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Effects of Highly or Relatively Selective 5-HT_{1A} Receptor Agonists on Lordosis in Female Rats

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ABSTRACT—To investigate the role of serotonin (5-HT) receptor 1A or 7 in regulating lordosis behavior in female rats, ovariectomized rats were treated with 3 kinds of receptor agonists and lordosis behavior was observed. The injected agents were the selective 5-HT_{1A} receptor agonist, buspirone (BUS), the highly selective 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-n-propylamino)tetralin ((±)8-OH-DPAT), and the 5-HT_{1A} and 5-HT_7 receptor agonist, (R)-8-hydroxy-2-(di-n-propylamino)tetralin ((+)8-OH-DPAT). A behavioral test was performed after ovariectomy and subcutaneous implantation of a silicon tube containing estradiol. Female rats in which the lordosis quotient (LQ) was over 70 were intraperitoneally injected with several doses of these agents. As a result, in the BUS group, the dose of 3 mg/kg bw, but not 1 mg/kg was effective for suppressing lordosis. On the other hand, an inhibitory effect was observed from 0.25 mg/kg and 0.5 mg/kg in the (+)8-OH-DPAT and (±)8-OH-DPAT groups, respectively. In the time-course experiment, in all drug-treated groups, LQ decreased to lower than 20 after 15 min and low LQ continued for 1 hr at least. Measurement of locomotor activity using an infrared sensor system showed no relation between the decrease in lordosis by these agents and spontaneous locomotion. These results indicate that 5-HT_{1A} is strongly involved in the lordosis-inhibiting circuit of the serotonin neurons.

Key words: lordosis, 5-HT_{1A} receptor, 8-OH-DPAT, buspirone, female rat

INTRODUCTION

Highly estrous female rats show lordosis and soliciting behaviors with male mounting. These characteristic sexual behaviors are regulated by facilitatory and inhibitory systems in the central nervous system. The ventromedial hypothalamic nucleus (VMH) exerts an estrogen-dependent facilitatory influence in regulating lordosis (Pfaff *et al*., 1994). On the contrary, the lateral septum (LS) and the preoptic area (POA) exert a lordosis-inhibitory influence (Yamanouchi, 1997). These facilitatory and inhibitory mechanisms in the forebrain are modified by the limbic system and the lower brainstem.

In the midbrain, the dorsal raphe nucleus (DRN) plays an important role in inhibiting lordosis behavior, because destruction or ventral cutting of this nucleus facilitated lordosis behavior in female rats (Yamanouchi and Arai, 1985; Kakeyama and Yamanouchi, 1996; Kakeyama *et al*., 1997). Electrical stimulation of the DRN inhibited lordosis in female rats (Arendash and Gorski, 1983). Furthermore, since a DRN lesion causes male rats to show lordosis, the quantity or quality of the inhibition of the DRN leads to sex differences in the brain (Kakeyama and Yamanouchi, 1992).

The DRN contains a large number of serotonergic neurons (Törk, 1985). Since lordosis is enhanced by treatment with the serotonin (5-HT) synthesis inhibitor, p-chlorophenylalanine (PCPA) (Zemlan *et al*., 1973), but is not enhanced in rats with a DRN lesion (Kakeyama and Yamanouchi, 1993), it appears that serotonergic neurons in the DRN play an inhibitory role in lordosis-regulation. The axons of serotonergic neurons in the DRN extend to the lordosis regulating mechanisms in the hypothalamus, including the VMH and the POA (Parent *et al*., 1981; Törk, 1985). Among the 5-HT receptors, 7 families (from 1 to 7) have been classified (Hoyer *et al*., 1994). In the hypothalamus 5-$HT_{1A,}$ 5-HT_{2c} and 5-HT_7 receptors have been found (Hoyer *et al*., 1994; Barnes and Sharp, 1999).

It has been suggested that the 5-HT_{1A} receptor is involved in the lordosis inhibiting mechanism, because 5-HT_{1A} receptor agonists, (±)8-OH-DPAT (Mendelson and Gorzalka, 1986b) or buspirone (Mendelson and Gorzalka, 1986a) decreased lordosis. In contrast, since lordosis is facilitated by treatment with the 5-$HT_{2A/2C}$ receptor agonist,

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DOI, and conversely, is inhibited by the antagonist, ketanserin (Wolf *et al.*, 1998; Wolf *et al.*, 1999), 5-$HT_{2A/2C}$ receptor plays an important role in the lordosis facilitating mechanism. Moreover, treatment with the 5-HT_3 receptor antagonist, tropisetron, decreased lordosis (Maswood *et al.*, 1997; Maswood *et al.*, 1998). In this study, to clarify the role of 5-HT_{1A} and $_7$ receptors in regulating lordosis, a comparative analysis was performed using the highly selective 5-HT_{1A} receptor agonist, (±)8-OH-DPAT, 5-HT_{1A} and 5-HT_7 receptor agonist, (+)8-OH-DPAT, or relatively selective 5-HT_{1A} receptor agonist, buspirone.

MATERIALS AND METHODS

Female Wistar rats (215–295 g) were purchased from Takasugi Animal Farm (Saitama, Japan). The rats were housed under conditions of controlled temperature (23–25°C) and photoperiod (14 : 10, light : dark). Food and water were available *ad libitum*. The present experiments were performed according to the Guidelines for the Care and Use of Laboratory Animals in the Human Science Department of Waseda University. All female rats were ovariectomized under ether anesthesia. Rats were implanted with a silicon tube (inner diameter, 1.57 mm; outer diameter, 3.18 mm; length, 30 mm; Kaneka Medix Co., Osaka, Japan) containing estradiol-17β (E_2; Sigma Chemical Co., St. Louis, MO, USA) subcutaneously within one week after ovariectomy. Three experiments were then performed.

In the 1st experiment, the effect of 3 kinds of 5-HT receptor agonist on lordosis behavior was investigated. Six days after the implantation of E_2, the first behavioral test was carried out. In the behavioral test, each animal was placed in a plastic observation cage (40×60×50 cm) with two vigorous male rats. The lordosis quotient (LQ; number of lordosis reflex / 10 mounts ×100) was recorded.

One hr after the 1st behavioral test, rats in which the LQ was over 70 in the 1st test were injected with 3 kinds of 5-HT receptor agonist and the 2nd behavioral test was performed. Eight rats in each group were injected with 1, 3, or 5 mg/kg bw buspirone (buspirone hydrochloride; BUS; 1 mg/ml saline; Sigma) intraperitoneally. In 7 rats of each group, the animals were injected with 0.25, 0.5 or 1 mg/kg 8-hydroxy-2-(di-n-propylamino)tetralin ((±)8-OH-DPAT; Sigma), or 0.25, 0.5 or 1 mg/kg (R)-8-hydroxy-2-(di-n-propylamino)tetralin ((+)8-OH-DPAT; Sigma) intraperitoneally. Fifteen females were injected with 1 ml/kg saline as the control group. Thirty minutes after injection, the second behavioral test was started.

In the 2nd experiment, to examine the time-course change of LQs after injection of the agonists, 1 hr after the 1st behavioral test, female rats were injected with 3 mg/kg BUS (n=6), 1 mg /kg (±)8-OH-DPAT (n=5), 1 mg/kg (+)8-OH-DPAT (n=5) or 1 ml/kg saline (n=10) and behavioral tests were performed at 15, 30, 60, and 120 min after injection.

In the 3rd experiment, to check the effect of 5-HT receptor agonists on locomotor activity, E_2-treated ovariectomized rats were injected with 3 mg/kg BUS (n=5), 1 mg /kg (±)8-OH-DPAT (n=5), 1 mg/kg (+)8-OH-DPAT (n=6) or 1 ml/kg saline (n=10) and just after injection, measurement of spontaneous locomotor activity was started. The regime of treatments with estrogen and 5-HT agonists was the same as those in the 1st experiment. Spontaneous locomotor activity was measured continuously for 3 hr from 14:00 by

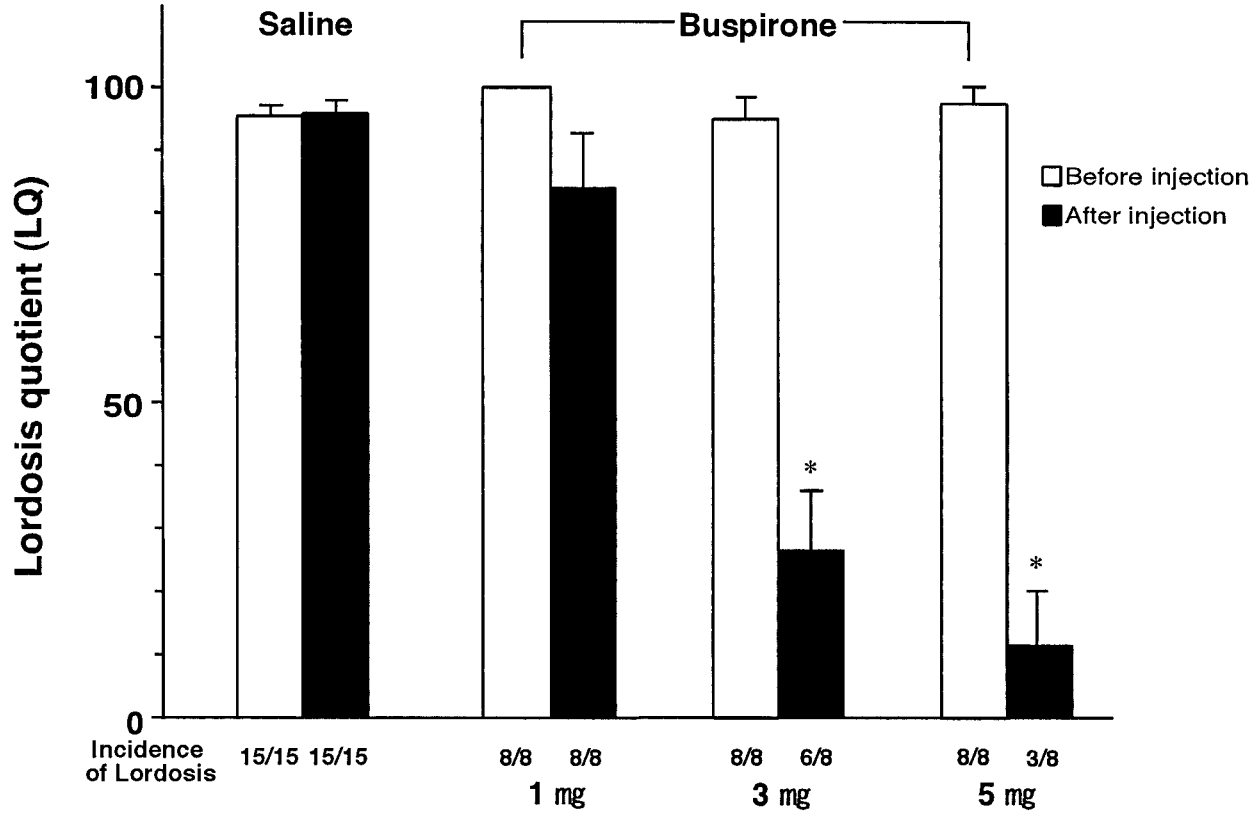

Fig. 1. The mean LQs±SEM and incidence of lordosis before and after injection with various doses of buspirone (1, 3, 5 mg/kg bw) in ovariectomized rats with subcutaneous implantation of a silicon tube containing estradiol-17β (E_2). *p<0.05 vs. before injection, p<0.001 vs. saline, p<0.01 vs. 1 mg group.

means of an infrared sensor system (SUPERMEX; Muromachi-Kikai, Tokyo, Japan). The measured locomotor activities were totaled every 15 min in each rat.

The differences in the mean LQ between before and after injection in each group were analyzed by Wilcoxon signed rank test. The differences in the mean LQ among groups were analyzed by the Kruskal-Wallis test and followed by the Mann-Whitney U-test. The differences in the mean LQ in the time-course test and locomotor activity among the groups were analyzed by analysis of variance (ANOVA) of repeated measures. The differences in the locomotor activities among the groups at each time were analyzed by t-test.

RESULTS

The mean LQs in the saline- and BUS-treated groups are shown in Fig. 1. In the saline-treated control group, the mean LQs were high both before and after injection. In the 1 mg/kg BUS-treated group, the mean LQ after injection was almost the same as that in the control group or before injection. In contrast, the mean LQs in the 3 and 5 mg BUS-treated groups were lower than those before injection (P<0.05) or in the control group and 1 mg group (P<0.0001) after injection.

The mean LQs in the (±) or (+)8-OH-DPAT-treated group are shown in Fig. 2. In both the (±) and (+)8-OH-DPAT-treated groups, after treatment at the doses of 0.5 or 1 mg/kg, the mean LQs were lower than those before injection (P<0.05). Furthermore, in the 0.25 mg/kg (+)8-OH-DPAT-treated group, the mean LQ was lower than that before injection (P<0.05). A comparison between the (±) and (+)8-OH-DPAT-treated groups revealed the absence of any significant differences in the mean LQ of each dose.

Time courses of the inhibition of the lordosis response by 5-HT_{1A} receptor agonists are shown in Fig. 3. High LQ was sustained after injection with saline during a period of 3 hr. In all the drug-treated groups, the mean LQs decreased to lower than 20 after 15 min, and low level of LQs continued for 1 hr. At 2 hr after injection, the mean LQs recovered to higher than 60. At each time, there was significant difference in the mean LQ between the control and drug-treated groups (P<0.0001).

Locomotor activity immediately after injection was high, but decreased soon thereafter and the level was sustained for 3 hr with small changes in the saline-treated control group (Fig. 4). In the 1 mg/kg (±)8-OH-DPAT-treated group, similar locomotor activity to that of the control was observed during a period of 3 hr. In contrast, (+)8-OH-DPAT-treated rats showed higher locomotor activity than that of the control during a 1-hr period, but then decreased to the same level of the control. In the BUS-treated group, the first 15-min locomotor activity was lower than those of other groups (P<0.001 vs. saline, P<0.01 vs. (±)8-OH-DPAT, P<0.0001 vs. (+)8-OH-DPAT).

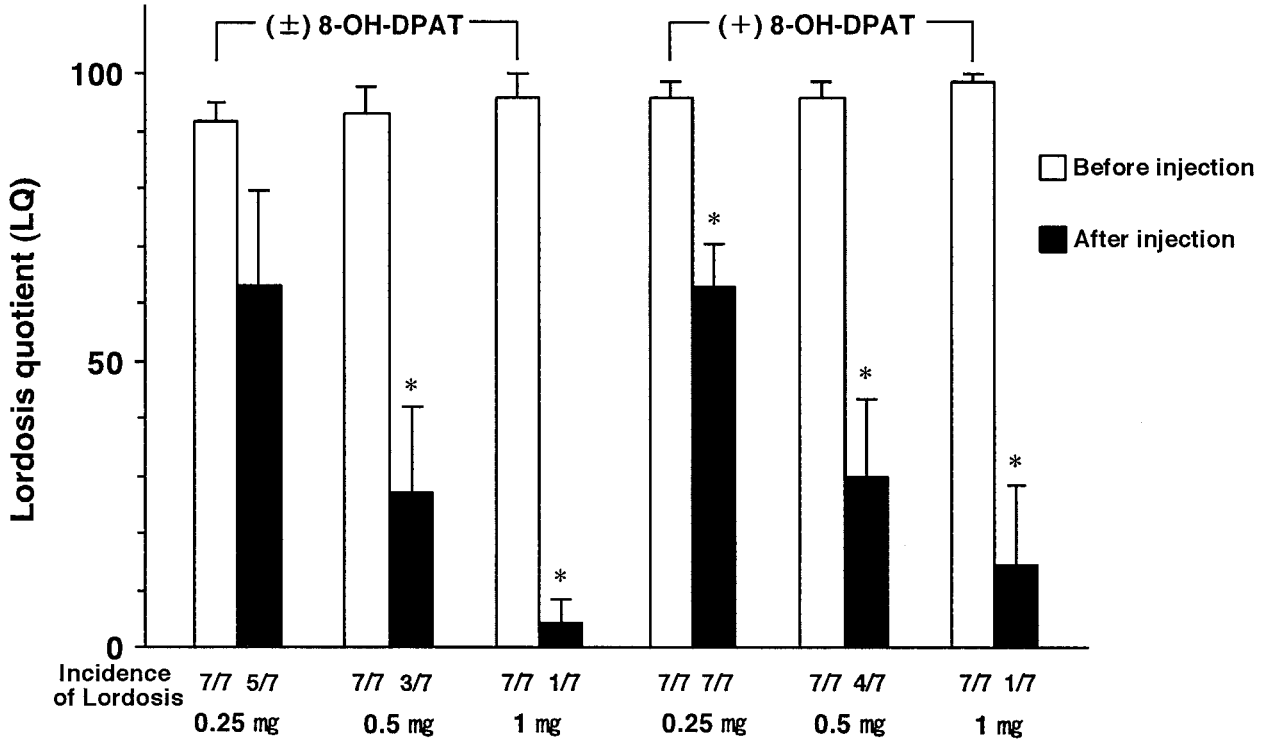

Fig. 2. The mean LQs±SEM and incidence of lordosis before and after injection with various doses (0.25, 0.5, 1 mg/kg bw) of (±)8-OH-DPAT or (+)8-OH-DPAT in ovariectomized rats with subcutaneous implantation of a silicon tube containing estradiol-17β (E_2). *p<0.05 vs. before injection.

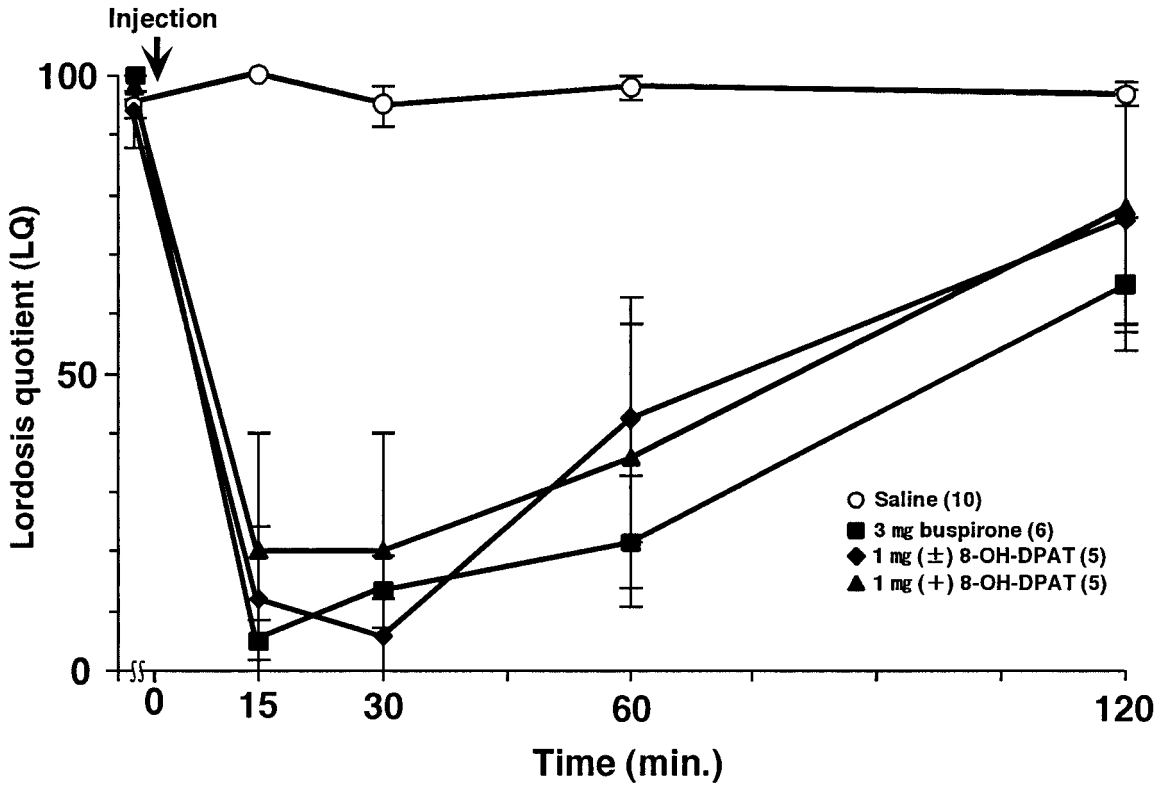

Fig. 3. Time course of the inhibition of the lordosis response after injection with 5-HT agonists in ovariectomized rats with subcutaneous implantation of a silicon tube containing estradiol-17β (E_2). The behavioral test was carried out at 15, 30, 60, and 120 min after injection.

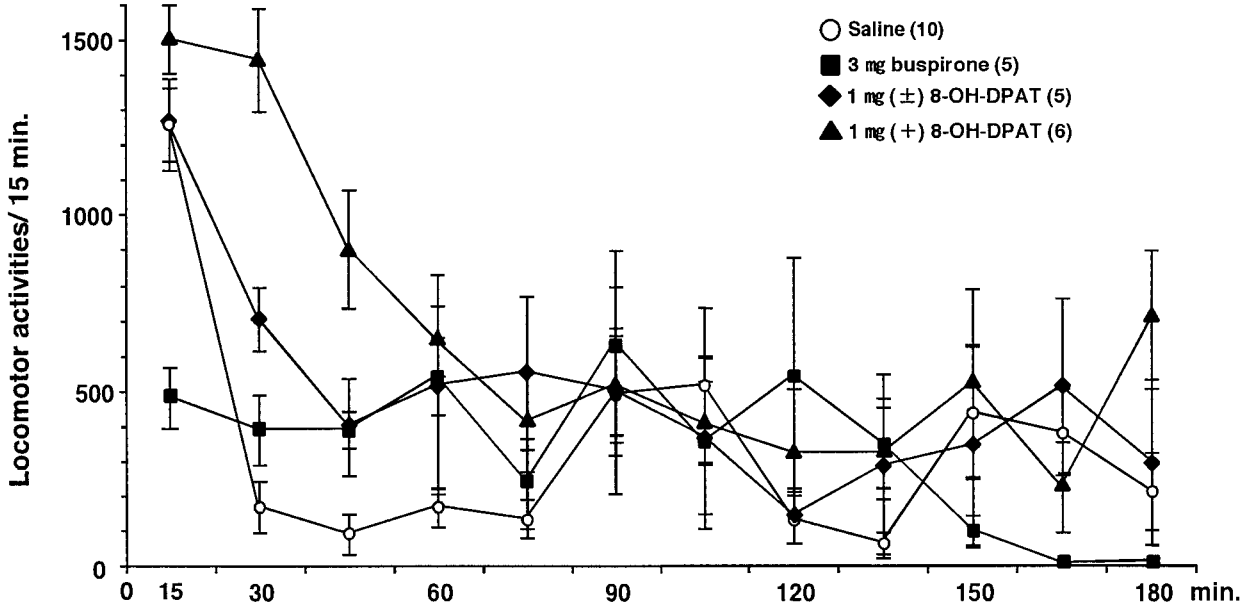

Fig. 4. Spontaneous locomotor activities after treatment with 3 mg/kg bw buspirone, 1 mg (±)8-OH-DPAT, 1 mg (+)8-OH-DPAT or saline in ovariectomized rats with subcutaneous implantation of a silicon tube containing estradiol-17β (E_2).

DISCUSSION

In the present experiment, the dose of 3 mg/kg bw, but not 1 mg/kg BUS inhibited lordosis behavior in female rats. On the other hand, in the (±)8-OH-DPAT-treated group, 0.5 mg/kg was sufficient to suppress lordosis. Furthermore,

(+)8-OH-DPAT was most effective, because the dose of 0.25 mg/kg inhibited lordosis behavior. These results are in agreement with the reports that 8-OH-DPAT has a strong influence on the inhibition of lordosis, compared with BUS (Smith and Peroutka, 1986; Uphouse *et al*., 1992).

BUS has been reported to act on 5-HT_{1A}, dopamine (DA) or noradrenaline (NA) receptors (Trulson and Henderson, 1984; Peroutka, 1985; Reader *et al*., 2000). It has been reported that DA receptors contribute to the stimulatory mechanism of lordosis behavior, because direct application of DA agonist into the brain was found to enhance lordosis (Foreman and Moss, 1978). The NA neuron is also involved in the lordosis facilitating mechanism (Crowley *et al*., 1978; Etgen, 1990). Therefore, stimulation of monoaminergic receptors other than 5-HT receptor may rather weaken the lordosis-inhibiting effect of BUS.

(±)8-OH-DPAT acts on 5-HT_{1A} receptor specifically in the brain (Uphouse *et al*., 1992; Uphouse and Caldarola-Pastuszka, 1993). Thus, (±)8-OH-DPAT and BUS are thought to act on 5-HT_{1A} receptors and inhibit lordosis behavior by binding to 5-HT_{1A} receptor in the female rat brain.

On the other hand, (+)8-OH-DPAT has been reported to act on 5-HT_{1A} and 5-HT_7 receptors (Cornfield *et al*., 1991; Barnes and Sharp, 1999). Some 5-HT receptors have been reported to play a facilitative role in regulating lordosis behavior, because lordosis is enhanced by treatment with a 5-$HT_{2A/2C}$ receptor agonist (Wolf *et al*., 1998; Wolf *et al*., 1999) and is suppressed by a 5-$HT_{2A/2C}$ antagonist (Wolf *et al*., 1998; Wolf *et al*., 1999) or a 5-HT_3 receptor antagonist (Maswood *et al*., 1997; Maswood *et al*., 1998). If 5-HT_7 receptor is involved in the lordosis-facilitating mechanisms of the serotonergic neuron, lordosis is expected to increase by treatment with (+)8-OH-DPAT. In the present experiment, rather, (+)8-OH-DPAT was more effective in suppressing lordosis than was (±)8-OH-DPAT. This suggests that similar to 5-HT_{1A} receptor, 5-HT_7 receptor is concerned with the lordosis-inhibiting system. However, there was no statistical difference in the mean LQ between the (+)8-OH-DPAT group and the (±)8-OH-DPAT group in all tests. Further experiments using a more selective 5-HT_7 receptor agonist than (+)8-OH-DPAT or direct application of the drug to the candidate portion in the brain are necessary.

In all of the drug-treated groups, LQs decreased 15 min after injection and the low level of LQs continued for 1 hr. LQs recovered to some extent after 2 hr. These results are in agreement with the report that a decreased LQ in female rats injected with BUS or 8-OH-DPAT into the VMH recovered in about 2 hr (Uphouse *et al*., 1992). Yu and Lewander (1997) reported that 15 min after subcutaneous injection of (+)8-OH-DPAT, this agonist had been found in the brain. This supports our finding of an acute inhibitory effect of these drugs on lordosis. There were no differences in the locomotor activities among the groups with some exceptions in the early period after injection in the (+)8-OH-DPAT and BUS groups. However, because the lordosis inhibiting effect was observed in all groups regardless of the locomotor condition, the effects of these agonists are thought to act on the lordosis inhibiting system without affecting the regulatory center of locomotion and decreased lordosis.

Direct hypothalamic application of 5-HT_{1A} receptor agonist has been reported to suppress lordosis in female rats (Uphouse *et al*., 1992). In the DRN, axons of serotonergic neurons, which exert a lordosis-inhibiting influence (Kakeyama and Yamanouchi, 1992), extended to the hypothalamus, the POA and the VMH (Parent *et al*., 1981; Törk, 1985). After a lesion formed in the DRN, the contents of serotonin in the POA and the VMH decreased in female and male rats (Kakeyama *et al*., 2002). In the POA and the VMH, the amount of serotonin decreased when female rats exhibited lordosis behavior (Luine, 1993; Gonzalez *et al*., 1997). 5-HT_{1A} receptors exist in the POA and the VMH (Gonzalez *et al*., 1997). From these results, the lordosis modulating functions of the POA and the VMH received an inhibiting influence from the DRN serotonergic neurons through the 5-HT_{1A} receptor system.

5-HT_{1A} receptor function is influenced by estrogen (Jackson and Uphouse, 1998). On the other hand, estrogen does not seem to have a direct effect on the lordosis regulating function in the DRN, because direct application of the crystal estrogen into the DRN did not facilitate lordosis in subthreshold doses of estrogen-treated ovariectomized rats (Satou and Yamanouchi, 1999**)**. Furthermore, it has been reported that the number of serotonin-immunopositive cells in the DRN is not influenced by estrogen (Lu *et al*., 2001). These reports suggest that regulation of 5-HT_{1A} receptors by estrogen may be via neurons other than the serotonergic neurons of the DRN. Further experiments are needed to clarify the relationship between 5-HT_{1A} receptor-modulation and sex steroid hormone.

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