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Increased Self-Administration of Cocaine Following Haloperidol: Sex-Dependent Effects of the Antiestrogen Tamoxifen

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DALTON, J. C. H., G. J. VICKERS AND D. C. S. ROBERTS. *Increased self-administration of cocaine following haloperidol: Sex-dependent effects of the antiestrogen tamoxifen.* PHARMACOL BIOCHEM BEHAV **25**(3) 497–501, 1986.—Intravenous self-administration of cocaine is extremely sensitive to the effects of antipsychotic drugs, making this behavior a useful screen for neuroleptic potency. A possible interaction between female sex hormones and antipsychotic activity was investigated, using increased rates of cocaine self-administration as a measure of neuroleptic action. We found that female rats were more sensitive to haloperidol than were male rats. Female rats treated with a single injection of the antiestrogen tamoxifen 24 hr prior to test showed a significantly reduced response to haloperidol. The normal response was found to have recovered by one week following the tamoxifen treatment. Tamoxifen had no significant effect in male rats. These data, along with previous observations, indicate that ovarian function can greatly influence the behavioral response to antipsychotic drugs. To the extent that the self-administration model may reflect the potency of an antipsychotic drug, these data may indicate that female rats are more sensitive to the activity of neuroleptic drugs. Secondly, pretreatment with tamoxifen results in a significant attenuation of the activity of haloperidol.

Haloperidol Cocaine Self-administration Tamoxifen

CONSIDERABLE evidence now suggests that female sex hormones modulate central dopaminergic function. Neurochemical data have shown that dopamine (DA) levels fluctuate across the estrous cycle of the rat [8, 11, 16, 25, 30, 36] and mouse [22]. Injections of estrogen have also been shown to affect dopamine turnover and release [2, 3, 12, 15, 31, 32, 35, 36, 44] and influence DA receptors [24, 25, 36]. Furthermore, there are many reports which indicate that the behavioral response to dopamine agonists [5, 6, 26] and antagonists [4, 10, 14, 23, 40] is affected by the estrous cycle and estrogen injections.

These data imply that hormonal status should be an important consideration during long-term treatment with antipsychotic drugs. It is noteworthy that in women, hormonal status is reportedly related to the occurrence of tardive dyskinesia (TD), a motor side-effect produced by long-term neuroleptic use [7, 21, 27]. In fact, TD is more frequently found in women than in men, particularly in the postmenopausal age group [27,42], and preliminary indications are that estrogen injections may improve TD in men [43] and post menopausal women [18].

It has also been suggested that the therapeutic efficacy of antipsychotic drugs fluctuates across the menstrual cycle [4, 14, 19, 20]. A better understanding of the interaction between steroid hormones and dopaminergic systems will indicate whether ovarian function is an important clinical factor to be considered during antipsychotic drug therapy.

In an attempt to delineate the influence of ovarian hormones on the behavioral response to antipsychotic drugs, we have employed an animal model which detects changes in neuroleptic potency [38]. This model is based upon the ability of antipsychotic drugs to block the rewarding effects of psychomotor stimulant drugs [13, 44, 45], which are presumed to be mediated by mesolimbic rather than striatal dopaminergic mechanisms. Rats trained to self-administer cocaine will increase their drug intake following pretreatment with low doses of a variety of neuroleptic agents [38]. We have recently reported that this response to haloperidol was shown to fluctuate across the estrous cycle and was attenuated by ovariectomy (OVX) [10, 39, 40, 46]. Interestingly, the OVX-induced effect was not reversible by various estrogen replacement regimens [39,40]. Although these data do not indicate which specific hormone is involved, they do suggest that ovarian status can affect the activity of neuroleptic drugs.

In the present experiments, we further examined the role of estrogen in this response through the use of the estrogen antagonist tamoxifen. Antiestrogens such as tamoxifen have been shown to antagonize estrogen-dependent behaviors in rats [1,17]. The mechanism(s) through which this effect is

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TABLE 1

BODY WEIGHT AND BASELINE COCAINE SELF-ADMINISTRATION IN MALE AND FEMALE RATS

	Weight (g)	Baseline intake/4 hr (ml)	(mg/kg)
Males (N =10)	315.3* (±7.65)	3.44 (±0.81)	55.003 (±2.36)
Females (N = 21)	265.3 (±5.31)	3.17 (±0.14)	56.63 (±2.26)

Data represent the mean (± S.E.M.) for each group. Drug intake was measured in ml and converted to mg of cocaine/kg body weight.
*Indicates a significant difference in body weight between groups ($p<0.001$). No other comparison was found to be significant.

achieved is at present unresolved, however a depletion of cytoplasmic estrogen receptors and/or an action of the antiestrogen-receptor complex with the genome are likely possibilities [9].

We now report that, in female but not male rats, tamoxifen produces a reversible attenuation of the effects of haloperidol using the self-administration model.

METHOD

Subjects

Female and male Wistar rats (Woodlyn Laboratories, Guelph), weighing 225±15 g and 257±21 g respectively at the start of the experiment, were housed two per cage. The vivarium had a 12 hr light/dark cycle and an ambient room temperature of 22°C. Food and water were continuously available prior to surgery.

Drugs

Haloperidol was provided by McNeil Laboratories Canada Ltd. (Stouffville). Tamoxifen citrate was purchased from the Sigma Chemical Co. (St. Louis) and cocaine hydrochloride was purchased from British Drug House (Toronto).

Training

Following 24 hr food deprivation, animals were trained to press a lever on a continuous reinforcement schedule for food reward (Noyes pellets). This method facilitates the subsequent acquisition of a lever response for intravenous cocaine reward [37]. The apparatus was similar for both food and drug testing. Each chamber was constructed of Plexiglas, having a wire grid floor, a removable response lever mounted on one wall and a water bottle fixed to the opposite wall.

Surgery

Subjects were anaesthetized with sodium pentobarbitol (65 mg/kg, IP) and implanted with a chronically indwelling jugular cannula, as described elsewhere [38]. Subjects were then housed singly in test chambers and permitted a 2 to 3 day recovery period. Food and water were available throughout the experiment.

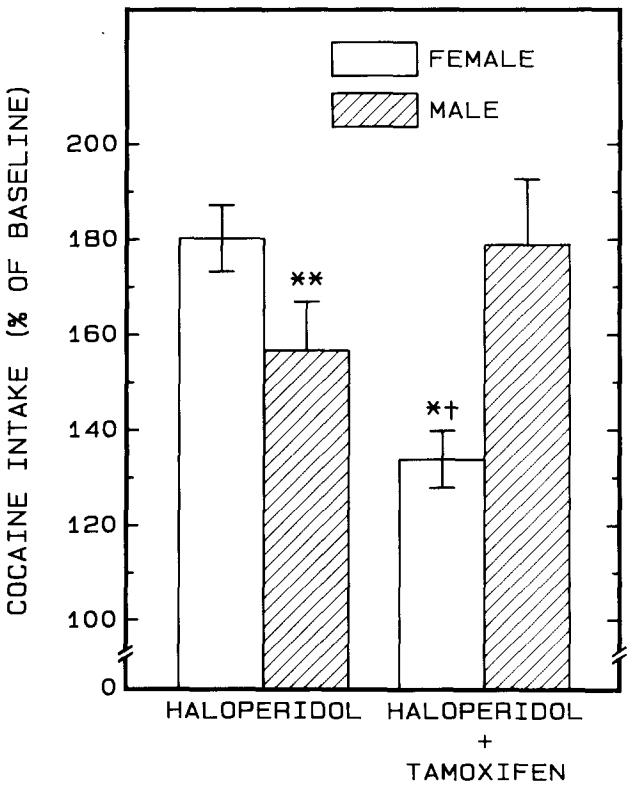

FIG. 1. The effect of tamoxifen pretreatment on the increase in cocaine self-administration produced by haloperidol in male and female rats. Data represent the mean (±S.E.M.) cocaine intake for each group expressed as a percent of baseline intake. Female rats showed a statistically significant greater response to haloperidol than male rats (**$p<0.05$). Also, females had a significantly reduced response to haloperidol following tamoxifen when compared to haloperidol treatment alone (*$p<0.001$). Male rats treated with tamoxifen showed a greater response to haloperidol than female rats treated with tamoxifen (†$p<0.005$).

Testing

A removable lever was introduced into the chamber each day for 4 hours, beginning at light offset (10 a.m.). When the lever was depressed the subject received a single 4 sec intrajugular infusion of cocaine (0.5 mg/0.1 ml saline). A stimulus light was co-activated for 20 sec and all responses during this period had no programmed effect. Lever responses were recorded by mechanical counters and cocaine intake was measured in ml. Animals that did not acquire a stable baseline cocaine intake (defined as 4 consecutive days during which intake did not vary by more than 10%) and animals whose cannula became blocked were replaced. Thus, the number of animals reported in these experiments refer to subjects successfully completing all phases of experimentation. For all experiments the dependent measure was intake of cocaine/session in ml.

Experiment 1

In order to control for possible residual drug effects of tamoxifen or haloperidol and to counterbalance drug experience two groups of female subjects were tested in parallel; with order of tamoxifen presentation reversed. In group 1

(N=11) subjects were injected with haloperidol (0.1 mg/kg, IP) one hour before the cocaine test session. One week later they received an injection of tamoxifen in propylene glycol (1.0 mg/kg, SC) and 24 hr after were injected with haloperidol as before, and tested. Group 2 (N=7) was tested in the reverse order.

Experiment 2

Male subjects were injected with haloperidol and/or tamoxifen in a counterbalanced design as outlined above (N=10).

RESULTS

Table 1 shows the average daily intake of cocaine for male and female rats. There was a tendency for the male animals to self-administer slightly more of the cocaine solution (measured in ml) than the female animals, however, when the data were expressed according to mg of cocaine/body weight (see Table 1) the resulting drug intake for each group was virtually identical ($F<1$).

All animals showed an increased intake of cocaine following injection with haloperidol. Individual data were expressed as a percent increase in cocaine intake over baseline values and subjected to an analysis of variance (ANOVA) with Sex as a between group comparison and Treatment (i.e., tamoxifen) as a within subject comparison. The overall ANOVA revealed a significant interaction between Sex and Treatment, $F(1,26)=29.51$, $p<0.001$, which indicated that the effect of tamoxifen was different in male and female animals. Analysis restricted to the female group revealed a significant reduction in the haloperidol response 24 hr after the tamoxifen treatment, $F(1,16)=29.76$, $p<0.001$. Order of drug testing (i.e., tamoxifen pretreatment prior to the first or second test), was included in the analysis as a between group comparison and showed no statistically significant effect ($F<1$).

Analysis restricted to the male rats showed that tamoxifen failed to attenuate the rate-increasing effects of haloperidol on cocaine self-administration, and in fact produced a non-significant increase in drug intake (see Fig. 1).

Male and female groups differed significantly under both test conditions. Female rats showed a greater response to haloperidol treatment alone, $F(1,26)=4.34$, $p<0.05$, while male rats showed a greater response to haloperidol following tamoxifen pretreatment, $F(1,26)=12.23$, $p<0.005$.

DISCUSSION

It has been demonstrated that a variety of antipsychotic drugs will, in a dose dependent manner, increase the self-administration of cocaine in male [38] and female rats [40]. This procedure can be employed as a useful animal model in determining the potency of antipsychotic drugs. Using this model we have previously reported that in the female rat the activity of haloperidol is affected by both ovariectomy and the estrous cycle [10, 39, 40].

In the present experiments, the data indicate a sex difference in the response to haloperidol. Haloperidol pretreatment caused a statistically larger increase in cocaine self-administration in female rats than in male rats. Inasmuch as this animal model is a useful screen for determining the therapeutic potency of antipsychotic drugs (see [38]), these data suggest that female rats may be more sensitive to the effects of haloperidol. Other studies have also shown that the behavioral response to both dopamine agonists and antagonists is greater in female rats than in male rats [2, 29, 33, 41].

We have previously shown that ovariectomy (OVX) attenuates the effect of haloperidol [39,40]. Thus, OVX animals are similar to males in that they are less responsive to this particular effect of haloperidol. The extent to which estrogen contributed to this effect could not be determined since ovariectomy produces a gross depletion of a number of female sex hormones. However, no statistically significant effect of a variety of estrogen pretreatments could be demonstrated. In light of this, we re-investigated the role of estrogen on the rate-increasing effects of haloperidol on cocaine self-administration using the estrogen antagonist tamoxifen.

In the present experiment, it was observed that a single injection of tamoxifen, which disrupted the normal estrous cycle (as determined by vaginal lavage), caused an attenuation of the effect of haloperidol on cocaine self-administration. When the rats were tested 24 hr after the tamoxifen injection the response to haloperidol was found to be attenuated by 50%. This effect was not seen one week later. Thus it appears that both short term pharmacological blockade of the estrous cycle and long term disruption (OVX) of ovarian function is sufficient to attenuate some effects of haloperidol According to our model this may reflect a reduced antipsychotic potency of haloperidol. These results confirm previous data which indicate that female hormonal status can affect the response to dopamine antagonists [4, 14, 40].

The effect of tamoxifen was sex-dependent since the antiestrogen did not affect the response to haloperidol in male rats. Rather than attenuating the action of haloperidol, there was a tendency for tamoxifen to increase the sensitivity of males to this drug. Whether this is a reliable difference which reflects some estrogenic or antiestrogenic effect of tamoxifen requires further study before comment should be made.

We have previously reported that estrogen pretreatment does not affect ovariectomy-induced attenuation of the haloperidol response [39,40]. Inasmuch as tamoxifen is a specific antiestrogen, we can conclude that one behavioral effect of haloperidol is estrogen sensitive and sex dependent. Despite the fact that tamoxifen exerts direct influences on estrogen receptors, we cannot conclude that the effects of tamoxifen on cocaine self-administration following haloperidol are due to estrogen alone, since disruption of the estrous cycle would also affect other female sex hormones.

Finally, it is possible that the presumed interaction between neuroleptic drugs and ovarian hormones may not be a centrally mediated phenomenon, but instead may be due to sex related differences in drug metabolism [28,34]. The fact that hepatic enzymes are affected by steroid treatment [28], together with the suggestion that estrogen can interfere with the metabolic clearance rate of some DA antagonists [4] indicates that peripheral metabolic actions could account for the data. We are presently examining this possibility.

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