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Ketanserin Effects on Rat Behavioral Responses: Modifications by the Estrous Cycle, Ovariectomy and Estradiol Replacement

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DÍAZ-VÉLIZ, G., DUSSAUBAT, N. AND MORA, S. *Ketanserin effects on rat behavioral responses: modifications by the estrous cycle, ovariectomy and estradiol replacement.* PHARMACOL BIOCHEM BEHAV **57**(4) 687–692, 1997.—The present investigation was designed to explore the influence of estrous cycle phase, ovariectomy, and estradiol replacement on the behavioral effects of the 5-HT_2 receptor antagonist, ketanserin.The parameters under investigation were ketanserin-influenced acquisition of conditioning avoidance responses (CARs), and the performance of some spontaneous motor behaviors. Ketanserin (KET 3 mg/kg) injected subcutaneously 30 min before testing improved active conditioned avoidance in intact female rats at estrus, and in ovariectomized (OVX) rats with estradiol replacement. Furthermore, KET impaired performance in female rats at diestrus and after ovariectomy. In male rats, which were included in this study in order to compare their behavioral responses with those exhibited by female rats, KET administration enhanced acquisition of CARs. These results provide behavioral evidence for the hypothesis that central serotonergic activity is a function of the hormonal status of the animal. An additional segment of the present study focussed on motoric behaviors. Spontaneous motor activity, number of rears, and time spent in grooming behavior were significantly increased by KET in all groups studied. In contrast, blockade of 5-HT_2 receptors failed to induce significant changes in the number of head shakes. Relationships between ovarian hormones and the central serotonergic system are discussed. © 1997 Elsevier Science Inc.

Serotonergic system Ketanserin Estrous cycle Conditioned avoidance responses Estradiol Ovariectomy

FLUCTUATIONS in ovarian hormones over the estrous cycle or following ovariectomy, with or without estradiol replacement, are associated with major perturbations in the acquisition of a conditioned avoidance response (CAR). Previously, we have reported that this behavioral response is facilitated at diestrus but it is diminished at estrus and metestrus (12). Furthermore, the systemic administration of a single dose of estradiol benzoate (EB 2 μg) to ovariectomized (OVX) rats impairs this behavior (13). Other authors have tested the effects of sex, estrous cycle and gonadal hormones upon acquisition of CARs without conclusive results (3,4,22,25).

The involvement of brain serotonergic (5-HT) neurons in mediating performance in various behavioral tests which assay learning and memory processes, has been proposed. Two of these tests are active and passive avoidance conditioning (1,2,15,19,20,24,28). Systemic administration of 5-HT receptor antagonists, both nonselective (metergoline, methysergide) and 5-HT_2 selective (pirenperona, ketanserin and mianserin) has been shown to facilitate the memory of a previously learned avoidance response (1,2). On the other hand, lesion of the raphe nuclei, the area containing 5-HT cell bodies, has been reported to produce facilitation of avoidance acquisition (20,24).

Several lines of evidence have shown a relationship between sex hormones and serotonergic neurotransmission in the CNS. In general, higher levels of 5-HT and the serotonin metabolite 5-HIAA have been found in the brains of female rats relative to the levels found in the brains of male rats (10). In addition, it has been reported that 5-HT synthetic capacity

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in the brains of female rats is higher than in male brains (10,27). Other studies have indicated that estrogen influences 5-HT receptor binding and metabolism, as well as electrophysiological responses to serotonin. Serotonin receptor levels undergo regular changes during the estrous cycle of the rat (7). Cortical [^{3}H]-5-HT binding is low on the morning of proestrus and increases during estrus (26,29). Treatment of OVX rats with estradiol also produces a significant increase in cortical [^{3}H]-5-HT binding, presumably reflecting an augmentation in 5-HT_2 receptors (8,29). Monoamine oxidase (MAO) activity in whole brain also changes during the estrous cycle of the rat, perhaps influenced by increasing estrogen levels; estrogen itself acts as an MAO inhibitor (18). Ovariectomized rats show a poor response to serotonin-induced hyperpolarization in hippocampal pyramidal cells, a response which can be restored by chronic estradiol treatment (5).

Taken together, these various findings strongly suggest that ovarian hormones may participate in the regulation of 5-HT neuronal function. The present investigation was designed to explore whether the hormonal status of the rat might influence the nonsexual behavioral effects of a 5-HT_2 antagonist drug. We studied the influence of ketanserin (KET) upon avoidance conditioning and some spontaneous motor responses, using intact cycling female rats at two stages of the estrous cycle, OVX rats, OVX-estrogen primed female rats, and male rats.

METHODS

Animals

A total of 80 female Sprague–Dawley rats, weighing 180–210 g, were housed in groups of six per cage in a temperature-controlled vivarium, with a 12 h light period beginning at 0800 h, and free access to food and tapwater.

Vaginal smears were taken daily from 40 intact female rats to determine the different stages of the estrous cycle. Only rats exhibiting at least three consecutive regular 4-day cycles were included in this study. Because a previous report (12) showed great differences in the acquisition of CARs between diestrous and estrous females, only these phases were considered for the pharmacological experiments.

Bilateral ovariectomy was performed on 40 female rats under light ether anesthesia. Fourteen days after surgical removal of the ovaries, rats were randomly divided into two groups that received either 2 μg estradiol benzoate (EB) or corn oil vehicle (0.2 ml/rat), injected subcutaneously (SC) into the dorsal region of the neck. Vaginal smears were taken for at least 4 days before commencement of estradiol administration; rats were invariably found to be in diestrus, confirming the completeness of ovariectomy.

A group of 20 male Sprague–Dawley rats were also included in the study in order to compare their behavioral responses with those exhibited by female rats.

All ovariectomized female rats, as well as male rats, were manipulated in the same manner as the intact females on several consecutive days before the experiments, in order to exclude handling-induced differences between groups.

Drug

Ketanserin tartrate (KET, Research Biochemicals Inc., Natick, MA) was dissolved in 0.9% saline and administered subcutaneously (SC) in an injection volume of 1 ml/kg (3 mg/kg). KET administration occurred 48 h after the administration of EB and 30 min before the behavioral testing. Control rats received saline at the same volume. Rats were injected with KET or saline only once and were tested between 1000 and 1400 h.

Spontaneous Motor Activity

The animals were individually placed in a plexiglass cage (30 × 30 × 30 cm), inside a soundproof room. Spontaneous motor activity was monitored automatically through an Opto-Varimex Mini (Columbus Instruments, Columbus, Ohio) and the following responses were recorded simultaneously: number of times each animal reared, time (in seconds) spent in grooming behavior, and number of head shakes. Each animal was observed continuously for 30 min, via a videocamera connected to a VHS tape-recorder. Scores were generated from live observations, and video sequences were used for subsequent reanalysis.

Active Avoidance Conditioning

The conditioning experiments were carried out with a two-way shuttle box (Lafayette Instrument Co., Lafayette, IN) composed of two stainless steel modular testing units, which were equipped with an 18-bar insulated shock grid floor, two 28V DC lights and a tone generator (2800 Hz; Mallory Sonalert, Lafayette, IN). Electric shocks were provided through the grid floor by a master shock supply (Lafayette Instrument Co., Lafayette, IN). Immediately after the spontaneous motor activity test, the rats were individually placed in the shuttle box and were trained over 50 trials, after a 5 min-period of habituation. Each trial consisted of the presentation of a tone which, after 5 s, was combined with a 0.20-mA foot-shock. The shock persisted until the animal escaped to the opposite chamber. The maximum shock duration was 10 s. A conditioned avoidance response (CAR) was defined as a crossing within the first 5 s (tone alone).

Statistical Analysis

For each experimental group ($n = 10$ rats) the results are expressed as mean ± SEM. All data were analyzed by two-way analysis of variance (ANOVA) followed by posthoc Newman-Keuls's multiple comparison test. Student's *t*-test was used to compare groups of male rats. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

Behavioral Effects of Ketanserin in Female Rats

Active avoidance conditioning. The results of the active avoidance experiment are shown in Fig. 1. ANOVA revealed a significant effect of hormonal status [$F(3,72) = 22.24$, $p < 0.01$], and KET treatment [$F(1,72) = 11.94$, $p < 0.01$], on the acquisition of CARs. Posthoc analysis indicated that the avoidance conditioning in saline injected rats was similar in diestrous and OVX rats, but this behavior was seriously impaired in rats at estrus and OVX after EB treatment ($p < 0.001$ in both cases). Administration of KET significantly improved the acquisition of CARs in estrous rats ($p < 0.025$) and in OVX rats after EB treatment ($p < 0.005$). However, KET significantly impaired the conditioned response in diestrous and OVX rats ($p < 0.0005$ in both cases). The significant interaction between KET treatment and hormonal status [$F(3, 72) = 22.80$, $p < 0.01$], suggests that the effect of KET is dependent upon the hormonal status of the rat. No significant differences were observed with regard to the footshock thresholds among the different groups.

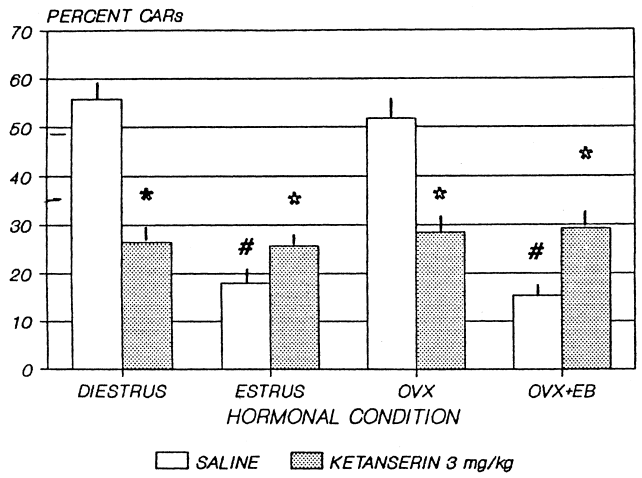

FIG. 1. Influence of hormonal status (intact female rats at diestrus and estrus, ovariectomized = OVX and ovariectomized with estradiol replacement = OVX + EB) on KET's effect on the acquisition of conditioned avoidance responses (CARs). Each bar represent the mean ± SEM of the percentages of CARs for 50 trials. Comparisons were made using two-way ANOVA followed by posthoc Newman-Keuls test. *Significantly different compared with its saline control group; #$p < 0.001$ comparing diestrus vs estrus or OVX vs OVX + EB rats. $n = 10$ rats/group.

Spontaneous motor activity. Mean motor activity counts are shown in Figure 2 (top panel). Data analysis revealed that hormonal status [$F(3, 72) = 5.97$, $p < 0.05$], and KET treatment [$F(1, 72) = 34.72$, $p < 0.01$], exert a statistically significant effect on spontaneous motor activity. Subsequent Newman-Keuls tests indicated that in saline-injected groups, motor activity was higher at diestrus than at estrus ($p < 0.01$). Furthermore, the EB treatment to OVX rats produced a significant decrease in motor activity compared with OVX rats ($p < 0.025$). KET treatment significantly increased the motor activity in the four hormonal conditions compared with the saline injected controls ($p < 0.05$ in all comparisons). Since the interaction of KET treatment with hormonal status was not significant, the effect of KET on motor activity appears not to be dependent upon the hormonal status of the rat.

Rearing behavior. ANOVA revealed significant effects of hormonal status [$F(3, 72) = 2.88$, $p < 0.05$], and KET treatment [$F(1, 72) = 20.05$, $p < 0.01$], on rearings. As shown in Figure 2 (bottom panel), ovariectomy decreased the number of rears ($p < 0.01$ compared with diestrous rats) and this effect was reversed by EB treatment ($p < 0.05$). Rearing behavior was also diminished in estrous rats ($p < 0.01$ compared with diestrous rats). All groups studied demonstrated a significant increase in rearing following KET administration ($p < 0.05$ in all comparisons).

Head shaking. Figure 3 (top panel) presents the mean number of head shakes for the experimental groups. Under our experimental conditions only a significant effect of the hormonal status was evident upon this behavior [$F(3, 72) = 6.92$, $p < 0.01$]. Subsequent Newman-Keuls tests revealed that the estrous saline-injected rats displeyed significantly fewer head shakes than any of other saline-injected groups ($p < 0.005$ compared with diestrous rats). EB administration enhanced this behavior in OVX rats ($p < 0.01$ compared with OVX rats). KET administration produced a significant decrease in head shakes only in the OVX rats injected with EB ($p < 0.01$).

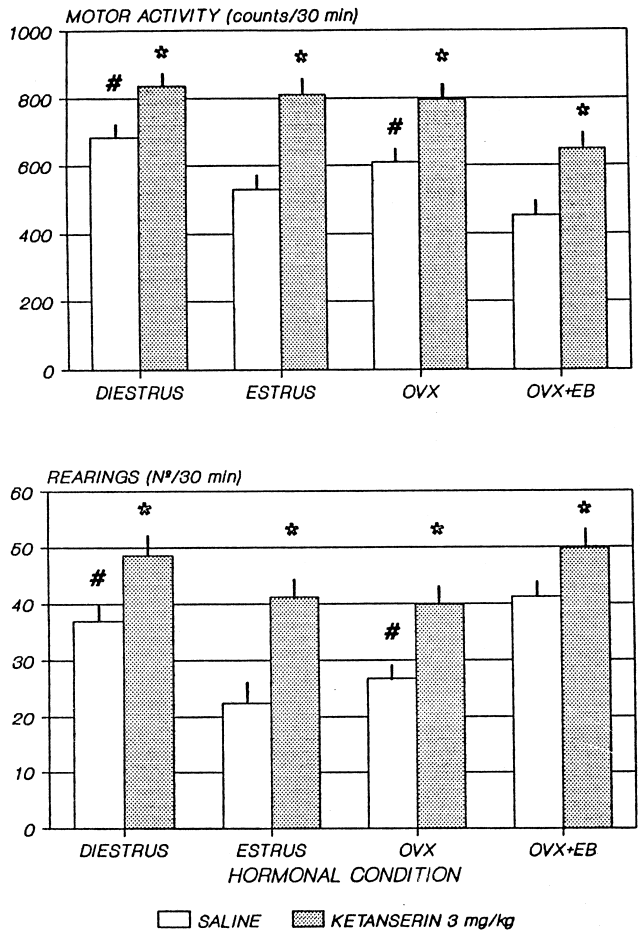

FIG. 2. Influence of hormonal status (intact female rats at diestrus and estrus, ovariectomized = OVX and ovariectomized with estradiol replacement = OVX + EB) on KET's effects on spontaneous motor activity and rearing behavior. Each bar represents the mean ± SEM of the motor activity counts (top panel) or of the number of rears (bottom panel) during 30 min of observation. Comparisons were made using two-way ANOVA followed by posthoc Newman-Keuls test. *$p < 0.05$ compared with its saline control group; #$p < 0.001$ comparing diestrus vs estrus or OVX vs OVX + EB rats. $n = 10$ rats/group.

Grooming behavior. The data representing the time spent in grooming are shown in Figure 3 (bottom panel). ANOVA revealed significant effects of hormonal status [$F(3, 72) = 9.40$, $p < 0.01$], and KET treatment [$F(1, 72) = 21.95$, $p < 0.01$]. Posthoc analysis indicated that ovariectomy significantly enhanced the time spent in grooming behavior ($p < 0.01$ compared with diestrous and estrous rats) and this effect was reversed by EB treatment ($p < 0.0025$). KET was able to elicited significantly more time spent in grooming in all experimental groups ($p < 0.05$).

Behavioral Effects of Ketanserin in Male Rats

The results summarized in Table 1 show that KET administration to male rats induced a significant increase in acquisition of CARs, motor activity, rearing, and grooming behavior. There was no effect of KET on head shakes.

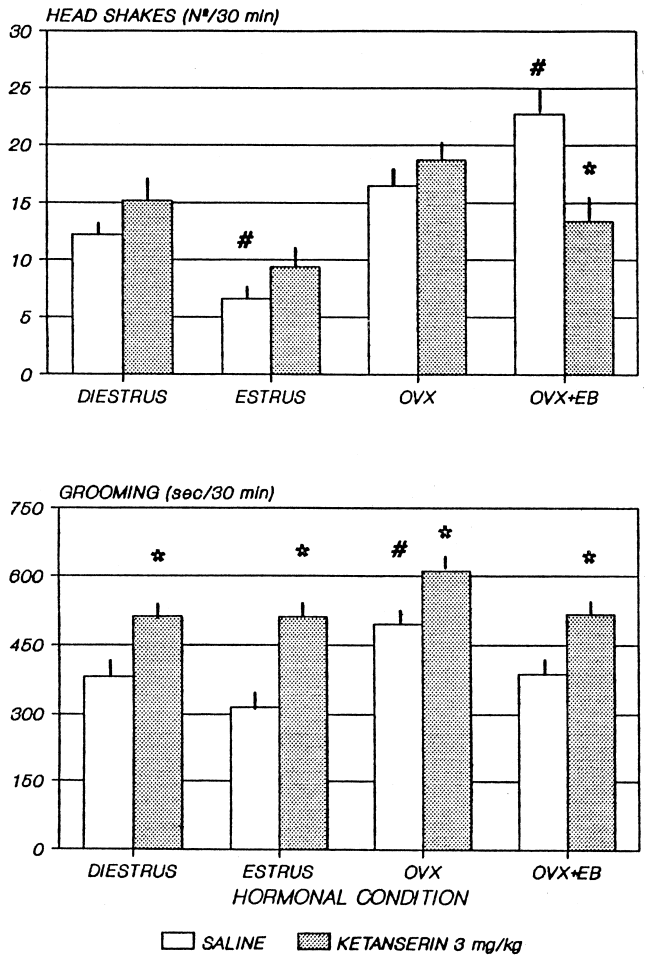

FIG. 3. Influence of hormonal status (intact female rats at diestrus and estrus, ovariectomized = OVX and ovariectomized with estradiol replacement = OVX + EB) on KET's effects on head shaking and grooming behavior. Each bar represents the mean ± SEM of the number of head shakes (top panel) or of the time spent in grooming behavior (bottom panel) during the 30 min of observation. Comparisons were made using two-way ANOVA followed by posthoc Newman-Keuls test. *$p < 0.05$ compared with its saline control group and #$p < 0.001$ comparing diestrus vs estrus or OVX vs OVX + EB rats. $n = 10$ rats/group.

DISCUSSION

The results presented here support previous evidence that avoidance conditioning is influenced by the female's estrous cycle and by estradiol administration to OVX rats (12,13). The major finding of the present study is that the hormonal changes which occur during the estrous cycle, after ovariectomy and after estradiol administration, can also have direct effects on the action of drugs which influence 5-HT transmission. Pharmacological studies have demonstrated that the central 5-HT neuronal system may functionally be involved in learning and memory processes (1,2,15,19,20,24,28). It has been demonstrated that systemic administration of both nonselective and 5-HT_2 selective receptor antagonists increase the acquisition of CAR (1,2). In the present study, a similar behavioral response was observed after the administration of KET, a selective 5-HT_2 antagonist, to male rats.

In female control groups treated with saline, it was observed that active avoidance conditioning was dependent on the hormonal status of the rat. However, these differences were abolished after KET treatment. In fact, KET effectively enhanced acquisition of CAR in cycling female rats at estrus and in OVX rats primed with estrogen, but the same dose of this drug impaired the acquisition behavior in rats at diestrus and in OVX rats without EB replacement (animals with low levels of gonadal steroids). The present finding that reducing central 5-HT activity eliminates differences in avoidance behavior related to the ovarian status of females strongly suggests that the role of 5-HT in mediating this behavior is hormone-dependent. Nevertheless, the KET effect was stronger in males than in females.

The above mentioned results indicate that the action of KET may be influenced by estradiol levels, since the stimulant effects of KET, in female rats, were observed only late after the peak plasma concentration of estradiol; that is, during estrus (9,12) and 48 hr after a single injection of EB to OVX rats (13). These results cannot be explained by changes in pain sensitivity or in motor activity. Although conditioned avoidance can vary according to the footshock intensity (4), in our experimental conditions no significant differences were observed in the footshock thresholds applied to the different groups. On the other hand, the effect of KET on acquisition of CARs was dependent upon the hormonal status of the rat, but spontaneous motor activity was enhanced in all groups studied, regardless of the hormonal condition. Since motor activity increased even in those groups which CAR performance decreased, there does not appear to be a correlation between the impairment in acquisition and performance of the spontaneous motor response.

Several lines of evidence support a relationship between estradiol and serotonergic neurotransmission in the CNS. There are studies indicating that estrogen influences serotonin receptor binding and metabolism (18), as well as electrophysiological (5) responses to serotonin. Serotonin receptors levels undergo regular changes during the estrous cycle of the rat (7); for example, in certain brain regions there was a significant increase in binding of [^{3}H]-5-HT during the day of proestrus when estrogen levels are high (26,29), and in OVX rats after estradiol treatment (8,29). Since estradiol levels are

TABLE 1

SUMMARY OF KETANSERIN EFFECTS IN MALE RATS

	CARs %	Motor Activity (Counts/30 min)	Rearings (No/30 min)	Head Shakes (No/30 min)	Grooming (S/30 min)
Saline	34.5 ± 3.7	660.7 ± 27.7	37.1 ± 1.5	15.8 ± 1.5	475.3 ± 19.3
Ketanserin (3 mg/kg)	50.2 ± 3.0*	768.8 ± 25.2*	42.8 ± 1.9*	17.6 ± 1.7	634.1 ± 26.0*

* $p < 0.025$ compared with its saline control group; $n = 10$ rats/group.

highest on the morning of proestrus and decline during that afternoon and evening (9), it has been suggested that the estrous increase in cortical [^{3}H]-5-HT binding reflected a withdrawal from the depressant effects of estradiol (26,29). In our experimental conditions, the impairment in acquisition is correlated with a delay of 24–48 hours after the estrogen peak. That time point corresponds to estrus or 48 hr after estradiol in OVX rats, when the serum estradiol levels are almost undetectable. The impairment in CAR acquisition, which is partially prevented by KET, could be considered as part of an estrogen withdrawal syndrome, or the expression of genomic actions of this hormone. Although the gonadal hormonal status appears to modulate behavioral responses to central 5-HT inhibition in animal models, the precise mechanism by which KET induced such behavioral differences across the estrous cycle or after estradiol treatment in the present study remains to be established. It is possible that female sex hormones may be acting directly on 5-HT receptors or influencing other neurotransmitter systems which, in turn, modulate 5-HT activity. Considering that KET is a selective 5-HT$_2$ antagonist, it may be that its stimulating effects during estrus and in OVX rats primed with EB could be correlated with a previous hyperactivity of this system. The fact that KET did not completely reverse the impairment of CARs in these groups suggests that either an insufficient dosage was used, or other modulatory agents are involved.

Although the head shaking response can be mediated by multiple neurotransmitter systems (17), drugs which increase synaptic concentration of 5-HT induce head-shake behavior in rodents (6), and this behavior is antagonized by selective 5-HT$_2$ receptor antagonists (6,11,16). In the present study, the enhancement in head shakes induced by EB was attenuated by KET. These results suggest that EB, which increases 5-HT$_2$ receptors (8,29), had an indirect 5-HT$_2$ agonist effect on head shakes. This action is not observed in estrous rats; a fact which maybe due to the action of progesterone which, in many behaviors, is opposite to that of estradiol (14). The interaction of progesterone with 5-HT system is presently under investigation.

In addition, KET was able to increase rearing behavior and time spent in grooming behavior in all groups studied, but these effects were not influenced by the hormonal status of the rat. There are reports suggesting the possibility that dopamine receptors are primarily involved in the expression of both rearing (21) and grooming behavior (23).

In summary, the 5-HT$_2$ antagonist KET was found to modify the performance of conditioned avoidance behavior, according to the hormonal status of the female rat at the time of behavioral testing. Nevertheless, cognitive abilities were more sensitive than motoric behaviors to the interaction between estradiol and the 5-HT system. This study provides additional evidence to support a role of central 5-HT in avoidance procedures, and contributes to a better understanding of the complex interaction between gonadal hormones and central neurotransmitter systems.

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