Inconsistencies in these reports may be related to differences in the hormone dosing regimens as well as strain and age differences of the subjects between the studies.

An additional mechanism that may underlie EST-dependent effects of PROG on cocaine seeking may be related to GABA neurotransmission. Decreased GABA release in the ventral pallidum is associated with increased dopamine release in addition to heightened drug-seeking behavior in rats (Tang et al., 2005; Callie and Parsons, 2004), while the administration of GABA agonists decrease dopamine release and cocaine seeking (Campbell et al., 1999, 2002). This suggests that decreased GABA is associated with heightened vulnerability toward cocaine abuse, while increased GABA may attenuate drug-taking behavior. Previous work indicates that EST inhibited activation of medium spiny GABAergic neurons in the striatum (Mermelstein et al., 1996), increased striatal GABA release (Hu et al., 2006), and enhanced dopamine metabolism and turnover (Di Paolo et al., 1985; Shimizu and Bray, 1993) and stimulant-elicited dopamine release in the striatum (Becker and Beer, 1986; Becker, 1990a, b; Castner et al., 1993). Conversely, PROG and its metabolites promoted striatal-GABA activity (Schumacher and McEwen, 1989; Schumacher et al., 1989) and decreased dopamine (Dazzi et al., 2002; Dluzen and Ramirez, 1984; Jaworska-Feil et al., 1998; Laconi et al., 2007; Shimizu and Bray, 1993) in the striatum. Thus, the different effects of ALLO and EST on cocaine seeking may be explained by their opposite effects on GABA and/or dopamine neurotransmission in areas of the brain that regulate drug seeking.

Progestins' interaction with cocaine pharmacokinetics

It is possible that PROG and/or its metabolites may interact with drug pharmacokinetics to affect drug-seeking behavior. Most of this research has been conducted with cocaine. However, previous findings do not support this notion and indicate little to no effect of the menstrual cycle on plasma cocaine levels in women following iv or smoked cocaine (Evans and Foltin, 2004; Mendelson et al., 1999; Sofuoglu et al., 1999). This suggests that PROG's suppressant effect on cocaine-induced behavior does not involve an interaction with cocaine metabolism. While studies examining the effects of menstrual cycle on cocaine metabolism following iv and smoked cocaine agree that pharmacokinetics is not an issue, findings from studies using intranasal cocaine administration have been inconsistent. For example, Lukas et al., (1996) reported lower peak plasma cocaine levels during the PROG-dominant luteal phase than during the follicular phase of the menstrual cycle (Lukas et al., 1996), while Collins et al., (2007) found no phase differences in plasma cocaine. Differences in experimental procedures such as cocaine dose, timing of cocaine administration, and number of self-administered doses may have accounted for these varied results. For example, Collins and co-workers (2007) used two doses separated by 40 min, while Lukas et al. (1996) used only one dose.

Findings showing a lack of effect of female gonadal hormones on blood cocaine levels are also supported by research in animals. There was no interaction between menstrual cycle

phase and cocaine levels in plasma in nonhuman primates (Evans and Foltin, 2004). Similarly, studies using hormone replacement in OVX rats failed to show a consistent role of PROG on plasma levels of cocaine's metabolite benzoylecgonine (Quinones-Jenab et al., 2000a; Perrotti et al., 2001; Niyomchai et al., 2006). Taken together most studies to date indicate that hormones such as PROG are most likely not exerting their inhibitory effects via alteration of cocaine pharmacokinetics.

Cocaine's effects on progestin levels

Studies have revealed that administration of several drugs of abuse increase circulating progestin levels. Plasma PROG levels were significantly higher during early cocaine abstinence in women (Fox et al., 2008). Also, in male and female rats PROG levels (Chin et al., 2002; Festa and Quinones-Jenab, 2004; Grobin et al., 2005; Quinones-Jenab et al., 2000a, 2008; Walker et al., 2001) and PROG receptor activation (Wu et al., 2006) increased following cocaine administration. Furthermore, cocaine-induced increases in PROG in freely-cycling female rats were dependent on the estrous cycle stage, with the highest levels occurring during proestrus when EST is high (Quinones-Jenab et al., 2000a; Walker et al., 2001). These results indicated that cocaine-induced elevation of PROG was independent of sex (occurs in both males and females) and was possibly influenced by EST in females. However, other research suggested that the effects of cocaine on plasma levels of ALLO were sex-dependent. For example, cocaine-induced increases in plasma levels of PROG's metabolite ALLO have been reported for female (Quinones-Jenab et al., 2008) but not male (Quinones-Jenab et al., 2008; Grobin et al., 2005) rats. These results indicated that cocaine affects PROG synthesis and receptor expression regardless of sex, while cocaine's influence on ALLO levels was specific to females.

Similar to cocaine, cortical and/or plasma concentrations of PROG and ALLO were elevated following administration of other drugs of abuse such as alcohol (Barbaccia et al., 1999; Morrow et al., 2001; VanDoren et al., 2000), nicotine (Concas et al., 2006; Porcu et al., 2003), morphine (Concas et al., 2006; Grobin et al., 2005), and tetrahydrocannabinol (Porcu et al., 2003). All of these drugs activate the HPA axis and elicit stress responses following their administration and/or during their withdrawal (Adinoff et al., 2005; Fox and Sinha, 2009; Junghanns et al., 2003; Lee et al., 2001; Shaham et al., 2000; Stewart, 2000). Thus, increases in PROG and ALLO may serve as a mechanism to restore homeostasis in the brain following drug-induced HPA dysregulation (Grobin et al., 2005). This is supported by a finding demonstrating that cocaine-induced increases in progestin levels were blocked following adrenalectomy (Walker et al., 2001). Findings also suggest that prolonged drug intake may suppress the ability of progestins to attenuate responses to stress. For example, Childs and de Wit (2009) demonstrated that following a public speaking procedure (i.e., the Trier Social Stress Test), chronic cigarette smokers scored higher on self-reported measures of stress and had lower baseline levels of ALLO in the plasma in addition to lower stress-induced increases of PROG compared to non-smokers. Thus, continued drug use may produce a dysregulation in the body's ability to cope with stress, and this may lead to further drug use.

Baseline measures of PROG and ALLO were also present to a greater extent in females compared to males during the luteal phase of the menstrual cycle (but are similar between sexes when women are in the follicular phase) (Genazzani et al., 1998; Pearson Murphy and Allison, 2000), and this may partially explain why females, compared to males, showed fewer withdrawal effects across numerous drugs such as alcohol (Alele and Devaud, 2007; Cicero et al., 2002; Devaud and Chadda, 2001; Varlinskaya and Spear, 2004; Woodstock-Striley et al., 2004), pentobarbital (Suzuki et al., 1985), methaqualone (Suzuki et al., 1988), and PCP (Carroll et al., 2009). These results suggest that increased levels of progestins may afford protection against the aversive affects of drugs of abuse in women.

Conclusion

Findings from human and animal research indicate a role for PROG and its metabolites in several aspects of drug abuse. This work highlights the importance of hormonal status of women in regulating behaviors maintained by drugs of abuse, particularly with respect to cocaine. In human research, phases of the menstrual cycle associated with high endogenous levels of progestins, or their systemic injection, corresponded with decreases in the subjective and physiological effects of cocaine. Similar results were found in animal research on the effects of endogenous and exogenous progestins on the rewarding (cocaine seeking) and aversive effects of cocaine across several phases of the drug abuse process. Findings from animal research have further explored PROG's actions, implicating its metabolite ALLO in the attenuation of many behavioral effects of cocaine. Thus, human research may benefit from examining the effects of ALLO on cocaine-induced subjective and physiological responses.

Of particular interest is the influence of progestins' on stress as it relates to drug abuse. Physiological and behavioral responses to stress were associated with rewarding and aversive aspects of cocaine abuse and results from human and animal research discussed here indicated a role for progestins in attenuating these responses. Stressful events or the administration of drugs of abuse increased levels of circulating progestins and a relationship between hormones, stress, and cocaine abuse was substantiated by findings from human and animal research.

Human and animal studies suggest that progestins influence responses to other drugs of abuse as well as cocaine. For example, progestins, especially ALLO, have a strong relationship with subjective and behavioral effects of alcohol. However, these effects are opposite to those of cocaine in that ALLO plasma levels were correlated with increased alcohol-induced positive-subjective effects and intoxication in women, while systemic administration of ALLO increased levels of alcohol-seeking behavior in rats. These results indicate that ALLO may be responsible for regulating the reinforcing effects of alcohol. Despite this finding, there is little support that progestins affect reinforcement maintained by other drugs of abuse. However, results indicate an important role for progestins in the alleviation of negative aspects of many of these drugs.

Similar to results with cocaine, findings from various studies using alcohol, benzodiazepines, nicotine, and morphine indicate that progestins afford protection against the aversive consequences of drug abuse such as withdrawal and the potentially lethal effects of overdose. This suggests their role as possible compensatory mechanisms in the regulation of negative aspects of drug use, and this may explain why females are more vulnerable than males to cocaine seeking across numerous phases of drug abuse (i.e., they are less likely to experience the negative consequences).

As discussed earlier, there is little support indicating that the inhibitory effects of progestins are due to their pharmacokinetic effects on cocaine. Rather, there is support that progestins alter drug-maintained behavior through their influence on neurochemical processes related to drug reward. This review presented findings indicating that neurochemical profiles associated with enhanced HPA activation, increased levels of dopamine, and decreased GABA in the striatum coincided with the expression of drug reward and/or drug-seeking behavior, while decreased HPA activity, decreased levels of dopamine, and increased GABA were associated with an attenuation of these behaviors. Interestingly, EST has been shown to produce effects similar to the former profile (increased HPA and dopamine, decreased GABA) while PROG and its metabolites produce effects that fit the latter profile (decreased HPA and dopamine, increased GABA). Thus, the fact that EST increases and

progestins decrease measures indicative of drug abuse may be related to their opposite effects on these neurochemical substrates.

An important consideration from the findings discussed in this review is that addictive disorders affect women differently than men. The hormones discussed here are present to a much greater degree in women, and symptomology associated with drug abuse disorders fluctuates with increases and decreases of progestins and EST in females. These fluctuations may mark periods of increased vulnerability to, or protection against, drug abuse in women. The findings presented in this review highlight the importance of sex-specific treatment strategies that take into account the unique interactions between female gonadal hormones (and their metabolites) and drug abuse. The feasibility of this strategy has been demonstrated in previous human research. These studies indicate that scheduling smoking quit dates around periods of the menstrual cycle that mark periods of increased vulnerability to relapse may be beneficial to treatment outcome in woman smokers (Franklin et al., 2008; Carpenter et al., 2008). Similar strategies could be implemented in the treatment of other excessive behaviors maintained by drug and nondrug rewards that are known to be influenced by menstrual cycle such as cocaine and amphetamine dependence.

In conclusion, the findings discussed in this review indicate that women and men respond differently to the effects of drugs of abuse. For women, fluctuations of progestins may mark periods of increased or decreased vulnerability to the development of drug dependence, reflected by their effects on both the reinforcing and negative aspects of this disorder. However, progestins' potential for therapeutic applications has yet to be examined for problems of drug dependence and other addictive disorders involving nondrug substances/events (e.g., food, gambling). The influence of progestins on addictive behaviors is a promising area of scientific inquiry, as the research presented here suggests the potential for progestins in the treatment of drug abuse.

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Figure 1.
Plasma concentrations of EST (solid line) and PROG (dashed line) across the human and nonhuman menstrual cycle

Figure 2.
Plasma concentrations of EST (solid line) and PROG (dashed line) across the rodent estrous cycle

Figure 3.

Data represent the mean ($\pm$ SEM) cocaine infusions self-administered each day of the LgA phase. Horizontal lines indicate the 3-day intervals during which there were significant group differences in drug deliveries ($p < 0.05$). Panel A: * = $p < 0.05$ block 1 < blocks 3–7; block 2 < blocks 5–7 in the OVX-EST group, # = $p < 0.05$ block 1 < blocks 4–7 in the SH-VEH group, and @ = $p < 0.05$ block 1 < blocks 5–7; block 2 < blocks 6 and 7; block 3 < block 7 in the OVX-VEH group. Panel B: † = $p < 0.05$ block 1 < blocks 3–7 in the VEH group.

Figure 4.

Black bars represent the mean ($\pm$ SEM) responses on the cocaine-paired lever following a 10 mg/kg cocaine priming injection and white bars refer to responses on the same lever after a saline priming injection. All groups responded more on the cocaine-paired lever after a 10 mg/kg cocaine i.p. than after a saline i.p. (* = $p < 0.05$). Significant group differences in cocaine-primed responding are represented by # ($p < 0.05$). Panel C: † = $p < 0.05$ VEH > ALLO in the female group.

Figure 5.

Mean ($\pm$ SEM) responses on the previously drug-paired lever following saline (S) or YOH (Y) priming injections during the reinstatement procedure. Asterisks indicate significantly greater responding following YOH compared to S priming injections ($p < 0.05$). # = a significant difference in YOH compared to responding following A+Y in the female group ($p < 0.05$), and † = a significant sex difference (females > males) in responding following the first YOH injection ($p < 0.05$).

Table 1

Summary of the effects of endogenous and exogenous PROG on subjective responses to amphetamine and cocaine in human research

Drug	Independent Variable	Dependent Measure	Findings ^a	Reference
Cocaine	Menstrual cycle state	Subjective measures	No phase differences	Lukas et al., 1996 Mendelson et al., 1999
		Feel high, want more drug	L < F	Sofuoglu et al., 1999
		Positive effect, want more drug	L < F	Evans et al., 2002
		Good drug effect	L < F	Evans and Foltin 2006
		Craving following cues	L < F	Sinha et al., 2007
		Subjective measures	No phase differences	Collins et al., 2007
	Systemic PROG administration during the follicular phase	Feel the effect of last dose	F+P < F	Sofuoglu et al., 2002
		Feel the effect of last dose, feeling high	F+P < F	Sofuoglu et al., 2004
		Good drug effect, drug quality	F+P < F	Evans and Foltin 2006

^aL: luteal phase; F: follicular phase; P: PROG

Table 2

Summary of the effects of endogenous and exogenous progestins on behavioral responses to cocaine across phases of the drug abuse process

Independent Variable	Dependent Measure	Finding ^a	Reference
Menstrual cycle state (Monkey)	Maintenance (PR)	BPs: L < F	Mello et al., 2007
Estrous cycle state	Maintenance (PR)	BPs: E < all other phases	Roberts et al., 1989
	Maintenance (FR)	Intake: E < all other phases	Feltenstein and See 2007 Lynch 2008
	Extinction	Resistance to extinction: E < all other phases	Feltenstein and See 2007 Kerstetter et al., 2008
	Cue-induced Reinstatement	no phase differences	Fuchs et al., 2005
	Cocaine-primed reinstatement	E < all other phases	Kippin et al., 2005 Feltenstein and See 2007 Kerstetter et al., 2008
Systemic PROG administration	Acquisition	Days to criteria: OVX+EB+P < OVX+EB	Jackson et al., 2006
	Maintenance (PR)	Intake: P < V	Anker and Carroll, unpublished data
		Intake: No effect	Larson et al., 2005
	Escalation	Intake: OVX+EB+P < OVX+EB; sham+P < sham+V	Larson et al., 2007
	Cocaine-primed reinstatement	OVX+EB+P < OVX+EB; sham+P < sham+V	Anker et al., 2007
		P < V	Feltenstein et al., 2009
		P < V; FIN+P = V	Anker et al., 2009
Systemic ALLO administration	Escalation	Intake: A < V	Anker and Carroll, unpublished data
	Overdose	Seizures and death: A & Preg < V	Kaminski et al., 2003 Leskiewicz et al., 2003
	Cocaine-primed reinstatement	A < V & P	Anker et al., 2009
	Stress-induced reinstatement	A < V	Anker and Carroll, 2010

^aL: luteal phase; F: follicular phase; E: estrus phase; EB: EST; P: PROG; V: vehicle; FIN: finasteride; A: ALLO; Preg: pregnanolone

Table 3

Summary of the effects of progestins on other behaviors elicited by cocaine

Independent Variable	Dependent Measure	Decreased Response ^a	Reference
Systemic PROG administration	Cocaine-induced CPP	P < V	Russo et al., 2003 Romieu et al., 2003 Russo et al., 2008
	Cocaine-induced locomotor activity	No effect	Sircar and Kim 1999 Quinones-Jenab et al., 2000b Perrotti et al., 2001 Yang et al., 2007
		P (24 hr after EB)+EB > V; P (<24 hr after EB)+EB < V	Perrotti et al., 2003
		P+EB > V; P+EB < V	Niyomachi et al., 2008
		EB+P > V	Yang et al., 2007
		P < V	Sell et al., 2000
Systemic pregnanolone	Cocaine discrimination	Blocked by Preg	Quinton et al., 2006

^aP: PROG; V: vehicle; EB: EST; Preg: pregnanolone

Table 4

The effects of endogenous and exogenous progestins on the intake of and subjective responses to other drugs of abuse

Drug	Independent Variable	Dependent Measure	Finding ^a	Reference
Amphetamine	Menstrual cycle phase	Feeling high	L < F	Justice and de Wit 1999
		Want more drug	L < F	Justice and de Wit 2000 White et al., 2002
Nicotine	Menstrual cycle phase	Intake and positive subjective measures	L > F	Mello et al., 1987
		Intake and/or withdrawal	L > F	DeBon et al., 1995 Allen et al., 2009b
		Intake	L > F	Snively et al., 2000
		Withdrawal	L > F	Allen et al., 1999
		Withdrawal	L > F	Perkins et al., 2000
		Craving	L > F	Franklin et al., 2004
			F > L	Carpenter et al., 2008
		Intake and subjective measures	No phase differences	Pomerleau et al., 1994 Allen et al., 1996, 1999, 2009a Marks et al., 1999 Pomerleau et al., 2000 Allen et al., 2004 Franklin et al., 2008
		Abstinence	F > L	Carpenter et al., 2008 Franklin et al., 2008
	Systemic PROG administration during the follicular phase	Positive subjective measures	P < placebo	Sofuoglu et al., 2001, 2009
Alcohol	Menstrual cycle phase	Intake	L > F	Garcia-Closes et al., 2002 Harvey and Beckman 1985
		Intake and positive subjective measures	No phase differences	Hay et al., 1984 Sutker et al., 1987 Freitag and Adesso 1993 Pomerleau et al., 1994 Holdstock and de Wit 2000 Nyberg et al., 2004
Marijuana	Menstrual cycle phase	Intake and subjective measures of positive effect, intoxication, and craving	No phase differences	Lex et al., 1984 Griffin et al., 1986
Opioids	Menstrual cycle phase	Intake and subjective measures of positive effect, intoxication, and craving	No phase differences	Gear et al., 1996 Sener et al., 2005

^aL: luteal phase; F: follicular phase; P: PROG

Table 5

Summary of hormone cycle effects on behaviors elicited by other drugs of abuse in animals.

Drug	Independent Variable	Dependent Measure	Finding ^a	Reference
Alcohol	Menstrual cycle phase (monkey)	Maintenance (FR)	Intake lower during menstruation	Mello et al., 1986
	Estrous cycle phase	Maintenance (FR)	Intake: D > all other phases	Forger and Morin 1982 Roberts et al., 1998
			Total intake: no phase differences; Duration of intake bout: Pro > all other phases	Ford et al., 2002
Nicotine	Estrous cycle phase	Maintenance (FR and PR)	No phase differences (FR)	Donny et al., 2000
			Intake: E > all other phases (PR)	Lynch 2009
		Withdrawal	No phase differences	Hamilton et al., 2009
PCP	Menstrual cycle phase (monkey)	Maintenance (FR)	L < F	Newman et al., 2006

^aD: diestrus phase; E: estrus phase; Pro: proestrus phase; L: luteal phase; F: follicular phase

Table 6

Summary of the effects of ALLO administration on behaviors elicited by other drugs of abuse in animals.

Drug	Independent Variable	Dependent Measure	Finding a	Reference
Nicotine	ALLO administration	Nicotine- precipitated seizure	A < V	Luntz-Leybmann et al., 1990 Martin-Garcia and Pallares 2005
Alcohol	ALLO administration	Maintenance	A > V in rats with a brief history of alcohol intake	Janak et al., 1998 VanDoren et al., 2000 Morrow et al., 2001
			No effect in rats with a brief history of alcohol intake	Martin-Garcia et al., 2007
			A < V in rats with a long history of alcohol intake	Morrow et al., 2001 Ford et al., 2005 Martin-Garcia et al., 2007
		Withdrawal	A < V	Hirani et al., 2002 Martin-Garcia and Pallares 2005
		Reinstatement	Reinstates alcohol seeking: A > V	Finn et al., 2008
Morphine	ALLO administration	Withdrawal	A < V	Reddy and Kulkarni 1997b
Benzodiazepine	ALLO administration	Withdrawal	A < V	Reddy and Kulkarni 1997a

A: ALLO; V: vehicle