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Cyclobenzaprine, a centrally acting muscle relaxant, acts on descending serotonergic systems

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Abstract

The centrally acting muscle relaxant cyclobenzaprine was thought to be an α_2-adrenoceptor agonist that reduced muscle tone by decreasing the activity of descending noradrenergic neurons. In the present study, we examined the effects of cyclobenzaprine on descending neurons by measuring the monosynaptic reflex in rats. Cyclobenzaprine reduced the monosynaptic reflex amplitude dose dependently and this effect was not inhibited by the α_2-adrenoceptor antagonists idazoxan and yohimbine. Cyclobenzaprine-induced monosynaptic reflex depression was not attenuated by noradrenergic neuronal lesions produced by 6-hydroxydopamine. However, cyclobenzaprine inhibited monosynaptic reflex facilitation induced by (±)-1-(4-iodo-2,5-dimethoxyphenyl)-2-aminopropane, a 5-HT_2 receptor agonist, in spinalized rats markedly, and 5-HT depletion by DL-*p*-chlorophenylalanine inhibited the depressive effect of cyclobenzaprine on the monosynaptic reflex. These results suggest that cyclobenzaprine is a 5-HT_2 receptor antagonist and that its muscle relaxant effect is due to inhibition of serotonergic, not noradrenergic, descending systems in the spinal cord.

Keywords: Cyclobenzaprine; 5-HT (5-hydroxytryptamine, serotonin); Monosynaptic reflex

1. Introduction

Cyclobenzaprine, a centrally acting skeletal muscle relaxant (Share and McFarlane, 1975), has been used widely to treat the musculoskeletal pain and sleep disturbances associated with fibromyalgia syndrome (Carette et al., 1994; Goldenberg, 1989; Santandrea et al., 1993). The monosynaptic reflex is the activity of α-motoneurons evoked via synapses from Ia sensory fibers originating from the same muscle. Cyclobenzaprine decreased the amplitude of the monosynaptic reflex in intercollicular decerebrated animals (Barnes et al., 1980), but a much higher dose of cyclobenzaprine was needed to depress the monosynaptic reflex in spinalized animals (Esplin and Capek, 1979). Therefore, cyclobenzaprine was thought to act mainly on the brainstem (Barnes, 1976; Barnes et al., 1980). The descending noradrenergic neurons originating from the locus coeruleus (Chan et al., 1986; Ono et al., 1988; Strahlendorf et al., 1980) and descending serotonergic neurons originating from the medullary raphe (Fung and Barnes, 1989) are major descending neurons regulating α-motoneuronal activity. Barnes et al. (1980) reported that cyclobenzaprine decreased the spontaneous firing rate of the locus coeruleus and thus reduced spinal α-motoneuronal activity. Fung et al. (1991), on the basis of the result that phenoxybenzamine inhibited the depressant effect of cyclobenzaprine on the monosynaptic reflex (Barnes et al., 1980), suggested that cyclobenzaprine is an α_2-adrenoceptor agonist. However, Commissiong et al. (1981) demonstrated that cyclobenzaprine increased the firing rate of the locus coeruleus.

In addition to the noradrenergic coeruleospinal system, the serotonergic raphe-spinal system has been suggested to play an important role in regulating spinal motor function (Fung and Barnes, 1989; Roberts et al., 1988). However, the effects of cyclobenzaprine on such systems have not, as far as we know, been investigated. Therefore, in the present study, we investigated the effects of cyclobenzaprine on serotonergic neuronal systems.

2. Materials and methods

2.1. General preparation

Male Wistar rats (NRC Haruna, Japan) weighing 250–420 g were used in all the experiments. They were anes-

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thetized with urethane (1.0 g/kg i.p.) and α-chloralose (25 mg/kg i.p.) and ventilated artificially. In order to spinalize rats, the vagus nerves were severed bilaterally at the cervical region and the spinal cord was transected at the C1 level. All the rats underwent laminectomy in the lumbo-sacral region, the ventral and dorsal roots below L4 were cut bilaterally and the dorsal and ventral roots of segments L4 and L5 were isolated. A skin pouch was formed at the dissection site so that the exposed tissues could be covered with liquid paraffin kept at 36 ± 0.5°C and the body temperature was maintained at 36 ± 0.5°C by a heating pad.

2.2. Neurotoxic lesions

The noradrenergic neurons were lesioned using 6-hydroxydopamine hydrobromide (36.7 μg/animal), which was dissolved in 0.9% (w/v) physiological saline containing 0.1 mg/ml ascorbic acid, and 20 μl was injected intracisternally (i.c.). Animals were used 2 weeks after the administration of 6-hydroxydopamine. Depletion of serotonin (5-hydroxytryptamine, 5-HT) was performed by administering DL-*p*-chlorophenylalanine (300 mg/kg/day i.p.) on days 1–3 before measuring the monosynaptic reflex. DL-*p*-Chlorophenylalanine was suspended in 0.5% (w/v) carboxymethyl cellulose sodium solution and 10 ml/kg was injected. The noradrenaline and 5-HT contents of the spinal cord and brainstem were measured by high-performance liquid chromatography with electrochemical detection.

2.3. Monosynaptic reflex measurement

The dorsal and ventral roots of segment L5 were placed on bipolar Ag-AgCl wire electrodes for stimulation (0.2 Hz, 0.05 ms, supramaximal voltages) and recording, respectively. The reflex potentials were amplified (Nihon Kohden, AVB-10), displayed on an oscilloscope (Nihon Kohden, VC-10) and averaged 8 times by an averaging computer (Nihon Kohden, DAT-1100), the analog output of which was recorded by a recorder (Nihon Kohden, WT-625G).

2.4. Drugs

Cyclobenzaprine hydrochloride and 6-hydroxydopamine hydrobromide were obtained from Sigma Chemical (St. Louis, MO, USA). Yohimbine hydrochloride, (±)-1-(4-iodo-2,5-dimethoxyphenyl)-2-aminopropane hydrochloride (DOI) and ketanserin tartrate were obtained from Research Biochemicals International (Natick, MA, USA). Idazoxan hydrochloride was obtained from Reckitt & Colman (Hull, Yorkshire, UK). Urethane was obtained from Aldrich Chemical (Milwaukee, WI, USA). α-Chloralose was obtained from Tokyo Kasei (Tokyo, Japan). DL-*p*-Chlorophenylalanine was obtained from Nakarai Chemicals (Kyoto, Japan). The doses of drugs used in this experiments reflect the weight of the salt.

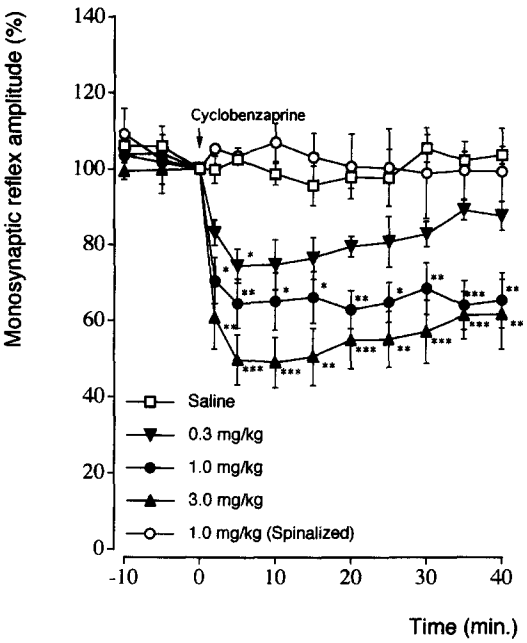

Fig. 1. Effect of cyclobezaprine on the monosynaptic reflex in non-spinalized (0.3, 1.0 and 3.0 mg/kg i.v.) and spinalized (1.0 mg/kg i.v.) rats. Each point represents the mean ± S.E. ($n = 4$) of the amplitude calculated as a % of the value immediately prior to cyclobenzaprine administration. The significance of each difference compared with saline (control) was determined by ANOVA followed by Bonferroni's multiple *t*-test, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

2.5. Statistics

All the data were expressed as means ± S.E. Student's *t*-test was used for comparison between two groups. One-way analysis of variance (ANOVA) followed by Bonferroni's multiple *t*-test was used for multiple comparison. Differences at $P < 0.05$ (two-tailed) were considered to be significant.

3. Results

3.1. Effect of cyclobenzaprine on monosynaptic reflex depression

Cyclobenzaprine (0.3, 1.0 and 3.0 mg/kg i.v.) reduced the monosynaptic reflex amplitude in non-spinalized rats dose dependently to 74 ± 4.5 ($n = 4$), 63 ± 5.0 ($n = 4$) and 46 ± 8.0% ($n = 4$) of the control levels, respectively, whereas cyclobenzaprine (1.0 mg/kg i.v.) did not change the monosynaptic reflex amplitude in spinalized rats (Fig. 1). As shown in Fig. 1, the maximum effect of each dose of cyclobenzaprine was obtained within 5 min after administration and the monosynaptic reflex amplitude recovered to the predrug level within 2 h of the 1.0 mg/kg injection.

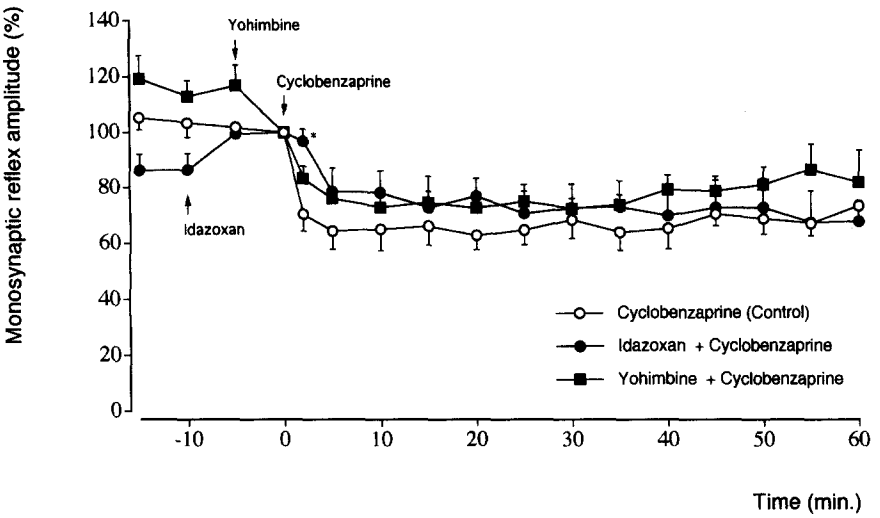

Fig. 2. Effects of idazoxan (0.5 mg/kg i.v.) and yohimbine (0.5 mg/kg i.v.) on cyclobenzaprine (1.0 mg/kg i.v.)-induced monosynaptic reflex depression in non-spinalized rats. Idazoxan and yohimbine were injected 10 and 5 min before cyclobenzaprine administration, respectively. Each point represents the mean ± S.E. ($n = 4$) of the amplitudes calculated as a % of the value immediately prior to cyclobenzaprine administration. The significance of each difference compared with cyclobenzaprine alone (control) was determined by ANOVA followed by Bonferroni's multiple t-test, * $P < 0.05$.

3.2. Effects of α_2-adrenoceptor antagonists on cyclobenzaprine-induced monosynaptic reflex depression in non-spinalized rats

The effects of α_2-adrenoceptor antagonists on the depressant action of cyclobenzaprine on the monosynaptic reflex in non-spinalized rats are shown in Fig. 2. Idazoxan (0.5 mg/kg i.v.) itself increased the monosynaptic reflex amplitude by 18% and yohimbine (0.5 mg/kg i.v.) alone decreased it by 23%. After idazoxan and yohimbine treatment, the monosynaptic reflex amplitudes 10 min after cyclobenzaprine administration were 78 ± 8.0 and 73 ± 4.7% (both $n = 4$) of those prior to cyclobenzaprine administration. Cyclobenzaprine itself also reduced the monosynaptic reflex to 65 ± 7.6% ($n = 4$) compared with the value immediately before cyclobenzaprine administration. Idazoxan significantly ($P < 0.05$) blocked the depressant effect of cyclobenzaprine at 2 min after cyclobenzaprine administration, but no significant differences in the maximal effect of cyclobenzaprine among the idazoxan-treated, yohimbine-treated and control groups were observed.

3.3. Effect of noradrenergic denervation on cyclobenzaprine-induced monosynaptic reflex depression in non-spinalized rats

6-Hydroxydopamine treatment did not affect the action of cyclobenzaprine (Fig. 3). The monosynaptic reflex amplitude 10 min after cyclobenzaprine administration was

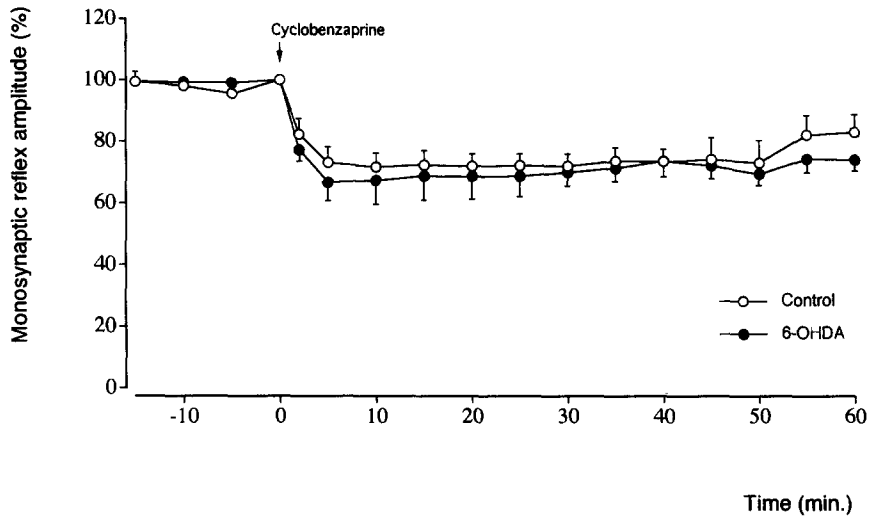

Fig. 3. Effects of cyclobenzaprine (1.0 mg/kg i.v.) on the monosynaptic reflex in 6-hydroxydopamine (6-OHDA)-lesioned non-spinalized rats. 6-OHDA (36.7 μg/animal, i.c.) was administered 2 weeks before the monosynaptic reflex was measured. Each point represents the mean ± S.E. ($n = 4$) of the amplitudes calculated as a % of the value immediately prior to cyclobenzaprine administration.

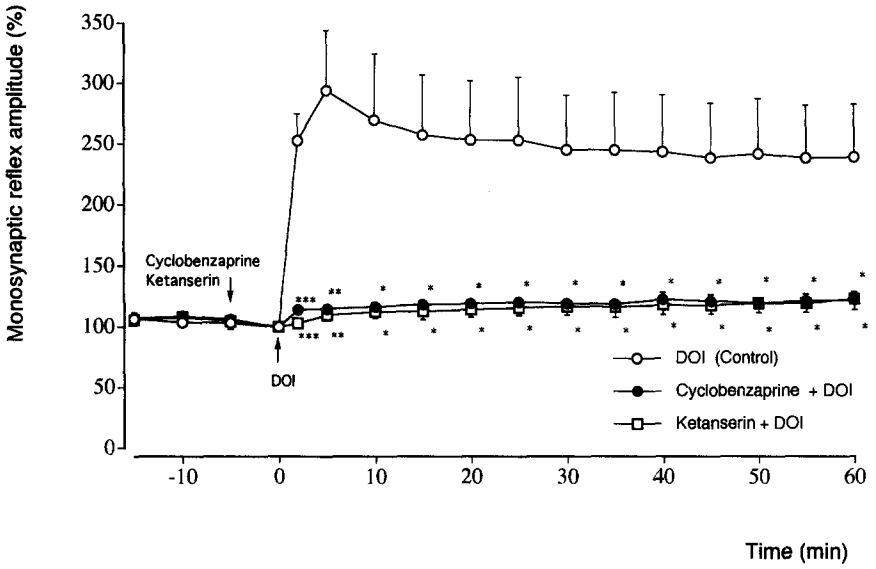

Fig. 4. Effects of cyclobenzaprine (1.0 mg/kg i.v.) and ketanserin (1.0 mg/kg i.v.) on the facilitative effect of DOI (0.1 mg/kg i.v.) on the monosynaptic reflex in spinalized rats. Cyclobenzaprine and ketanserin were injected 5 min before DOI administration. Each point represents the mean ± S.E. ($n = 4$) of the amplitude calculated as a % of the value immediately prior to DOI administration. The significance of each difference compared with the DOI (control) value was determined by ANOVA followed by Bonferroni's multiple t-test, * $P < 0.05$, * * $P < 0.01$.

67 ± 7.7 and 72 ± 4.6% (both $n = 4$) in 6-hydroxydopamine-treated and control groups, respectively. The difference between these values was not significant.

The noradrenaline content was reduced by 99.2% in the spinal cord of the 6-hydroxydopamine-treated non-spinalized rats. The net noradrenaline content was 262.2 ± 14.3 (control, $n = 4$) and 2.1 ± 0.14 (6-hydroxydopamine-treated, $n = 5$) ng/g wet tissue in the spinal cord. The 5-HT content was 446.8 ± 24.6 (control, $n = 4$) and 319.1 ± 35.0 (6-hydroxydopamine-treated, $n = 5$) ng/g wet tissue in the spinal cord. The decrease in noradrenaline ($P < 0.001$) and 5-HT ($P < 0.05$) was significant.

3.4. Effect of cyclobenzaprine against the action of serotonergic receptor agonist in spinalized rats

The 5-HT_2 receptor agonist DOI (0.1 mg/kg i.v.) increased the monosynaptic reflex in spinalized rats markedly (Fig. 4). The monosynaptic reflex amplitude 5 min after DOI injection increased to 294 ± 50% ($n = 4$) of the value immediately before cyclobenzaprine administration and this increase lasted for over 60 min. This effect of DOI was virtually abolished ($P < 0.01$, at 5 min) by treatment with 1.0 mg/kg cyclobenzaprine (Fig. 4). Ketanserin tartrate (1.0 mg/kg i.v.), a 5-HT_2 receptor antag-

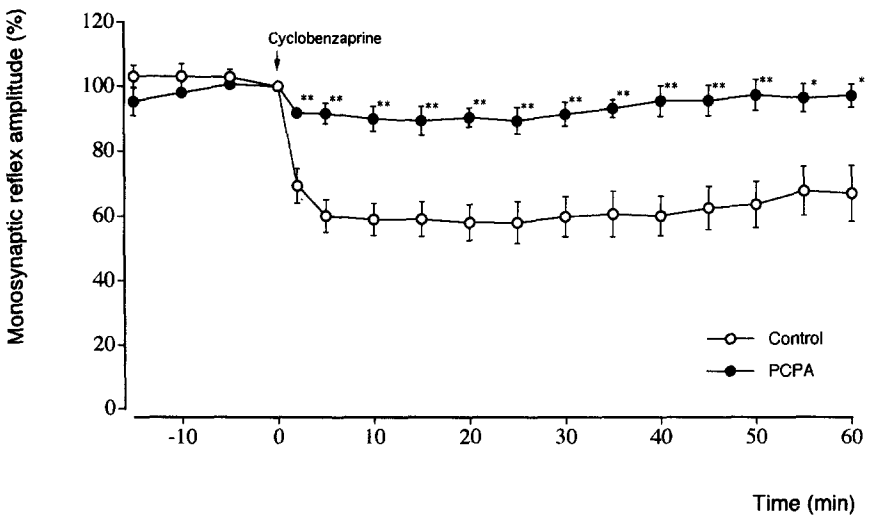

Fig. 5. Effect of cyclobenzaprine on the monosynaptic reflex in p-chlorophenylalanine (PCPA)-treated rats. PCPA (300 mg/kg/day i.p.) was given on days 1–3 before the monosynaptic reflex measurement. Each point represents the mean ± S.E. ($n = 4$) of the amplitude calculated as a % of the value immediately prior to cyclobenzaprine administration. The significance of each difference was determined by Student's t-test, two-tailed, * $P < 0.05$, * * $P < 0.01$.

onist, also significantly ($P < 0.005$, at 5 min) inhibited this effect of DOI. The monosynaptic reflex amplitudes were 115 ± 1.2 and $110 \pm 4.7\%$ (both $n = 4$) of the values immediately before DOI administration in cyclobenzaprine- and ketanserin-treated rats, respectively. In spinalized rats, cyclobenzaprine and ketanserin, at the above doses, themselves had no significant effect on the monosynaptic reflex amplitude.

3.5. Effect of DL-p-chlorophenylalanine treatment on the cyclobenzaprine-induced monosynaptic reflex depression in non-spinalized rats

The inhibitory action of cyclobenzaprine on the monosynaptic reflex in non-spinalized rats was virtually abolished by DL-*p*-chlorophenylalanine treatment (Fig. 5). The monosynaptic reflex amplitude 10 min after cyclobenzaprine administration was reduced to $59 \pm 4.9\%$ ($n = 4$) of the preadministration value in the control rats, whereas that in the DL-*p*-chlorophenylalanine-treated rats was $90 \pm 3.8\%$ ($n = 4$). These values differed significantly ($P < 0.01$).

The 5-HT content was reduced by 96.6% in the spinal cord of the DL-*p*-chlorophenylalanine-treated non-spinalized rats. The net 5-HT content was 457.4 ± 55.1 (control, $n = 5$) and 15.6 ± 0.7 (DL-*p*-chlorophenylalanine-treated, $n = 5$) ng/g wet tissue in the spinal cord. The noradrenaline content was 288.1 ± 19.3 (control, $n = 5$) and 169.7 ± 16.7 (DL-*p*-chlorophenylalanine-treated, $n = 5$) ng/g wet tissue in the spinal cord. The decrease in noradrenaline ($P < 0.01$) and 5-HT ($P < 0.001$) was significant.

4. Discussion

It is reported that cyclobenzaprine (Barnes et al., 1980), as well as the α_2-adrenoceptor agonist tizanidine (Palmeri and Wiesendanger, 1990), decreases the spontaneous firing rate of the locus coeruleus. Also, it is reported that the effect of cyclobenzaprine on the monosynaptic reflex in cats is antagonized by phenoxybenzamine (Barnes et al., 1980). In the light of these results, Fung et al. (1991) suggested that the action of cyclobenzaprine on the monosynaptic reflex was mediated by α_2-adrenoceptors. However, the selectivity of phenoxybenzamine is relatively poor, and 5-HT_2 receptors (Gaddum and Picrelli, 1957; Hindle, 1994) and 5-HT-induced inositol phospholipid hydrolysis (Kendall and Nahorski, 1985) are also blocked by phenoxybenzamine treatment, showing that it is difficult to separate the noradrenergic and serotonergic effects of cyclobenzaprine. Taking these findings into account, we used the more selective α_2-adrenoceptor antagonists idazoxan and yohimbine in the present study. Idazoxan blocked the depressant effect of cyclobenzaprine during the first few minutes after its administration, but did not affect the maximum cyclobenzaprine-induced depression (Fig. 2). This blockade may have been due to the facilitatory effect of idazoxan on the descending noradrenergic neurons and subsequent enhancement of α-motoneuronal excitation. Unlike idazoxan, yohimbine itself reduced the monosynaptic reflex amplitude, but had no effect on the cyclobenzaprine-induced monosynaptic reflex depression (Fig. 2). In some respects, idazoxan and yohimbine appear to differ pharmacologically. Idazoxan, but not yohimbine, was demonstrated to bind to imidazoline receptors existing in the rat brainstem (Boyajian et al., 1987; MacKinnon et al., 1989). The opposite actions of idazoxan and yohimbine on the monosynaptic reflex may be attributable to these differences, but this is uncertain from the results of the present study. The finding that neither drug inhibited the effect of cyclobenzaprine suggests that the monosynaptic reflex depressant effect of cyclobenzaprine is not mediated by α_2-adrenoceptors.

It has been thought that the muscle relaxant effect of cyclobenzaprine is due to the decrease of the firing rate of the locus coeruleus, because descending noradrenergic neurons originating from the locus coeruleus increase the excitability of spinal α-motoneurons (Fung et al., 1991). 6-Hydroxydopamine almost completely destroyed noradrenergic neurons and depleted NE in the spinal cord in the present study, and the effect of the descending noradrenergic neurons on spinal α-motoneurons should be abolished after 6-hydroxydopamine treatment. It is also reported that noradrenergic locus coeruleus neurons project to raphe neurons, and that 6-hydroxydopamine treatment may change the characteristics of the facilitation of α-motoneurons via descending serotonergic neurons. Thus, we cannot totally exclude the interactions between raphe and locus coeruleus nuclei at the brainstem level in the effect of cyclobenzaprine. However, the effect of cyclobenzaprine on the monosynaptic reflex was not inhibited by 6-hydroxydopamine treatment in the present study (Fig. 3), which indicates that descending noradrenergic neurons had little effect on the muscle relaxant action of cyclobenzaprine.

5-HT-containing neurons originating from the medullary raphe nuclei innervate the ventral horn of the spinal cord (Jones and Light, 1990). In general, raphe nuclei neurons are autoactive and discharge tonically. It has been shown that 5-HT_{1B}, 5-HT_{1C} and 5-HT_2 receptors mediate motoneuronal excitation (Jackson and White, 1990; Yamazaki et al., 1992). Direct stimulation of the nucleus raphe pallidus (Fung and Barnes, 1989) and raphe obscurus (Roberts et al., 1988) excites α-motoneurons and the descending serotonergic neurons probably influence the spinal motor systems. In fact, Han-Wistar rats, which are mutant spastic animals, have high brain contents of 5-HT and their rigidity is considered to be due to hyperactivity of serotonergic systems (Kehr, 1981). The evidence that stimulation of the nucleus raphe pallidus and raphe obscurus evokes hindlimb muscle rigidity (Hammond and Yaksh,

1984) also suggests a relationship between muscle rigidity and the descending serotonergic system.

DL-*p*-Chlorophenylalanine inhibits 5-HT synthesis and causes extensive 5-HT depletion. DL-*p*-Chlorophenylalanine treatment blocked cyclobenzaprine-induced monosynaptic reflex depression significantly (Fig. 5). DL-*p*-Chlorophenylalanine depletes 5-HT almost completely, but also reduces noradrenaline and dopamine contents to some extent. However, a contribution of a DL-*p*-chlorophenylalanine-induced decrease in the spinal cord noradrenaline content on the action of cyclobenzaprine can be excluded, because, in the present study, destruction of the descending noradrenergic neurons by 6-hydroxydopamine did not inhibit the action of cyclobenzaprine. Furthermore, the functional role of descending dopaminergic systems in the monosynaptic reflex was found to be negligible in comparison with that of the noradrenergic and serotonergic systems in a previous study (Kamijo et al., 1993). Therefore, serotonergic neurons appear to be necessary for the action of cyclobenzaprine.

In the present study, cyclobenzaprine reduced the monosynaptic reflex amplitude in intact rats, but had no effect in spinalized rats (Fig. 1). However, cyclobenzaprine abolished the facilitatory effect of the 5-HT_2 receptor agonist DOI on the monosynaptic reflex in spinalized rats. As the 5-HT_2 receptor antagonist ketanserin also blocked this DOI-induced facilitation (Fig. 4; Yamazaki et al., 1992), we concluded that this effect of DOI is mediated by 5-HT_2 receptors and therefore cyclobenzaprine seems to act as a 5-HT_2 receptor antagonist. It was also found that cyclobenzaprine bound strongly to 5-HT_2 receptors (K_i to 5-HT_1 receptor = 2900 nM, 5-HT_2 receptor = 62 nM) in a preliminary study (not shown in results). [^{3}H]5-HT and [^{3}H]RP62203 were used to identify 5-HT_1 and 5-HT_2 receptor, respectively. Thus, we propose that the mechanism responsible for the muscle relaxant action of cyclobenzaprine is inhibition of α-motoneuronal excitation as a result of the blockade of postsynaptic 5-HT_2 receptor in the spinal cord. The monosynaptic reflex amplitude was reduced by cyclobenzaprine in non-spinalized, but not spinalized, rats. As spinalized animals are disconnected from the serotonergic nerve nuclei, the lack of an effect of cyclobenzaprine on the monosynaptic reflex is not surprising in view of the above findings. This agrees with the reports that cyclobenzaprine had little effect on postsynaptic inhibition (Esplin and Capek, 1979) and spinal interneurons (Barnes and Adams, 1978) in spinalized cats.

Lang and Barnes (1983) have explained the contradictory effects of cyclobenzaprine on the locus coeruleus. They showed that cyclobenzaprine increased the firing rate of slow-firing locus coeruleus neurons and decreased that of fast-firing locus coeruleus neurons. In the present study, cyclobenzaprine was shown to attenuate the action of a 5-HT_2 receptor agonist (DOI) at the spinal cord level, and it seems that cyclobenzaprine also acts as a 5-HT_2 receptor antagonist in the brainstem. As serotonergic neurons are reported to project to the locus coeruleus and 5-HT_2 receptor agonists have been reported to decrease the firing rate of the locus coeruleus (Chiang and Aston-Jones, 1993; Gorea and Adrien, 1988), it is suggested that cyclobenzaprine increases the activity of the locus coeruleus via 5-HT_2 receptor blockade, but this does not explain the depressive effect of cyclobenzaprine on the firing rate of the locus coeruleus. There may be other types of receptors that participate in the effect of cyclobenzaprine on the locus coeruleus, but it is not clear from the present study. Species differences may also contribute to this complex change in the firing rate of the locus coeruleus.

In conclusion, different from other centrally acting muscle relaxants, cyclobenzaprine blocks tonic α-motoneuronal excitation produced by serotonergic descending neurons. The blockade of 5-HT_2 receptors seems to be the major action of cyclobenzaprine as muscle relaxant.

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