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# Neural Mechanisms of Reproduction in Females as a Predisposing Factor for Drug Addiction

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## Abstract

There is an increasing awareness that adolescent females differ from males in their response to drugs of abuse and consequently in their vulnerability to addiction. One possible component of this vulnerability to drug addiction is the neurobiological impact that reproductive physiology and behaviors have on the mesolimbic dopamine system, a key neural pathway mediating drug addiction. In this review, we examine animal models that address the impact of ovarian cyclicity, sexual affiliation, sexual behavior, and maternal care on the long-term plasticity of the mesolimbic dopamine system. The thesis is that this plasticity in synaptic neurotransmission stemming from an individual's normal life history contributes to the pathological impact of drugs of abuse on the neurobiology of this system. Hormones released during reproductive cycles have only transient effects on these dopamine systems, whereas reproductive behaviors produce a persistent sensitization of dopamine release and postsynaptic neuronal responsiveness. Puberty itself may not represent a neurobiological risk factor for drug abuse, but attendant behavioral experiences may have a negative impact on females engaging in drug use.

### Keywords

Sexual behavior; Pair bonding; Maternal care; Estradiol; Progesterone; Dopamine; Sensitization; Neuronal signaling; Neural Plasticity

## 1. Introduction

In recent decades there has been an increase in drug use and abuse (both legal and illicit) among adolescent girls and women [233]. Along with this shift in the demographics of drug use is a developing sensitivity to particular experiential variables that co-vary with addiction in females [130]. Because drug use among females may require special approaches to prevention and therapy [164], a good starting point for determining addiction vulnerability in women would be to address life experiences of particular relevance to women. As drug use often begins during adolescence, life history events associated with reproduction may impact the consequences of drug use.



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There is growing appreciation of a shared neurobiology between naturally-occurring motivated behaviors, such as reproductive behaviors, and the neural mechanisms of repeated drug use that contribute to addiction vulnerability (e.g. [97]). Two primary features of this shared neurobiology are the importance of limbic and striatal targets of dopamine innervation and cellular mechanisms underlying neural plasticity in response to both drugs of abuse and behavioral experiences [50]. Clearly such processes would occur in both males and females. However, in this review our focus is on females, taking a life-history approach, to evaluate the effects of reproductive cycles, sexual and social experiences, and maternal care on striatal dopamine pathways, as well as on the cellular events relevant to the actions of abused drugs. We provide evidence that synaptic plasticity resulting from a female's life experiences enhances responsiveness to drugs of abuse in a way than can predispose the individual to addiction.

## 2. Drugs of abuse affect neuronal plasticity in the nucleus accumbens

Common to all drugs of abuse is the activation of the mesolimbic dopamine pathway (for more extensive reviews see [39,50,100,146,147]). When dopaminergic projection neurons originating in the ventral tegmental area are activated by drugs of abuse there is a corresponding increase in extracellular dopamine within a number of forebrain regions, most notably for our purposes, the nucleus accumbens. One consequence of repeated exposure to drugs of abuse is a sensitized increase in dopamine neurotransmission, which is postulated to cause consequent morphological and functional changes within medium spiny neurons of the nucleus accumbens. These alterations in neuronal morphology through dynamic dendritic spine remodeling are believed to underlie the persistent behavioral and psychological changes following chronic drug administration [177]. Focusing on dopamine receptor-mediated events, we will provide an overview of some of the molecular mechanisms (Figure 1), which may ultimately lead to the aforementioned changes in dendritic spine morphology and function. For many of these mechanisms, we appreciate that there could be differences between males and females. Unfortunately, the bulk of this literature has been done exclusively in males. We are summarizing this literature with the assumption that these same mechanisms also apply to females.

There is a vast literature on experience-based plasticity in dendritic spines [81,124,139,177,187], yet little direct evidence relates this structural plasticity to particular behaviors. Dendritic spine synaptogenesis consequent to drug administration is hypothesized to involve mostly excitatory synapses [177]. Spines themselves also have diverse morphology with varying sizes and shapes, believed to reflect the physiology of the spines, with larger spine heads correlating to stronger synaptic connections [81,187]. Importantly, in the case of chronic drug use, dendritic spines exhibit stability following cessation of stimulation. This atypical stability makes them likely candidates to mediate the long-term underlying cellular plasticity leading to the behavioral effects seen in drug addicts that ultimately cause them to relapse [50]. In fact, previous research has established that exposure to psychostimulants causes an increase in dendritic spine density in nucleus accumbens medium spiny neurons [49,107,121,122,153,174–177].

What are some of the intervening molecular events that can cause changes in dendritic morphology? Transcription factors such as Fos and cyclic AMP response element binding protein (CREB) are likely molecular mediators of dendritic spine formation and long-term cellular plasticity [50]. Multiple cell signaling pathways, including the mitogen activated protein kinase (MAP kinase) pathway, can stimulate transcription factor activity [1]. Entry into the MAP kinase pathway can be achieved via various signaling pathways originating from G-protein coupled receptors, ionotropic glutamate receptors, and growth factor receptors (Figure 1) [1,37,127,131,212]. Binding of these receptors in turn stimulates a

cascade of phosphorylation events, including the activation of ERK1/2. Using one example [131], illustrated in Figure 1, increased extracellular dopamine will activate dopamine D1 receptors leading to heightened activation of adenylyl cyclase, an increase in the production of cytosolic cAMP, and activation of protein kinase A (PKA). This increase in PKA activity ultimately increases the activity of multiple downstream targets including Akt (also known as protein kinase B), the 32 kDa dopamine and cAMP dependent phosphoprotein (DARPP-32), as well as directly phosphorylating the transcription factor CREB. When DARPP-32 is activated by phosphorylation it can inhibit activity of protein phosphatase 1. This inhibition of phosphatase activity effectively results in increased phosphorylation of ERK1/2. CREB activation has been shown to be an important component of the behavioral rewarding effects of drugs of abuse, although its direct role in dendritic spine formation has yet to be elucidated. Alternatively, activation of the D2 receptor inhibits adenylyl cyclase, which in turn activates the inositol triphosphate pathway as well as inhibiting the phosphorylation of DARPP-32 (Figure 1). Therefore, D2 receptor stimulation has the effect of counteracting D1 receptor activation.

Whereas an increase in dendritic spine formation has been associated with both D1 and D2 receptor containing medium spiny neurons within the nucleus accumbens, it seems that D1 neurons display more stable changes in dendritic spines [117]. ΔFosB [82], a highly stable transcription factor, is a potential mediator of these long-lasting structural changes, although a molecular connection between dopamine D1 receptors and ΔFosB has not been determined. Unlike other Fos family proteins which are induced transiently following acute activation, ΔFosB accumulates following repeated stimulation and remains elevated for extended periods of time. Putative downstream targets of ΔFosB signaling have been examined by both microarray experiments and overexpression paradigms [5,6,67,80,[157],186,215,223,229]. These targets include cyclin dependent kinase 5 (Cdk5) [223], the transcription factor nuclear factor κB (NF-κB) [6], and the GluR2 subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazole (AMPA) receptor [103] (Figure 1). These downstream targets have also been shown to contribute to the long-term cellular and behavioral plasticity following repeated drug use. The importance of both Cdk5 and NF-κB in drug induced dendritic spine formation has been examined following chronic cocaine administration [153,186]. In addition, the insertion of GluR2 subunits into AMPA receptors decreases $Ca^{2+}$ permeability, potentially affecting the expression of drug-related behaviors [103].

Despite the extensive literature evaluating cell signaling and drug addiction, little is known about how these well characterized pathways respond to natural behavioral experiences. In an effort to better understand the meaning of drug-induced plasticity, we must first appreciate how these pathways respond to natural stimuli. This review will focus on how different components of reproduction in females may act within these well-established signaling pathways to potentially sensitize synaptic neurotransmission in a way that predisposes an individual to addiction.

## 3. Impact of ovarian hormones on mesolimbic dopamine systems and drug taking

Female rats have been the preponderant species used to model the effects of ovarian hormones on parameters of drug use in human females. The issue with using rodents to model human reproductive cycles is that rats have what is termed an estrous cycle, whereas women have a characteristic menstrual cycle. Hormonal fluctuations across these cycles are depicted in Figure 2. For women, there is a 2 week follicular phase during which estradiol rises, which terminates with ovulation. After ovulation, the corpus luteum that is formed from the ruptured ovarian follicle secretes progesterone for approximately another 2 weeks;

this is termed the luteal phase. Thus, the follicular phase (especially the late follicular phase) is characterized by high levels of estradiol, whereas the luteal phase has both elevated estradiol and progesterone.

Rats, in contrast, have a 4 day estrous cycle in which there are rising levels of estradiol early in the cycle, with a surge in progesterone on the 4$^{th}$ day. The surge in progesterone is coincident with ovulation. Therefore, with respect to hormonal secretion, rats have a cycle that is a calendar order of magnitude shorter than women (4 days versus 4 weeks). Two approaches have been used in rats to model ovarian hormone effects on parameters of drug use in women. One is to manipulate ovarian hormones within the timing of the rat's cycle. Here, females are examined at different points of their endogenous cycle, or the ovaries are removed and acute hormone replacement is given to mimic different phases of the cycle. The other approach is to give prolonged estradiol and/or progesterone treatments on the order of weeks. Certainly, under normal circumstances female rats are not exposed to high, chronic levels of either estradiol or progesterone. Still, many investigators, including ourselves, have effectively used this hormonal regimen to tease out questions that are difficult to answer with more acute, physiologically-based approaches. In addition, maintaining the exposure of a female rat to high levels of estradiol or progesterone may be relevant to modeling hormonal exposure during a woman's menstrual cycle. Nonetheless, in this section we will take a physiologically conservative approach in reviewing the literature on rats, limiting our discussions to steroid treatments that are within the realm of the timing of a 4-day estrous cycle.

There is a rather limited literature in women examining the relation between steroid hormone levels and psychological responses to drugs or their associative cues. The approach in these studies has either been to examine women at different stages of their menstrual cycle or to look at some type of hormone replacement in normally cycling women (see review [57]).

The contributions of estradiol to drug responsiveness have been evaluated by comparing women in the early and late follicular phases of the menstrual cycle. In the late follicular phase small increases were noted in the subjective evaluation of how much the women 'liked' a low dose of amphetamine [95]. Two other studies approached this question by supplementing estradiol levels during the early follicular phase. Women given an estradiol patch during the early follicular phase reported more pleasant responses to amphetamine and an increased desire to want more drug compared to the non-treated women [94]. In a similar vein, women who were taking oral contraceptives were given sublingual estradiol during the 'placebo' days of the treatment regimen [123]. Compared with controls, the estradiol-treated women showed a greater discriminative ability for the detection of amphetamine and also reported a greater 'liking' for the drug.

Comparisons between the follicular and luteal phases of the menstrual cycle are designed to examine the added contribution of progesterone given a background of estradiol exposure. One interesting finding from these studies is that women taking cocaine during the luteal phase had attenuated elevations in heart rate and blood pressure relative to cocaine effects during the follicular phase. This was true for either exposure to cocaine or to cocaine-related cues [56,197,199]. Subjective responses to cocaine or amphetamine were also blunted during the luteal phase. Reports of feeling 'high', liking the drug, wanting more of the drug, or craving were all lower during the luteal phase of the cycle [56,96,197,199,218]. Compared to a 'no hormone' condition it appears that estradiol augments the subjective components of drug use, whereas progesterone may counteract these effects of estradiol in women.

Analogous studies of estrous cycle effects or specific hormonal treatments on responsiveness to psychostimulants have been conducted in rats. This literature has been effectively reviewed elsewhere [12,32,64], so we will summarize it only briefly.

The simplest approach to testing the hypothesis that ovarian hormones can modulate drug effects is to compare gonadally intact female rats across the estrous cycle with ovariectomized females. Surprisingly, this literature is rather sparse. Ovariectomized female rats show a clear decrease in cocaine stimulated activity compared with intact females [40,110]. For estrous cycle effects we will use two examples. Cocaine-treated female rats had higher activity levels during proestrus and estrus compared with activity measured during either of the diestrus days [192]. In a self-administration study, hormone levels (rather than vaginal cytology) were used to track the estrous cycle [60]. In this case, self-administration of cocaine did not correlate with fluctuations in estradiol levels, though elevations in progesterone were associated with reductions in self-administration.

Estradiol treatments consistently augment locomotor activation in conjunction with either cocaine or amphetamine [58,85,93,165,231,232]. A similar set of results is found with estradiol facilitating self-administration of drugs [7,83,84,90,[111],112,128,129,184]. One interesting set of observations is that estradiol may have a nonmonotonic dose-response curve in its interactions with psychostimulants [83,150]. At low doses estradiol may actually inhibit the effects of cocaine. Moderate doses facilitate cocaine's effects on activity, whereas supraphysiological doses of estradiol may also antagonize cocaine's actions. Progesterone secretion appears to antagonize these effects of estradiol [7,53,54,231].

The time course of estradiol effects on drug-induced activity typically has had a duration of several days, consistent with an activation of intracellular receptors. Indeed, both estrogen receptors α and β have been implicated in estradiol effects on locomotor activity and self-administration [112,190]. An alternative approach has been to test the effects of cocaine or amphetamine on activity 30 min after estradiol administration [17,148,149]. The rationale behind this treatment is that such a rapid time course for estradiol effects must be mediated by membrane estrogen receptors [12]. In this case, estradiol facilitated amphetamine-induced activity [17], though oddly enough attenuated activity following cocaine [148]. Estradiol appeared to reduce cocaine availability in the brain, which may have mediated cocaine's diminished effect on activity [149]. In contrast, estradiol enhanced dialysate dopamine levels in response to amphetamine [17,35]. The measurements of dialysate dopamine or cocaine availability explain the behavioral observations, though it is unclear why estradiol should interact differentially with cocaine and amphetamine.

Ovarian hormones have been shown to influence the magnitude of a conditioned place preference to psychostimulants in rats. Relative to gonadally-intact females, ovariectomy decreased cocaine-induced conditioned place preference [185]. Either estradiol alone, or in combination with progesterone, facilitated conditioned place preference to either amphetamine or cocaine [38,185,196]. Preliminary evidence suggests that the effects of estradiol on conditioned place preference are mediated by interactions with estrogen receptor β [196].

Different mechanisms have been explored that potentially could mediate the effects of estradiol on drug action. Consistent with the effects of estradiol on drug-induced activity is the pattern of dopamine release following estradiol treatment. Even in the absence of drugs, basal dopamine is elevated in estrus relative to diestrus [16]. Estradiol administration increases dopamine synthesis/turnover [45,118,163], dopamine release [14,15], and methamphetamine potentiated dopamine release [156]. Part of the basis for the elevated dopamine could be estradiol inhibition of dopamine uptake [52,206]. The inference from

these studies that estradiol acts directly on the striatum, is supported by similar effects on dopamine in superfused striatal dissections [51,225]. Further, the observation that catechol estrogens or estradiol conjugated with bovine serum albumen (a membrane impermeable estradiol complex) mimic the effects of estradiol itself points to a membrane action of estradiol on dopamine release [19,20].

Finally, estradiol can modulate postsynaptic mechanisms of dopamine neurotransmission. Dopamine D1 receptor expression is lower during proestrus than diestrus of the female rat's cycle [119]. Similarly, estradiol potentiates D1 mediated neuronal excitability [47]. In contrast, D2 receptor binding is diminished with estradiol pretreatment [10,42,118], though the neurophysiological consequences of these receptor changes have not been tested. Again, these effects are transient and though they may contribute to the rewarding effects of drugs, they are unlikely to contribute to addiction vulnerability.

## 4. Sexual experience sensitizes the mesolimbic dopamine system

Adolescence is characterized by the onset of reproductive cyclicity. The potential impact of ovarian hormones on the mesolimbic dopamine system was discussed in the previous section. The presence of reproductive cycles does not require the female to engage in sexual activity, though some 60% of girls in the US have had sexual intercourse by the age of 19 [29]. We know from rodent studies that mechanisms mediating sexual responses are neurobiologically separable from the motivational control of sexual interest. Most notably, lesions of the nucleus accumbens in rats will spare the expression of sexual responsiveness to mounts by a male at the same time that these females resist the male's mounting attempts [171,172]. In this section, we will review the impact of the motivational consequences of sexual interactions in female rodents on dopamine neurotransmission. The goal here is to identify cellular changes that result from sexual experience which impact the initial response to taking potentially addictive drugs.

Among animals, sexual interactions have evolved in a way that reproductive success is maximized. This pattern of optimal sexual interaction has been well characterized in rodents and is referred to as the 'species vaginal code', established by Milton Diamond [48]. Diamond argued that particular patterns of vaginal stimulation by the male's intromissions were key to inducing pregnancy, establishing that "species-related neural stimuli from the vagina, integrated with other sensory inputs accompanying mating, are crucial for the initiation of neural and endocrine mechanisms supporting pregnancy and pseudopregnancy" [48].

The majority of the work done to dissect these behaviors has been performed in rats and hamsters, and although females of both species express lordosis (a characteristic dorsoflexion of the spine) the two species have rather different mating patterns. For female rats, mating behavior is a very active process that includes darting away from the male and then stopping to permit the male to mount. Flank stimulation provided by the mounting male is a sensory trigger for lordosis in the female. Once the male dismounts, the female terminates lordosis and goes back to darting about the mating area. For female rats, the ability to dart away from the male provides an opportunity for the female to regulate the timing of the male's mounting attempts, a process termed 'pacing' [136].

Mating for female hamsters is not as overtly active as that of female rats. In the presence of a male, a receptive female hamster will enter lordosis for minutes on end, even without any tactile stimulation from the male [151,152]. While in lordosis, the female hamster will move her perineum in the direction of the male's thrusts in an effort to facilitate intromission [151,152]. In this case, the male determines the pacing of mounting attempts, though the

female has considerable control over the extent to which a mounting attempt includes intromission [21,151,152].

Erskine [55] has detailed the ways in which paced mating controlled by the female induces neuroendocrine mechanisms necessary for successful pregnancy. Our view [139] is that pacing in rats or perineal movements in hamsters activate reward circuits in a way that provides sensory feedback to the females, thus optimizing copulatory contacts with the male to maximize reproductive success based on the 'vaginal code' for each of these species. The primary way in which the rewarding consequences of sexual behavior in females have been tested is through the conditioned place preference (CPP) paradigm. Not surprisingly, sexual behavior has been shown to induce CPP in both female rats and hamsters [140,158]. For rats, CPP is primarily evident when the female is permitted to pace her sexual interactions with the male [74,91,132,161,162].

Repeated exposure to drugs of abuse also induces CPP in laboratory animals and this CPP can be inhibited by blocking dopamine action using selective dopamine antagonists [209,210], establishing the importance of dopamine action in inducing the rewarding effects of drugs. Although the role of dopamine in inducing CPP with drugs of abuse appears to be relatively clear cut, there are conflicting reports as to the effect on CPP when dopamine transmission has been disrupted during sexual behavior. We evaluated the contribution of dopamine receptor binding to the induction of CPP in female hamsters following repeated sexual bouts. Consistent with findings from the drug literature, systemic injection of selective D2 receptor antagonists resulted in an attenuation of CPP in female hamsters [141]. Horsman and Paredes evaluated [69] the effects of both a non-selective D1/D2 antagonist and a selective D2 antagonist on CPP induced by paced sexual behavior in female rats. In this study, neither dopamine antagonist affected the acquisition of CPP. Because the literature is so limited on this topic, we do not know what might form the basis for these discrepant results.

The regulation of the male's intromission by female hamsters can be measured indirectly through the male's 'hit rate', which is the proportion of mounts by the male hamster that results in intravaginal intromission. Female hamsters given sexual experience consisting of 6 weekly 10 min tests can improve the hit rate of sexually naive males compared with the performance of males tested with sexually inexperienced females [21]. This increased hit rate remains even after a subsequent 6 week absence from mating with a male, implying a sustained change in the female's behavior resulting from the initial sexual experience [21]. To evaluate the contribution of nucleus accumbens dopamine to this experience-based change in the female's behavior, 6-hydroxydopamine (6-OHDA) lesions were made in the nucleus accumbens prior to giving female hamsters sexual experience. After 6-OHDA lesions, the increased hit rate otherwise observed in experienced females was negated, demonstrating that dopamine release in the nucleus accumbens is necessary for the change in female sexual behavior that is observed over time with sexual experience [21].

A more direct relation between sexual behavior and nucleus accumbens dopamine release was established using in vivo microdialysis to monitor extracellular levels of dopamine in female rats and hamsters during sexual behavior [13,92,105,138,143,166]. In sexually receptive female hamsters, increases in extracellular dopamine, as measured by dialysate dopamine concentration, were measured in the nucleus accumbens during mating behavior [138]. This elevation in dialysate dopamine in the nucleus accumbens during mating was dependent upon intromissive stimulation from the male [106].

Similar increases in extracellular dopamine have been demonstrated in receptive female rats by in vivo microdialysis. Initially, it was demonstrated that female rats able to pace their

sexual behavior showed the greatest increases in dopamine release in the nucleus accumbens when compared to females who were not responsible for pacing sexual behavior [143]. However, subsequent work has demonstrated that it is not the females pacing behavior per se, but the timing of the copulatory stimuli, regardless of whether the female is responsible for regulating the pacing of sexual contacts [11]. Pfaus et al. [166] took this work a step further, making an effort to dissect the contributions of different components of female sexual behavior to elevations in dialysate dopamine. By evaluating dopamine release during locomotion in a novel environment and during sexual behavior, Pfaus and colleagues [166] demonstrated that increases in extracellular dopamine detected within the nucleus accumbens during mating behavior were a result of contact with the copulating male, and not a side-effect of neuronal stimulation resulting from physical activity or exploration of a novel environment [166].

Jenkins and Becker [92] refined their microdialysis procedure to collect samples every minute during copulation in female rats. By time-locking these samples to particular behaviors, Jenkins and Becker [92] were further able to demonstrate that dopamine release in the nucleus accumbens actually occurs before coital stimulation from the male. This observation supports the hypothesis that dopamine release in the nucleus accumbens is involved in the anticipation of sexual behavior and not necessarily related to the explicit expression of lordosis [92].

‘Sensitization’ is the term used in the drug literature to describe an enhanced dopamine release following repeated exposure to a drug [98,99,167,200]. We were also able to demonstrate that sexual experience sensitized dopamine release in the nucleus accumbens, and that this augmented dopamine release was not accompanied by alterations in lordosis expression [105]. These data suggests that sensitization of the dopamine system is a natural consequence of certain types of repeated behavioral experiences.

Based on the demonstration that sexual behavior can sensitize the mesolimbic dopamine system in a manner analogous to that of drugs of abuse, we tested whether cross-sensitization of the mesolimbic dopamine response to amphetamine would occur following repeated sexual experiences (Figure 3). When exposed to amphetamine, drug naïve, sexually experienced female hamsters showed a sensitized locomotor response upon their first exposure to amphetamine compared with the response of sexually inexperienced females [24]. Interestingly, the reverse phenomenon has been demonstrated in rats, in that females with previous drug exposure will display increased appetitive behaviors, i.e. hopping and darting towards a copulating male rat, without a change in the expression of lordosis [3]. These data suggest that previous exposure to drugs of abuse enhances the “motivational” control of sexual behavior without affecting the reflexive lordotic components.

Thus far, we have established the importance of repeated dopamine release driving the sensitization of the mesolimbic dopamine system on a behavioral and presynaptic level, but what are the neurochemical underpinnings of this sensitization? What changes occur at the synapse of nucleus accumbens neurons that mediate this persistent sensitized response? For the remainder of this section, we will piece together components of intracellular pathways that may contribute to this long-lasting plasticity in neurobiology and behavior.

Mentioned previously, a hallmark of sensitization is an increase in synaptic dopamine concentration in response to fixed stimulus. To date, whether the sensitized synaptic dopamine elevations result from changes in presynaptic release, decreased dopamine reuptake, or some combination of the two has not been tested. What is clear is that this increase in synaptic dopamine concentration enhances postsynaptic dopamine signaling.

It has long been known that drugs of abuse not only sensitize the mesolimbic dopamine system but also alter receptor-mediated intracellular signaling [179,188,189,208,211,213]. In an effort to resolve components of intracellular sensitization that result from sexual experience, we measured cAMP accumulation in homogenates from the nucleus accumbens of female hamsters after in vitro pharmacological stimulation [22]. In this experiment, cAMP accumulation was evaluated following stimulation of the dopamine D1 receptor, activation of the G-protein using Gpp(NH)p, or direct forskolin stimulation of adenylyl cyclase. Homogenates from both sexually naïve and experienced animals showed a dose dependent response to either forskolin or Gpp(NH)p in the nucleus accumbens and caudate, with no differences in response between sexually experienced and inexperienced females. In contrast, preparations taken from sexually experienced female hamsters displayed a significantly enhanced accumulation of cAMP in the nucleus accumbens in response to dopamine when compared to homogenates from sexually-naïve controls. The enhanced cAMP accumulation in the accumbens of sexually-experienced females suggests that in addition to presynaptic dopamine sensitization, repeated sexual behavior may also trigger an increased coupling of the dopamine D1 receptor to its G-protein, which in turn yields an increased efficacy in the activation of cAMP production. These data further the idea that drugs of abuse take advantage of reward circuitry in the brain that is in place to promote naturally occurring behaviors in the animal.

Given the sensitized accumulation of cAMP, it is logical to next evaluate which potential downstream targets are activated, and how this augmented activation may contribute to sensitization and long term changes in the mesolimbic dopamine circuit following sexual experience. When gene expression in the dorsal and ventral striatum of sexually experienced or sexually naïve female hamsters was compared by microarray, a number of gene expression changes were observed, including but not limited to genes involved with neurotransmission, signal transduction, transcriptional regulation, receptors, and cytoskeletal remodeling [23]. In contrast to the effects of repeated exposure to drugs (e.g., [25]), our microarray study found no differences in dopamine receptor expression following sexual experience. Further, our unpublished observations are consistent with the microarray results in that there is no effect of sexual experience on either dopamine D1 or D2 receptor densities (V.J. Watts, B.R. Chemel and R.L. Meisel, unpublished data) or total D1 or D2 receptor protein levels (N.A. Staffend, V.L. Hedges and R.L. Meisel, unpublished data), bolstering the hypothesis that accumulation of cAMP through D1 receptor activation is indeed a result of increased coupling of dopamine D1 receptor to G proteins rather than to receptor changes.

Although a comprehensive view of signaling pathways affected by sexual experience is lacking, there are demonstrations of immediate early gene activation such as c-Fos, as well as accumulation of FosB/ΔFosB in the nucleus accumbens after repeated sexual experience [24,43,139,215]. We demonstrated that sexual behavior induces c-Fos expression in the core of the nucleus accumbens, which is further elevated (i.e. sensitized) if the animal has had prior sexual experience [105]. These results support the contention that sexual experience not only sensitizes dopamine release, but also postsynaptic cellular activation in the nucleus accumbens. Recently, Coria-Avila and Pfaus [43] demonstrated the induction of Fos expression in the nucleus accumbens core of female rats who were conditioned to associate a particular odor or strain of male rat with sexual experience. Unique to these results is the report of neuronal Fos activation in the *anticipation*, and not receipt, of sexual reward [43], bolstering the hypothesis that dopamine release in the nucleus accumbens core is associated with sexual behavior reflective of the motivational or appetitive state of the female animal.

Most Fos family members are rapidly degraded after transcription. The transient expression of these immediate early genes allows for controlled activation of downstream affectors.

ΔFosB is a truncated member of the FosB family of immediate early genes [144] and is unusual because ΔFosB is very stable and accumulates in the brain after chronic stimuli such as drugs of abuse, natural reward and chronic stress (for review see [145]). Due to the transient nature of full length FosB, pan-FosB antibodies are commonly used with confidence for immunohistochemical detection of ΔFosB in brain tissue. Using this approach, sexual experience resulted in a significant accumulation of FosB selectively in the core of the nucleus accumbens of female hamsters when compared to sexually naïve female controls [139]. This accumulation was independent of sexual behavior immediately prior to sacrifice, indicating persistent, long-term accumulation of the ΔFosB isoform.

Because of its stability, ΔFosB is able to produce greater levels of transcriptional activity when compared to more transient Fos family members, and it has been speculated that ΔFosB contributes to long-term behavioral and cellular plasticity associated with previous experience (for review see [137]). In an effort to delineate behavioral consequences of ΔFosB accumulation, transgenic and viral vector methods have been implemented to manipulate the level of ΔFosB gene expression [67,80,157,215]. As discussed previously, sexual experience is known to induce conditioned place preference in female rodents, and these data are taken to indicate rewarding consequences of sex behavior. Previous work has demonstrated that sexual pairings once a week for 5–6 weeks is sufficient to induce conditioned place preference in female hamsters [80,140,141] as well as provide adequate experience enabling the female to increase the hit rate of a sexually naïve male partner [24]. However, 2 weeks of sexual experience is inadequate to produce conditioned place preference or to affect copulatory interactions with a male [80]. When ΔFosB was overexpressed by an adeno-associated virus in the nucleus accumbens, female hamsters showed significant conditioned place preference after only 2 weeks of sexual pairing. These female hamsters overexpressing ΔFosB when given 2 weeks of sexual pairings were also able to significantly increase the hit rate of males compared to males mated with GFP-transfected control females [80]. These results suggest that ΔFosB is augmenting the consequences of sexual behavior thereby reinforcing the effects of behavioral experience at earlier stages of behavioral acquisition. A possible action of ΔFosB in this regard is through sustained downstream transcription of gene products important for neuronal plasticity.

In addition to intracellular and behavioral modifications, sexual experience has the ability to induce plastic changes of the neuronal architecture, perhaps altering synaptic connectivity in various brain regions [139]. After 6 weeks of sexual experience, significant increases in dendritic spine density were noted in Golgi stained sections from the nucleus accumbens of sexually experienced female hamsters, a characteristic commonly resulting from a sensitizing dosing regimen of many drugs of abuse [104,122,194].

Taken together, it is clear that previous sexual experience has the ability to sensitize the mesolimbic dopamine system in a manner analogous to that of drugs of abuse. Although there are many gaps in our knowledge of the specific signaling molecules and intracellular pathways involved, it is apparent that repeated sexual behavior leads to increased dopamine release in the nucleus accumbens of female rodents and this increased dopamine release has significant postsynaptic effects on signaling, transcription, and synaptic morphology.

## 5. Activation of the mesolimbic dopamine system by pair bonding in voles

Social interactions can be viewed more broadly than simply sexual behavior, as other types of intersexual social interactions activate the mesolimbic dopamine pathway. Most notable among these social interactions is pair bonding in prairie voles [89]. Pair bonds are defined as long-term, selective and affiliative social attachments. Voles are microtine rodents, which display an array of social systems, ranging from highly social to solitary. Prairie voles

exhibit selective pair bonding and monogamous affiliation with an established partner, as well as biparental care in a shared nest. In the field, pair bonds in prairie voles are characterized by the preferential association with a single partner and the failure to take on a new mate upon the death of that partner [70–72,169]. In the laboratory, the formation of a pair bond is first assessed by the presence of a partner preference. In this paradigm, a presumably pair-bonded vole is given a choice to spend its time with either its partner or a conspecific stranger. Importantly, mating facilitates partner preference between an individual male and female [34,87,193]. Short-term cohabitation (which would produce a pair bond in mated animals) in the absence of mating is insufficient to produce a partner preference [87,219,222], however, long-term cohabitation with a male (in the absence of mating) can induce partner preference [219]. In this section we will focus on the importance of the mesolimbic dopamine system in pair bond formation in the prairie vole. In addition to discussions of synaptic dopamine neurotransmission and the interaction of dopamine with the neuropeptide oxytocin in the female vole, we will also examine this pair bond model in terms of its relevance to susceptibility to drug addiction.

One question that has been asked is whether mating in the female prairie vole is sufficient to activate the mesolimbic dopamine system. Stimuli from the male are required for the display of female sexual behavior in prairie voles [33]. An in vivo microdialysis experiment in estrous female prairie voles found an increase in extracellular dopamine levels within the nucleus accumbens during mating [73]. Dopamine was increased 50% over baseline in the first 15 min sample following introduction of the male and remained elevated at 30% for the following 3 hrs [73]. Non-mated non-estrous females given oil vehicle did not show an increase in extracellular dopamine levels, indicating that the increased dopamine is not due to nonspecific social interactions, but instead to the sexual interaction itself. This finding is reminiscent of dopamine changes during mating in non-pair bonding species, such as female rats [143,166] and hamsters [106,138], indicating that an increase in extracellular dopamine does not fully explain the formation of a pair bond. What may be significant here is the protracted maintenance of the extracellular dopamine levels in voles as these elevations can be more transient in other species [106].

Both monogamy and pair bonding are rarely found in nature. As sexual behavior can stimulate dopamine release in the nucleus accumbens of promiscuous species, how is it that dopamine release underlies pair bonding in the vole? In this regard, a pharmacological approach was taken to determine the significance of dopamine in the formation of partner preferences. In one study, the nonspecific dopamine agonist, apomorphine, was administered to estrous females, which were then tested in a partner preference test after cohabitation with a male in the absence of mating. Administration of varying doses of apomorphine was able to produce a partner preference in the absence of mating [216]. In contrast, haloperidol, a general dopamine antagonist, blocked the formation of a partner preference in females that were allowed to mate for 24 hr with a male. To further elucidate the dopamine receptor subtype of importance, Wang et al. [216] repeated the experiment with specific D1 and D2 receptor antagonists. The D1 receptor antagonist SCH23390 did not affect the vole's ability to form a partner preference. However, administration of the D2 receptor antagonist, eticlopride, blocked mating induced partner preference regardless of whether the drug was administered systemically or directly into the nucleus accumbens. It appears that the D2 antagonist, while not affecting mating, specifically disrupted the formation of a partner preference, which parallels the effect of D2 antagonism on conditioned place preference in female hamsters. The importance of D2 receptor activation was further validated by a formation of partner preferences in the absence of mating following treatment with the D2 agonist quinpirole given either systemically or by direct infusion into the nucleus accumbens. Again, this effect was not seen with the D1 agonist SKF38393 [216].

The involvement of the neuropeptide oxytocin and its interaction with dopamine within the mesolimbic system was studied in the context of the regulation of pair bonding [224]. Monogamous prairie voles have higher densities of both oxytocin receptor oxytocin receptor gene expression in the nucleus accumbens than do promiscuous voles [228]. This species difference alludes to the importance of oxytocin receptor activation in pair bond formation. Indeed, extracellular concentrations of oxytocin are increased in the nucleus accumbens of female prairie voles during unrestricted interactions with a male [182]. Unilateral 6-OHDA lesions in the nucleus accumbens of female prairie voles resulted in diminished binding of the dopamine transporter, while leaving oxytocin receptor binding unaffected [227]. This indicates that the oxytocin receptors are likely located on postsynaptic targets within the nucleus accumbens, rather than on dopaminergic terminals originating from the ventral tegmental area. . The studies reviewed here focus on voles, though it is important to note that the distribution of oxytocin immunoreactive fibers within the nucleus accumbens is conserved in voles, mice, and rats [182].

The interaction between dopamine and oxytocin systems has been demonstrated to critical for pair bonding in female prairie voles. Intracerebroventricular (icv) infusions of oxytocin in female voles increase social contact with males, as well as facilitate partner preference in the absence of mating [41,221]. Similar icv infusions of an oxytocin receptor antagonist block the formation of a partner preference even after extensive mating [87]. Indeed, direct nucleus accumbens infusions of an oxytocin receptor antagonist block partner preference [227], identifying the nucleus accumbens as a site of action for the ventricular treatments. In the absence of mating, blocking oxytocin receptor activation during extended cohabitation with a male also prevented the formation of a partner preference [227].

A study by Ross et al. [183] used adeno-associated viral vectors to overexpress oxytocin receptor in the nucleus accumbens of both adult monogamous female prairie voles and nonmonogamous female meadow voles to examine how oxytocin receptor density in the accumbens was related to social behaviors. Overexpression of the oxytocin receptor in the already monogamous prairie vole resulted in accelerated partner preference after cohabitation with a male. Interestingly, when the oxytocin receptor was overexpressed in the promiscuous meadow vole, there was no effect on partner preference. This study suggests that oxytocin receptor expression within the nucleus accumbens is not sufficient to produce a partner preference in nonmonogamous species [183]. Still, species difference in oxytocin neurotransmission may impact whether a species shows a monogamous or polygamous mating strategy.

The oxytocin results taken together with the data presented earlier regarding dopamine D2 receptor activation indicate the involvement of both systems in pair bonding, but do not necessarily demonstrate an interaction between these systems. The interaction of oxytocin with dopamine was demonstrated by co-administration of the D2 receptor agonist quinpirole with either the D2 receptor antagonist eticlopride or an oxytocin antagonist into the shell of the nucleus accumbens [125]. These combined treatments blocked quinpirole-induced partner preference. Complementing these results, co-administration of oxytocin with either an oxytocin or D2 receptor antagonist into the nucleus accumbens shell blocked oxytocin-induced partner preference. These data indicate that oxytocin and dopamine D2 receptors indeed interact to facilitate the development of partner preference in female prairie voles [125]. One interpretation is that the oxytocin-dopamine interaction is unique in the monogamous pair bonding vole, when compared to other promiscuous species, a theory partially supported by the species-specific distribution of oxytocin receptors within the nucleus accumbens [88,227]. A similar oxytocin-D2 interaction, as well as receptor distribution, is found in the medial prefrontal cortex of female prairie voles, another area

within the mesolimbic dopamine pathway that could be important for pair bond formation [198].

There exist two hypotheses for mechanisms of oxytocin action in pair bond formation after mating. First, oxytocin transmission within brain areas of high oxytocin receptor density (e.g., nucleus accumbens and prefrontal cortex) is known to play an important role in reward processing and acts to reinforce the association with the partner male. Another hypothesis is that while D2 receptors may mediate the maintenance of the pair bond, oxytocin acts on social recognition, which is critical for pair bond formation. Indeed, the administration of a low dose of oxytocin facilitates social recognition in rats [170]. Rodents usually recognize previously encountered conspecifics by olfactory recognition cues. Olfactory cues are certainly important in voles, as olfactory bulb removal inhibits the formation of a partner preference and estrus induction in female prairie voles [220]. Additionally, oxytocin knockout mice have been shown to exhibit social amnesia [62], a behavior that can be rescued by direct infusion of oxytocin into the medial amygdala [61]. The inability to recognize individuals in these knockout mice is not due to problems involving learning and memory or olfactory processing because these animals perform similarly to wild types in the Morris water maze and habituate to nonsocial odors. In addition, Fos induction does not differ in brain regions involved in olfactory processing between knockouts and wild types after a social encounter, however knockouts fail to show Fos induction in the medial amygdala [62]. The medial amygdala receives both direct and indirect projections from the accessory olfactory bulbs and mediates socially significant olfactory cues [142], as shown by lesions of the vomeronasal organ inhibiting pair bond formation in female prairie voles [44]. Further experimentation is needed to fully elucidate the specific details underlying the interaction between dopamine and oxytocin within the nucleus accumbens, but the importance of both neuromodulators is undeniable in the formation of pair bonds in female prairie voles.

Young et al. [226] proposed a neural circuitry model of social bonding in monogamous prairie voles (Figure 4). In short, sensory information from the vagina traveling via spinal projections from the lumbrosacral spinal cord converges onto both the nucleus tractus solitarius and the midbrain periaqueductal gray, which in turn project to the nucleus accumbens. Olfactory information is processed by the accessory olfactory bulb, which then projects to the oxytocin receptor rich medial amygdala, where oxytocin facilitates social recognition. The subsequent activation of the mesolimbic reward pathway resulting from copulation results in a surge in dopamine release in both the nucleus accumbens and the prefrontal cortex. The nucleus accumbens may act as a coincidence detector, so that when dopaminergic and peptidergic signals occur simultaneously a selective pair bond can result.

The neural circuitry critical to the expression of pair bonding in the female vole certainly overlaps pathways that underlie addiction. Most notable in this shared circuitry is the placement of the mesolimbic dopamine pathway as a final common output to both the regulation of pair bonding and functional consequences of drugs of abuse. The beauty of the intrinsic neurobiology of the vole model system is that it is uniquely placed to uncover possible contributions of oxytocin to mechanisms mediating addiction vulnerability. Although a few studies on dopamine-oxytocin interactions with respect to drugs of abuse have been done in male rats [108,109], clearly this research area deserves more study.

## 6. Activation of the mesolimbic dopamine system by maternal behavior

Maternal care is a highly motivated behavior, where the dam engages in many pup-directed behaviors including licking and grooming, nursing, nest building, and retrieving pups to the nest site [65,155,201,202]. While it is clear this highly motivated state that allows the

immediate care of offspring is brought about by both the hormonal events of pregnancy and parturition, there is also substantial evidence that similar to drugs of abuse, activation of the mesolimbic dopamine system is key to the expression of this behavior [204]. This section of the review will focus on research that has investigated the rewarding properties of pups, the presynaptic facilitation of dopamine release during maternal behavior, and the importance of post-synaptic D1 and D2 receptor activation.

The onset of maternal care behaviors is rapid at birth, but can also be induced in virgin female rats following 6 to 8 days of repeated exposure to pups [65,180]. Although it was initially reported that postpartum lactating females behave in a manner indistinguishable from pup-sensitized virgin females, Bridges et al. [26] showed that lactating females performed superiorly to pup-sensitized females in a T-maze pup retrieval task. To further investigate the mechanism underlying this difference in behavior, Stern and Mackinnon [202] attached a T-maze to the dam's home cage and tested a variety of conditions, comparing normal postpartum females, thelectomized (nipple removal) females, hormonally-facilitated maternal behavior, and non-hormonal conditions (pup-sensitized) in their ability to choose the most rewarding stimulus (the pup). Over the 5 days of testing, one arm of the T-maze would hold a previously suckled pup and the other a pup-sized toy, with arm assignments randomly chosen each test day. Interestingly, nearly every postpartum, thelectomized and hormonally primed female retrieved the pup and returned it to the nest (while ignoring the toy). In contrast, only half of the pup-sensitized females were able to perform this task. This study implicated the obvious importance of hormones in the specific rewarding maternal behavior of pup retrieval [202].

The rewarding value of pups for maternal female rats has been further investigated using traditional paradigms. In one such behavioral test, a pup 'self-administration' procedure, dams would readily bar press to gain access to pups, suggesting that the pups were highly rewarding to these females [116]. An unusual approach was taken in a study examining cocaine self administration throughout the reproductive cycle of female rats [79]. Female rats were able to self administer cocaine in their home cage with pups present. The highest intake of cocaine was seen during estrus and the first trimester of pregnancy, whereas intake rapidly dropped at parturition and remained at a decreased level throughout the first 8 days of lactation [79]. This decrease in cocaine self administration at the time of parturition suggested that pups are such a highly valued natural stimulus that they are preferred over cocaine. The idea that female rats would prefer pups over cocaine was supported in a functional magnetic resonance imaging study [63]. In this study, both nursing dams and cocaine-exposed virgin females had activation of the mesolimbic dopamine system. When the lactating dams were exposed to cocaine, there was suppression of activation within this reward system [63], demonstrating that for the dam nursing is more rewarding than cocaine.

A condition place preference paradigm, where dams chose between a pup-paired or cocaine-paired environment, was utilized to test whether females would exhibit a place preference to a pup-conditioned environment following parturition [133]. The place preference for pups was maintained for a short time after parturition, but decreased over time such that dams eventually changed their preference to the cocaine-paired environment [134,135]. This pattern of preference (pup preferring in early postpartum and cocaine preferring in late post partum) was maintained even when the incentive salience of the cocaine-paired condition was increased by both route of cocaine administration and the duration of the conditioning session [191]. Mattson and Morrell [135] went on to investigate the differential distribution of the immediate early gene c-Fos and cocaine and amphetamine-regulated transcript expression in these cocaine- and pup-preferring dams. They found dams that prefer the cocaine associated compartments had a greater increase in c-Fos immunoreactivity in both the nucleus accumbens core and shell than either dams that preferred the pup associated

compartments or unconditioned (control) dams. Interestingly, when these animals were tested for locomotor sensitization, only the cocaine-preferring dams showed a sensitized response following the cocaine conditioning compared to pup-preferring dams [191].

To determine if pup reward shares circuitry with drugs of abuse, several laboratories have examined how different aspects of maternal care affect extracellular dopamine within the nucleus accumbens. Consistent with this hypothesis, a microdialysis experiment showed that the reuniting of separated pups with the dam significantly increased dopamine and its metabolites within the nucleus accumbens [76]. Further, 6-OHDA lesions of either the dopaminergic ventral tegmental projection neurons or the nucleus accumbens terminals impaired the maternal pup retrieval [78]. Apparently this treatment only produced a partial disruption of maternal retrieval, as it was overridden by extending the time of maternal separation from the pups to 3–6 hours [77]. Champagne et al. [36] further examined nucleus accumbens dopamine during maternal licking/grooming using in vivo voltammetry within the nucleus accumbens shell. It was found that there was an increase in extracellular dopamine while the dam was in a nursing posture and immediately before the onset of a licking/grooming bout. Dopamine levels remained at an elevated level throughout the bout, but then decreased immediately before the termination of the behavior. Additionally, the amplitude of the dopamine response was correlated to whether dams had been characterized as either low or high licking/grooming dams, with high licking/grooming dams having an augmented dopamine signal compared to low licking/grooming dams [36]. These observations were supported by a microdialysis experiment that compared normal Sprague-Dawley rats with Flinders sensitive rats, which display low levels of maternal behavior [113]. The Flinders rats were found to be deficient in affiliative maternal behaviors, and these decreased maternal behaviors correlated with a decrease in dopamine during microdialysis. One interpretation of these results is that the Flinders rats do not properly interact with pups because they do not find them appropriately rewarding [113].

Previous maternal and reproductive experiences also effect extracellular dopamine concentrations within the nucleus accumbens shell, as well as dopamine dependent behaviors. A study by Felicio et al. [59] examined the impact of prior parity on dopaminergic activity. Dams with two prior pregnancies exhibited significantly higher striatal dopamine levels compared to dams with only one prior pregnancy, suggesting that previous maternal experience had the ability to sensitize striatal dopamine levels [59]. Another study used nulliparous (no prior births) and multiparous (multiple prior births) female rats given pup exposure along with microdialysis during a period that elicits little to no maternal behavior in any females [2]. Despite the lack of observable maternal behavior at this time, an increase in dopamine was still observed during the first 8 min of pup exposure, with multiparous females having higher dopamine levels than nulliparous females. This effect on dopamine quickly dissipated in the following 8 min test sample. Still, the experience-dependent increase in dopamine supports the idea that nucleus accumbens dopamine plays a part in mediating the rewarding consequences of pup exposure in females with previous maternal experience [2].

To further evaluate how previous reproductive experience can affect dopamine neurotransmission, Byrnes et al. [31] examined the effects of dopamine agonists on the striatal dependent behaviors, prepulse inhibition and oral stereotypy, in nulliparous females and in multiparous females that had previously weaned their litters. Apomorphine, a mixed D1/D2 receptor agonist disrupted prepulse inhibition and oral stereotypy in multiparous, but not nulliparous females. Consistent with these behavioral effects, multiparous females had higher striatal dopamine content compared to nulliparous females [31]. These results suggest that prior pregnancies can sensitize striatal dopamine systems, potentially making these females more susceptible to drugs of abuse.

If previous maternal experience has the ability to sensitize dopamine release, it could then be possible for maternal behavior to cross sensitize to drugs of abuse. To test this possibility nulliparous and multiparous female rats were given amphetamine and tested for locomotor activity [86]. Compared to nulliparous females, multiparous females showed higher locomotor activity following amphetamine administration. These results demonstrate that prior reproductive experience can cross sensitize to amphetamine [86].

Several pharmacological approaches have been taken to understand the role of dopamine in the nucleus accumbens on maternal behavior. Administration of a mixed D1/D2 receptor antagonist directly into the nucleus accumbens disrupted normal maternal behavior in rats [101] and the biparental female prairie vole [126]. To further parse out which dopamine receptor subtype could be mediating these effects, a D1 receptor antagonist was directly injected in the nucleus accumbens of female rats. This manipulation decreased pup retrieval (a D2 antagonist was ineffective) only if applied to the nucleus accumbens as opposed to other neural sites (i.e., the ventral pallidum or medial preoptic area) [154].

Surgical termination of pregnancy is a procedure that produces a short-latency onset of maternal behavior [181]. Direct injection of a D1, but not a D2, agonist into the nucleus accumbens of pregnancy terminated rats facilitated the maternal response to donor pups [204], implicating D1 receptor activation for the onset of maternal behavior. While these studies demonstrate the importance of D1 receptor activation in the onset of maternal care, another aspect of maternal behavior termed maternal memory, has also been shown to be mediated by dopamine receptor activation in the nucleus accumbens [27,28]. Maternal memory is the long term retention of maternal behavior following partuition and is believed to be important in maintaining high levels of maternal care that remains following the immediate post-partum period. Indeed, the long-term effects of pup removal at parturition results in almost the complete loss of maternal behavior so that the dam acts in a similar manner to virgin females [28]. Research showing that lesions of the entirety of the nucleus accumbens or the shell alone flanking the time of pup exposure is sufficient to disrupt maternal memory [115,120], but not other maternal behaviors such as licking and nursing [120].

The separate administration of both D1 and D2 receptor antagonists throughout parturition has been found to significantly attenuate maternal behaviors tested at the time of parturition [30], as well as the maintenance of maternal care [195]. Females treated with either a D1 or D2 antagonist following parturition failed to group pups in the nest and crouch over them appropriately, however only the D2 receptor antagonist affected the retention of maternal behavior and maternal memory when these same dams were tested 7 days following parturition [30]. Parada et al. [160] has also shown that a D2 antagonist microinfusion into the nucleus accumbens shell produces deficits in maternal memory when tested following the 7 day latency between pup exposures, without any effect of the D1 antagonists. They surprisingly found that the combined D1/D2 antagonist infusion showed an additive effect, which would suggest that blocking both receptor subtypes is necessary to completely disrupt maternal behavior [160]. Both D1 and D2 antagonists have also been employed to examine ongoing maternal behavior in lactating rats. A mixed D1/D2 antagonist, haloperidol, significantly reduced pup retrieval, pup grouping, and nest building, with similar results observed from the D2 receptor blocker pimozide and the D1 antagonist SKF-83566 [195].

The results of these studies highlight the importance of nucleus accumbens dopamine neurotransmission in maternal behavior, and its responsiveness to drugs of abuse. In addition to maternal behavior itself, prior parity also seems to sensitize dopamine systems in a way that make females more vulnerable to the effects of drugs. A valuable addition to this literature would be studies comparing the commonalities of the molecular mechanisms

underlying the effects of maternal behavior and reproductive experience with mechanisms of drug induced plasticity, for example as outlined in Figure 1.

## 7. Conclusions

We began this review with the thesis that life experiences, particularly those related to reproduction, can affect the mesolimbic dopamine system in a way that makes females susceptible to the addictive properties of drugs. This idea stems from the proposition that the mesolimbic dopamine system retains a high degree of synaptic plasticity that is functionally related to an individual's changing needs. Activation by a variety of drug classes usurps this plasticity, yielding persisting sensitized cellular and behavioral responses to these drugs. If under certain conditions, naturally-occurring behaviors promote a similar sensitization of these dopaminergic circuits, a given pattern of drug use becomes more potent in accelerating the stages leading from drug use to abuse. In this regard, there should be parity in the effects of drugs and motivated behaviors on the long-term sensitization of dopamine neurotransmission and its functional consequences. That is, repeated drug administration should impact the expression of normal motivated behaviors just as behavioral experience can affect an individual's responsiveness to drugs. In fact, animal studies have convincingly demonstrated that a variety of drugs that people abuse can affect different parameters of female sexual behavior (reviewed by [75]). We have provided an overview of mechanisms through which different components of a female's reproductive experiences can alter dopamine neurotransmission in a way that the system shows a sensitized response to drugs even upon the initial exposure. Our focus has been on reproductive events in females, though it is important to note that there is a rich literature in rats demonstrating that male sexual experience sensitizes the mesolimbic dopamine system [8,9,68,159,168,205] in much the same way as we have described for females.

Common to all stages of reproduction in females reviewed here is an activation of the mesolimbic dopamine system. Ovarian hormone levels impact dopamine neurotransmission in the nucleus accumbens in a way that can acutely impact the rewarding and psychomotor potency of drugs. These effects are dynamic, changing with the integrated fluctuations of estradiol and progesterone across an individual's cycle. In contrast, reproductive behaviors and prior pregnancies produce a sensitization of dopaminergic neurotransmission, which leads to a long-lasting potentiation of receptor mediated signaling. It is thought that transcriptional activation consequent to these signaling events induces the formation and stabilization of dendritic spines that presumably impact neuronal excitability [50]. Though this plasticity is biologically adaptive as our examples of sexual behavior, social affiliation, and maternal behavior demonstrate, an undesirable outcome is that it can potentiate cellular responses to drugs.

A number of voices have expressed the view that mesolimbic dopamine pathways are common ground for both the neurobiological control of motivated behaviors and the rewarding and addictive properties of drugs (e.g., [97,102,173]). By extension, the argument, which is eminently reasonable, is that addiction is therefore a pathology of motivation. The question commonly raised is why aren't motivated behaviors addictive [214]? One simple answer to this question is that they indeed are addictive, if we consider extremes of sexual behavior, shopping, eating, or gambling [4,46,178,230]. Nonetheless, the conventional answer is that our normal life experiences do not activate the mesolimbic system to the extent that potent pharmacological agents do, so addiction represents crossing a neurobiological threshold that is not reached as a result of simple life experiences [214].

Perhaps more illuminating is the observation that not all drug users become addicts. Drug use in people goes through a series of stages in which drugs initially produce a subjective

rewarding experience [97]. With repeated drug use, tolerance to the pleasant effects of drugs develops, causing people to take higher doses to achieve the same subjective experience. It is this escalation of drug use that presumably leads to the neurobiological changes underlying addiction [97]. These changes in the addicted brain are extremely resistant to therapeutic intervention, and even when treatment is effective, people are vulnerable to relapse [203]. Even so, we are left with the questions of why there are individual differences in vulnerability to addiction and why once an individual is addicted that treatment is ineffective.

Plasticity in the mesolimbic dopamine system in response to natural behavioral experiences speaks to these essential issues related to drug addiction. One factor that certainly contributes to addiction vulnerability is genetics [114]. Early life experiences have also been identified as critical variables, especially with respect to an individual's negative or stressful life experiences [114]. An additional factor that we have highlighted here is an individual's normal behavioral life history. Our hypothesis is that these experiences affect neurotransmission in the mesolimbic dopamine system in a biologically advantageous manner; though an unfortunate consequence is that drug use in this case may accelerate the individual through the stages of addiction more quickly.

What then is the basis for the resistance to therapeutic intervention? Reproductive behaviors are fully developed in the absence of explicit associative processes. The incentive properties of relevant cues for the behaviors are well-established prior to an individual's initial experience. Female rats engage in effective copulatory interactions with males when paired for the first time, assuming appropriate physiological conditions are met. Similarly, parturient female rats effectively care for their newborn pups. As we have discussed, these behavioral 'reflexes' are controlled by a mesolimbic dopamine circuitry that has the special property of responding to biologically-meaningful incentive stimuli. In the case of drugs, Belin et al. [18] articulated a learning-based neural model in which repeated stimulation of the ventral striatum produces a shift in neural processing from the nucleus accumbens shell to the accumbens core and dorsal striatum that is matched by behavioral associations that become less malleable, producing what they term an 'incentive habit'. This neural plasticity is exemplified by dendritic spine studies in which cocaine administration is sufficient for spine induction in the shell, whereas behaviorally sensitizing cocaine treatments are required for spine formation in the nucleus accumbens core [122]. Because sensitization following sexual experience preferentially targets the core of the nucleus accumbens, such experience may facilitate this drug-mediated shift in neural processing. Collectively, these learned responses to drugs acquire the characteristics of natural motivated behaviors. The unusual strength of these associations [18], as with the motivated behaviors in our examples, makes addicted patterns of behavior extremely difficult to extinguish (e.g., [217]).

In sum, we propose that female reproductive processes, broadly considered, can produce enduring effects on synaptic dopamine neurotransmission in the nucleus accumbens. Under normal conditions, the neural consequences of these behavioral experiences serve important adaptive functions by presumably increasing reproductive success. Developing our mechanistic understanding of mesolimbic dopamine systems with respect to motivated behaviors that are part of an individual's natural life is certainly important in its own right. An added benefit of this research is that it will impact new developments in the prevention and treatment of addiction [214].

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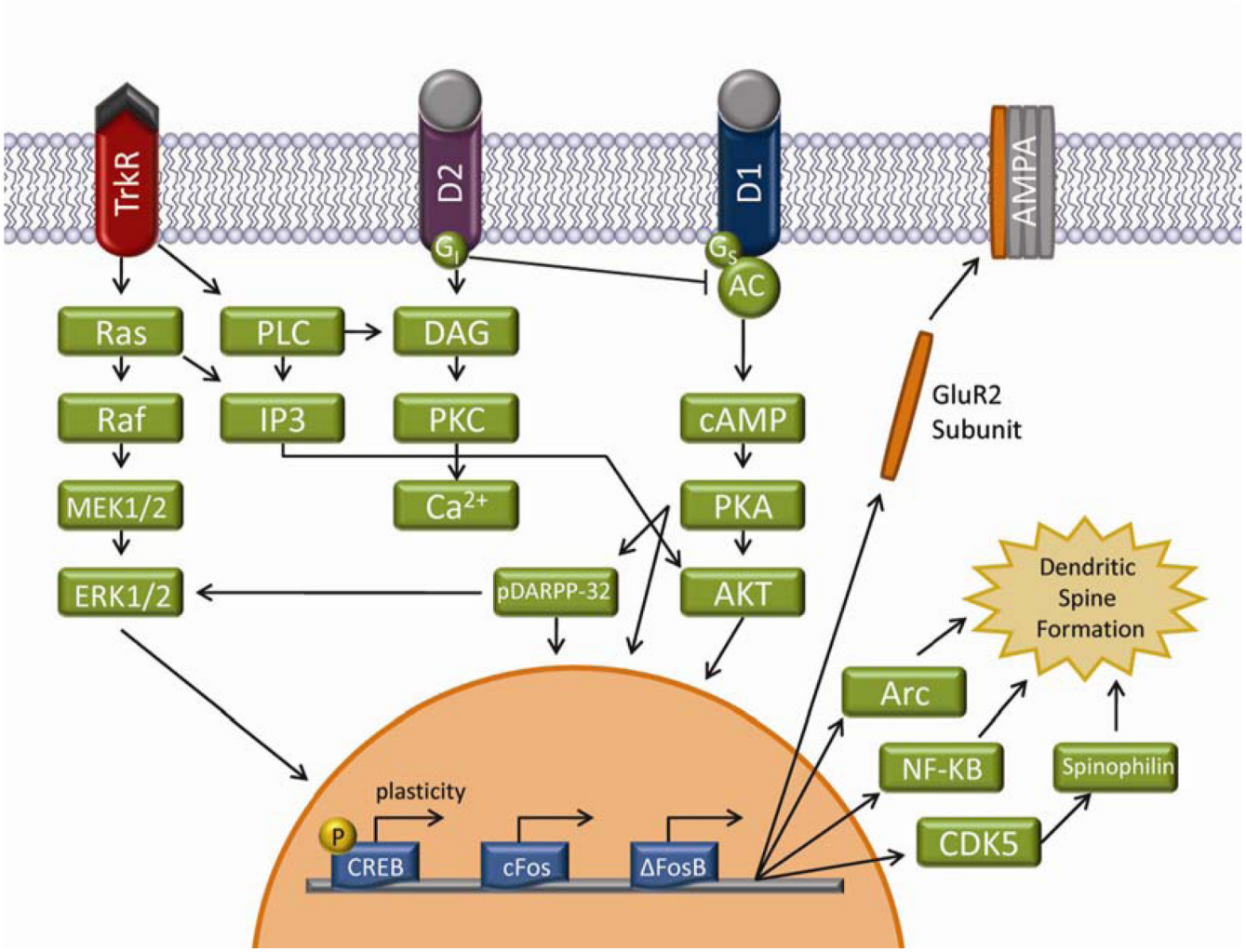


**Figure 1.**

Schematic representation of select cell signaling pathways involved in drug addiction. Activation of cell membrane receptors, such as D1 and Trk receptors, results in the propagation of that signal through multiple intracellular signaling cascades. Specifically, the MAPK and adenylate cyclase/PKA signaling cascades have been shown to be activated via dopaminergic signaling. Ultimately, activation of these intracellular signaling cascades results in gene transcription within the nucleus of the cell. Two of the many downstream gene targets of such signaling are CREB and ΔFosB. Whereas CREB phosphorylation is believed to mediate some of the behavioral plasticity resulting from drugs of abuse, the accumulation of the stable transcription factor ΔFosB is postulated to underlie drug induced structural plasticity. Targets of ΔFosB transcription in turn can affect intrinsic membrane excitability through the insertion of GluR2 subunits into AMPA receptors, as well as structural changes through dendritic spine plasticity via cdk5 activation. Importantly, D2 receptor activation counteracts D1 receptor activation [50].

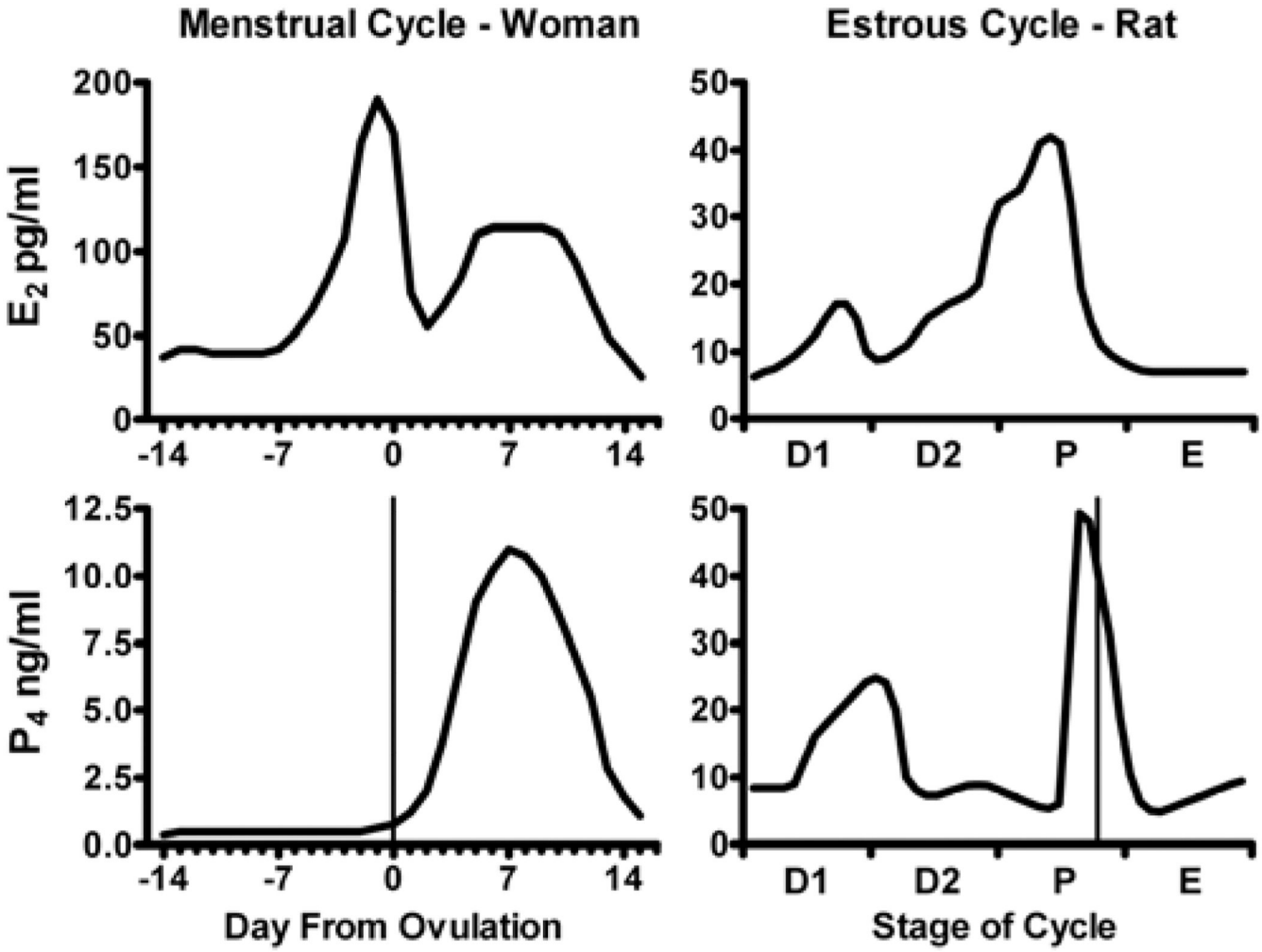


**Figure 2.**

Plasma concentrations of estradiol ($E_2$) and progesterone ($P_4$) throughout the human menstrual and rat estrous cycles. Values represent the means of measurements taken daily from women and at two-hour intervals from rats. The four-day estrous cycle is broken down into its stages: diestrus-1 (D1), diestrus-2 (D2), proestrus (P), and estrus (E). Vertical lines indicate ovulation. Modified from [207] and [66].

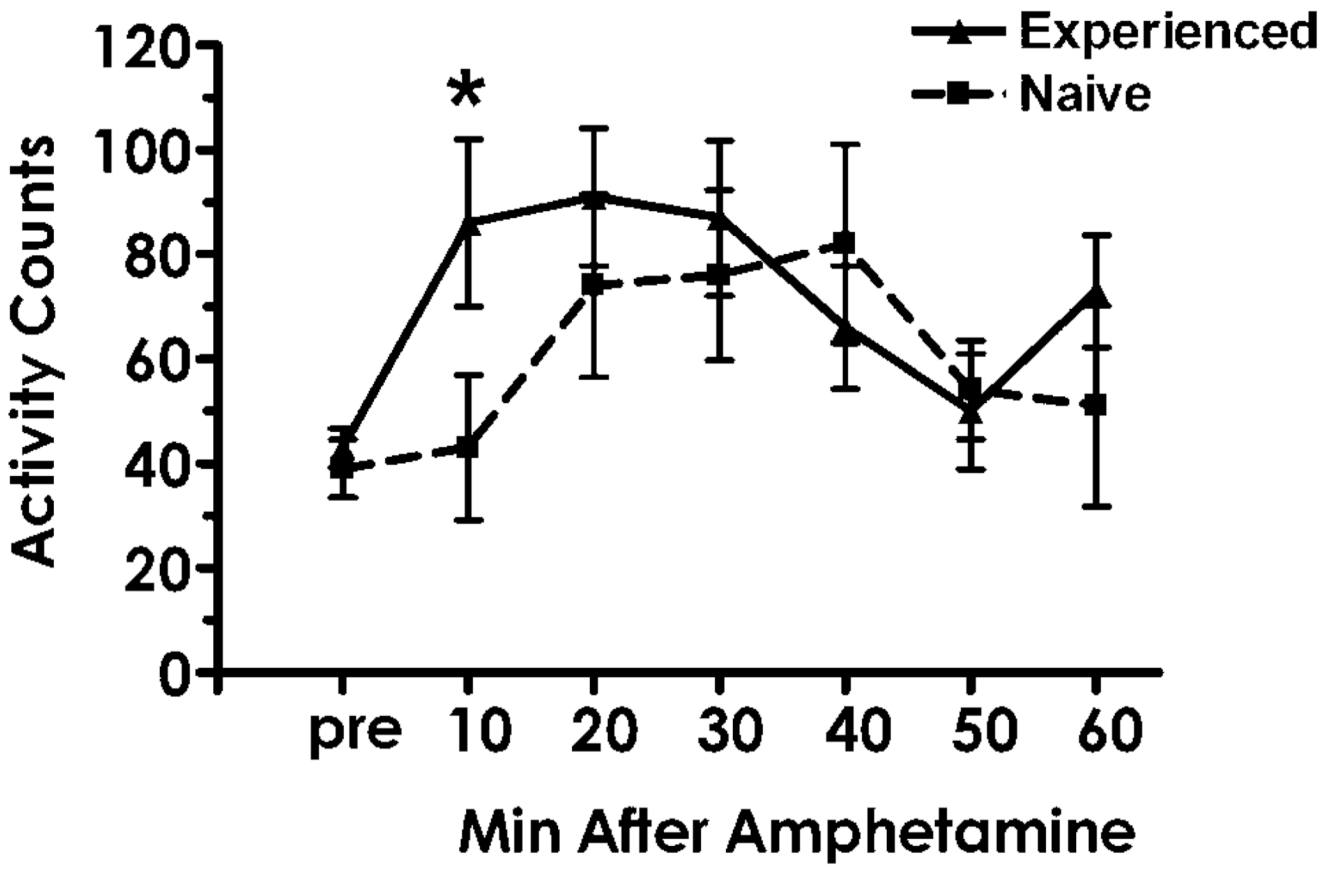


**Figure 3.**
Female sexual experience sensitizes the activity response to amphetamine. When exposed to amphetamine for the first time, sexually experienced female hamsters show a significant increase in activity at the 10 min time point (*) when compared to sexually naïve female hamsters. This activity level remains elevated in sexually experienced females through the first 30 min of the test period (data from [24]).

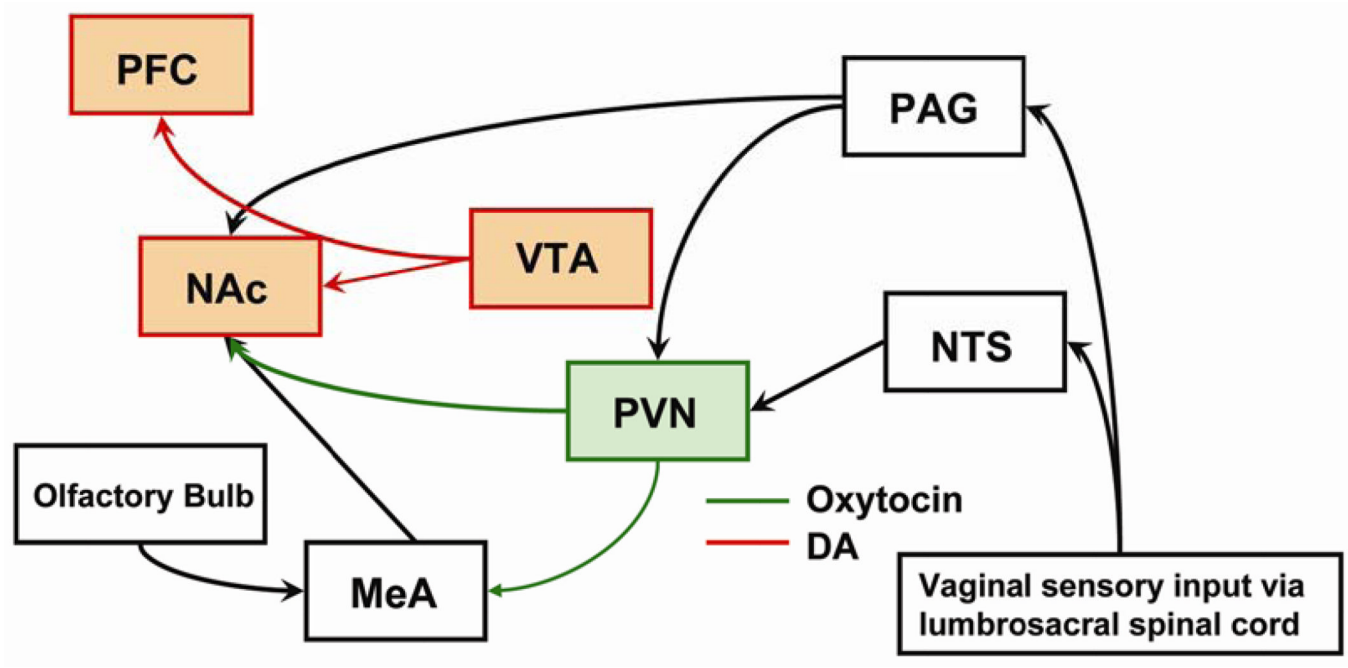


**Figure 4.**
Schematic representation of the proposed circuitry for pair bonding in female prairie voles. Various sensory stimuli ultimately result in dopaminergic and peptidergic release at the level of the nucleus accumbens, thereby positioning the nucleus accumbens in an optimal anatomical location to act as a coincidence detector for pair bond formation [226]. DA, dopamine; MeA, medial amygdala; NAc, nucleus accumbens; NTS, nucleus tractus solitarius; PAG, periaqueductal gray; PFC, prefrontal cortex; PVN, paraventricular nucleus; VTA, ventral tegmental area.