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Additive inhibition of lordosis by simultaneous treatments with $GABA_A$ and $GABA_B$ receptor agonists, muscimol and baclofen, in female rats

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ABSTRACT

In order to investigate the relationship between $GABA_A$ and $GABA_B$ receptors in the induction of lordosis behavior, agonists of these receptor subtypes were injected simultaneously to estrogen-treated ovariectomized rats and lordosis behavior was observed before and after the injections. The $GABA_A$ receptor agonist, muscimol (MUS), at a dose in the range from 1.0 to 1.4 mg/kg body weight (bw) or the $GABA_B$ receptor agonist, baclofen (BAC) at a dose in the range from 1 to 10 mg/kg bw, was injected intraperitoneally. The lordosis quotient (LQ) decreased after treatments with MUS or BAC and a dose-dependent decrease of LQ was observed in MUS or BAC-treated rats. When 1.2 mg/kg bw MUS and 5 mg/kg bw BAC were injected simultaneously, the mean LQ decreased strongly and was significantly lower than the values obtained after single injections of the agonists at these doses ($P<0.05$). In addition, to ascertain the time-course of changes, a behavioral test was carried out 7 times from 15 to 180 min after the injection of agonists. The low LQ in the rats injected with both MUS and BAC continued longer than in rats given single injections. These results indicate that both $GABA_A$ and $GABA_B$ receptors are involved in lordosis-inhibiting mechanisms by the GABA neuron and operate independently.

1. Introduction

Female typical sexual behavior, lordosis, is dependent on the blood levels of estrogen. Estrogen acts on the lordosis-facilitative system in the ventromedial hypothalamic nucleus (Pfaff et al., 2006) and inhibiting system in the lateral septum (Yamanouchi, 1997) in the induction of lordosis. These facilitatory and inhibitory influences in the forebrain regulate the governing center for lordosis in the midbrain central gray (Sakuma and Pfaff, 1979; Tsukahara and Yamanouchi, 2001).

Many kinds of neurotransmitters are thought to be involved in the lordosis-regulating neural system. In the induction of lordosis behavior, monoamines, such as dopamine and serotonin play both inhibitory and facilitative roles. It have been reported that direct infusions of dopamine antagonist into the brain inhibited lordosis (Foreman and Moss, 1979) conversely, chemical depletion of caudate dopamine with 6-hydoroxydopamine facilitated lordosis (Caggiula et al., 1979). This discrepancy can be speculated to be caused by opposite role of dopamine in different regions of the brain. In the role of serotonin in regulating lordosis, different serotonin receptors have opposing effect, because lordosis was suppressed by injections of 5-HT_{1A} receptor agonist (Uphouse et al. 1996; Kishitake and Yamanouchi, 2003), but facilitated by injection with a 5-HT_3 receptor agonist (Maswood et al., 1997).

GABAergic neurons are thought to play an important inhibitory role in the regulation of lordosis, because direct application of GABA into the brain was found to suppress lordosis behavior (Mascó et al., 1986). This amino-acid neuron operates through 2 types of receptor: $GABA_A$ and $GABA_B$ (Matsumoto, 1989). The $GABA_A$ and $GABA_B$ receptors in the brain are distinct in the signal transduction systems (Kuriyama et al., 1993). Both receptors exist widely in the central nervous system and their distributions have been reported to overlap in the brain (Tohyama and Takatsuji, 1998). However, there is a quantitative regional difference in the amounts of $GABA_A$ and $GABA_B$ receptors (Bowery et al., 1987).

The $GABA_B$ receptor is known to be involved in lordosis inhibition by GABAergic neurons, because systemic injections (Ågmo et al., 1989; Luine et al., 1991; Kakeyama and Yamanouchi, 1996) with an agonist, baclofen were found to inhibit lordosis behavior. On the other hand, systemic injections with the $GABA_A$ receptor agonist, 4,5,6,7, -tetrahydroisoxazolo (5,4-c) pyrideine-3-ol (THIP), also suppressed lordosis behavior in female rats (Ågmo et al., 1989). On the other hand, in the experiments using another $GABA_A$ receptor agonist, muscimol

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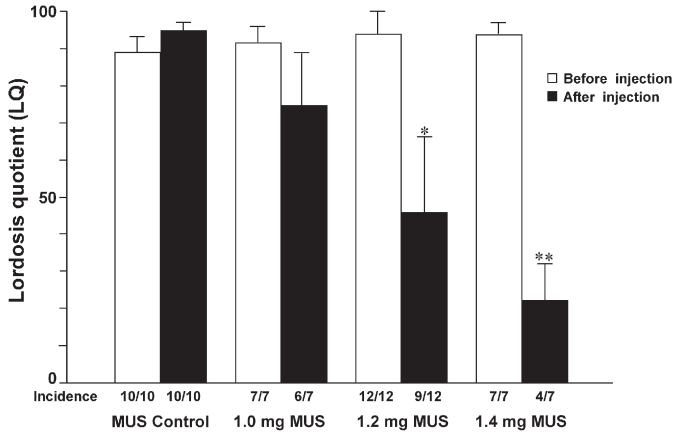

Fig. 1. The mean LQs±S.E. and incidence of lordosis before and after injection with 1.0, 1.2, 1.4 mg/kg bw muscimol (MUS) or placebo (control) in estrogen-treated ovariectomized rats. *$P<0.05$ vs before injection and control. **$P<0.05$ vs before injection, control and 1.0 mg MUS group.

by the direct infusion technique in the brain, lordosis inhibition and facilitation have been reported depending on the injected sites (McCarthy et al., 1991a).

However, the relationships between the role of $GABA_A$ and $GABA_B$ receptors in the neural system for expression of lordosis behavior has not yet been analyzed. For that purpose, different doses of muscimol or baclofen were injected intraperitoneally and a lordosis behavior test was carried out in estrogen-treated ovariectomized rats. Next, the effects of simultaneous injection with muscimol and baclofen on lordosis were observed.

2. Materials and methods

Adult female Wistar rats (215–320 g, Takasugi Animal Farm, Saitama) were kept under a controlled temperature (23–25 °C) and photoperiod (LD 14:10, light off at 1900 h). Food and water were accessed freely. All experiments were conducted according to the Regulations for Animal Experimentation at Waseda University (Permission No.06 J0009).

All rats were ovariectomized under ether anesthesia. One week after the surgery, all rats were implanted subcutaneously with a silicon tube (inner diameter, 1.57 mm; outer diameter, 3.18 mm; length, 30 mm; Kaneka Medix Co., Osaka) containing estradiol-17β (E_2; Sigma Chemical Co., St. Louis, MO, USA) to induce the estrous state.

Behavioral tests were performed 2, 4 and 6 days after implantation of E_2. On day 6, after the behavioral test, the $GABA_A$ agonist, muscimol, the $GABA_B$ agonist, baclofen, or both agonists were injected intraperitoneally and behavioral tests were carried out again.

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.

In the 1st experiment, at day 6 after E_2 implantation, immediately after the behavioral observation, the animals were injected with muscimol and/or baclofen and a behavioral test was carried out again 30 min after the injection. In order to determine the degree of lordosis-inhibiting effect of muscimol administered by intraperitoneal injection, in 1.0, 1.2 or 1.4 mg/kg muscimol (MUS, 5-(Aminomethyl)-3-isoxazolol), BIOMOL, USA, 2.5, 3 or 3.5 mg/ml saline, respectively) was injected in 7, 12 or 7 rats, respectively. As the control (MUS-control group), 0.4 ml/kg saline was injected in 10 rats. One, 5 or 10 mg/kg bw (±) baclofen (BAC, SIGMA, USA 2.5, 12.5 or 25 mg/1 ml 0.2 NHCl) or 0.4 ml/kg 0.2 NHCL (BAC-control group) was injected intraperitoneally in 9, 10, 5 or 5 rats, respectively. In the MUS+BAC group, both 1.2 mg/kg MUS and 5 mg/kg BAC were injected in 12 rats. As the control for MUS+BAC, 5 rats received placebo of MUS or of BAC.

In the 2nd experiment, to examine the time-course of changes after injection with MUS and/or BAC, at 6 days after E_2 implantation, after conducting the behavioral test, 1.2 mg/kg MUS (7 rats) or 5 mg/kg BAC (4 rats) or both 1.2 mg/kg MUS and 5 mg/kg BAC (8 rats) were injected intraperitoneally and the behavioral test was performed again at 15, 30, 45, 60, 90, 120 min after the injection. As control group, 7 rats were injected with placebo.

Statistical difference of the mean LQs between before and after injection with drugs in each group was analyzed by Wilcoxon signed rank test. The differences in the mean LQs after injection with drugs among the groups were analyzed by the Kruskal–Wallis test followed by the Mann–Whitney *U*-test. In the time-course experiment, difference (treatment and time) was analyzed by two-way ANOVA with repeated measures. Statistical difference of the mean LQs between two groups on each time was determined by two-way ANOVA with repeated measures followed by the Bonferroni test. The level of $P<0.05$ was considered to be statistically significant. To examine additive or synergistic effects, the two-way ANOVA test was used.

3. Results

Mean LQs both before and after saline-injection in the MUS-control group were high (Fig. 1). Among the mean LQs after injections with several doses of MUS, there was a statistical difference found by the Kruskal–Wallis test ($P<0.05$). When 1.0 mg/kg bw MUS was injected, the mean LQ decreased slightly, but there was no statistical difference between the values before and after the injections. In the 1.2 mg MUS group, the mean LQ decreased to 50.8±10.1 and was lower than that before injection ($P<0.05$) and in the control group ($P<0.05$). After treatment with 1.4 mg/kg bw MUS, a further decrease was seen and the mean LQ was lower than that before treatment ($P<0.05$) and the values in the control and 1.0 mg MUS groups ($P<0.05$).

Among the mean LQs after injections with several doses of BAC, there was a statistical difference found by the Kruskal–Wallis test ($P<0.001$) (Fig. 2). In 1, 5 or 10 mg/kg BAC groups the mean LQs decreased and were lower than the values before injection ($P<0.05$) and in the BAC-control group ($P<0.05$). When the mean LQs were compared, there were significant differences in the BAC-treated groups ($P<0.05$).

After simultaneous injections with 1.2 mg MUS and 5 mg BAC, the mean LQ decreased severely to 15.8±3.5 and was also lower than in the MUS+BAC BAC-control group ($P<0.05$) (Fig. 3). This value was

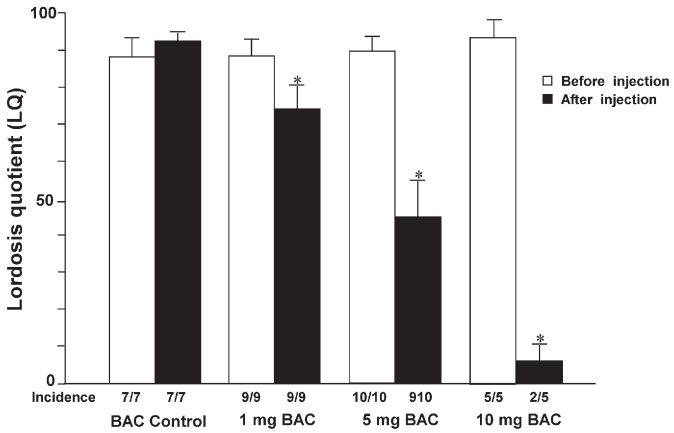

Fig. 2. The mean LQs±S.E. and incidence of lordosis before and after injection with 1, 5, 10 mg/kg bw baclofen (BAC) or placebo (control) in estrogen-treated ovariectomized rats. *$P<0.05$ vs before injection and control group. $P<0.05$ each other in BAC groups.

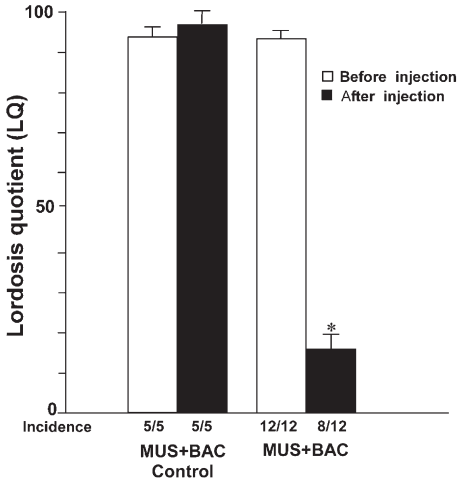

Fig. 3. The mean LQs ± S.E. and incidence of lordosis before and after injection with both 1.2 mg/kg bw muscimol and 5 mg/kg bw baclofen (MUS+BAC) or placebo (MUS+BAC control) in estrogen-treated ovariectomized rats. *$P<0.05$ vs before injection and control group.

lower than those in the 1.2 mg MUS (Fig. 1) or 5 mg BAC groups (Fig. 2) ($P<0.05$). Furthermore, the two-way ANOVA analysis for interactions among MUS, BAC and MUS+BAC showed no significant difference ($P=0.324$). This indicates that the effect of simultaneous injections with MUS and BAC is additive but not synergistic.

Changes in the mean LQ in the time-course experiment can be seen in Fig. 4. Two-way ANOVA analysis with repeated measures showed that treatments with the drugs produced significant differences in the mean LQs (F 3,23 = 14.98, $P<0.001$) and change in times after injections also produced significant changes in the mean LQs (F 7, 161 = 45.795, $P<0.01$). Significant effects of treatments–time interactions were found (F (21,161) = 10.483, $P<0.01$). Control rats showed high LQs throughout the tests. In the 1.2 mg/kg MUS group, the mean LQs were significantly lower than those in the control group from 30 to 45 min after injection ($P<0.05$, Bonferroni test). In the 5 mg/kg bw BAC group, statistical differences of mean LQs were seen from 15 to 60 min ($P<0.05$). In the MUS+BAC group, low mean LQs were continued from 15 to 120 min when compared to those of the control group ($P<0.05$). At 120 min, mean LQ of the MUS+BAC group was lower than those in the 1.2 mg MUS and the 5 mg BAC groups ($P<0.05$).

4. Discussion

In the present experiment, intraperitoneal injection with muscimol inhibited lordosis behavior in estrogen-treated ovariectomized rats. A dose of more than 1.2 mg/kg bw of muscimol was necessary to inhibit lordosis by systemic injection. Inhibitory effects on lordosis of muscimol administered by intraperitoneal injection were dose-dependent for doses from 1.0 to 1.4 mg/kg bw, as well as an inhibitory effect of another $GABA_A$ agonist, THIP (Ågmo et al., 1989).

The result of the present study of baclofen also inhibiting lordosis was in agreement with the results cited in many reports (Ågmo et al., 1989; Luine et al., 1991; Kakeyama and Yamanouchi, 1996; Kishitake and Yamanouchi, 2005). The report of Ågmo et al. (1989) of the dose-dependent effect of peritoneal injection of baclofen at doses from 1 to 10 mg/kg bw was almost the same as the present results. Thus, both $GABA_A$ and $GABA_B$ receptors play an inhibitory role in the expression of lordosis behavior.

Simultaneous treatment with 1.2 mg/kg bw muscimol and 5 mg/kg bw baclofen suppressed lordosis more strongly than a single injection of each drug. The time-course experiment showed that inhibition of lordosis by simultaneous injections with muscimol and baclofen continued longer than inhibition after a single injection with muscimol or baclofen. These findings suggest that the inhibitory effects of muscimol and baclofen on lordosis occurred additively, although the possibility that it was due to pharmacokinetic actions cannot be excluded.

Since muscimol (Chan-Palay et al., 1978) and baclofen (van Bree et al., 1991) have been reported to pass through the blood-brain barrier, the GABAergic neuron-$GABA_A$ receptor and -$GABA_B$ receptor systems may operate in an independent manner in the inhibition of lordosis in the brain.

$GABA_A$ receptors are ionotropic receptors gating chloride ion channels (Barnard et al., 1987). $GABA_B$ receptors belong to the family of metabotropic G-protein-coupled receptors (Bowery et al., 2002). These indicate a possible functional difference in the $GABA_A$ and $GABA_B$ receptors in neurons. There have been few reports of colocalization of $GABA_A$ and $GABA_B$ receptors in a neuron. In the human basal ganglia, it has been shown that the $GABA_A\alpha1$ and $GAGA_BR1$ subunits are colocalized (Waldvogel et al., 2004). The role of the basal ganglia in the regulation of lordosis in the rat has not been reported. There is no evidence of the functional independency of $GABA_A$ and $GABA_B$ receptors in a neuron.

Functional independency of the $GABA_A$ and $GABA_B$ receptors in this result may be rather an event within an intranuclear circuit of a nucleus involved in lordosis regulation, because, many nuclei have neurons containing $GABA_A$, moreover, neurons containing $GABA_B$ receptors in the brain (Tohyama and Takatsuji, 1998) and the GABA neuron are known to possess short axons in a nucleus (Ottersen et al., 1995).

Another possibility is that different nuclei containing $GABA_A$ or $GABA_B$ operate independently in the neural circuit for the induction of the lordosis. $GABA_A$ (Pirker et al., 2000) and $GABA_B$ (Bowery et al., 1987) receptors have been reported to exist widely (Tohyama and Takatsuji, 1998) in the neural substrates that are involved in lordosis regulation.

The rostral midbrain central gray (MCG) is known as the most important integration center for lordosis (Pfaff et al., 2006). Microinjection of the $GABA_A$ antagonist, bicuculline or the agonist, muscimol, into the MCG decreased or facilitated lordosis in rats (McCarthy et al., 1991a,b). In contrast, direct infusion of muscimol into the caudal part of the MCG suppressed lordosis behavior (Salzberg et al., 2002). Thus, the GABAergic system including the $GABA_A$ receptor plays a biphasic role in the MCG, although experiments including the present result showed that stimulation of the $GABA_A$ receptor in the whole brain resulted in the inhibition of lordosis expression.

Facilitative and inhibitory roles of GABA receptors have been reported in other areas. Direct injection of muscimol into the preoptic

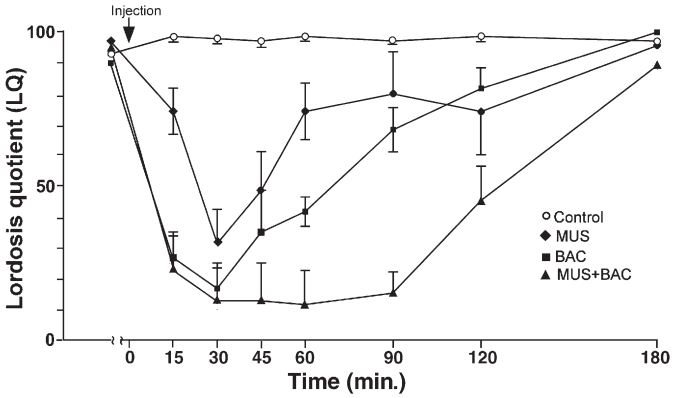

Fig. 4. Time-course of inhibition of the lordosis response by injection with placebo, 1.2 mg muscimol (MUS) and/or 5 mg baclofen (BAC) in estrogen-treated ovariectomized rats.

area (POA) resulted in inhibition of lordosis, whereas injection into the ventromedial hypothalamus caused lordosis facilitation (McCarthy et al., 1990). Furthermore, GABA levels in the hypothalamus were higher in receptive females than that in postreceptive rats, but the GABA level in the POA was lower in receptive females than that in postreceptive rats (McCarthy et al., 1991b).

In the ventromedial hypothalamic nucleus (VMN), different results from those of McCarthy et al., described above have been reported. Direct application of muscimol into the VMN or the vicinity of the VMN is effective in inhibiting lordosis (Qureshi et al., 1988; Hoffman et al., 2002; Guptarak et al., 2004). Because the VMN exerts a lordosis-facilitative influence (Pfaff et al., 2006), these findings suggest the possibility that the GABA neurons in the VMN also play a biphasic role in lordosis facilitation.

The lateral septum exerts a strong inhibitory influence on lordosis behavior (Yamanouchi, 1997). Baclofen was effective in inhibiting lordosis in female rats even after dysfunction of the lateral septum (Kakeyama and Yamanouchi, 1996). Although both receptors have been reported to exist in this area, the $GABA_B$ receptor can be excluded from the lordosis-inhibitory system in the septum.

In the function of the $GABA_B$ receptor, the dorsal raphe nucleus that has an inhibitory role in lordosis regulation (Kakeyama and Yamanouchi, 1992) may be the site of baclofen action, because lesions of this nucleus prevented the inhibitory effect of baclofen on lordosis (Kakeyama and Yamanouchi, 1996).

These results suggest that muscimol and baclofen act on each subtype of GABA receptor in different parts of the medial basal hypothalamus or midbrain and induce an additive inhibitory effect on lordosis by simultaneous injections.

Induction of lordosis is a prerequisite for the action of estrogen in the forebrain areas such as VMN (Baefield and Chen, 1977) and the lateral septum (Satou and Yamanouchi, 1999). GABA neurons possess estrogen receptors (Herbison, 1994). It has been reported that the injection of estrogen decreases action of the $GABA_B$ receptor in the hypothalamus (Lagrange et al., 1996). Estrogen and progesterone influence the function of GABAergic neurons (McCarthy, 1995). Long-term exposure to estrogen changes the GABA receptor biochemically and functionally (Hamon et al., 1983). Thus, further studies are needed to clarify the relationships between the subtypes of GABA and steroid receptors in regulating lordosis behavior.

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