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Differential effects of (*R*)- and (*S*)-8-hydroxy-2-(di-*n*-propylamino)tetralin on the monosynaptic spinal reflex in rats

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Abstract

We examined the effects of (*R*)- and (*S*)-8-hydroxy-2-(di-*n*-propylamino)tetralin hydrobromide (8-OH-DPAT) on the monosynaptic spinal reflex in rats. In intact rats, (*R*)-8-OH-DPAT (10 μg/kg, i.v.) enhanced the amplitude of the monosynaptic reflex, whereas at 100 μg/kg, it reduced the amplitude. (*S*)-8-OH-DPAT enhanced the monosynaptic reflex dose-dependently. In spinalized rats, (*R*)-8-OH-DPAT produced dose-dependent inhibition, but the (*S*)-enantiomer did not affect the monosynaptic reflex. Pretreatment with spiroxatrine or 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)butyl]-piperazine (NAN-190) inhibited (*R*)-8-OH-DPAT-induced monosynaptic reflex enhancement in intact rats, as did 5-hydroxytryptamine (5-HT) depletion. Ketanserin reduced the effect of (*R*)-8-OH-DPAT. These pretreatment regimens had no effect on the monosynaptic reflex depression produced by the (*R*)-enantiomer in intact and spinalized rats. Pretreatment with prazosin inhibited (*S*)-8-OH-DPAT-induced monosynaptic reflex enhancement in intact rats, as did noradrenaline and 5-HT depletion. These results suggest that supraspinal 5-HT_{1A} receptors and the descending serotonergic system are involved in the stimulatory effect of (*R*)-8-OH-DPAT on the monosynaptic reflex, while both the descending serotonergic and noradrenergic systems, the latter acting via α_1-adrenoceptors, are involved in the effect of the (*S*)-enantiomer on this reflex.

Keywords: Spinal reflex; 8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin); Spinal cord

1. Introduction

Serotonergic neurons descend from the nucleus raphe pontis and nucleus raphe medullae oblongatae to the spinal ventral horn and terminate in the region of the somata and dendrites of motoneurons in the spinal cord (Willis, 1984; Björk et al., 1989; Marlier et al., 1991). Several workers have examined the various functional roles of 5-hydroxytryptamine (5-HT) in spinal motor systems. 5-HT receptor agonists have been shown both to increase and to decrease spinal motor transmission. Motoneurons possess somatodendritic 5-HT_2 (probably 5-HT_{2A}) receptors, which account for the increased excitability caused by many 5-HT-related ligands (Yamazaki et al., 1992; Elliott and Wallis, 1993). However, afferent input to motoneurons is depressed via 5-HT_{1A} (Clarke et al., 1997) and 5-HT_{1D} (Manuel et al., 1995) receptors.

8-Hydroxy-2-(di-*n*-propylamino)tetralin hydrobromide (8-OH-DPAT) has been used as a selective ligand to study the function of 5-HT_{1A} receptors. In a previous study, we found that 8-OH-DPAT significantly enhanced the amplitude of the monosynaptic reflex in intact rats, whereas in spinalized rats, it reduced the amplitude of this reflex in a dose-dependent manner (Hasegawa and Ono, 1996). Receptor binding (Björk et al., 1989) and forskolin-stimulated adenyl cyclase (Cornfield et al., 1991) assays and in vivo microiontophoresis (Hadrava et al., 1996) have revealed that the (*R*)- and (*S*)-enantiomers of 8-OH-DPAT have different effects and different affinities for 5-HT_{1A} receptors. These enantiomers also showed different profiles in a behavioral study (Cao and Rodgers, 1996). In the light of these observations, the different effects of 8-OH-DPAT in

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intact and spinalized animals may have resulted from the use of a racemic mixture. In this study, the supraspinal/spinal effects of (*R*)- and (*S*)-8-OH-DPAT were examined and the 5-HT receptor subtypes and descending systems involved in their effects were studied.

2. Materials and methods

2.1. Measurement of monosynaptic reflexes

Male Wistar rats (8–9 weeks old) were anesthetized with α-chloralose (25 mg/kg, intraperitoneally [i.p.]) and urethane (1000 mg/kg, i.p.) and cannulae were inserted into the trachea to maintain respiration and into the femoral vein for drug administration. To produce spinalized rats, the vagus nerves were cut bilaterally in the cervical region to eliminate parasympathomimetic effects on the heart, and the spinal cord was transected at the C1 level under lidocaine anesthesia (4%, 50 μl). A dorsal laminectomy was performed in the lumbo-sacral region of each rat, in which both the ventral and dorsal roots below L4 were cut just distal to their points of exit from the vertebral column. The entire exposed surgical area was covered with liquid paraffin and kept at 36 ± 0.5°C by radiant heat. Bipolar Ag–AgCl wire electrodes were then used for stimulation and recording. An L5 dorsal root was stimulated with 0.2 Hz rectangular pulses, 0.05 ms in duration, at a supramaximal voltage approximately twice that required to evoke a maximal reflex response. Monosynaptic reflex potentials were recorded from the ipsilateral L5 ventral root and displayed on an oscilloscope. Eight consecutive responses were averaged by an averager.

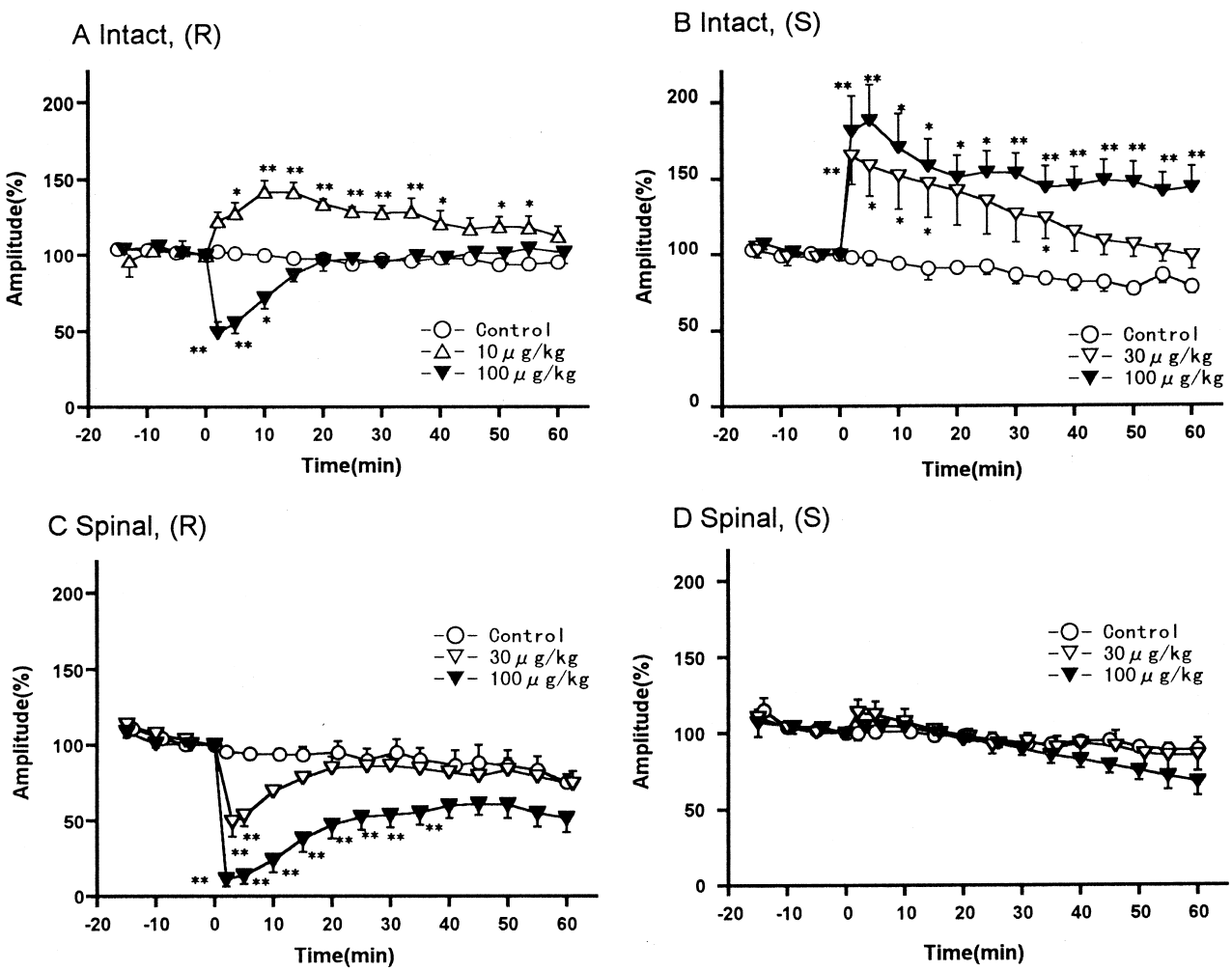

Fig. 1. Effects of (*R*)- and (*S*)-8-OH-DPAT HBr on the amplitude of the monosynaptic reflex in intact (A,B) and spinalized (C,D) rats. Each point represents the mean ± S.E.M. of four to six rats per group. Ordinates: mean monosynaptic reflex amplitudes expressed as percentages of the corresponding values at time 0. Abscissae: time in minutes after the injection of (*R*)- or (*S*)-8-OH-DPAT HBr. The significance of the differences between the test and control values was determined by one-way analysis of variance (ANOVA) followed by Bonferroni's multiple *t*-test (two-tailed); $^{*}P < 0.05$ and $^{**}P < 0.01$.

2.2. Neurotoxic lesions

Serotonergic neurons were lesioned by an intracisternal (i.c.) injection of 20 μl 5,6-dihydroxytryptamine creatinine sulfate (75 μg/animal) dissolved in 0.9% w/v physiological saline containing 100 μg/ml ascorbic acid. Control animals received 0.9% w/v physiological saline containing ascorbic acid. The animals were used in the experiments two weeks after 5,6-dihydroxytryptamine administration. Depletion of noradrenaline was prevented by administering desipramine hydrochloride (25 mg/kg, i.p.) dissolved in distilled water 1 h before 5,6-dihydroxytryptamine administration. Depletion of noradrenaline was achieved by administering 6-hydroxydopamine hydrobromide (36.7 μg/animal, i.c.) dissolved in 0.9% w/v physiological saline containing 100 μg/ml ascorbic acid. Control animals received 0.9% w/v physiological saline containing ascorbic acid. Two weeks after inducing the neurotoxic lesion, the noradrenaline and 5-HT contents of the spinal cords were measured by high-performance liquid chromatography with electrochemical detection.

2.3. Drugs

(*R*)- and (*S*)-8-OH-DPAT hydrobromide, 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)butyl]-piperazine (NAN-190) hydrobromide, spiroxatrine and ketanserin tartrate were obtained from Research Biochemicals International (Naick, MA, USA). Prazosin hydrochloride, 5,6-dihydroxytryptamine creatinine sulfate, 6-hydroxydopamine hydrobromide and desipramine hydrochloride were obtained from Sigma (St. Louis, MO, USA). Urethane and α-chloralose were obtained from Aldrich Chemical (Milwaukee, WI, USA) and Tokyo Kasei (Tokyo, Japan), respectively, and were both dissolved in distilled water. All the test compounds, except ketanserin tartrate and prazosin hydrochloride, which were dissolved in distilled

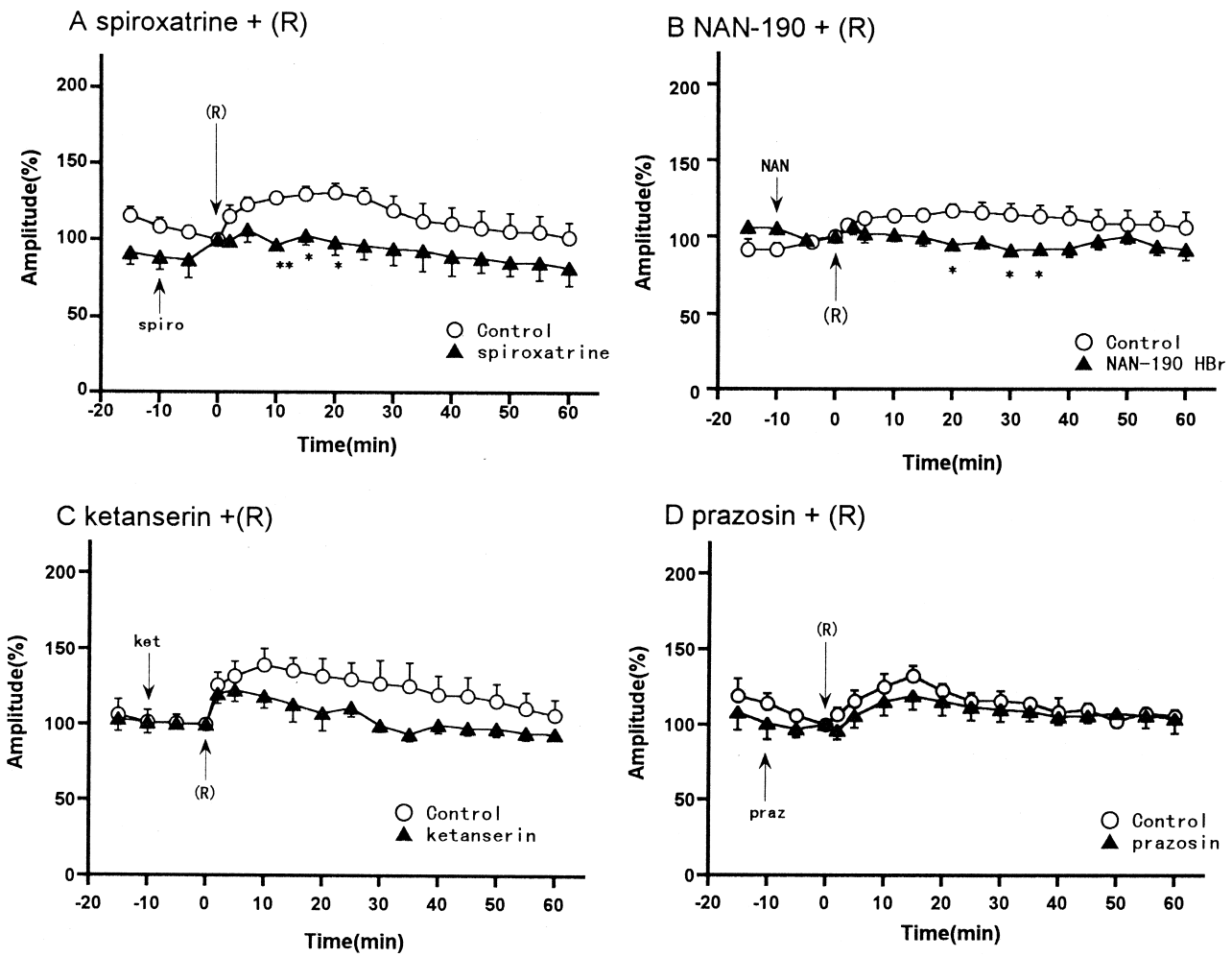

Fig. 2. Influence of pretreatment with spiroxatrine (10 μg/kg, i.v., A), NAN-190 HBr (3 μg/kg, i.v., B), ketanserin tartrate (1 mg/kg, i.v., C) or prazosin HCl (500 μg/kg, i.v., D) on the effect of (*R*)-8-OH-DPAT HBr (10 μg/kg, i.v.) on the monosynaptic reflex in intact rats. Each point represents the mean ± S.E.M. of four to five rats per group. Ordinates: mean monosynaptic reflex amplitudes expressed as percentages of the corresponding values at time 0. Abscissae: time in minutes after the injection of (*R*)-8-OH-DPAT HBr. The significance of the differences between the test and control values was determined by Student's *t*-test (two-tailed); $^{*}P < 0.05$ and $^{**}P < 0.01$.

water, were dissolved in 0.9% w/v physiological saline and 1 ml/kg was administered i.v. Each antagonist was administered 10 min before injection of the required agonist. The dose of each drug used in these experiments is expressed as the weight of the salt. Control rats received 1 ml/kg vehicle. Drugs were administered to the spinalized rats at least 2 h after spinalization.

2.4. Statistical analysis

The monosynaptic reflex amplitudes recorded after drug administration were calculated as percentages of the corresponding predrug (time 0) amplitudes. All data are expressed as means ± S.E.M. Student's *t*-test was used to compare data between two groups, while one-way analysis of variance (ANOVA) followed by Bonferroni's multiple *t*-test was used for multiple comparisons of the control and treated groups. Differences at $P < 0.05$ (two-tailed) were considered significant.

3. Results

3.1. Effects of (R)- and (S)-8-OH-DPAT in intact rats

In intact rats, (*R*)-8-OH-DPAT at a dose of 10 μg/kg significantly enhanced the amplitude of the monosynaptic reflex to 142.0 ± 7.4% ($n = 4$, Fig. 1A), but at 30 μg/kg, it evoked no change (not illustrated), and at 100 μg/kg, it reduced the amplitude significantly to 49.3 ± 6.9% ($n = 4$, Fig. 1A). Enhancement of the monosynaptic reflex in intact rats by the (*R*)-enantiomer peaked 10–15 min after administration, while inhibition peaked after 2 min and the amplitude returned to the control level within 20 min. (*S*)-8-OH-DPAT significantly enhanced the amplitude of the monosynaptic reflex in a dose-dependent manner, increasing the amplitude of the monosynaptic reflex to 165.0 ± 18.7% ($n = 5$) and 188.3 ± 23.1% ($n = 4$) at 30 and 100 μg/kg, respectively (Fig. 1B). Its effect peaked 2–5 min after administration.

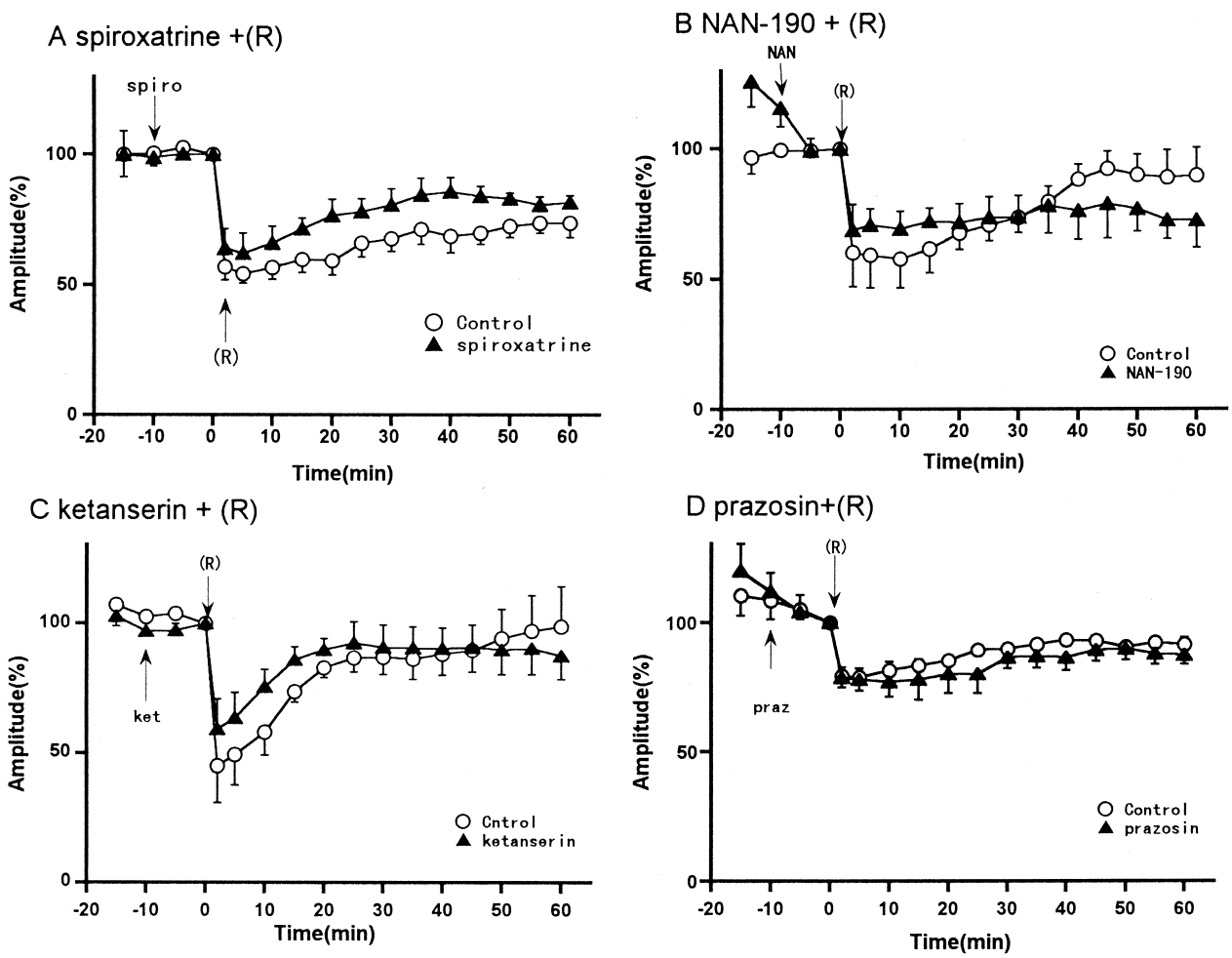

Fig. 3. Influence of pretreatment with spiroxatrine (10 μg/kg, i.v., A), NAN-190 HBr (3 μg/kg, i.v., B), ketanserin tartrate (500 μg/kg, i.v., C) or prazosin HCl (500 μg/kg, i.v., D) on the effect of (*R*)-8-OH-DPAT HBr (30 μg/kg, i.v.) on the monosynaptic reflex in spinalized rats. Each point represents the mean ± S.E.M. of four rats per group. Ordinates: mean monosynaptic reflex amplitudes expressed as percentages of the corresponding values at time 0. Abscissae: time in minutes after the injection of (*R*)-8-OH-DPAT HBr. The significance of the differences between the test and control values was determined by Student's *t*-test (two-tailed).

3.2. Effects of (R)- and (S)-8-OH-DPAT in spinalized rats

In spinalized rats, (*R*)-8-OH-DPAT at doses of 30 and 100 μg/kg significantly reduced the amplitude of the monosynaptic reflex to 49.0 ± 9.7% ($n = 4$) and 11.4 ± 4.9% ($n = 6$), respectively (Fig. 1C). This effect peaked 2 min after administration. The (*S*)-enantiomer did not affect the monosynaptic reflex (Fig. 1D).

3.3. Influences of 5-HT receptor and α_1-adrenoceptor antagonists on (R)-8-OH-DPAT-induced effects

Pretreatment with the 5-HT_{1A} receptor antagonists spiroxatrine (10 μg/kg, i.v.) or NAN-190 (3 μg/kg, i.v.) inhibited (*R*)-8-OH-DPAT (10 μg/kg, i.v.)-induced monosynaptic reflex enhancement in intact rats (Fig. 2A,B). Although the 5-HT_2 receptor antagonist ketanserin (1 mg/kg, i.v.) reduced (*R*)-8-OH-DPAT-induced monosynaptic reflex enhancement, complete antagonism was not observed (Fig. 2C). The α_1-adrenoceptor antagonist prazosin (500 μg/kg, i.v.) had no effect (Fig. 2D). In spinalized rats, these pretreatment regimens had little effect on the monosynaptic reflex depression produced by the (*R*)-enantiomer (30 μg/kg, i.v.) (Fig. 3A,B,C,D).

3.4. Influences of 5-HT receptor and α_1-adrenoceptor antagonists on (S)-8-OH-DPAT-induced effects

Pretreatment with prazosin (500 μg/kg, i.v.) inhibited (*S*)-8-OH-DPAT (30 μg/kg, i.v.)-induced monosynaptic reflex enhancement in intact rats (Fig. 4D), whereas the 5-HT_{1A} and 5-HT_2 receptor antagonists listed above had no effects (Fig. 4A,B,C).

3.5. Influence of serotonergic or noradrenergic denervation on (R)- and (S)-8-OH-DPAT-induced effects

The 5-HT content of the spinal cords of intact rats was reduced by 79.4% ($n = 5$) by 5,6-dihydroxytryptamine treatment, and this 5-HT depletion significantly inhibited

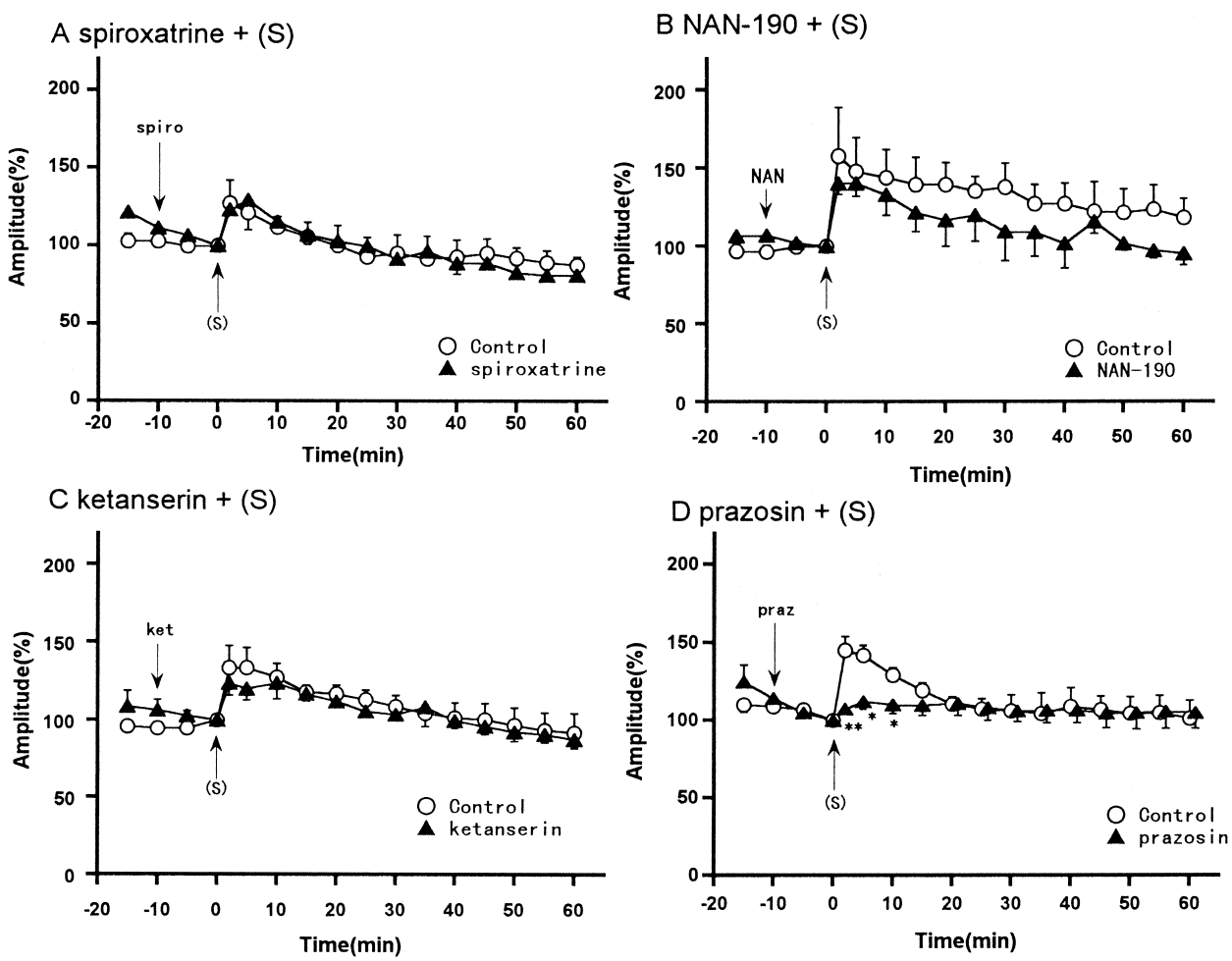

Fig. 4. Influence of pretreatment with spiroxatrine (10 μg/kg, i.v., A), NAN-190 HBr (3 μg/kg, i.v., B), ketanserin tartrate (1 mg/kg, i.v., C) or prazosin HCl (500 μg/kg, i.v., C) on the effect of (*S*)-8-OH-DPAT HBr (30 μg/kg, i.v.) on the monosynaptic reflex in intact rats. Each point represents the mean ± S.E.M. of four rats per group. Ordinates: mean monosynaptic reflex amplitudes expressed as percentages of the corresponding values at time 0. Abscissae: time in minutes after the injection of (*S*)-8-OH-DPAT HBr. The significance of the differences between the test and control values was determined by Student's *t*-test (two-tailed); $^*P < 0.05$ and $^{**}P < 0.01$.

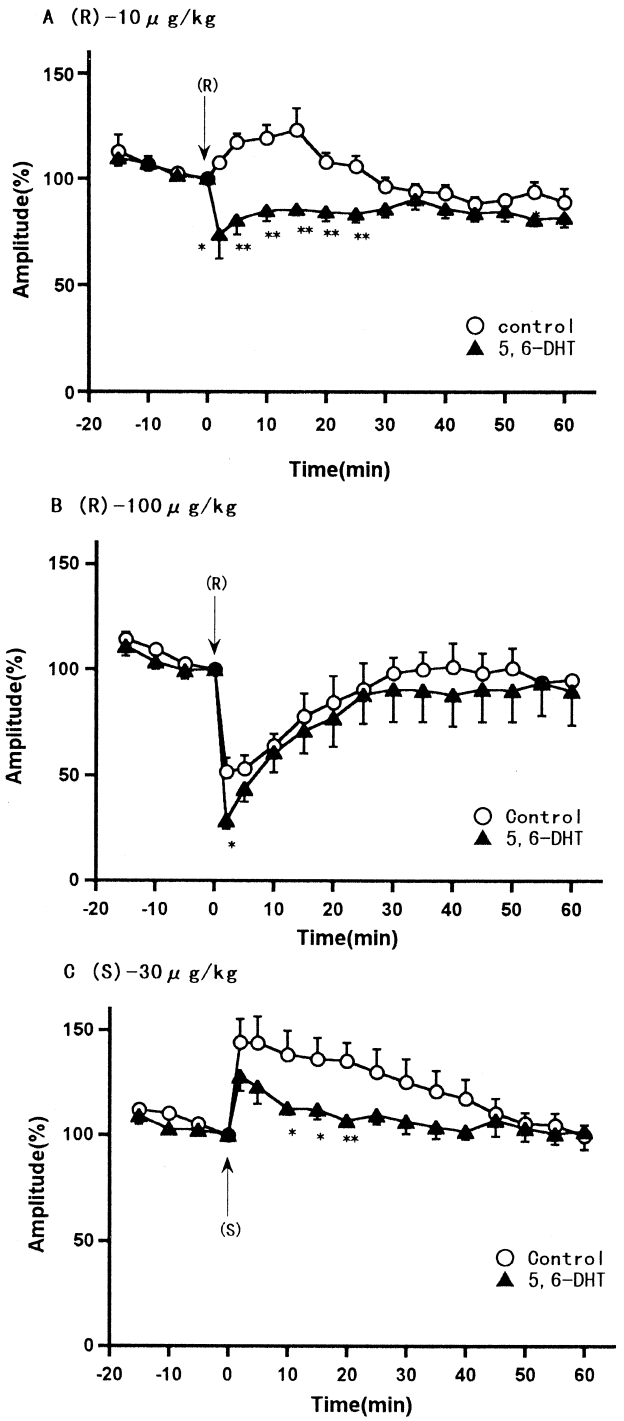

Fig. 5. Effects of (*R*)- (10 μg/kg, i.v., A; 100 μg/kg, i.v., B) and (*S*)-8-OH-DPAT (30 μg/kg, i.v., C) on the monosynaptic reflex in 5,6-dihydroxytryptamine creatinine sulfate-treated intact rats. 5,6-Dihydroxytryptamine creatinine sulfate (75 μg/animal, i.c.) was administered 2 weeks before the monosynaptic reflex was measured. Control animals received vehicle (i.c.). Each point represents the mean ± S.E.M. of four to six rats per group. Ordinates: mean monosynaptic reflex amplitudes expressed as percentages of the corresponding values at time 0. Abscissae: time in minutes after the injection of (*R*)- or (*S*)-8-OH-DPAT HBr. The significance of the differences between the test and control values was determined by Student's *t*-test (two-tailed); $^{*}P < 0.05$ and $^{**}P < 0.01$.

(*R*)-8-OH-DPAT (10 μg/kg, i.v.)-induced enhancement of the monosynaptic reflex, reversing it to produce inhibition. The amplitude of the monosynaptic reflexes in 5,6-dihydroxytryptamine-treated and control rats 15 min after (*R*)-enantiomer administration were 85.6 ± 3.1% ($n = 5$) and 123.3 ± 10.1% ($n = 5$), respectively (Fig. 5A). 5-HT depletion also significantly enhanced the monosynaptic reflex depression produced by a high dose (100 μg/kg, i.v.) of the (*R*)-enantiomer, and inhibited the monosynaptic reflex enhancement produced by the (*S*)-enantiomer (30 μg/kg, i.v.) in intact rats.

The noradrenaline content of the spinal cords of intact rats was reduced by 54.1% ($n = 8$) by 6-hydroxydopamine treatment. This affected neither the stimulatory nor the inhibitory actions of (*R*)-8-OH-DPAT (Fig. 6A,B). However, (*S*)-8-OH-DPAT-induced enhancement of the monosynaptic reflex was significantly inhibited by 6-hydroxydopamine pretreatment (Fig. 6C). Two minutes after (*S*)-8-OH-DPAT administration, the amplitude of the monosynaptic reflex had increased to 136.2 ± 4.1% ($n = 6$) in control and 115.1 ± 5.6% ($n = 8$) in 6-hydroxydopamine-treated rats, respectively. Significant rebound reflex facilitation was observed after a high dose of (*R*)-8-OH-DPAT in 6-hydroxydopamine-treated rats (Fig. 6B).

4. Discussion

In this study, there was a possibility that changes in the amplitude of the monosynaptic reflex could be due to changes in blood pressure caused by the i.v. injections of 8-OH-DPAT. The effects of (*R*)- and (*S*)-8-OH-DPAT on blood pressure were therefore monitored from the carotid artery (not shown). (*R*)-8-OH-DPAT did not alter blood pressure significantly within 10 min of administration to intact (10.0 ± 6.4 mmHg increase, $n = 4$) or spinalized rats (0.0 ± 3.6 mmHg increase, $n = 4$), but (*S*)-8-OH-DPAT increased it significantly in intact rats (by 15.0 ± 1.5 mmHg, $n = 4$). However, in previous studies, we showed that changes in reflex amplitude were not affected by large changes in blood pressure (Ono et al., 1991, 1993). These results suggest that the effects of 8-OH-DPAT on the spinal reflex were not due to changes in blood pressure.

In intact rats, (*R*)-8-OH-DPAT 10 μg/kg enhanced the amplitude of the monosynaptic reflex, whereas at 100 μg/kg, it reduced the amplitude (Fig. 1A). In spinalized rats, (*R*)-8-OH-DPAT inhibited the monosynaptic reflex in a dose-dependent manner (Fig. 1C). These results suggest that (*R*)-8-OH-DPAT stimulated the spinal motor systems indirectly via a supraspinal structure, but inhibited the reflex pathway in the spinal cord itself. Pretreatment with the 5-HT_{1A} receptor antagonists spiroxatrine or NAN-190 inhibited (*R*)-8-OH-DPAT-induced enhancement of the monosynaptic reflex in intact rats (Fig. 2A,B), as did ketanserin to a lesser extent (Fig. 2C). Although the spinal 5-HT content of the 5,6-DHT-treated rats was not com-

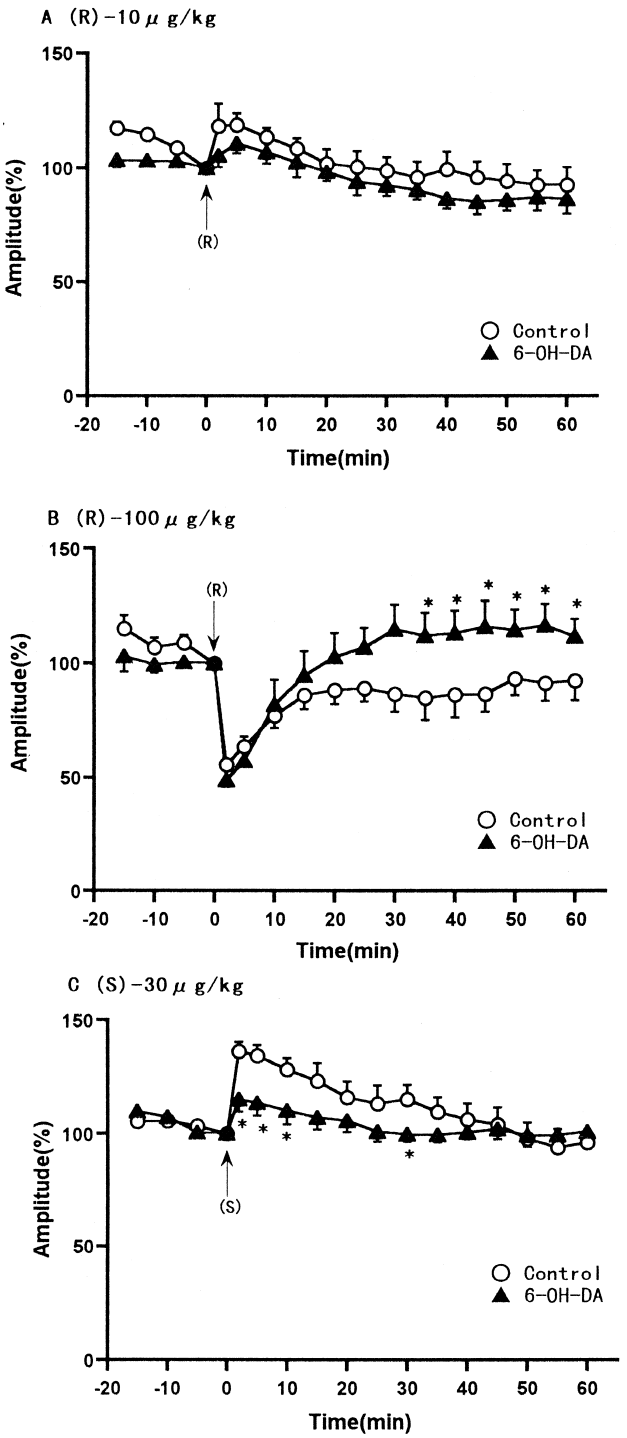

Fig. 6. Effects of (*R*)- (10 μg/kg, i.v., A; 100 μg/kg, i.v., B) and (*S*)-8-OH-DPAT (30 μg/kg, i.v., C) on the monosynaptic reflex in 6-hydroxydopamine HBr-treated intact rats. 6-Hydroxydopamine HBr (36.7 μg/animal, i.c.) was administered 2 weeks before the monosynaptic reflex was measured. Control animals received vehicle (i.c.). Each point represents the mean ± S.E.M. of six to eight rats per group. Ordinates: mean monosynaptic reflex amplitudes expressed as percentages of the corresponding values at time 0. Abscissae: time in minutes after the injection of (*R*)- or (*S*)-8-OH-DPAT HBr. The significance of the differences between the test and control values was determined by Student's *t*-test (two-tailed); $^{*}P < 0.05$.

pletely depleted, (*R*)-enantiomer-induced enhancement of the monosynaptic reflex was abolished (Fig. 5A). In a previous study, we showed that 5-methoxy-*N*,*N*-dimethyltryptamine and 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) enhanced the excitability of spinal cord motoneurons directly through 5-HT_2 receptors in vivo (Yamazaki et al., 1992). In the present study, although the effect did not reach statistical significance, pretreatment with the 5-HT_2 receptor antagonist ketanserin inhibited (*R*)-enantiomer-induced monosynaptic reflex enhancement (Fig. 2C). These findings suggest that supraspinal 5-HT_{1A} receptors and the descending serotonergic system are involved in the stimulatory effect of (*R*)-8-OH-DPAT on the monosynaptic reflex. In another previous study, we found that descending noradrenergic pathways enhanced the monosynaptic reflex through α_1-adrenoceptors in the spinal cord (Ono and Fukuda, 1995). Neither the noradrenergic neuronal lesion produced by 6-hydroxydopamine nor the α_1-adrenoceptor antagonist prazosin affected the action of (*R*)-8-OH-DPAT on the monosynaptic reflex (Fig. 6A, Fig. 2D), suggesting that the descending noradrenergic system and α_1-adrenoceptors are not involved in (*R*)-8-OH-DPAT-induced enhancement of the monosynaptic reflex.

(*S*)-8-OH-DPAT enhanced the monosynaptic reflex in intact rats in a dose-dependent manner (Fig. 1B), but had no effect in spinalized rats (Fig. 1D), suggesting an effect exerted via the supraspinal system, but no action on the spinal cord itself. Pretreatment with NAN-190, spiroxatrine or ketanserin had no effect on the enhancement of the monosynaptic reflex produced by the (*S*)-enantiomer (Fig. 4A,B,C). Although 5-HT depletion by 5,6-dihydroxytryptamine significantly inhibited the monosynaptic reflex enhancement produced by the (*S*)-enantiomer, complete antagonism was not observed (Fig. 5C). These results suggest that the supraspinal 5-HT system, but not spinal 5-HT_{1A} or 5-HT_2 receptors, is involved in the monosynaptic reflex-enhancing effect of (*S*)-8-OH-DPAT. The spinal 5-HT receptors involved remain to be identified. Pretreatment with the α_1-adrenoceptor antagonist prazosin inhibited (*S*)-8-OH-DPAT-induced enhancement of the monosynaptic reflex in intact rats (Fig. 4D). In addition, although the spinal noradrenaline content was not completely depleted in the 6-hydroxydopamine-treated rats, (*S*)-8-OH-DPAT-induced enhancement of the monosynaptic reflex was inhibited (Fig. 6C). These findings suggest that the descending noradrenergic system and α_1-adrenoceptors are involved in the stimulatory action of (*S*)-8-OH-DPAT on the monosynaptic reflex. The residual activity might be attributable to effects mediated via the serotonergic pathway. 6-Hydroxydopamine depletes dopamine levels in dopaminergic fibers. There is little dopaminergic innervation in the spinal cord (Björklund and Skagerberg, 1982), and in a previous study, we have shown that stimulation of dopamine D_1/D_2 receptors has little influence on the monosynaptic reflex, suggesting that descend-

ing dopaminergic systems have little effect on monosynaptic reflex transmission (Kamijo et al., 1993). Thus, the involvement of dopaminergic systems can be discounted. Recently, noradrenaline release has been shown to be increased after the administration of 8-OH-DPAT to mice (Prow et al., 1996). Spinal antinociception mediated by 5-HT is blocked by α-adrenoceptor antagonists and depletion of endogenous noradrenaline (Sawynok and Reid, 1996). Spontaneous tail-flicks have been observed after administration of 8-OH-DPAT, and these were inhibited by 5-HT_{1A} receptor and α_1-adrenoceptor antagonists (Millan et al., 1994). Therefore, it may be that the effects of 8-OH-DPAT involving α_1-adrenoceptors are exerted by its (*S*)-enantiomer.

In this study, a high dose (100 μg/kg, i.v.) of (*R*)-8-OH-DPAT inhibited the monosynaptic reflex in intact and spinalized rats (Fig. 1A,C), suggesting that, at this dose, (*R*)-8-OH-DPAT inhibits the spinal cord itself. 5-HT may inhibit the motoneuronal reflex in neonatal rat isolated spinal cord via presynaptic 5-HT_{1A} (Wu et al., 1991), 5-HT_1-like (Elliott and Wallis, 1992) or 5-HT_{1D} receptors (Manuel et al., 1995). (*R*)-8-OH-DPAT also depressed the monosynaptic reflex via 5-HT_{1D} receptors in neonatal rat spinal cord (Manuel et al., 1995). In our study, none of the pretreatment regimens affected the depression of the monosynaptic reflex produced by a high dose of the (*R*)-enantiomer in intact or spinalized rats (Fig. 3, Fig. 5B, Fig. 6B). Thus, it is unclear which receptors and/or neurons are involved in this effect. 8-OH-DPAT has been suggested to be a ligand of the 5-HT_7 receptor (Lovenberg et al., 1993; Eglen et al., 1997) and of 5-HT_7 or 5-HT_{1D} receptors (Manuel et al., 1995; Clarke et al., 1997). Therefore, these receptors may be involved in the inhibitory effect of (*R*)-8-OH-DPAT on the monosynaptic reflex. The inhibitory effect seen 2 min after a high dose of (*R*)-8-OH-DPAT was increased by 5,6-dihydroxytryptamine treatment (Fig. 5B), perhaps due to the removal of any descending facilitatory effects. A significant rebound effect was observed in 6-hydroxydopamine-treated rats after a high dose of (*R*)-8-OH-DPAT (Fig. 6B), for reasons yet to be discovered.

5. Conclusion

It is evident that a racemic mixture of 8-OH-DPAT should not be regarded as a selective 5-HT_{1A} receptor agonist because the (*R*)- and (*S*)-enantiomer components have different pharmacological effects. Our results suggest that, in intact rats, supraspinal 5-HT_{1A} receptors and the descending serotonergic system are involved in the stimulatory action of (*R*)-8-OH-DPAT on the monosynaptic reflex, whereas the descending noradrenergic system and α_1-adrenoceptors are involved in the stimulatory action of (*S*)-8-OH-DPAT on this reflex.

Acknowledgements

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