Evidence suggests that sex differences in response to cocaine administration may be regulated by activation of progesterone and estrogen receptors. To test this hypothesis, rats were pretreated with either RU 486 (progesterone antagonist; 0, 3, or 25 mg/kg), tamoxifen (estrogen antagonist; 0, 1, or 3 mg/kg), or vehicle followed by saline or cocaine administration (15 mg/kg). Although RU 486 did not affect cocaine-induced locomotor activity in female rats, it dose-dependently decreased such activity in males (3 mg/kg significantly attenuated locomotor responses in cocaine-treated rats as compared with vehicle treatment or 25 mg/kg of RU 486). RU 486 also affected baseline serum levels of corticosterone. Males treated with 3 mg/kg of RU 486 plus cocaine had higher progesterone and corticosterone serum levels than vehicle-treated groups. In females, both doses (3 and 25 mg/kg) of RU 486 significantly attenuated corticosterone serum levels compared with vehicle treatment. For both sexes overall, tamoxifen neither significantly influenced cocaine-induced ambulatory and rearing responses nor altered cocaine-induced progesterone and corticosterone serum levels. Taken together, our results suggest that progesterone receptors have a sexually dimorphic role in cocaine-induced effects, but estrogen receptors have only a limited role. Moreover, both receptor antagonists modulate neurochemical responses differentially. (Ethn Dis. 2008;18[Suppl 2]:S2-81–S2-86)

Key Words: Cocaine, Progesterone Receptor, Estrogen Receptor, Sex Differences

INTRODUCTION

Accumulating evidence suggests sex differences in response to cocaine administration. For example, women report more drug cravings, use greater amounts of drugs, and are admitted to the emergency department more frequently than men.1–3 Similarly, female rats acquire cocaine discrimination at a faster rate, display a greater motivation to self-administer cocaine, and exhibit more augmented behavioral responses to cocaine than do male rats.4 Female rats also develop conditioned place preference to cocaine with lower doses and fewer conditioning days than male rats require.5 These results suggest that females are more sensitive than males to the addictive properties of cocaine.

Through different experimental approaches, it has been shown that gonadal hormones may contribute in part to sex differences in behavioral and endocrinologic responses to cocaine. For example, rodent studies have shown that hormonal fluctuations during the female reproductive cycle modulate cocaine-induced behavioral responses; higher locomotor activities have been shown during estrus and proestrus than diestrus.6–8 Gonadectomy of female rats decreases overall cocaine-induced locomotor responses, but in male rats the effects of gonadectomy are inconsistent.9–12 In female rats, gonadal hormone replacement affects cocaine-induced locomotor response, ie, estrogen increases cocaine-induced locomotor responses, whereas progesterone attenuates them.7,13–15 However, the mechanisms by which estrogen and progesterone influence cocaine-stimulated responses are not well understood.

EFFECTS OF RU 486 AND TAMOXIFEN ON COCAINE-INDUCED BEHAVIORAL AND ENDOCRINOLOGIC ACTIVATIONS IN MALE AND FEMALE FISCHER RATS

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RU 486 (mifepristone), a progesterone receptor antagonist, and tamoxifen, a selective estrogen-receptor modulator, are commonly used to study the role of steroid receptors in the modulation of behavioral activities since both compounds inhibit lordosis behaviors.16–18 In this study, these pharmacologic agents were used to test the hypothesis that activation of progesterone or estrogen receptors is a necessary step in mediating some behavioral effects of gonadal hormones on cocaine-induced activity in both male and female rats.

METHODS

Animals

Eight-week-old intact male and female Fischer rats purchased from Charles River (Raleigh, NC) were individually housed in standard cages with free access to standard chow and water ad libitum. Rats were maintained on a 12-hour light/dark cycle (lights on at 9 AM) and handled for 1 week before experimental manipulations. RU 486 and tamoxifen studies were run separately. Each study consisted of three cohorts, run 1 month apart, with 8–12 rats per group. Because vaginal lavages cause behavioral and neurochemical changes that may account for the differences observed between female and male rats, females were randomly assigned to experimental groups regardless of their estrous cycles.8 All National Institutes of Health guidelines for the care and use of laboratory animals were strictly followed and were approved by the Institutional Animal Care and Use Committee of Hunter College.