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# Tricyclic analogs cyclobenzaprine, amitriptyline and cyproheptadine inhibit the spinal reflex transmission through 5-HT$_2$ receptors

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**Abstract**

The centrally acting muscle relaxant cyclobenzaprine decreases the amplitude of monosynaptic reflex potentials by inhibiting the facilitatory descending serotonergic influences in the spinal cord. Interestingly, the structure of cyclobenzaprine is much similar to those of amitriptyline and cyproheptadine. In the present study, we attempted to elucidate the relationship between 5-HT$_2$ receptor antagonistic and inhibitory effects of cyclobenzaprine, amitriptyline, cyproheptadine and ketanserin on the spinal reflexes. Cyclobenzaprine, amitriptyline, cyproheptadine, and ketanserin significantly inhibited facilitatory effects of 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) on flexor reflexes and mono- and polysynaptic spinal reflex potentials in spinalized rats. In intact rats, these drugs significantly reduced the mono- and polysynaptic reflex potentials. 5-HT depletion significantly prevented the depression of the spinal reflex potentials induced by these drugs. These results suggest that the inhibitory effects of cyclobenzaprine, amitriptyline, and cyproheptadine on mono- and polysynaptic reflex potentials are due to the inhibition of descending serotonergic systems through 5-HT$_2$ receptors in the spinal cord.


*Keywords:* Cyclobenzaprine; Amitriptyline; Cyproheptadine; Flexor reflex; Spinal reflex

## 1. Introduction

Cyclobenzaprine (Fig. 1A), a centrally acting muscle relaxant, has been used to treat the musculoskeletal pain and sleep disturbances associated with fibromyalgia syndrome (Goldenberg, 1989; Santandrea et al., 1993; Carette et al., 1994). It is believed that cyclobenzaprine acts mainly on the brainstem (Barnes, 1976; Barnes et al., 1980). The descending monoaminergic pathways modulate the functions of spinal cord (Björklund and Skagerberg, 1982). In the ventral horn, the descending noradrenergic neurons originating from the locus coeruleus and descending serotonergic neurons originating from the medullary raphe regulate α-motoneuronal activity (Strahlendorf et al., 1980; Chan et al., 1986; Ono et al., 1988), while the noradrenergic and serotonergic neurons projected to the dorsal horn modulate the pain transmission from sensory nerves (Yaksh and Aimone, 1989). In a previous study, we showed that cyclobenzaprine depressed the monosynaptic reflex potential in spinal cord by inhibiting descending serotonergic systems, but not noradrenergic systems (Kobayashi et al., 1996). Interestingly, the structure of cyclobenzaprine is similar to those of amitriptyline (a tricyclic antidepressant, Fig. 1B) and cyproheptadine (5-HT receptor antagonist, Fig. 1C). In the present study, we attempted to elucidate the relationship between 5-HT$_2$ receptor antagonistic and inhibitory effects of cyclobenzaprine, amitriptyline, cyproheptadine and ketanserin (a 5-HT$_2$ receptor antagonist) on the spinal reflexes. To evaluate the antagonistic effects on 5-HT$_2$ receptors of these drugs in vivo, we studied their effects on the facilitatory actions of 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), a selective 5-HT$_2$ receptor agonist, on flexor reflexes and spinal mono- and polysynaptic reflex potentials in spinalized rats (Yamazaki et al., 1992b). The involvement of serotonergic nervous system in the inhibitory effects of

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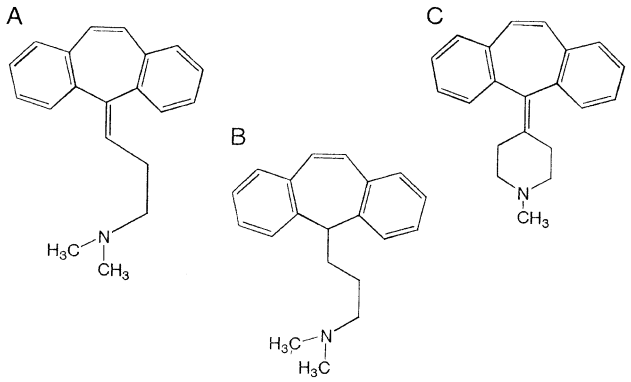


Fig. 1. Chemical structures of cyclobenzaprine (A), amitryptirine (B) and cyproheptadine (C).

these drugs on spinal reflex potentials was studied in 5-HT depleted intact (nonspinalized) rats.

## 2. Materials and methods

### 2.1. Measurement of flexor reflexes

All experimental protocols used were approved by the Animal Care and Use Committee of Tokyo University of Science and Nagoya City University and were conducted in accordance with the guidelines of the National Institutes of Health and the Japanese Pharmacological Society.

Male Wistar rats (8–9 weeks old) were anesthetized with ether, and cannulae were inserted into the trachea for respiration and the femoral vein for drug administration. 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). To minimize hemorrhage and to damage the function of higher centers, cotton balls were pressed rostrally into the intracranial hole. The rat was placed in ventral recumbent position and ventilated artificially. The left hind foot was stimulated through needle electrodes inserted into the skin of the toe (7 V, 2 ms duration, 4 pulses separated by a 20-ms interval, every 20 s). The parameters of stimulation were sufficient to elicit afferent nociception. The withdrawal movement of the hindlimb was recorded using a force–displacement transducer and a recorder. The administration of drugs was conducted 1 h after spinalization and discontinuation of ether-induced anesthesia.

### 2.2. Measurement of mono- and polysynaptic spinal reflex potentials

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 for respiration and the femoral vein for drug administration. In the 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, both the ventral and dorsal roots below L4 were cut distally at their points of exit from the vertebral column, and the entire exposed surgical area was covered with liquid paraffin that was maintained at $36 \pm 0.5$ °C by radiant heat. Bipolar Ag–AgCl wire electrodes were 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. Mono- and polysynaptic reflex potentials were recorded from the ipsilateral L5 ventral root, displayed on an oscilloscope, and eight consecutive responses were averaged by an averager. The amplitudes of monosynaptic reflex potential and polysynaptic reflex potential, which has a latency corresponding to the disynaptic reflex, were then measured (Fig. 3F). The latency of the monosynaptic reflex potential was 2–3 ms, and the delay of the polysynaptic reflex peak from the monosynaptic reflex peak was 0.8–1 ms.

### 2.3. Neurotoxic lesions

Depletion of 5-HT was performed by administering DL-*p*-chlorophenylalanine (300 mg/kg/day, i.p.) on days 1–3 before measuring the mono- and polysynaptic reflex potentials. DL-*p*-chlorophenylalanine was suspended in 0.5% w/v carboxymethyl cellulose sodium solution and 10 ml/kg was injected. Control animals received 0.5% w/v carboxymethyl cellulose sodium solution.

### 2.4. Drugs

Cyclobenzaprine hydrochloride and amitriptyline hydrochloride were obtained from Sigma (St. Louis, MO, USA). Cyproheptadine hydrochloride were obtained from Merck-Banyu (Tokyo, Japan). DOI and ketanserin tartrate were obtained from Research Biochemicals International (Natick, MA, USA). Carboxymethyl cellulose sodium and α-chloralose were obtained from Tokyo Kasei (Tokyo, Japan). Urethane and DL-*p*-chlorophenylalanine were obtained from Aldrich Chemical (Milwaukee, WI, USA) and Wako (Tokyo, Japan), respectively. Urethane and α-chloralose were dissolved in distilled water. For the measurements of flexor reflex and spinal reflex potentials, all of the test compounds were dissolved in 0.9% w/v physiological saline and 1 ml/kg was administered intravenously (i.v.). Each antagonist was administered 10 min before injection of DOI. The dose of each drug used in these experiments is expressed as the weight

of the salt. Control rats received vehicle at 1 ml/kg. Drugs were administered to the spinalized rats at least 2 h after spinalization.

### 2.5. Statistical analysis

The flexor reflex and mono- and polysynaptic reflex potentials recorded after drug administration are expressed as percentages of the corresponding predrug (time 0) values. All data are expressed as means ± S.E.M. Student's *t*-test was used to compare the data for two groups, while the two-tailed Bonferroni type multiple *t*-test following one-way analysis of variance (ANOVA) was used for multiple comparisons of control and treated groups (Wallenstein et al., 1980). Differences at $P < 0.05$ (two-tailed) were considered to be significant.

## 3. Results

### 3.1. Effects of drugs on the flexor reflexes

DOI (1–10 μg/kg, i.v.) increased flexor reflexes dose-dependently in spinalized rats (Fig. 2A). The effect peaked

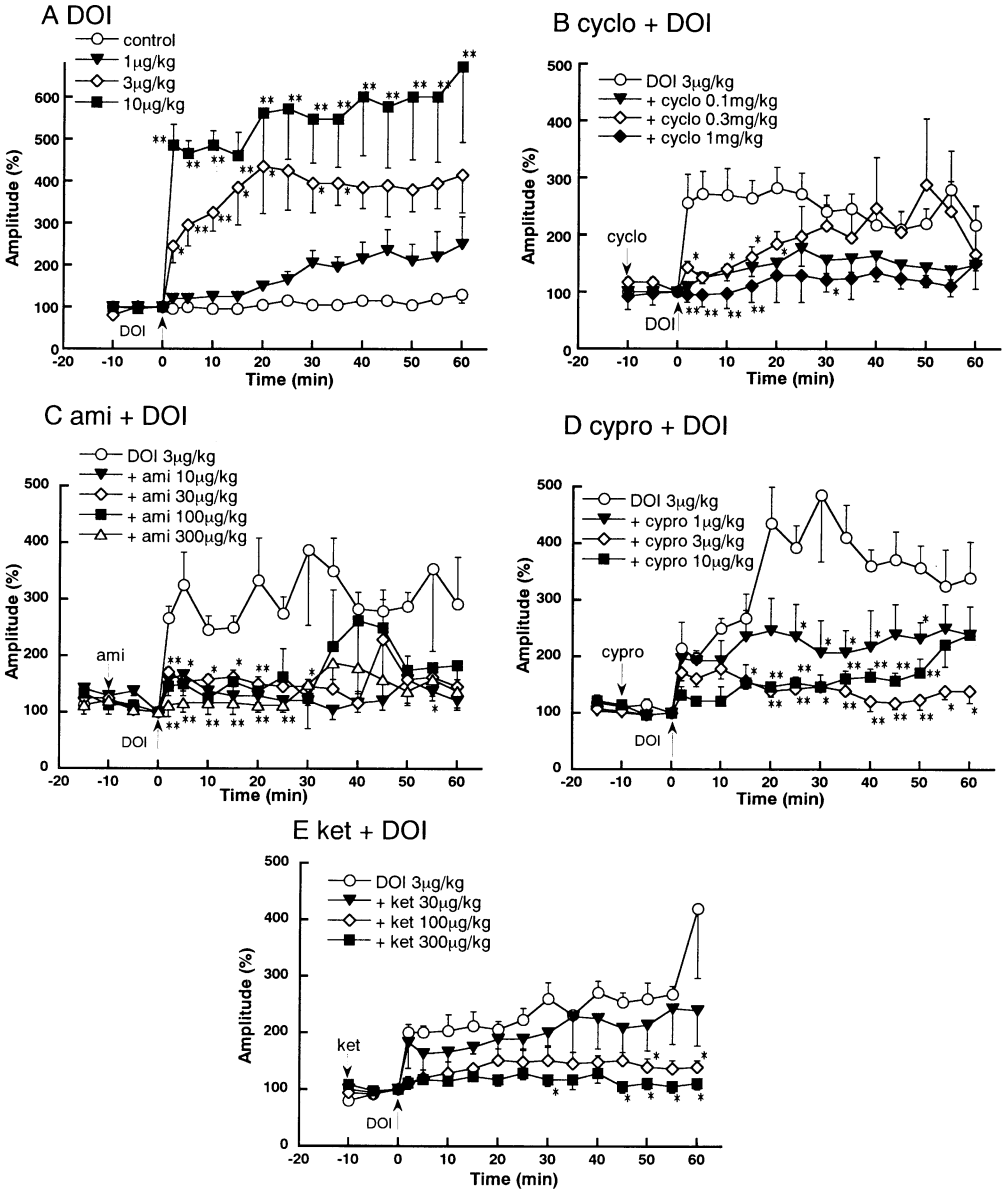


Fig. 2. Effect of 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI; 1, 3 and 10 μg/kg, i.v., A) on the flexor reflex in spinalized rats, and the effects of cyclobenzaprine hydrochloride (0.1, 0.3 and 1 mg/kg, i.v., B), amitriptyline hydrochloride (10, 30, 100, and 300 μg/kg, i.v., C), cyproheptadine hydrochloride (1, 3 and 10 μg/kg, i.v., D) and ketanserin tartrate (30, 100 and 300 μg/kg, i.v., E) on the DOI-induced (3 μg/kg, i.v.) enhancement of the flexor reflex in spinalized rats. Each point represents the means ± S.E.M. of four rats per group. Ordinate: means of amplitudes of reflexes expressed as percentages of the corresponding values at time 0. Abscissae: time in minutes after the injection of DOI. The significance of the differences between the test and control values was determined by Bonferroni-type multiple *t*-test following ANOVA; $*P < 0.05$ and $**P < 0.01$.

20 min after administration and it persisted for over 60 min. Cyclobenzaprine hydrochloride (0.1–1 mg/kg, i.v.) significantly blocked the DOI-induced (3 μg/kg, i.v.) enhancement of the flexor reflex (Fig. 2B). Amitriptyline hydrochloride (10–300 μg/kg, i.v.) and cyproheptadine hydrochloride (1–10 μg/kg, i.v.) also blocked the DOI-induced (3 μg/kg, i.v.) enhancement of flexor reflex; these effects were significant (Fig. 2C and D). Although the pretreatment with ketanserin tartrate (30–300 μg/kg, i.v.) showed the tendency to block the DOI-induced enhancement, this effect was not significant because of the weak effect of DOI in the control group (Fig. 2E). Neither cyclobenzaprine, amitriptyline, cyproheptadine nor ketanserin themselves exhibited any effects on the flexor reflex (Fig. 2).

### *3.2. Effects of drugs on the DOI-induced enhancement of spinal reflex potentials in spinalized rats*

In our previous study, 100 μg/kg DOI enhanced the mono- and polysynaptic reflex potentials and increased the excitability of motoneurons, and ketanserin antagonized these DOI-induced effects, suggesting that 5-$HT_2$ receptors are involved in these facilitatory effects of DOI on motoneurons in the spinal cord (Yamazaki et al., 1992b). Thus, we used DOI at 100 μg/kg in the present study. DOI (100 μg/kg, i.v.) enhanced the mono- and polysynaptic reflex potentials (Figs. 3A and 4A); this enhancement was significant and peaked 2–5 min after administration. The maximum amplitudes of mono- and polysynaptic reflex

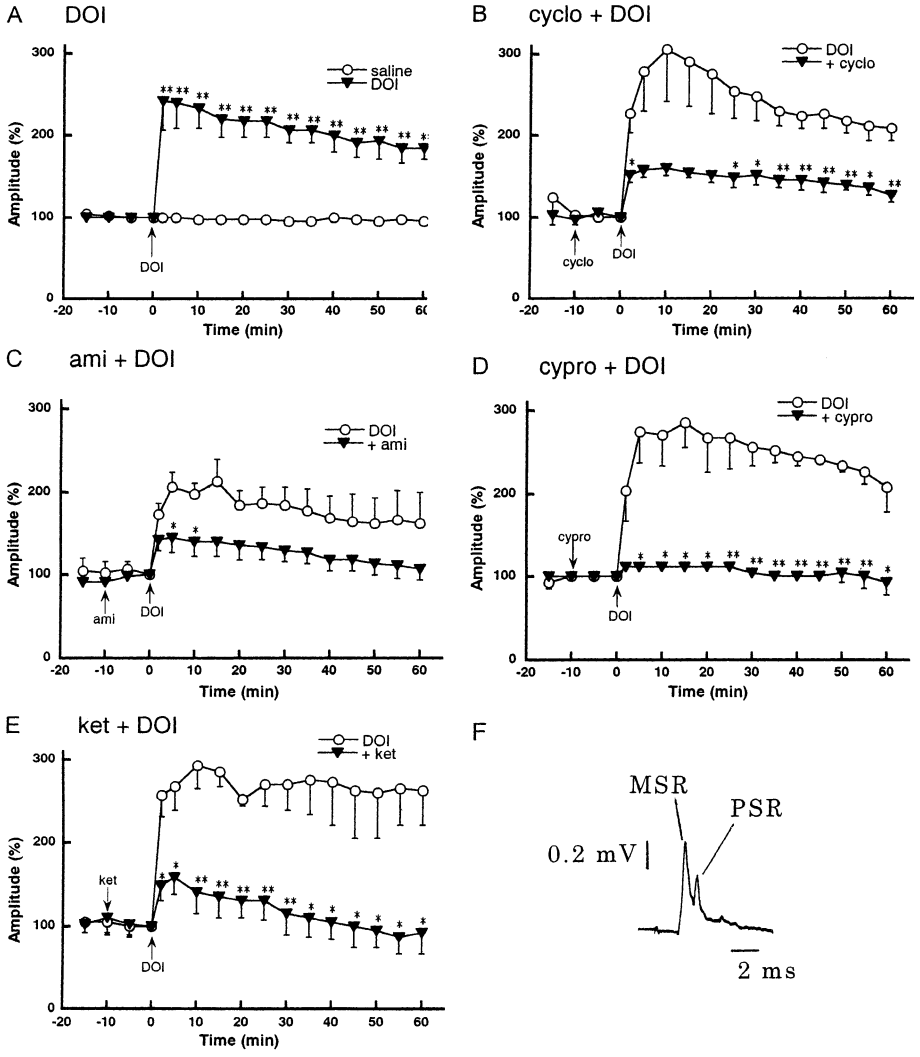


Fig. 3. Effect of DOI (100 μg/kg, i.v., A) on the monosynaptic reflex potential in spinalized rats, and the effects of cyclobenzaprine hydrochloride (300 μg/kg, i.v., B), amitriptyline hydrochloride (300 μg/kg, i.v., C), cyproheptadine hydrochloride (300 μg/kg, i.v., D) and ketanserin tartrate (300 μg/kg, i.v., E) on the DOI-induced (100 μg/kg, i.v.) enhancement of monosynaptic reflex potential. Each point represents the means ± S.E.M. of four rats per group. Ordinate: means of amplitudes of reflexes expressed as percentages of the corresponding values at time 0. Abscissae: time in minutes after the injection of DOI. The significance of the differences between the test and control values was determined by two-tailed Student's *t*-test; $*P<0.05$ and $**P<0.01$. F: a sample of record of mono- (MSR) and polysynaptic (PSR) reflex potentials.

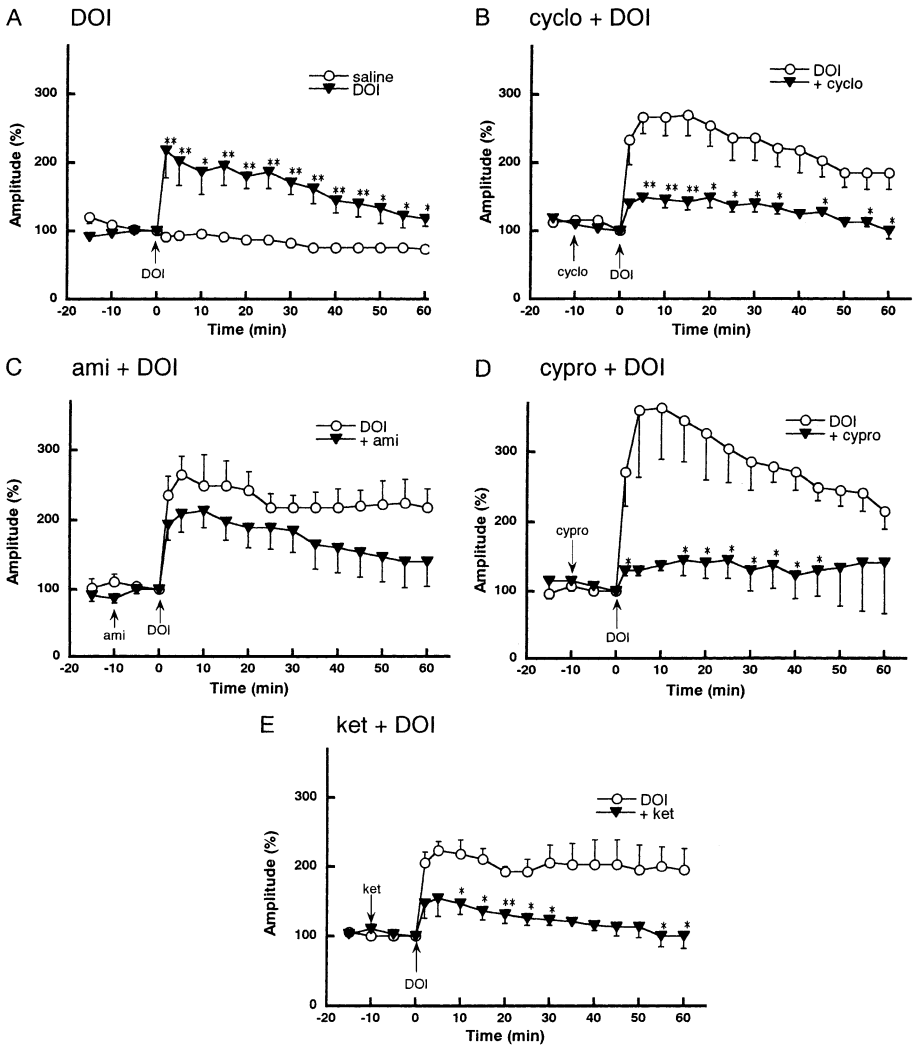


Fig. 4. Effect of DOI (100 μg/kg, i.v., A) on the polysynaptic reflex potential in spinalized rats, and the effects of cyclobenzaprine hydrochloride (300 μg/kg, i.v., B), amitriptyline hydrochloride (300 μg/kg, i.v., C), cyproheptadine hydrochloride (300 μg/kg, i.v., D) and ketanserin tartrate (300 μg/kg, i.v., E) on the DOI-induced (100 μg/kg, i.v.) enhancement of the polysynaptic reflex potential. Each point represents the means ± S.E.M. of four rats per group. Ordinate: means of amplitudes of reflexes expressed as percentages of the corresponding values at time 0. Abscissae: time in minutes after the injection of DOI. The significance of the differences between the test and control values was determined by two-tailed Student's *t*-test; $*P<0.05$ and $**P<0.01$.

amplitudes after administration of DOI were about 250% and 200% of the pretreatment level, respectively. Pretreatment with cyclobenzaprine hydrochloride (300 μg/kg, i.v.) significantly inhibited the DOI-induced enhancement of mono- and polysynaptic reflex potentials (Figs. 3B and 4B). In cyclobenzaprine-treated rats, the mono- and polysynaptic reflex amplitudes were increased to about 150% of control level after DOI treatment. Pretreatment with amitriptyline hydrochloride (300 μg/kg, i.v.), cyproheptadine hydrochloride (300 μg/kg, i.v.), and ketanserin tartrate (300 μg/kg, i.v.) also inhibited the DOI-induced enhancement of mono- and polysynaptic reflex potentials (Figs. 3C–E and 4C–E). With the exception of amitriptyline, these effects were significant. Cyclobenzaprine, amitriptyline, cyproheptadine, and ketanserin themselves had no effect on the mono- and polysynaptic reflex potentials in the spinalized rats (Figs. 3 and 4).

### 3.3. Effects of drugs on mono- and polysynaptic reflex potentials in intact rats

In intact (nonspinalized) rats, cyclobenzaprine hydrochloride (300 μg/kg, i.v.) significantly reduced the amplitude of mono- and polysynaptic reflex potentials (Figs. 5A and 6A). The maximum effect of cyclobenzaprine was obtained within 15 min after administration, and this persisted for over 60 min. Cyclobenzaprine inhibited the mono- and polysynaptic reflex amplitude by about 20% and 40%, respectively. Amitriptyline hydrochloride (300 μg/kg, i.v.), cyproheptadine hydrochloride (300 μg/kg,

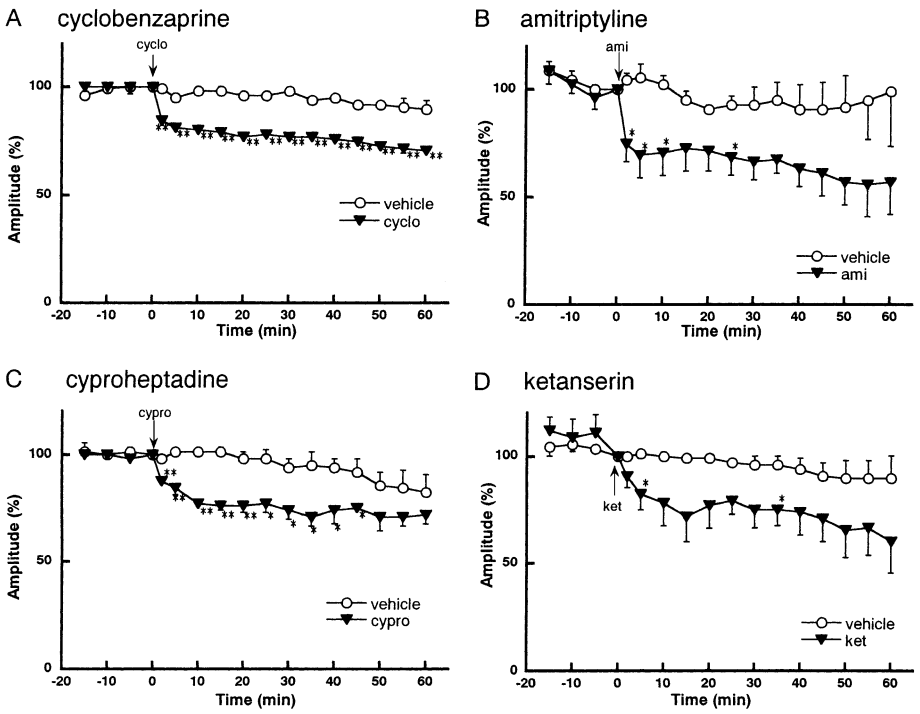


Fig. 5. Effects of cyclobenzaprine hydrochloride (300 μg/kg, i.v., A), amitriptyline hydrochloride (300 μg/kg, i.v., B), cyproheptadine hydrochloride (300 μg/kg, i.v., C) and ketanserin tartrate (300 μg/kg, i.v., D) on the amplitude of the monosynaptic reflex potential in intact rats. Each point represents the means ± S.E.M. of four rats per group. Ordinate: means of amplitudes of reflexes expressed as percentages of the corresponding values at time 0. Abscissae: time in minutes after the injection of each drug. The significance of the differences between the test and control values was determined by two-tailed Student's *t*-test; $*P<0.05$ and $**P<0.01$.

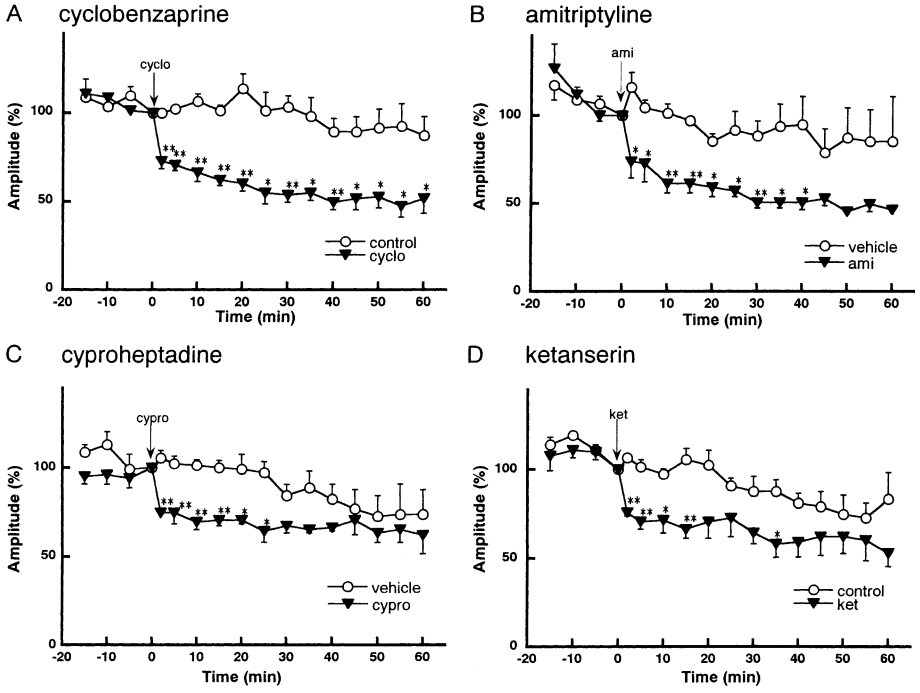


Fig. 6. Effects of cyclobenzaprine hydrochloride (300 μg/kg, i.v., A), amitriptyline hydrochloride (300 μg/kg, i.v., B), cyproheptadine hydrochloride (300 μg/kg, i.v., C) and ketanserin tartrate (300 μg/kg, i.v., D) on the amplitude of the polysynaptic reflex potential in intact rats. Each point represents the means ± S.E.M. of four rats per group. Ordinate: means of amplitudes of reflexes expressed as percentages of the corresponding values at time 0. Abscissae: time in minutes after the injection of each drug. The significance of the differences between the test and control values was determined by two-tailed Student's *t*-test; $*P<0.05$ and $**P<0.01$.

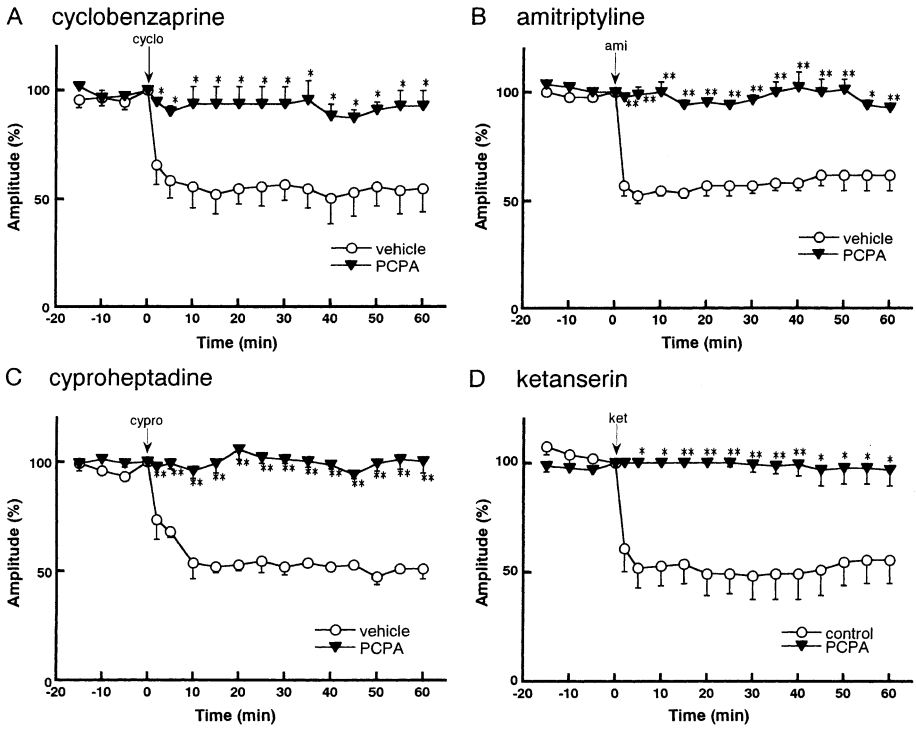


Fig. 7. Effects of cyclobenzaprine hydrochloride (300 μg/kg, i.v., A), amitriptyline hydrochloride (300 μg/kg, i.v., B), cyproheptadine hydrochloride (300 μg/kg, i.v., C) and ketanserin tartrate (300 μg/kg, i.v., D) on the amplitude of the monosynaptic reflex potential in DL-*p*-chlorophenylalanine-treated rats. Each point represents the means ± S.E.M. of four rats per group. Ordinate: means of amplitudes of reflexes expressed as percentages of the corresponding values at time 0. Abscissae: time in minutes after the injection of each drug. The significance of the differences between the DL-*p*-chlorophenylalanine-treated and control values was determined by two-tailed Student's *t*-test; $*P<0.05$ and $**P<0.01$.

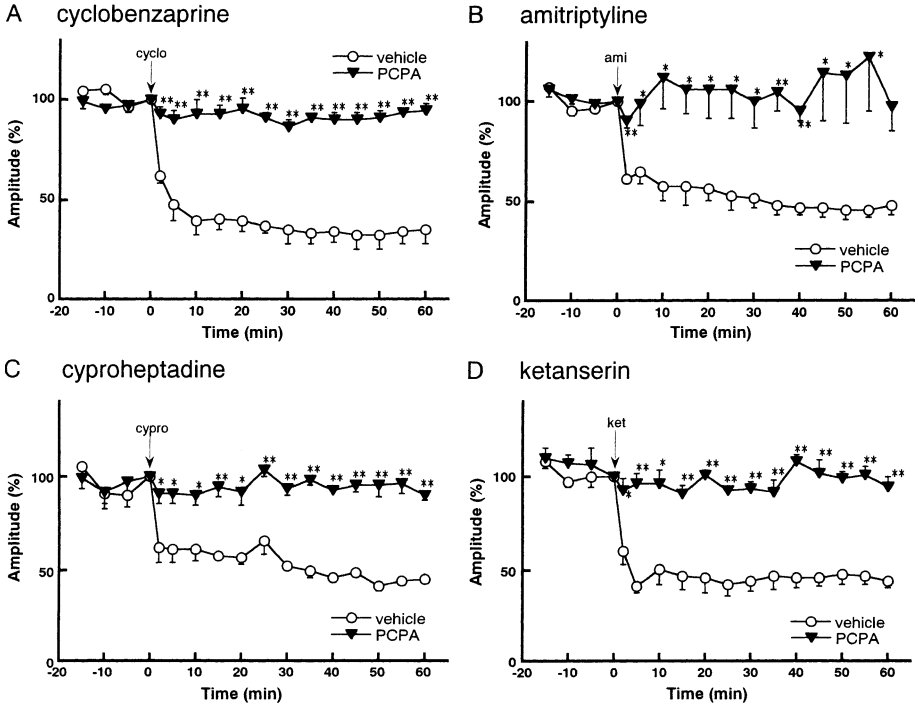


Fig. 8. Effects of cyclobenzaprine hydrochloride (300 μg/kg, i.v., A), amitriptyline hydrochloride (300 μg/kg, i.v., B), cyproheptadine hydrochloride (300 μg/kg, i.v., C) and ketanserin tartrate (300 μg/kg, i.v., D) on the amplitude of the polysynaptic reflex potential in DL-*p*-chlorophenylalanine-treated rats. Each point represents the means ± S.E.M. of four rats per group. Ordinate: means of amplitudes of reflexes expressed as percentages of the corresponding values at time 0. Abscissae: time in minutes after the injection of each drug. The significance of the differences between the DL-*p*-chlorophenylalanine-treated and control values was determined by two-tailed Student's *t*-test; $*P<0.05$ and $**P<0.01$.

i.v.), and ketanserin tartrate (300 μg/kg, i.v.) also reduced these reflex amplitudes, by about 30–50% (Figs. 5B–D and 6B–D).

### 3.4. Effects of drugs on mono- and polysynaptic reflex potentials in DL-p-chlorophenylalanine-treated intact rats

In intact rats, 5-HT depletion significantly inhibited the cyclobenzaprine hydrochloride-induced (300 μg/kg, i.v.) depression of the mono- and polysynaptic reflex potentials (Figs. 7A and 8A). In control rats, the mono- and polysynaptic reflex amplitudes measured 15 min after cyclobenzaprine administration were reduced to about 40–50% of the preadministration value, whereas in the DL-*p*-chlorophenylalanine-treated rats amplitudes were about 90–100% of preadministration levels. These values differed significantly. Amitriptyline hydrochloride (300 μg/kg, i.v.), cyproheptadine hydrochloride (300 μg/kg, i.v.), and ketanserin tartrate (300 μg/kg, i.v.) exhibited similar effects (Figs. 7B–D and 8B–D).

## 4. Discussion

In the previous study, we showed that DOI (1–100 μg/kg) produced a dose-dependent increase in the mono- and polysynaptic reflex potentials of spinalized rats and in the excitability of motoneurons, and that ketanserin and ritanserin antagonized these facilitatory effects. These results suggest that DOI increases the activity of motoneurons through 5-$HT_2$ receptors at the level of the spinal cord (Yamazaki et al., 1992b). Kobayashi et al. (1996) showed that cyclobenzaprine inhibits the DOI-induced enhancement of the monosynaptic reflex, and that cyclobenzaprine binds strongly to 5-$HT_2$ receptors ($K_i$ to 5-$HT_1$ receptor = 2900 nM, 5-$HT_2$ receptor = 62 nM) in a receptor binding assay. Hatanaka et al. (1996) showed that in rat frontal cortex, amitriptyline inhibits the binding for 5-$HT_{2A}$ receptors with $K_i$ of 20 nM. Cyproheptadine also has a high affinity for 5-$HT_2$ receptors (p$K_i$ value to 5-$HT_{2A}$ and 5-$HT_{2C}$ are $8.80 \pm 0.11$ and $8.71 \pm 0.08$, respectively; Honrubia et al., 1997). These results suggested that cyclobenzaprine, amitriptyline and cyproheptadine bind to 5-$HT_2$ receptors with a high affinity.

In the present study, the 5-$HT_2$ receptor agonist DOI, enhanced the flexor reflex and mono- and polysynaptic reflex potentials of spinalized rats, and pretreatment with cyclobenzaprine, amitryptiline (a tricyclic antidepressant), cyproheptadine (a 5-HT receptor antagonist), and ketanserin (a 5-$HT_2$ receptor antagonist) inhibited this effect (Figs. 2–4). These results suggested that cyclobenzaprine, amitryptiline, cyproheptadine, and ketanserin antagonized the DOI-induced enhancement of these parameters at the spinal level through 5-$HT_2$ receptors.

In intact rats, cyclobenzaprine, amitriptyline, cyproheptadine, and ketanserin depressed the amplitudes of mono- and polysynaptic reflex potentials. In a previous study, the pretreatment with DL-*p*-chlorophenylalanine reduced the 5-HT content of the spinal cords by 96.6% (Kobayashi et al., 1996). The same treatment with DL-*p*-chlorophenylalanine resulted in a significant inhibition of the depressant effect of cyclobenzaprine, amitriptyline, cyproheptadine, and ketanserin. This suggests that descending serotonergic systems are involved in the depressant effect of these four drugs in rats in which connection between brain and spinal cord is intact. At the spinal level, 5-HT regulates the α-motoneuron activity through 5-$HT_2$ receptors (Yamazaki et al., 1992a). In the intercollicular decerabrated animal model, sustained facilitation of muscle tone of the limbs was demonstrated, and 5-HT depletion attenuated the muscle tone, suggesting that the descending serotonergic systems are essential for the induction of excessive muscle tone in these rats (Sakai et al., 2000). Jacobs and Fornal (1993) showed that the activity of 5-HT-containing neurons in the brain is activated preferentially in association with motor output in cats. Recently, Gerin et al. showed that the extracellular concentration of 5-HT in the ventral horn changed during locomotion in treadmill-trained cats (Gerin et al., 1995; Gerin and Privat, 1998). In chronic spinal rats, transplantation of embryonic monoaminergic neurons and serotonergic neurons into the spinal cord produced rhythmic motor activities in hindlimbs (Feraboli-Lohnherr et al., 1997; Giménez y Ribotta et al., 1998, 2000). In the isolated spinal cord of neonatal rats, 5-HT induces a long-lasting reflex facilitation via activation of 5-$HT_{2C}$ receptors (Machacek et al., 2001). Thus, it appears that cyclobenzaprine, amitriptyline, cyproheptadine and ketanserin block the effect of descending serotonergic systems through the 5-$HT_2$ receptors at the spinal level.

In conclusion, cyclobenzaprine, amitriptyline and cyproheptadine act via 5-$HT_2$ receptors to block the tonic α-motoneuronal excitation produced by descending serotonergic systems.

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