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Research Report

Effects of short- and long-term estrogen and progesterone replacement on behavioral responses and c-fos mRNA levels in female rats after acute cocaine administration

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ABSTRACT

It is well established that there are estrous cycle differences in cocaine-induced behavioral activity, implicating fluctuations in levels of estrogen and progesterone throughout the cycle in these alterations in behavior. However, the mechanisms by which steroids alter cocaine-induced behavioral responses have yet to be determined. The aim of this study was to determine whether short- or long-term estrogen and progesterone administration differentially alters behavioral responses to cocaine. Estrogen (50 μg) was administered 30 min or 48 h before cocaine (15 mg/kg, i.p.) administration; progesterone (500 μg) was administered 30 min or 24 h before cocaine. Short-term estrogen replacement decreased cocaine-induced ambulations. Short-term progesterone decreased rearing, whereas long-term progesterone decreased ambulations. Although cocaine increased levels of c-fos mRNA, none of the estrogen or progesterone replacement paradigms affected this measure. Because long-term estrogen replacement has been shown to have no effect on locomotor activity after acute cocaine administration, our observations suggest that short-term estrogen may underlie behavioral alterations. These findings suggest that after acute cocaine administration, while estrogen may activate only membrane receptors to alter behavioral responses to cocaine, progesterone activates both nuclear and membrane receptors.

1. Introduction

Previously published studies have shown that female rats exhibit greater behavioral activity responses to cocaine than do male rats (Caihol and Morméde, 1999; Chin et al., 2001, 2002; Craft and Stratmann, 1996; Festa and Quinones-Jenab, 2004; Festa et al., 2004; Sircar and Kim, 1999; Van Haaren and Meyer, 1991). These sexually dimorphic patterns have been attributed to fluctuating levels of estrogen and progesterone during the female reproductive cycle (Festa et al., 2003, 2004; Quinones-Jenab et al., 2000; Sell et al., 2000); cocaine-induced behavioral activity is lower during diestrus than during proestrus or estrus (Sell et al., 2000). Chronic estrogen replacement (administrated via Silastic capsules) potentiate acute cocaine's behavioral effects (Perrotti et al., 2003; Sell et al., 2000). On the other hand, pulsatory estrogen administra-

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tion (via subcutaneous injections) does not affect the behavioral responses to acute cocaine administration (Hu and Becker, 2003; Sircar and Kim, 1999). Progesterone, when administered via Silastic capsules, inhibits cocaine-induced responses (Sell et al., 2000). However, when administered acutely, progesterone has no effect on cocaine-induced locomotor or stereotypic activity (Perrotti et al., 2003; Quinones-Jenab et al., 2000; Sircar and Kim, 1999). As yet, the underlying causes of the discrepancies in behavior after hormone replacement and the mechanisms by which steroids alter behavioral activity have not been determined.

Recent findings have suggested that gonadal hormones may alter behavioral responses via two distinct mechanisms. First, after the steroids bind to intracellular receptors, these complexes act as transcription factors that regulate the expression of genes (Beato and Klug, 2000; Beato et al., 1996; Evans, 1988). For example, in male rats mRNA levels of c-*fos*, an immediate-early gene, is activated after cocaine administration (Daunais and McGinty, 1995; Graybiel et al., 1990; Hope et al., 1992). C-fos is also under the regulation of both estrogen and progesterone (Hyder et al., 1999; Priest and Roberts, 2000; Ueyama et al., 2006). The second mechanism relates to the capability of both estrogen and progesterone to exhibit rapid nongenomic effects through activation of plasma membrane receptors (Pappas et al., 1995; Towle and Sze, 1983). For example, there is a rapid attenuation in the potency of μ-opioid hyperpolarization after estrogen administration (Lagrange et al., 1997). Similarly, progesterone has been shown to modulate GABAergic membrane ion channels through non-progesterone receptor mechanisms (Bitran et al., 1993, 1995; Fernandez-Guasti and Picazo, 1995; Kokate et al., 1999; Majewska, 1992; Reddy et al., 2004). It is yet to be established whether estrogen and progesterone modulate cocaine-induced alterations through activation of membrane and/or genomic receptors. The aim of this study was to test that possibility.

2. Results

2.1. *Effects of time of estrogen administration on cocaine-induced alterations*

As shown in Fig. 1, cocaine increased ambulatory activity, rearing, and total locomotor activity ([$F(48,1)=31.227$, $p<0.001$], [$F(48,1)=18.261$, $p<0.001$], [$F(48,1)=24.106$, $p<0.001$], respectively). Because estrogen affected behavioral responses in saline-treated rats ([$F(25,3)=4.560$, $p=0.011$], wherein activity was the highest among rats receiving a 48-h pretreatment with estrogen, behavioral activation is presented and analyzed as percentages of their respective controls (summarized in Table 1). When corrected for baseline effects, cocaine's effects on ambulatory activity were lower in animals pretreated with estrogen for 30 min than in the control group ([$F(23,3)=3.348$, $p<0.037$], Table 1). Although cocaine increased serum levels of corticosterone and c-*fos* mRNA in the CPu ([$F(50,3)=7.477$, $p=0.008$], Fig. 2 and [$F(28,1)=7.4778$, $p=0.017$], Table 2, respectively), none of the estrogen replacements had an effect on either measure.

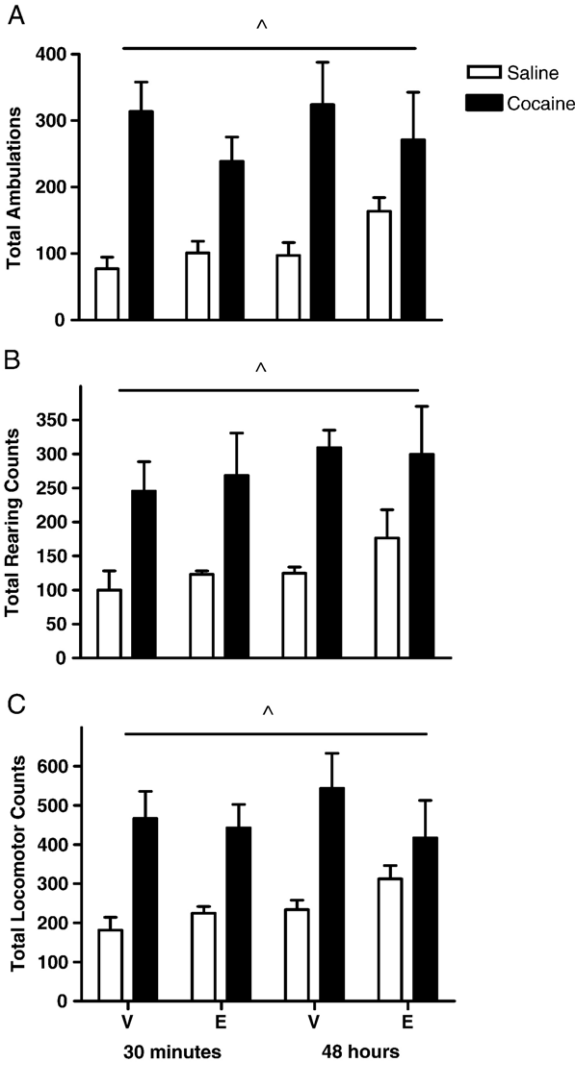

Fig. 1 – Influence of short- and long-term estrogen replacement on cocaine-induced (A) ambulatory, (B) rearing, and (C) total locomotor counts. Graphs summarize behavioral activity ± SEM after administration of saline (white bars) or cocaine (black bars) for OVX Fischer rats pretreated for 30 min or 48 h with vehicle (V) or estrogen (E; 50 μg). Data represent cumulative behavioral counts for the 30 min of behavioral testing. ^ Represents a statistically significant drug effect.

2.2. *Effects of time of progesterone administration on cocaine-induced alterations*

As shown in Fig. 3, ambulatory, rearing, and locomotor activity increased after acute cocaine administration ([$F(48,1)=31.227$, $p<0.001$], [$F(48,1)=18.261$, $p<0.001$], and [$F(50,1)=24.106$, $p<0.0001$], respectively). Because progesterone affected baseline behavioral responses ([$F(26,3)=4.710$, $p<0.007$], where activity was the highest in rats receiving a 24-h pretreatment with progesterone), behavioral activations are presented and analyzed as percentages of their respective controls. Pretreatment with progesterone 24 h before cocaine administration attenuated only ambulatory activity when compared with its control group ([$F(26,1)=6.666$, $p<0.016$], Table 1).