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Increased Self-Administration of Cocaine Following Haloperidol: Effect of Ovariectomy, Estrogen Replacement, and Estrous Cycle

D. C. S. ROBERTS, J. C. H. DALTON AND G. J. VICKERS

Department of Psychology, Carleton University, Ottawa, Canada, K1S 5B6

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ROBERTS, D. C. S., J. C. H. DALTON AND G. J. VICKERS. *Increased self-administration of cocaine following haloperidol: Effect of ovariectomy, estrogen replacement, and estrous cycle.* PHARMACOL BIOCHEM BEHAV **26**(1) 37–43, 1987.—Rats which have been trained to self-administer cocaine intravenously show a dose-dependent increase in drug intake when pretreated with dopamine antagonists. This neuroleptic-induced increase in cocaine intake may be related to the antipsychotic potency and suggests that self-administration behavior may provide a useful model for evaluating neuroleptic activity. The present study examines the influence of ovarian hormones on the potency of the neuroleptic haloperidol using the cocaine self-administration model. It was found that the potency of haloperidol fluctuated across the estrous cycle with subjects in diestrus self-administering more cocaine than animals tested in estrus or proestrus. It was also demonstrated that the potency of haloperidol was reduced significantly following ovariectomy (OVX), however this OVX-induced attenuation could not be reversed with a number of estrogen or catechol-estrogen treatments. To the extent that the self-administration model can reflect the potency of antipsychotic drugs, these data indicate that ovarian function can affect neuroleptic activity, although the hormone(s) involved remain unclear. The clinical implications of these data underscore the need to further examine the influence of female sex hormones on the therapeutic efficacy of antipsychotic drugs.

Self-administration Cocaine Haloperidol Ovariectomy Estrous cycle Catechol-estrogen

CLINICAL data indicate that sex hormones may influence both the antipsychotic and extrapyramidal side effects of neuroleptic drugs. For example, it has been suggested that the antipsychotic potency of neuroleptic drugs fluctuates across the menstrual cycle [5, 13, 21, 22, 43]. Of equal clinical importance are the observations that the Parkinsonian-like effects of neuroleptics are more often seen in women than in men [1] and that estrogen administration can exacerbate these symptoms [52]. Similarly, tardive dyskinesia (TD), a severe movement disorder precipitated by prolonged antipsychotic treatment, is more frequent in women than in men, and this prevalence is exaggerated in the post-menopausal age group [7,28]. Such reports have stimulated basic research into the influence of sex hormones on central dopaminergic systems [20, 24, 25] and on their interaction with dopamine (DA) antagonist drugs [4, 5, 40].

In the present series of experiments, we have investigated the interaction of ovarian hormones with neuroleptics by using an animal model which may be sensitive to antipsychotic potency. This model is based on the observation that neuroleptic drugs, regardless of chemical class, increase the rate of cocaine self-administration in direct proportion to their clinical dose [46]. This increase in cocaine self-administration rate has been interpreted as a compensatory response to the partial blockade of the reinforcing effects of cocaine [11,55]. A variety of data indicate that the rewarding effects are mediated by mesolimbic and/or mesocortical dopaminergic systems [19, 35, 45, 56], and may be unrelated to striatal mechanisms. Therefore, neuroleptic effects on cocaine self-administration may be more sensitive to cortical and limbic function than striatal (extrapyramidal) effects.

Ovariectomy and various estrogen (and catechol-estrogen) treatments have been reported to influence neuroleptic-induced catalepsy [4, 5, 40]. Inasmuch as catalepsy reflects an extrapyramidal response, we were interested in examining whether manipulations of ovarian function would produce different effects in the cocaine self-administration model.

Here we report that the cocaine self-administration model indicates that ovarian status significantly influences antipsychotic activity and this appears unrelated to the extrapyramidal actions of haloperidol.

METHOD

Subjects

Female Wistar rats (Woodlyn Laboratories, Guelph)

weighing approximately 230 g at the beginning of the experiment were used. Animals were housed in pairs. 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). 17-β-Estradiol benzoate and 2-hydroxyestradiol were purchased from Sigma Chemical Company (St. Louis). Cocaine HCl was purchased from BDH (Toronto).

Apparatus

Food-training chambers (25×30×30 cm) were constructed of Plexiglas with metal grid floors. Depression of a lever mounted on the side wall activated a food-pellet dispenser (BRS/LVE, MD), which delivered one pellet (P. J. Noyes Co., NH) per lever press and activated a stimulus light. A water bottle was mounted on the opposite side of the chamber. Self-administration chambers were identical to the food-training chambers except that the lever activated a syringe pump (Razel Scientific Instruments, CT) which resulted in an intravenous infusion of cocaine. An event recorder (Easterline Angus, IN) and electromechanical counters were used to record the pattern and number of infusions. The house lights were maintained on a 12 hr light/dark cycle (lights off at 10 a.m.) by an automated timer.

Preliminary Training and Surgery

Following a 10 day acclimitization period, animals were deprived of food for 24 hr then trained to press a lever for food reinforcement. This procedure reliably facilitates subsequent acquisition of drug self-administration. Once trained, each animal was anaesthetized with sodium pentobarbitol (65 mg/kg, Somnotol, IP) and implanted with a jugular cannula as described elsewhere [45]. For the remainder of the experiment, animals were housed individually in one of 18 identical self-administration chambers, with water and food freely available. Following a two day recovery period, daily 4 hr test sessions began approximately 1 hr after light offset (10 a.m.) with the introduction of a removable lever. Each depression of the lever produced an infusion of cocaine (0.5 mg/0.1 ml saline/4 sec). A 20 sec stimulus light was co-activated and all responses during this period had no programmed effect. Animals were replaced if they did not acquire a stable baseline (defined as 4 consecutive days during which cocaine intake did not vary by more than 10%) or if the cannula became blocked. The number of animals reported in each experiment refer to the number of subjects completing all phases of each experiment.

Experiment 1

Animals received either bilateral ovariectomies (OVX) or were sham-operated (SHAM) during the same surgical session as the cannula implantation. After a stable cocaine self-administration baseline was established, each animal was tested with a single dose of haloperidol (0.25, 0.05, 0.1, 0.15, or 0.2 mg/kg, IP) which was administered one hour before the cocaine test session. Increases in cocaine intake were expressed as percentages of the mean intake for the previous 4 baseline days.

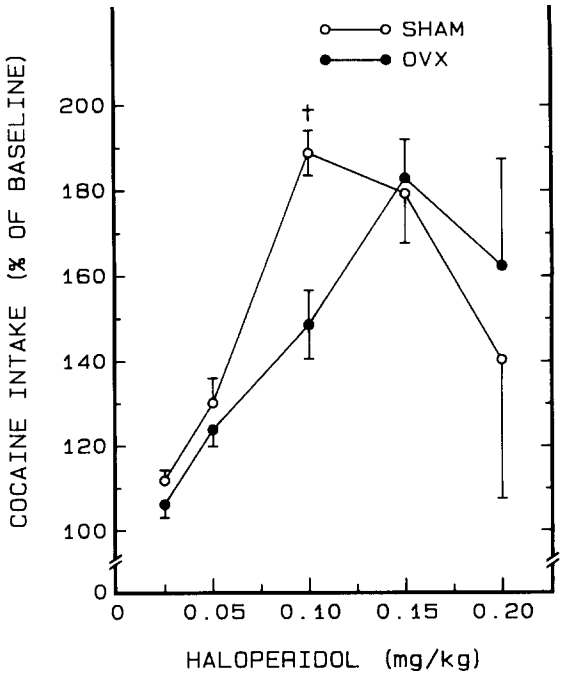

FIG. 1. The effect of various doses of haloperidol on cocaine self-administration. Data represent the increase in cocaine intake expressed as a percentage of baseline intake. Each point represents the mean (±SEM) cocaine intake for ovariectomized (OVX) and sham operated (SHAM) groups. See Table 1 for exact Ns. †Indicates significantly different from OVX group ($p<0.001$, ANOVA).

Experiment 2

Sexually mature female rats were prepared with intravenous cannulae, and permitted to self-administer cocaine as described above. The estrous cycle was determined daily by vaginal lavage taken at light offset. Nissl stained samples were examined under light microscopy, and categorized into proestrus, estrus, or diestrus. Animals that did not establish a stable pattern of cocaine self-administration or did not display 2 regular estrous cycles were dropped from the experiment. Animals were assigned to groups according to estrous cycle classification (as determined by the presence of leucocytes, nucleated epithelial, and cornified epithelial cell types) on the morning of the drug test. A clear metestrus stage was seldom observed, so that for the purposes of this study, animals showing a preponderance of leucocytes were categorized as diestrus, whereas those showing cornified epithelial cells were grouped together into an "estrus/metestrus" group. Each subject was tested once with a single dose of haloperidol (0.1 mg/kg, IP) 1 hour before access to cocaine, and then replaced. As in Experiment 1, the dependent variable was the increase in cocaine intake following haloperidol, expressed as a percent of baseline intake.

Experiment 3

Subjects were ovariectomized and prepared with intravenous cannulae as described in Experiment 1. Upon establishing a stable cocaine self-administration baseline, animals received various hormone treatments prior to their daily self-administration session. One group received a single injection of 17-β-estradiol benzoate (EB, 50 μg/kg, SC) 4 hr before the

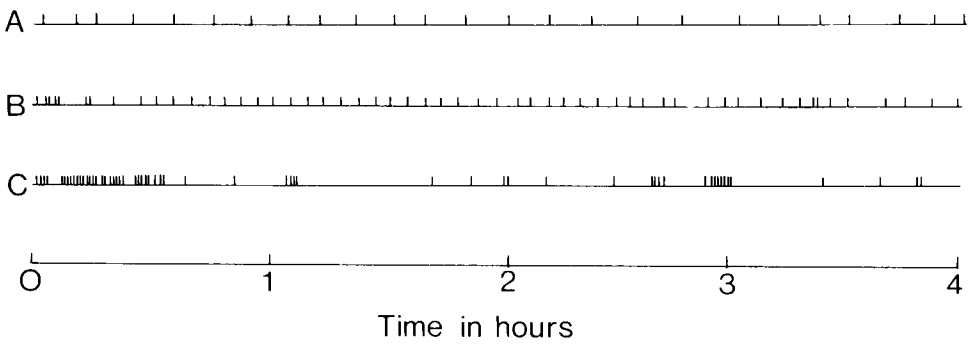

FIG. 2. Illustration of 3 event records of cocaine self-administration during a 4 hr test session. Each pen deflection represents an IV infusion of cocaine. Panel A shows an example of cocaine self-administration (baseline). Panel B illustrates the effect of haloperidol pretreatment (0.15 mg/kg) in which the response rate is increased and the response pattern remains regular. Panel C shows the event record of an animal which displayed an irregular pattern of cocaine self-administration following haloperidol pretreatment (0.15 mg/kg).

TABLE 1

NUMBER OF SUBJECTS DISPLAYING IRREGULAR PATTERN OF COCAINE INTAKE FOLLOWING HALOPERIDOL/N

	Dose of Haloperidol (mg/kg, IP)				
	0.025	0.05	0.1	0.15	0.2
Sham-operated	1/11	2/12	4/12	4/6	5/6
Ovariectomized	0/13	1/13	1/12	5/8	3/3

self-administration session. Two other groups received 3 daily EB injections (50 μg/kg, SC) and the haloperidol response was tested 4 or 24 hr following the last EB treatment. Subjects were injected with haloperidol (0.1 mg/kg, IP) one hour before access to cocaine. Control animals received injections of vehicle (vegetable oil, 1.0 ml/kg) and were tested in parallel with experimental subjects. Subjects in the fourth experimental group received the catechol-estrogen 2-hydroxyestradiol (2-OHE, 100 μg/kg, SC) or vehicle ten minutes before access to cocaine. The increase in cocaine self-administration was calculated as a percent of baseline drug intake (preceding 4 days).

RESULTS

In Experiment 1, an analysis of variance (ANOVA) revealed that haloperidol produced a statistically significant dose-dependent increase in cocaine self-administration, $F(4,85)=16.75$, $p<0.001$. ANOVA also revealed a significant treatment effect, $F(4,85)=2.43$, $p<0.05$, indicating that the ovariectomy significantly influenced the haloperidol response. The difference between groups was accounted for by the statistically significant separation, $F(1,22)=17.16$, $p<0.001$, obtained at the 0.1 mg/kg (see Fig. 1). Ovariectomy had no effect ($F<1$) on mean baseline cocaine intake. Mean intake for OVX and SHAM subjects was 3.12 ml (±0.11) and 2.99 ml (±0.11) respectively.

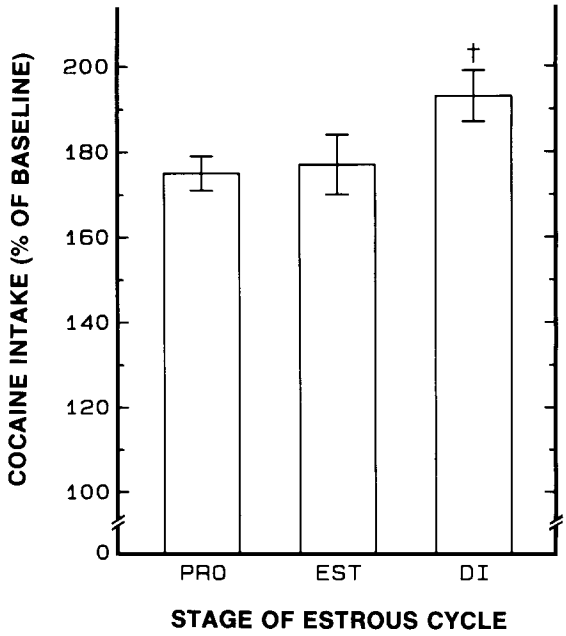

FIG. 3. The effect of the estrous cycle on haloperidol-induced increases in cocaine self-administration. Data represent the increase in cocaine intake expressed as a percentage of baseline intake. Each point represents the mean (±SEM) cocaine intake for proestrus (N=14), estrus (N=14), and diestrus (N=14) groups. †Indicates significantly different from other groups ($p<0.05$, Newman-Keuls).

An event record of a cocaine self-administration session, which illustrates the regular nature of the response, is represented in Fig. 2 (top panel). Panel B in Fig. 2 shows the event record of an animal in which haloperidol produced an increase in cocaine intake without affecting the regular response pattern. The lower panel illustrates an example of an animal which showed an irregular response pattern following a high dose of haloperidol. Table 1 shows the proportion of both SHAM and OVX subjects which displayed this response disruption following various doses of haloperidol.

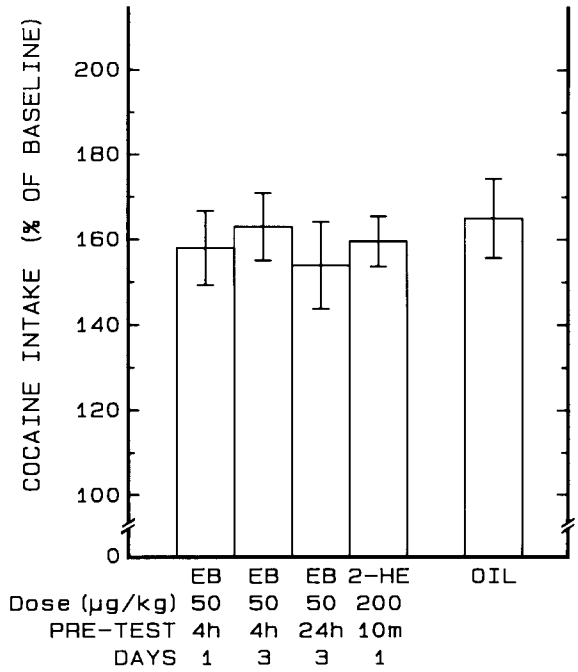

FIG. 4. The effect of estrogen pretreatment in OVX animals on cocaine self-administration following haloperidol. Data represent the increase in cocaine intake expressed as a percentage of baseline intake. Each point represents the mean (±SEM) cocaine intake for 7–13 animals per group. Animals received either estradiol benzoate (EB), 2-hydroxyestradiol (2-HE) or vehicle (OIL). The number of daily treatments is shown (Days) as well as the interval between the final injection and the test session (Pre-Test).

In the second experiment ANOVA revealed a statistically significant effect of the estrous cycle on self-administration of cocaine following haloperidol, $F(2,42)=4.22$, $p<0.05$. Newman-Keuls analysis showed that animals injected with haloperidol during diestrus self-administered statistically more cocaine than animals in proestrus, or estrus, $F(1,41)=4.77$, $p<0.035$ (ANOVA) (see Fig. 3). No statistically significant effect of the estrous cycle was observed on cocaine baseline intake ($F<1$).

An acute treatment with EB failed to produce a significant change in the self-administration response to haloperidol in OVX animals, $F(1,19)=0.33$, n.s. Three daily treatments with EB also failed to affect the response, whether tested 4 hr, $F(1,19)=0.54$, n.s., or 24 hr, $F(1,12)=1.31$, n.s., after the last injection. Similarly, pretreatment with the catechol-estrogen 2-hydroxyestradiol failed to affect the response, $F(1,15)=0.33$, n.s. The mean baseline cocaine intake for EB-treated animals was 3.19 ml (±0.07) and 3.24 ml (±0.16) for vehicle injected control subjects.

DISCUSSION

Animals given limited access to cocaine (e.g., 4 hr/day) demonstrate a remarkably invariant pattern of self-administration behavior (see Fig. 2). Within a test session, rats display a regular interinfusion interval, and self-administer almost exactly the same number of infusions from day to day. This baseline rate of cocaine intake is not influenced by hormonal variables. Neither ovariectomy nor various hormonal treatments (Experiments 1 and 3) were found to significantly alter cocaine self-administration. We have previously reported that male and female rats self-administer similar dosages, and such baseline rates were unaffected by the antiestrogen, tamoxifen [10]. Furthermore, in Experiment 2, we found no difference in the baseline rate of cocaine intake between groups tested at different phases of the estrous cycle. (While baseline rates are calculated across the four days of the estrous cycle, these baseline means would not reflect daily estrous related fluctuations in cocaine intake, but systematic comparisons of days within the estrous cycle have failed to reveal fluctuation in self-administration behavior for either cocaine or apomorphine.) We therefore conclude that hormonal variables do not appreciably alter the self-administration rate for either direct or indirect dopamine agonists. Paradoxically, however, our data suggest that the action of dopamine antagonists on cocaine self-administration behavior seems to be influenced by ovarian hormones.

Control rats pretreated with haloperidol show a dose-dependent increase in cocaine intake. At lower doses, the animals increase their cocaine intake up to 80–100% over baseline with the pattern of self-administration remaining regular. At higher doses of haloperidol, animals show an irregular response pattern, a behavior which has been interpreted as "extinction-like" responding [54,55], and usually precedes response cessation. Thus, the dose-response curve for haloperidol in control animals peaks at 0.1 mg/kg. The decline in the dose-response curve at the higher dosages (0.15 and 0.2 mg/kg), is associated with an increasing proportion of animals showing an irregular response pattern and reduced cocaine intake (see Table 1).

The potency of haloperidol appeared to be altered in ovariectomized rats. At the dose of 0.1 mg/kg, the SHAM group showed a 90% increase in the cocaine intake, with 25% of the animals starting to show an irregular pattern of self-administration. By contrast, the OVX group showed only a 48% increase in cocaine intake at this dose and only one out of the twelve animals displayed an irregular response pattern. It appears that the effect represents a shift in the dose-response curve to the right. The OVX group showed a regular response pattern at all doses until a maximal response was observed at 0.15 mg/kg. The OVX animals were clearly capable of responding at rates equal to the control group, if a high enough dose of haloperidol was administered, but simply appeared to be less sensitive to the effects of the neuroleptic in this paradigm.

We have previously reported that the antiestrogen, tamoxifen, also reduced the potency of haloperidol in female rats [10]. While this drug has its primary action on estrogen receptors, all other sex hormones are secondarily affected, with the result that the estrous cycle is arrested. Therefore it appears that either surgical (OVX) or pharmacological disruption (tamoxifen) of the estrous cycle attenuates the potency of haloperidol in the cocaine self-administration paradigm. It is of interest to note that using this procedure we have shown that male rats are less sensitive than female rats to the effects of haloperidol [10] and that a comparison of the rates of self-administration following haloperidol (0.1 mg/kg) reveals that after OVX or tamoxifen female rats respond at a lower rate comparable to the male rate. Thus female rats seem more sensitive to haloperidol than males, and this difference is negated by OVX or tamoxifen.

Inasmuch as estrous related hormones seem to influence the response to haloperidol, we investigated in the second

experiment whether the potency would fluctuate across the estrous cycle of the female rat. We observed that in our animal model there was a significant change in neuroleptic potency, however the finding that haloperidol was most potent during diestrus was unexpected. If OVX and antiestrogens reduce the potency of haloperidol by interfering with the action of 17-β-estradiol, then one would predict that the greatest potency should be observed when the plasma concentration of 17-β-estradiol is at or following its peak (i.e., during proestrus or estrus). The reason why haloperidol shows a slight (but statistically significant) increase in potency during diestrus when 17-β-estradiol levels are low is unclear, although the data imply that (A) either some change in dopamine receptor sensitivity is initiated by the peak in estradiol but has a long latency, or (B) estradiol is not involved at all (see below).

While it is recognized that results from the 4 day estrous cycle of the rat cannot be directly extrapolated to the human menstrual cycle, these data suggest that hormonal fluctuations might lead to alterations in the therapeutic effect of neuroleptics. Many authors have repeated the suggestion that the antipsychotic potency of neuroleptics varies with the menstrual cycle in humans (see the Introduction) however there does not appear to be any direct evidence in the literature. While a review by Stevens [50] has been cited for this effect, this paper makes no mention of the phenomenon. In laboratory animals, it has been shown that the behavioral response to amphetamine [3], intrastriatal infusions of dopamine [27] or stimulation of the nigrostriatal pathway [48] varies across the estrous cycle of the rat, and neurochemical studies have also indicated that the cyclic fluctuations in hormonal levels can affect dopamine function in the rat [8,32] and mouse [23,26]. These and the present data underscore the need for a re-examination of the clinical evidence concerning fluctuations in neuroleptic efficacy.

The present studies illustrate that the potency of haloperidol is affected by ovariectomy, and by fluctuations within the estrous cycle. While hormonal rhythms are most likely involved, these data do not implicate the specific hormone(s) responsible. Many steroid and peptide hormones fluctuate with the estrous cycle, and any one or combination of these might be important. In an effort to reinstate the haloperidol effect in the self-administration model, which was attenuated by ovariectomy, we chose to focus our attention on the effect of estrogen pretreatments. This was in large part due to the substantial literature which has demonstrated a direct interaction of estrogen on dopaminergic systems [51]. For example, it has been shown that estradiol and neuroleptics act synergistically in several behavioral paradigms [5, 13, 15, 40], and neurochemical data indicate that estrogen treatments can influence dopamine turnover [9, 33, 34, 44, 53], release [2], dopamine-stimulated adenylate cyclase activity [30], and DA receptor binding [12–14, 24, 25]. These neurochemical effects are paralleled by behavioral data which indicate that the response to DA agonist and antagonist drugs is influenced by ovarian status [6, 17, 31, 37, 39, 43].

Estradiol benzoate (EB) treatment regimens were chosen since they have previously been shown to affect the behavioral response to neuroleptic drugs [21,22]. We were unable to demonstrate a significant effect on the potency of haloperidol in the self-administration model following an acute injection of EB, three day treatment with EB, or withdrawal from EB treatment. This may indicate that the model is not sufficiently sensitive to detect changes in neuroleptic potency produced by EB, however, since we have demonstrated that the model can detect small fluctuations in potency across the estrous cycle, we conclude that these treatments are not sufficient to reinstate the efficacy of haloperidol following ovariectomy.

The catechol-estrogen, 2-OHE, was also tested for a possible influence on the haloperidol response. Catechol-estrogens are hydroxylated metabolites of estrogen, which can be formed in brain and have been shown to have significant physiological and pharmacological actions (see [42]). Recently, it has been demonstrated that catechol-estrogens can also affect dopaminergic function in rats [18,41]. Catechol-estrogens have been shown to compete for neuroleptic binding sites in tissue taken from anterior pituitary and striatum [36,49] and behavioral data show that catechol-estrogens can affect the response to dopaminergic agonist and antagonist drugs [16,40]. With respect to neuroleptic drugs, Nicoletti *et al.* [40] have demonstrated a potentiation of haloperidol-induced catalepsy following an acute injection of the catechol-estrogen 2-OHE. Using a similar treatment we were unable to affect the potency of haloperidol in OVX animals. These data again suggest that hormonal treatments that affect the extrapyramidal actions of neuroleptic drugs do not necessarily affect the self-administration model of antipsychotic drug potency.

We have shown that neither estrogen nor catechol-estrogen treatments reverse the OVX attenuation of the haloperidol response. One interpretation of these data might be that estrogen depletion is not the primary cause of the OVX effect, and that some other hormone is involved (e.g., prolactin, progesterone), or possibly that the coordinated cyclicity of many hormones is necessary for the higher sensitivity in the female rat. Further studies of the effects of other hormones, either alone or in combination with estrogen, will be necessary before the nature of the hormonal involvement can be established.

It should be recognized that the interaction between sex-hormones and neuroleptic action could be a peripheral effect, possibly related to drug clearance. Sex related differences in drug clearance have been reported [29,38], and drug metabolism by hepatic enzymes can be inhibited by steroid action. This point is particularly relevant since Chiodo *et al.* [5] have demonstrated that estrogen can affect the clearance of [^{3}H]-spiperone from brain. However, clearance rates of [^{3}H]-apomorphine and [^{3}H]-amphetamine were not affected by estrogen pretreatment [5]. Regardless of the site(s) of action, whether peripheral or central, the demonstration of an influence of hormones on neuroleptic action could have important clinical implications in the treatment of psychoses or tardive dyskinesia.

Finally, the usefulness of the cocaine self-administration model for exploring the effects of neuroleptic drugs deserves comment. A distinction will be made here between a screening procedure and a "model." The underlying mechanisms which allow a screening procedure to predict a particular drug effect may only be superficially related to a physiological response, the important thing being only that the screen predicts the therapeutic effect. For example, one screen takes advantage of the dopamine receptor binding characteristics in the retina to predict neuroleptic potency, but there is clearly no assumption made that these drugs normally achieve their antipsychotic effect in patients by acting on dopamine receptors in the eye. Theoretical arguments are secondary to the important aspect of whether or not the screen can predict a particular drug effect. As a screen, therefore, the cocaine self-administration procedure seems

useful. It detects neuroleptic potency in a wide variety of chemical classes, and predicts the clinical potency of atypical neuroleptics better than other behavioral or biochemical techniques (see [46]). Whether the prediction that clinical (neuroleptic) potency fluctuates with the reproductive cycle or that estrogen supplements will influence the antipsychotic effect must await clinical investigation.

An animal model, as opposed to a screen, must be judged on more theoretical grounds. There is the implied assumption that the mechanisms underlying the clinical response and the model are identical or at least analogous, and that investigations into the neural mechanisms underlying the model will yield insights into the clinical disorder. There is reason to believe that neuroleptics achieve their antipsychotic effect and influence cocaine self-administration at identical loci and that is limbic/cortical dopamine receptors. The modulation of both of these effects may be similarly affected by ovarian hormones and the site of this interaction could be the same. To this extent, the model shows some promise.

However, every model is encumbered with interpretational difficulties, and the self-administration model has several. (A) The dependent variable is rate of cocaine self-administration and the factors which govern this rate are poorly understood (see [47]). (B) The behavior is dependent on an interaction between two drugs, which have different pharmaco-dynamic properties. (C) There is the paradox that the hormonal influence is only observed with the antagonist and not on the baseline self-administration rates of the agonist. This last point may be a manifestation of points (A) and (B). Clearly, there is much to be understood about the neural bases of self-administration behavior before it will contribute toward our understanding of antipsychotic action. The value of the cocaine self-administration model therefore depends on the level of interpretation. The paradigm may succeed as a useful behavioral screen to predict neuroleptic potency and hormonal interactions, but it has serious limitations as a "model" for studying the neural basis of antipsychotic action.

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