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Progesterone and allopregnanolone are induced by cocaine in serum and brain tissues of male and female rats

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Abstract

Acute and chronic-cocaine administration increase serum levels of progesterone in both male and female rats. This study aimed to determine whether progesterone and its bioactive metabolite allopregnanolone (ALLOP) are altered in the hippocampus and striatum (areas known to modulate cocaine-induced behavioral response) after acute cocaine administration. To this end, male and female rats were administered 20 mg/kg and 5 mg/kg of cocaine, respectively (doses that produce equivalent behavioral responses between the sexes). Thirty minutes after drug treatment, serum and brain were collected and later analyzed for progesterone and ALLOP levels using HPLC measurements. At these cocaine doses, no sex differences in the overall behavioral responses after drug treatment were observed. In saline-treated controls, female rats had overall higher levels of progesterone in the serum than did male rats. After cocaine administration, progesterone and ALLOP levels in serum, hippocampus, and striatum were increased at similar levels in both sexes. In the hippocampus, progesterone levels were increased in both males and females, but ALLOP levels were increased only in females.

Keywords: Cocaine; Gender differences; Progesterone; Alloprogesterone

1. Introduction

Recent studies have demonstrated that progesterone plays a role as a mediator of cocaine addiction. For example, human female cocaine users have attenuated subjective responses and less desire to smoke cocaine during the luteal phase than during the follicular phase of the menstrual cycle (Evans and Foltin, 2006; Sofuoglu et al., 2002, 2001). In rodents, cocaine-induced behavioral activity and self-administration are lowest during the diestrus phase (Quiñones-Jenab et al., 1999; Roberts et al., 1989; Sell et al., 2002; Walker et al., 2001). Both the luteal phase in humans and the diestrous phase in rats are characterized by increases in serum levels of progesterone. Furthermore, progesterone attenuates locomotive responses to cocaine and counteracts the facilitory effects of estrogen on cocaine self-administration in gonadectomized (GDX) rats (Jackson et al., 2006; Niyomchai et al., 2005; Russo et al., 2003a). Progesterone treatment during both the acquisition and the expression phases of cocaine conditioning blocks cocaine-induced conditioned place preference (CPP; (Russo et al., 2003a)). Progesterone also attenuates some of the subjective effects of cocaine in both men and women (Evans and Foltin, 2006; Sofuoglu et al., 2002, 2001) and prevents the relapse to cocaine self-administration in female rats (Anker et al., 2007). Collectively, these reports suggest that increases in progesterone serum levels attenuate the subjective and some psychomotive responses to cocaine.

Besides the fact that progesterone mediates the subjective effects of cocaine, there is evidence that progesterone levels can vary with cocaine administration. After single-, binge-, and chronic-cocaine administration paradigms, in intact or pregnant

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female and intact male rats cocaine also increases serum levels of progesterone (Quiñones-Jenab et al., 2000; Walker et al., 2001). However, it is yet to be determined whether a similar increase in the level of progesterone occurs in brain tissues after cocaine administration.

Some of progesterone's effects are mediated through actions of its metabolite 5α-pregnan-3α-ol-20-one (allopregnanolone, ALLOP). Progesterone is converted rapidly in the brain and many peripheral tissues to ALLOP by actions of the metabolizing enzymes, 5α-reductase and 3α- hydroxysteroid oxidoreductase (Majewska et al., 1986; Morrow et al., 2005). Progesterone administration alters ALLOP levels in the serum and brain. For example, among both men and women a single dose of progesterone increases ALLOP serum levels (Soderpalm et al., 2004). Moreover, among women receiving progesterone-based hormone replacement therapy, ALLOP concentrations rise with increasing progesterone doses during hormonal replacement (Sundstrom et al., 2003). Both progesterone and ALLOP have been extensively documented as potent regulators of behavioral responses, including locomotor, anxiety, pain, and ethanol intake (reviewed in (Engel and Grant, 2001; Levin, 2001; Morrow et al., 2001; Walf et al., 2006)). Regardless of the individual's sex, increases in progesterone/ALLOP are associated with changes in mood and mild sedative-like effects (Soderpalm et al., 2004; Sundstrom et al., 2003). Evidence that progesterone's metabolism to ALLOP mediates its behavioral effects includes the fact that administration of finasteride, an enzymatic inhibitor that blocks the metabolism of progesterone into ALLOP, attenuates facilitation of sexual behavior in rats and hamsters, as well as anti-anxiety behavior (Bitran et al., 1995; Frye and Gardiner, 1996; Frye et al., 2004; Walf et al., 2006). Thus, cocaine-induced alterations of progesterone serum levels may in turn increase brain and serum concentration of this metabolite. The aim of this study was to determine whether cocaine administration increases progesterone and ALLOP levels in the serum and the striatum and hippocampus (areas known to mediate cocaine motor responses and memory formation, respectively) and whether there are sex differences in cocaine activation of these neurosteriods.

2. Methods

2.1. Animals

Intact male and female Fischer rats (8 weeks old) purchased from Charles River were housed in single-animal cages with free access to food and water and maintained on a 12-hour light/dark cycle. To minimize stress, animals were kept in our facility for 1 week before experimental manipulation and handled daily. Rats were randomly assigned to cocaine or saline administration. Animals run for behavioral testing were different from those used for hormonal measurements. Behavioral ($n=10$ per group) and neurochemical ($n=6$ per group) measurements were done in two separate groups of rats. Each study consisted of at least three cohorts. Because vaginal lavages have been shown to cause behavioral and neurochemical changes that may account for the differences when compared with male rats and to produce CPP (Walker et al., 2002), female rats were randomly assigned to experimental groups regardless of their estrous cycle. Animal care was in accordance with the Guide for the Care and Uses of Laboratory Animals (National Institute of Health, publication 865-23, Bethesda, MD) and approved by the Institutional Animal Care and Use Committee of Hunter College. All chemicals were purchased from Sigma Scientific (Saint Louis, MO).

2.2. Drug treatments

For all experimental paradigms, cocaine was diluted in saline (0.9%) immediately before each injection. Cocaine or saline was administered via intraperitoneal injections. Males received 20 mg/kg and females received 5 mg/kg of cocaine or saline. These doses have previously been shown to represent the optimal doses needed to produce equivalent CPP and locomotor responses between the sexes (Russo et al., 2003a,b). We used a cocaine dose that produces the same behavioral responses assures that the behavioral and reward differences are not responsible for differences in ALLOP and progesterone levels.

2.3. Behavioral activity determinations

Ambulatory and rearing responses were measured to corroborate that this cocaine administration paradigm produced equivalent behavioral responses between the sexes. Throughout the study all locomotor measurements were administered in each rat's home cage and measured as previously described (Festa et al., 2003, 2004). Ambulatory (break of 2 beams of lights) and rearing (vertical movement) activities were monitored, after cocaine or saline treatment using a Photobeam Activity System from San Diego Instruments (San Diego, CA). Behavioral counts represent the sum of all beams counts for 1 h after drug treatment.

2.4. Tissue collection

Animals were sacrificed by decapitation (after a brief [20-sec] exposure to CO_2). Trunk blood was collected and centrifuged at 3000 rpm for 20 min at 4 °C. Serum was stored at −80 °C until use. The hippocampus and striatum were dissected from sections (1 mm) prepared fresh just after decapitation. Tissue was then rapidly frozen in 2-methyl-butanol (−40 °C) and stored at −80 °C until use. The striatum was chosen because (1) we have previously demonstrated cocaine-induced changes in gene and protein levels (Jenab et al., 2005, 2002; Sun et al., 2007) and (2) it is an important area in the regulation of cocaine-induced motor activation. The hippocampus was chosen because it is an area essential in the mediation of formation and recall of cocaine rewards.

2.5. Radioimmunoassay of serum and brain progesterone

Progesterone and ALLOP concentrations were determined by radioimmunoassay using previously published methods (Frye et al., 1998). Steroids were extracted from plasma with diethyl ether and then rapidly frozen in a bath of dry ice and acetone.

Solvents were decanted and evaporated in a savant. Samples were resuspended to the original plasma volume in assay buffer (pH=7.4). Whole frozen brains were gently thawed on ice and the hippocampus and striatum were dissected. Brain tissue was homogenized with a glass/glass pestle in 50% MeOH, 1% acetic acid. Following centrifugation at 3,000 ×*g*, the supernatant was then chromatographed (first with 50% and then 100% MeOH) on a Sepak cartridge that had been equilibrated with 50% MeOH, 1% acetic acid. The final fractions were dried using a speed drier and then reconstituted in phosphate assay buffer.

Radioimmunoassay for progesterone was performed using [^{3}H] progesterone (NET-208, specific activity 48.4 ci/mmol, New England Nuclear (NEN), Boston, MA) and antisera (P#337 from Dr. G.D. Niswender, Colorado State University) in a 1:30,000 dilution that bound between 30% and 50% of [^{3}H] progesterone. Radioimmunoassays for ALLOP was performed using [^{3}H] ALLOP (NET-1047, 51.3 ci/mmol; New England Nuclear (NEN), Boston, MA) and sheep antibody (Dr. Robert Purdy, Veterans Medical Affairs, La Jolla, CA), in a 1:5000 dilution that bound between 40% and 60% of [^{3}H] 3α,5α-THP. Standard curves for progesterone and ALLOP were prepared in duplicate to give a range of concentrations from 50 to 8000 pg/mL. Samples and/or standards were incubated with radioactive tracer and antibodies at 4 °C for 24 h. Binding was terminated by the rapid addition of charcoal, and 15 min later, samples were centrifuged at 1500 ×*g* for 10 min. The supernatant was pipetted and activity was determined by standard scintillation spectroscopy. Sample concentrations were calculated using the logit-log method (Rodbard and Hutt, 2007), interpolation of the standards, and correction for recovery. The minimum detectable limit of the progesterone assay was 50 pg, and the intra-assay and inter-assay coefficients of variance were 0.06 and 0.07, respectively. The minimum detectable limit of the ALLOP assay was 50 pg, and the intra-assay and inter-assay coefficients of variance were 0.08 and 0.09, respectively.

2.6. Statistical analysis

To assess the effect of cocaine and its interaction with progesterone on locomotive activities, ANOVAs were used [Drug (saline, cocaine)×Sex (male, female)×Measurements (behavioral or endocrinological)]. Within each sex, 1-way ANOVAs were also run to examine the effects of cocaine on the level of progesterone or ALLOP in each different tissue. When significant interactions were obtained, a Newman–Keuls post hoc test was used to assess the differences between treatment groups. Significance was at the 0.05 level for all comparisons.

3. Results

3.1. Cocaine's effects on ambulatory and rearing activities

Overall, cocaine increased rearing and ambulatory activities [Fig. 1, main drug interaction; *rearing*: $F=38.18$, $p<0.000001$; *ambulatory*: $F=28.56$, $p<0.000001$]. At these cocaine doses (20 mg/kg and 5 mg/kg for males and females, respectively), both sexes demonstrated equivalent ambulatory and rearing activities after cocaine administration (*ambulations*: $F=0.36$, $p=0.553$; *rearing*: $F=0.273$, $p=0.273$).

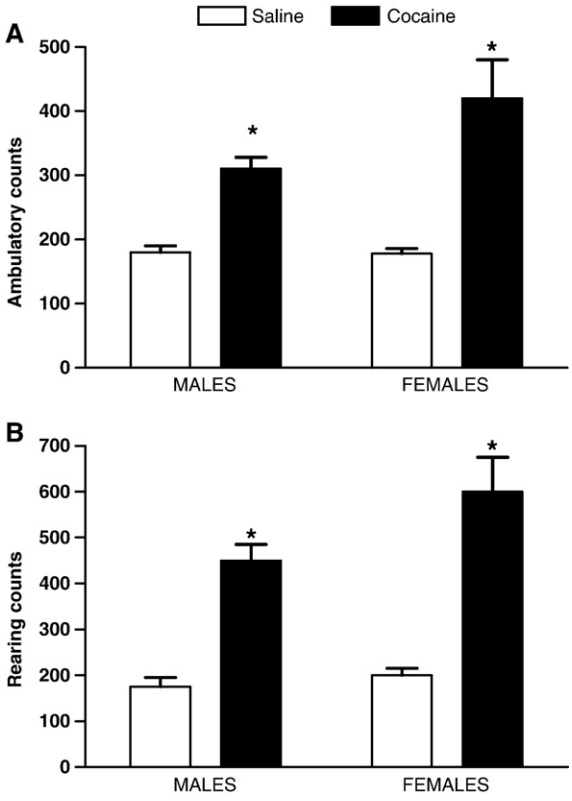

Fig. 1. Ambulatory (A) and rearing (B) responses after saline or cocaine (20 mg/kg in males and 5 mg/kg in females). White bars represent saline treatment, and black bars represent cocaine treatment. * Indicates a statistically significant difference ($p<0.05$) as compared with respective saline group. ($N=10$ per group).

3.2. Progesterone levels after cocaine administration

As illustrated in Fig. 2A, a main drug interaction was observed in progesterone levels in all three tested areas [*Serum*: $F=39.257$, $p<0.00001$; *Hippocampus*: $F=5.077$, $p<0.05$; *Striatum*: $F=4.450$, $p<0.05$]; overall, in all three tissues cocaine-induced progesterone levels in both male and female rats ($p<0.05$ for all comparisons). A main effect of sex was observed only in progesterone serum levels [$F=4.345$, $p<0.005$]; regardless of the drug treatment, females had overall higher progesterone serum than males ($p<0.05$ for all comparisons).

3.3. ALLOP levels after cocaine administration

As illustrated in Fig. 2B, a main effect of the drug on ALLOP levels was observed for all three tissues tested [*Serum*: $F=10.127$, $p<0.0001$; *Hippocampus*: $F=3.073$, $p<0.01$; *Striatum*: $F=7.863$, $p<0.01$]. Overall, cocaine-induced ALLOP levels in all three tissues both male and female rats ($p<0.05$ for all comparisons) with the exception of the male hippocampus ($p=0.067$). A main effect of sex was observed only in ALLOP hippocampus levels [$F=4.247$, $p<0.05$]; regardless of the drug treatment, females

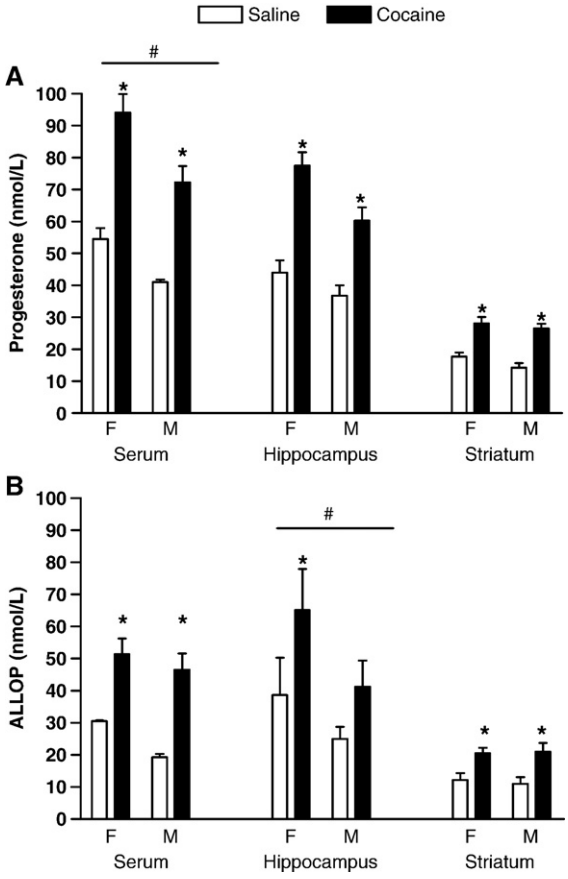

Fig. 2. Progesterone (A) and ALLOP (B) levels in serum, hippocampus, or striatum in male and female rats after saline or cocaine (20 mg/kg in males and 5 mg/kg in females). White bars represent saline treatment; black bars represent cocaine treatment. *Indicates a statistically significant difference ($p<0.05$) as compared with respective saline group. ($N=6$ per group). # Indicates a sex interaction within tissues was found.

had overall higher ALLOP hippocampus levels than males ($p<0.05$ for all comparisons). ALLOP and progesterone levels were significantly correlated in the striatum and serum, but not in the hippocampus (see Table 1).

4. Discussion

Results presented here are novel in that they show cocaine-induced progesterone and ALLOP in brain and serum tissues in both male and female rats. Recent studies have directly demonstrated that progesterone is an important contributing factor to the sex differences observed in response to cocaine in rats (Frye and Gardiner, 1996; Jackson et al., 2006; Kudo et al., 1991; Niyomchai et al., 2005; Russo et al., 2003a) and humans (Evans and Foltin, 2006; Sofuoglu et al., 2002; White et al., 1991). Most studies suggest that progesterone inhibits or attenuates cocaine's reward and subjective effects. That progesterone is altered in CNS tissues following cocaine exposure further supports the hypothesis that progestins play a pivotal role in the modulation of progesterone's effects on cocaine-mediated responses.

There is evidence that ALLOP may play an important role in mediating effects of cocaine. ALLOP can protect completely against cocaine-induced seizures in mice at dosages that do not cause motor toxicity (Gasior et al., 2005; Leskiewicz et al., 2003). Kaminski et al. (2003) further demonstrated the protective efficacy of ALLOP against cocaine-kindled seizures in male mice. The interaction of progesterone metabolites with cocaine extends to pharmacological actions beyond their anticonvulsant efficacy (Vandoren et al., 2000a,b). Taken together, these studies strongly suggest that ALLOP may also play an important role in behavioral responses that are influenced by cocaine. Because progesterone's effects on other behavioral models are mediated in part by ALLOP metabolism, and ALLOP itself affects drug-induced reward responses and drug-consumption (i.e., ethanol

Table 1
Correlation analysis of progesterone and ALLOP levels

	Males	Females
Serum	$R^2=0.530$*	$R^2=0.617$*
	$p=0.007$	$p=0.001$
Hippocampus	$R^2=0.160$	$R^2=0.001$
	$p=0.099$	$p=0.456$
Striatum	$R^2=0.308$*	$R^2=0.229$*
	$p=0.031$	$p=0.049$

*Represents significant ($p<0.05$) correlations between progesterone and ALLOP levels.

addiction and anxiety (Finn et al., 2003, 2004; Johansson et al., 2002; Melchior and Ritzmann, 1996; Sinnot et al., 2002; Vandoren et al., 2000a,b)), it is feasible that ALLOP is also an important mediator of cocaine-induced responses.

Here, in both male and female rats, striatal and serum progesterone levels were correlated with ALLOP levels. This finding is consistent with a previous report that progesterone administration alters ALLOP serum levels in both men and women (Soderpalm et al., 2004). Moreover, in women receiving progesterone-based hormone replacement therapy, ALLOP rises with increasing progesterone doses during hormonal replacement (Sundstrom et al., 2003). However, in our study a significant correlation between progesterone and ALLOP levels was not observed in the hippocampus. It has been observed that ALLOP metabolism in the brain can be independent from plasma progesterone (Baulieu et al., 2001). The lack of a significant correlation between progesterone and ALLOP levels in the hippocampus suggests that in this brain area cocaine-induced regulation of ALLOP levels may also be independent of progesterone serum/brain levels. Thus, it is possible that cocaine administration may directly stimulate brain production of this bioactive neurosteroid.

Although we used a cocaine administration paradigm that produced equivalent behavioral responses and progesterone/ALLOP induction between the sexes, gender differences in cocaine-induced alteration of ALLOP levels in the hippocampus were still observed. This finding suggests intrinsic sex differences in mechanisms mediating cocaine-induced alterations of ALLOP levels in the hippocampus and further demonstrates that, in the hippocampus, ALLOP and progesterone levels are independent from each other. Evans and Foltin (2006) demonstrated progesterone's inhibition of cocaine's subjective effects only in women. It remains to be determined whether these sex disparities in progesterone's regulation of cocaine's subjective effects are mediated through intrinsic differences between the sexes in progesterone-/ALLOP-mediated responses. However, because the hippocampus is a pivotal area involved in the formation and recall of cocaine reward and subjective effects, our data indirectly support the hypothesis that gender differences in cocaine-induced alterations of ALLOP levels in the hippocampus may in part be responsible for known differences in how the sexes both develop and recall the reward and subjective effects of this psychostimulant.

Given that cocaine administration can enhance progesterone secretion in the brain, an important question is how progesterone may then have an effect on altering subjective experiences. After increases in serum levels of progesterone, there is an induction of PR-A protein levels and DNA-PR binding complex formation in the nucleus accumbens (Wu et al., 2006) and striatum (unpublished results). That progesterone and ALLOP are increased peripherally and centrally after cocaine administration further suggests that progesterone receptor mediated mechanisms may be part of the cellular responses associated with cocaine responses in the CNS. Due to the differential distribution of PR receptors in the CNS between sexes, even equivalent increases in progesterone levels in the striatum and hippocampus may contribute to sex differences in cocaine-induced reward and behavioral responses.

In addition to classic actions at intracellular progestin receptors and membrane-mediated actions of progesterone, some of progesterone's effects could be through actions of ALLOP. ALLOP is devoid of affinity for intracellular progestin receptors (Rupprecht, 2003). However, ALLOP is a potent positive allosteric modulator of $GABA_A$ receptors. It enhances $GABA_A$-stimulated chloride flux in the brain in a noncompetitive manner at nanomolar concentrations (Belelli and Gee, 1989; Morrow et al., 1987). Thus, alterations in brain levels of both progesterone and ALLOP may have profound effects on the neuroplasticity of the CNS by activating rapid membrane-mediated intracellular responses.

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References

Anker JJ, Larson EB, Gliddon L, Carroll ME. Effects of progesteron on the reinstatement of cocaine-seeking behaviors in female rats. Exp Clin Psychopharmacol 2007;15:472–80.

Baulieu EE, Robel P, Schumacher M. Neurosteroids: beginning of the story. Int Rev Neurobiol 2001;46:1–32.

Belelli D, Gee K. 5α-Pregnan-3α,20α-diol behaves like a partial agonist in the modulation of GABA-stimulated chloride ion uptake by synaptoneurosomes. Eur J Pharmacol 1989;167:173–6.

Bitran D, Shiekh M, McLeod M. Anxiolytic effects of progesterone is mediated by the neurosteriod allopregnanolone at brain GABA A receptors. J Neuroendocrinol 1995;7:171–7.

Engel SR, Grant KA. Neurosteriods and behavior. Int Rev Neurobiol 2001;46:321–48.

Evans SM, Foltin R. Exogenous progesterone attenuates the subjective effects of smoked cocaine in women but not in men. Neuropsychopharmacology 2006;31:659–74.

Festa ED, Jenab S, Chin J, Gazi FM, Wu HBK, Russo SJ, Quinones-Jenab V. Frequency of cocaine administration affects behavioral and endocrine responses in male and female Fischer rats. Cell Mol Biol 2003;49:1275–80.

Festa ED, Russo SJ, Gazi FM, Niyomchai T, Kemen LM, Lin S-N, et al. Sex differences in cocaine-induced behavioral responses, pharmacokinetics, and monoamine levels. Neuropharmacology 2004;46:672–87.

Finn DA, Roberts AJ, Long S, Tanchuck M, Phillops TJ. Neurosteroid consumption has anxiolytic effects in mice. Pharmacol Biochem Behav 2003;76:451–62.

Finn DA, Roberts AJ, Long S, Tanchuck M, Phillops TJ. Interaction of chronic ethanol exposure and finasteride: sex and strain differences. Pharmacol Biochem Behav 2004;76:451–62.

Frye CA, Gardiner SG. Progestins can have a membrane-mediated action in rat midbrain for facilitation of sexual receptivity. Horm Behav 1996;30:682–91.

Frye CA, Bayon LE, Pursnani NK, Purdy RH. The neurosteroids, progesterone and 3-5 THP enhance sexual motivation, receptivity and proceptivity in female rats. Brain Res 1998;808:72–83.

Frye CA, Walf AA, Sunida K. Progestins' actions in the VTA to facilitate lordosis involve dopamine-like type 1 and 2 receptors. Pharmacol Biochem Behav 2004;78:405–18.

Gasior M, Carter RB, Witkin JM. Neuroactive steroid: potential therapeutic use in neurological and psychiatric disorders. Trends Phamacol Sci 2005;20:107–12.

Jackson LR, Robinson TE, Becker JB. Sex differences and hormonal influences on acquisition of cocaine self-administration in rats. Neuropsychopharmacology 2006;31:129–38.

Jenab S, Festa ED, Nazarian A, Wu HB, Sun WL, Hazim R, et al. Cocaine induction of ERK proteins in dorsal striatum of Fischer rats. Brain Res Mol Brain Res 2005;142:134–8.

Jenab S, Niyomchai T, Chin J, Festa ED, Russo SJ, Perrotti LI, et al. Effects of cocaine on c-fos and preprodynorphin mRNA levels in intact and ovariectomized Fischer rats. Brain Res Bull 2002;58:295–9.

Johansson IM, Birzniece V, Lindblad C, Olsson T, Backstrom T. Allopregnanolone inhibits learning in the Morris water maze. Brain Res 2002;934:125–31.

Kaminski RM, Gasior M, Carter RB, Witkin JM. Protective efficacy of neuroactive steroids against cocaine kindle seizures in mice. Eur J Pharmacol 2003;474:217–22.

Kudo M, Kudo T, Matsuki A. Role of prostaglandin E1 in steroidogenesis by isolated rat adrenal cells. Masui 1991;40:1819–24.

Leskiewicz M, Budziszewaska B, Jaworska-Feil L, Kubera M, Basta KA, Lason W. Inhibitory effects of some neuroactive steroids on cocaine-induced kindling in mice. Pol J Pharmacol 2003;55:1131–6.

Levin ER. Cell localization, physiology, and nongenomic actions of estrogen receptors. J Appl Physiol 2001;91:1860–7.

Majewska MD, Harrison NL, Schwartz RD, Barker JL, Paul SM. Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor. Science 1986;232:1007.

Melchior CL, Ritzmann RF. Neurosteroids block the memory-impairing effects of ethanol in mice. Pharmacol Biochem Behav 1996;53:51–6.

Morrow AL, Suzdak PD, Paul SM. Steroid hormone metabolites potentiate GABA receptor-mediated chloride ion flux with nanomolar potency. Eur J Pharmacol 1987;142:483–5.

Morrow AL, Vandoren MJ, Devaud LL. Effects of progesterone or neuroactive steroid? Nature 2005;395:652–3.

Morrow AL, Vandoren MJ, Penland SN, Matthews DB. The role of GABAergic neruoactive steroids in ethanol action, tolerance and dependence. Brain Res Rev 2001;37:98–109.

Niyomchai T, Russo SJ, Festa ED, Akhavan A, Jenab S, Quinones-Jenab V. Progesterone inhibits behavioral responses and estrogen increases corticosterone levels after acute cocaine administration. Pharmacol Biochem Behav 2005;80:603–10.

Quiñones-Jenab V, Ho A, Schlussman SD, Franck J, Kreek MJ. Estrous cycle differences in cocaine-induced stereotypic and locomotor behaviors in Fischer rats. Behav Brain Res 1999;101:15–20.

Quiñones-Jenab V, Perrotti LI, Ho A, Jenab S, Schlussman SD, Franck J, et al. Cocaine affects progesterone plasma levels in female rats. Pharmacol Biochem Behav 2000;66:449–53.

Roberts DCS, Bennett SAL, Vickers GJ. The estrous cycle affects cocaine self-administration on a progressive ratio schedule in rats. Psychopharmacology 1989;98:408–11.

Rodbard D, Hutt DM. Statistical analysis of radioimmunoassays and immunoradiometric assays: a generalized, weighted interactive, least squares method for logistic curve fitting. International Atomic Energy Agency. New York: Uniput; 2007.

Rupprecht R. Neuroactive steroids: mechanisms of action and neuropsychopharmacological properties. Psychoneuroendocrinology 2003;28:139–68.

Russo SJ, Festa ED, Fabian SJ, Gazi FM, Kraisch M, Jenab S, et al. Gonadal hormones differentially modulate cocaine-induced place preference in male and female rats. Neuroscience 2003a;120:523–33.

Russo SJ, Jenab S, Fabian SJ, Festa ED, Kemen LM, Quinones-Jenab V. Sex differences in the conditioned rewarding effects of cocaine. Brain Res 2003b;970:214–20.

Sell SL, Thomas ML, Cunningham KA. Influence of estrous cycle and estradiol on behavioral sensitization to cocaine in female rats. Drug Alcohol Depend 2002;67:281–90.

Sinnot RS, Phillips TJ, Finn DA. Alteration of voluntary ethanol and saccharin consumption by the neurosteroid allopregnanolone in mice. Psychopharmacology 2002;162:438–47.

Soderpalm AH, Lindsey S, Purdy RH, Hauger R, Wit de H. Administration of progesterone produces mild sedative-like effects in men and women. Psychoneuroendocrinology 2004;29:339–54.

Sofuoglu M, Babb DA, Hatsukami DK. Progesterone treatment during the early follicular phase of the menstrual cycle: effects on smoking behavior in women. Pharmacol Biochem Behav 2001;69:299–304.

Sofuoglu M, Babb D, Hatsukami DK. Effects of progesterone treatment on smoked cocaine response in women. Pharmacol Biochem Behav 2002;72:431–5.

Sun W, Zhou L, Hazim R, Quinones-Jenab V, Jenab S. Effects of acute cocaine on ERK and DARPP-32 phosphorylation pathways in the caudate-putamen of Fischer rats. Brain Res 2007;1178:9–12.

Sundstrom PI, Smith S, Gulinello M. GABA receptors, progesterone and premenstrual dysphoric disorder. Arch Women Mental Health 2003;6:23–41.

Vandoren MJ, Matthews DB, Janis GC, Crobin AC, Devaud LL, Morrow AL. Neuroactive steriods 3-alpha-hydroxy-5alphs-pregnan-20-one modulates electrophysiological and behavioral actions of ethanol. J. Neurosci. 2000a;20:1982–9.

Vandoren MJ, Matthews DB, Janis GC, Grobin AC, Devaud LL, Morrow AL. Neuroactive steroid 3α-hydroxy-5α-pregnan-20-one modulates electrophysiological and behavioral actions of ethanol. J Neurosci 2000b;20:1982–9.

Walf AA, Sumida K, Frye CA. Inhibiting 5 alpha-reductase in the amygdala attenuates antianxiety and antidepressive behavior of naturally receptive and hormone-primed ovariectomized rats. Psychopharmacology 2006;186:302–11.

Walker QD, Frances R, Cabbassa J, Kuhn CM. Effect of ovarian hormones and estrous cycle on stimulation of the hypothalamo-pituitary-adrenal axis by cocaine. J Pharmacol Exp Ther 2001;297:291–8.

Walker QD, Nelson CJ, Smith D, Kuhn CM. Vaginal lavage attenuates cocaine-stimulated activity and establishes place preference in rats. Pharmacol Biochem Behav. 2002;73:743–52.

White FJ, Henry DJ, Hu XT, Jeziorski M, Ackerman JM. Electrophysiological effects of cocaine in the mesoaccumbens dopamine system. In: Lakoski JM, M.P.G. a. F.J.W., editors. Cocaine: Pharmacology, Physiology and Clinical Strategies, vol. 221. Boca Raton: CRC Press; 1991.

Wu HBK, Fabian SJ, Jenab S, Quinones-Jenab V. Progesterone receptor activation after acute cocaine administration. Brain Res 2006;1126:188–92.