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Efficacy of pramipexole, a new dopamine receptor agonist, to relieve the parkinsonian-like muscle rigidity in rats

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Abstract

The aim of the present study was to assess the efficacy of pramipexole (2-amino-4,5,6,7-tetrahydro-6-propyl-amino-benzthiazole-dihydrochloride), a new dopamine D_2/D_3 receptor agonist, to attenuate parkinsonian-like muscle rigidity in rats. Muscle tone was examined using a combined mechano- and electromyographic (EMG) method, which simultaneously measured the muscle resistance of a rat's hindlimb to passive extension and flexion at the ankle joint, and the EMG acitivity of the antagonistic muscles of that joint: gastrocnemius and tibialis anterior. Muscle rigidity was produced by reserpine (5 mg/kg) injected in combination with α-methyl-p-tyrosine (250 mg/kg) or by haloperidol (0.5 mg/kg). Pramipexole in doses of 0.5–5 mg/kg antagonized both reserpine + α-methyl-*p*-tyrosine- and haloperidol-induced muscle rigidity. Pramipexole also reduced reserpine-enhanced tonic and reflex EMG activities in the gastrocnemius muscle. The present results suggest that stimulation of the postsynaptic dopamine receptor may be chiefly responsible for the antiparkinsonian action of pramipexole. The ability of pramipexole to diminish the parkinsonian-like muscle rigidity seems to indicate a therapeutic value of this compound in the treatment of Parkinson's disease.

Keywords: Dopamine receptor agonist; Electromyogram; Mechanomyogram; Muscle rigidity; Parkinsonism; Pramipexole

1. Introduction

It is widely accepted that the primary cause of Parkinson's disease is a progressive degeneration of nigral dopamine neurons (Bernheimer et al., 1973; Forno, 1982; Hornykiewicz, 1998) which leads to a substantial decrease in the dopamine level in the caudate nucleus and putamen (Hornykiewicz, 1982, 1993; Hornykiewicz and Kish, 1986). A deficit of this neurotransmitter is directly linked to the appearance of numerous symptoms of this disease, such as akinesia, muscle rigidity and tremor (Hornykiewicz, 1989; Hornykiewicz and Kish, 1986; McGeer et al., 1989). Substitutive administration of levodopa (L-DOPA) is the most effective and commonly used treatment in Parkinson's disease (Piccoli and Riuggeri, 1995). However, this therapeutic strategy is often complicated by severe side-effects such as psychoses, dyskinesia and on–off phenomena (Forno, 1982; Rinne, 1983; Fahn, 1992; Hagan et al., 1997). This disadvantage of L-DOPA therapy imposes major limitations on long-term, effective application of this drug. Dopamine receptor agonists comprise a class of drugs which are efficacious in the treatment of both early and advanced stages of Parkinson's disease (Lieberman et al., 1987; Molho et al., 1995).

Pramipexole (SND 919; 2-amino-4,5,6,7-tetrahydro-6-propyl-amino-benzthiazole-dihydrochloride) is a novel, highly active, full dopamine receptor agonist which acts on the D_2 receptor family with a preferential affinity for the D_3 type (Schneider and Mierau, 1987; Carter and Müller, 1991; Mierau and Schingnitz, 1992; Mierau et al., 1995; Sautel et al., 1995). On one hand, this compound was found to inhibit dopamine synthesis and release (Carter and Müller, 1991; Mierau, 1995; Mierau and Schingnitz, 1992), as well as dopaminergic firing rate (Piercey et al., 1995) by a negative feedback mechanism via dopamine autoreceptors. On the other hand, by stimulating dopamine D_2 postsynaptic receptors, pramipexole induces contralateral rotations in rats with a unilateral 6-hydroxydopamine (6-OHDA) lesion of the medial forebrain bundle and an-

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tagonizes parkinsonian-like symptoms in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) pretreated monkeys (Mierau, 1995; Mierau and Schingnitz, 1992). It was also shown that pramipexole antagonizes the reserpine-induced akinesia and neuroleptic-induced catalepsy (Maj et al., 1997). The above data show that due to stimulation of dopamine D_2 postsynaptic receptors, pramipexole appears to have a high antiparkinsonian potential.

We have recently demonstrated that muscle rigidity induced by reserpine or haloperidol in rats (Lorenc-Koci et al., 1995, 1996) is similar to that in parkinsonian patients (Mortimer and Webster, 1979). This rigidity develops in response to passive movements and is characterized by both enhanced muscle resistance and an increased electromyographic (EMG) reflex activity.

The aim of present study was to find out whether pramipexole, a new dopamine D_2/D_3 receptor agonist, is capable of counteracting reserpine- or haloperidol-induced muscle rigidity in rats.

2. Materials and methods

The experiment was carried out in compliance with the Animal Protection Bill of August 21, 1997 (published in Poland's Current Legislation Gazette [Dziennik Ustaw] no. 111/1997 item. 724), and according to the NIH guide for the Care and Use of Laboratory Animals.

2.1. Animals and drugs

The experiment was carried out in two groups of male Wistar rats weighing 270–340 g. Muscle rigidity was induced by reserpine (5 mg/kg, i.p.) or haloperidol (0.5 mg/kg, i.p.) administration. Reserpine (Polfa, Warszawa) was dissolved in a solution containing 0.25% citric acid, 2% benzyl alcohol and 10% Tween 80. Haloperidol (RBI, Research Biochemicals International) was dissolved in a small volume of 1% lactic acid and diluted to a final concentration with distilled water. Pramipexole (Boehringer-Ingelheim) was dissolved in a physiological solution of saline.

In the first group, rats treated with reserpine (5 mg/kg, i.p.) received additionally, 16 h later, α-methyl-*p*-tyrosine (250 mg/kg). The mechano- and electromyographic experiment started 20 h after administration of reserpine, 4 h after α-methyl-*p*-tyrosine and 15 min after pramipexole (0.5 and 1 mg/kg, s.c.), and lasted 90 min. In the second group, rats were pretreated with haloperidol (0.5 mg/kg), and 45 min later pramipexole in doses of 3 and 5 mg/kg was injected s.c. Mechano- and electromyographic measurements began 1 h after administration of haloperidol and 15 min after pramipexole, and lasted 60 min. Control animals received the vehicle only instead of pramipexole.

2.2. Mechano- and electromyographic measurements

Each rat was placed in a Metaplex cage, well ventilated and adapted to the animal's size. The hindfoot of rat, which protruded from an opening at the bottom of the cage, was placed on an appropriately matched Metaplex block and gently fixed to it with adhesive tape as in the previously described experiment of Ossowska et al. (1996). Two pairs of flexible stainless-steel wire electrodes (Cooner Wire, Chatsworth, CA, USA; e.d. 0.25 mm), were inserted percutaneously into the gastrocnemius (extensor, plantar flexor) and tibialis anterior (flexor, dorsal flexor) muscles to record EMG activity. Due to its influence on reflex activity, no local anaesthetic could be given for the insertion of electrodes. The distance between the two electrodes of a pair in each muscle was ca. 5 mm. A ground electrode was attached to the rat's tail.

The experiment consisted of 90 or 60 successive episodes of down and up movements (30 s apart) of the block which flexed and extended the rat's hindfoot at the ankle joint by 25°. Each movement lasted 250 ms. A force sensor recorded the resistance of the foot to passive movements (a mechanical moment, torque). EMG signals from the electrodes were amplified and band-pass-filtered (80 Hz to 10 kHz; Polygraph Grass, model 78). The recording of mechano- and electromyographic signals started 200 ms earlier, and was continued for 250 ms throughout each passive movement and 550 ms after its termination. Mechano- and electromyographic signals were sampled by analog–digital converters, with a frequency of 10 kHz per channel, and were fed into a PC. The maximum resistance (maximum torque (gcm); in comparison with the pre-movement value) of hindlimb muscles for each down (extension) or up (flexion) movement was determined.

The EMG activity of the gastrocnemius and tibialis anterior muscles was rectified and averaged with a time constant of 20 ms for each down and up movement. The EMG curves thus formed were composed of points spaced 20 ms apart. A further analysis was carried out using the averaged EMG curves. The following parameters were estimated for each movement.

(1) The mean pre-movement amplitude (EMG baseline, resting EMG activity); (2) components computed as differences between the maximum amplitude of the averaged EMG curves at three time points after the start of a movement, and the baseline: (a) EMG-A (0–20 ms); b) EMG-B (60–160 ms) and EMG-C (220–340 ms). Any cycles disturbed by voluntary movements of an animal were discarded. In order to visualize the main tendency of a time course of the EMG activity during a movement, all individual EMG curves for each group of rats were superimposed and averaged for either muscle or movement.

2.3. Statisics

Statistical analysis of maximum resistance values was carried out using the means calculated for each group of

rats. First, mean maximum resistance values were calculated for the whole experimental session (90 or 60 min, depending on the experimental group) for each rat; afterwards, mean maximum resistance values were calculated for each experimental group. Mean values of the EMG parameters were calculated likewise. The statistical significance of differences was estimated using the Kruskal–Wallis and the Wilcoxon tests.

3. Results

3.1. Mechanogram

In the first experimental group, reserpine, 5 mg/kg, administered in combination with α-methyl-*p*-tyrosine (250 mg/kg), induced muscle rigidity, measured in rats as increased muscle resistance developed in response to passive extension or flexion of the rat's hindlimb at the ankle joint. Twenty hours after injection of this dose of reserpine, when dopamine in a rat's brain was almost completely depleted from nigrostriatal terminals (Elverfors and Nissbrandt, 1991), the recorded muscle tone was significantly enhanced in comparison with that in control, solvent-treated rats. The observed increase in muscle tone was slightly stronger during flexion than during extension (Fig. 1A,B). Pramipexole, 0.5 and 1 mg/kg, injected subcutanously 15 min before the start of measurements, antagonized the reserpine-induced muscle rigidity during both extension and flexion of the hindfoot (Fig. 1A,B). The effect of pramipexole to decrease the reserpine-enhanced muscle tone persisted throughout the whole measurement period (90 min).

In the second experimental group, haloperidol, 0.5 mg/kg, was used, this being the lowest dose which could still produce muscle rigidity measured as enhanced muscle resistance to passive movements (Lorenc-Koci et al., 1996). One hour after haloperidol administration, muscle tone was significantly increased compared to that in a control, solvent-treated group (Fig. 2A,B). Moreover, the above dose of haloperidol did not evoke a complete blockade of dopamine receptors. Pramipexole, 3 and 5 mg/kg, caused a significant decrease in the haloperidol-induced muscle resistance to passive movements during both extension and flexion of the rat's hindlimb at the ankle joint.

3.2. Electromyogram

Tonic and reflex EMG activities are regarded as equivalents of muscle tone, and are recorded from the two antagonistic muscles: m. gastrocnemius and m. tibialis anterior before and during passive extension and flexion of the rat's hindlimb at the ankle joint. The rectified and averaged EMG activities, shown in Figs. 3 and 6 in the form of curves, illustrate the time-course and the intensity of EMG activities in two experimental groups. The first part of each curve (between −200 and 0 ms), recorded before the start of a movement, represents tonic (resting)

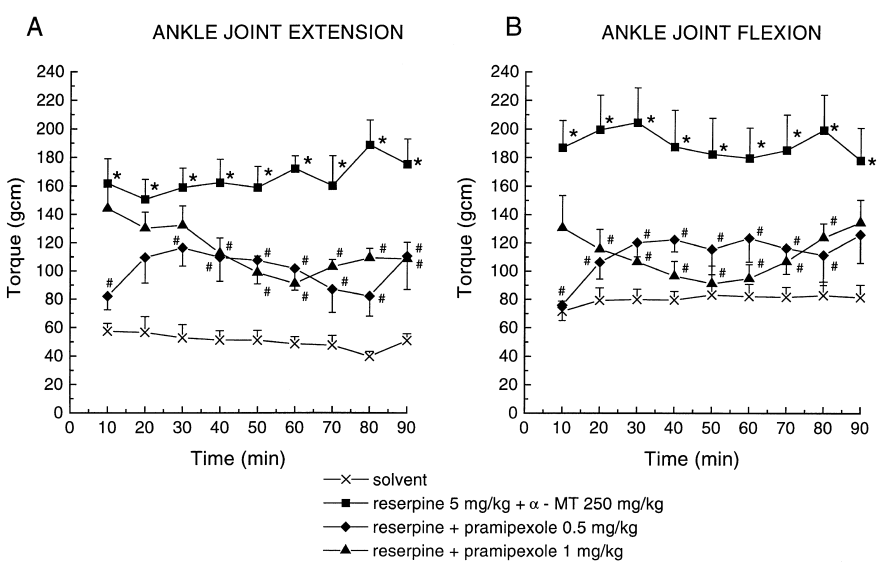

Fig 1. The effect of pramipexole (0.5 and 1 mg/kg) administration on the reserpine (5 mg/kg) + α-methyl-*p*-tyrosine (α-MT, 250 mg/kg)-enhanced muscle tone, developed during passive extension (A) and flexion (B) of the rat's hindfoot at the ankle joint. Measurements started 20 h after reserpine, 4 h after α-methyl-*p*-tyrosine, and 15 min after pramipexole injection. Abscissa, time in min; ordinate maximum torque in gcm. The results are shown as means ± S.E.M.; statistically significant differences (the Kruskal–Wallis and Wilcoxon tests) at the level $p < 0.01$ (*) vs. control, solvent-treated animals, $p < 0.05$ (#) vs. reserpine 5 + α-MT. The number of animals in experimental groups — control: $n = 10$; reserpine: 5 + α-MT $n = 9$; pramipexole: 0.5 mg/kg $n = 9$, 1 mg/kg $n = 10$.

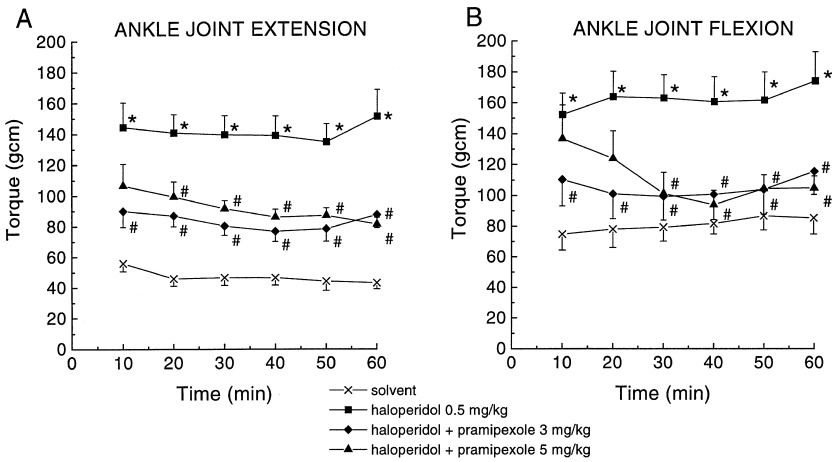

Fig 2. The effect of pramipexole (3 and 5 mg/kg) on the haloperidol-induced muscle tone developed during passive extension (A) and flexion (B) of the rat's hindfoot at the ankle joint. Measurements started 1 h after haloperidol, and 15 min after pramipexole injection. Abscissa, time in min; ordinate maximum torque in gcm. The results are shown as means ± S.E.M.; statistically significant differences (the Kruskal–Wallis and Wilcoxon tests) at the level $p < 0.01$ (*) vs. control, solvent-treated animals; $p < 0.05$ (#) vs. haloperidol 0.5 mg/kg. The number of animals in experimental groups — control: $n = 10$; haloperidol: 0.5 mg/kg $n = 10$; pramipexole: 3 mg/kg $n = 9$ and 5 mg/kg $n = 10$.

EMG activity (EMG baseline). Reflex EMG activity started within 20 ms; it is the so-called short-latency activity (EMG-A), which is of spinal origin. Afterwards, the EMG activity increased gradually (EMG-B, EMG-C) until the

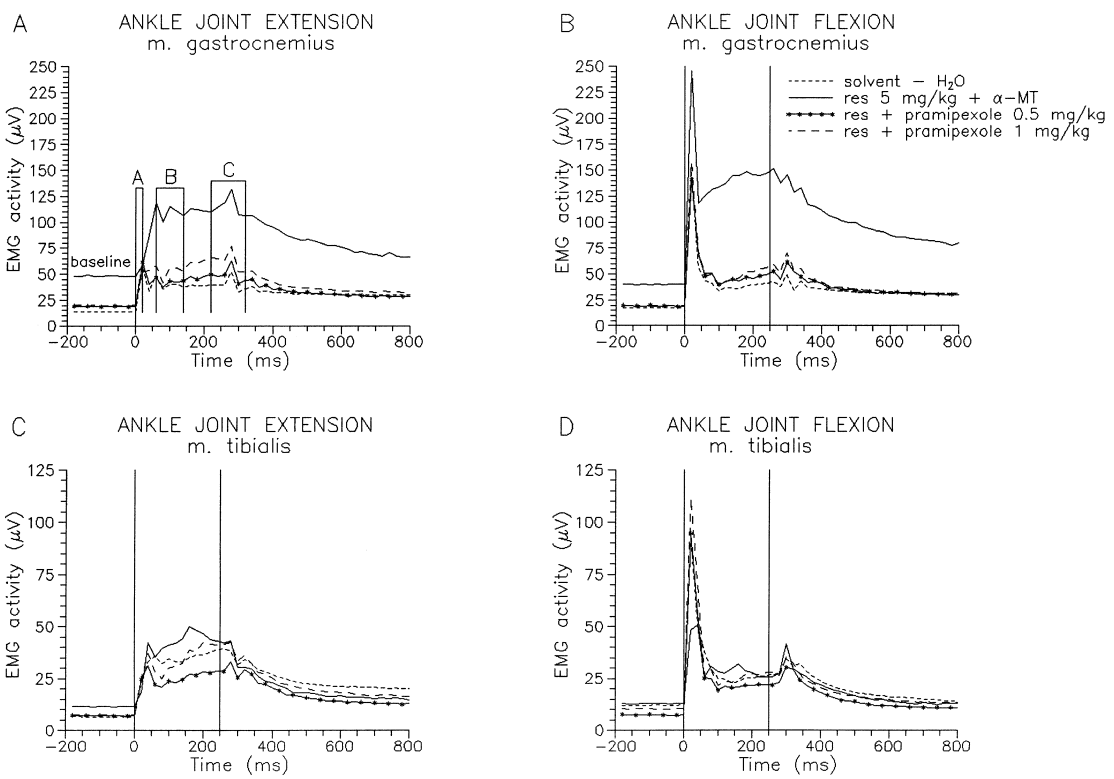

Fig 3. Electromyographic activity (EMG), recorded from the gastrocnemius (A,B) and tibialis anterior (C,D) muscles, during ankle joint extension and flexion in control, reserpine (res) + α-methyl-*p*-tyrosine (α-MT) and reserpine + α-MT + pramipexole-treated rats. EMG activity was rectified and averaged with a time constant of 20 ms. Curves were obtained by superimposing the EMG curves of all the undisturbed individual cycles, recorded for all rats in each group. The number of animals in each group — control: $n = 10$; haloperidol: 0.5 mg/kg $n = 10$; pramipexole: 0.5 mg/kg $n = 9$ and 1 mg/kg $n = 10$. (A) Four components are shown: EMG baseline (estimated before movements), EMG-A, EMG-B and EMG-C (estimated at 0–20, 60–160, and 220–340 ms after the start of movements). (B–D) Vertical lines denote the start and the end of a movement, respectively. Abscissa, time in ms; ordinate, EMG activity in μV.

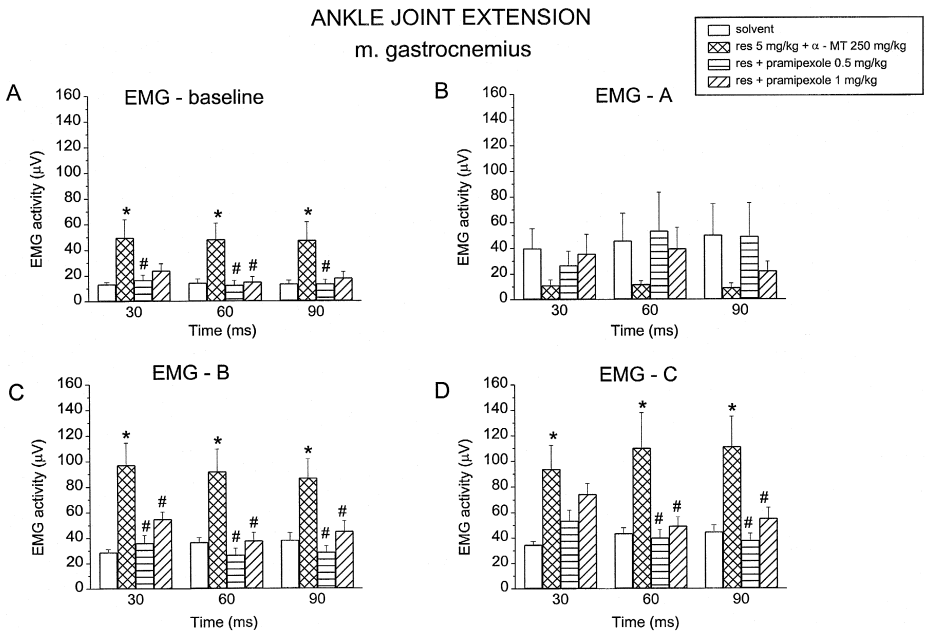

Fig 4. Quantitative comparison of the EMG activity recorded from the gastrocnemius muscle during extension in control, reserpine (res) + α-methyl-*p*-tyrosine (α-MT) and reserpine + α-MT + pramipexole-treated rats. The results are shown as means + S.E.M.; statistically significant differences (the Kruskal–Wallis and Wilcoxon tests) at the level $p < 0.01$ (*) vs. control, solvent-treated animals; $p < 0.05$ (#) vs. reserpine 5 + α-MT. For further explanations, see Fig. 3.

end of movements (250 ms), after which it slowly decreased. The other part of EMG activity had a long latency and is considered to be of supraspinal origin.

In the first experimental group, systemic injection of reserpine 5 mg/kg given jointly with α-methyl-*p*-tyrosine (250 mg/kg), at 20 h after administration potently affected the EMG activity in the gastrocnemius muscle during both extension and flexion, whereas in the tibialis anterior muscle, this combination did not change the physiological EMG response to movements (Fig. 3A–D). In the gastroc-

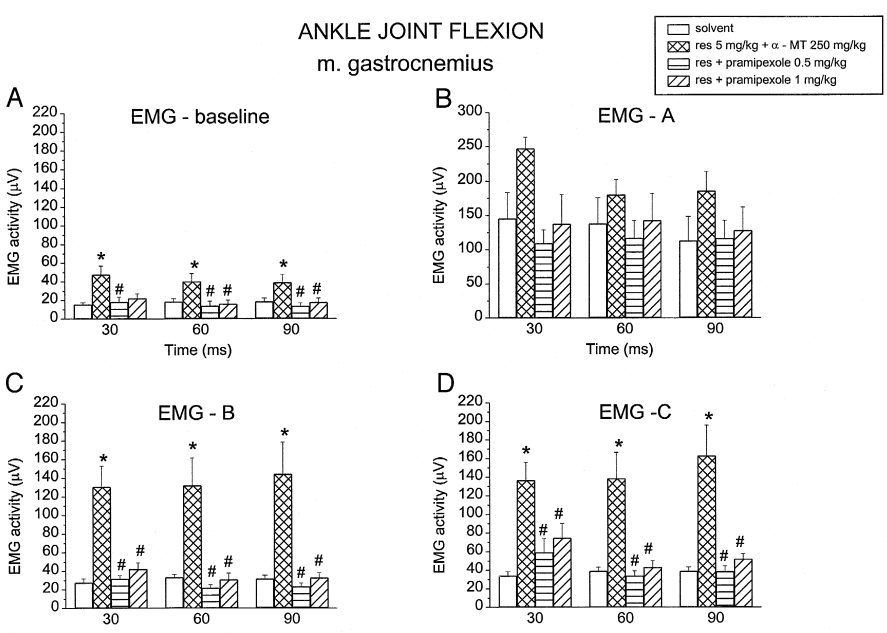

Fig 5. Quantitative comparison of EMG activity recorded from the gastrocnemius muscle during flexion in control, reserpine (res) + α-methyl-*p*-tyrosine (α-MT) and reserpine + α-MT + pramipexole-treated rats. The results are shown as means + S.E.M.; statistically significant differences (the Kruskal–Wallis and Wilcoxon tests) at the level $p < 0.01$ (*) vs. control, solvent-treated animals; $p < 0.05$ (#) vs. reserpine 5 + α-MT. For further explanations, see Fig. 3.

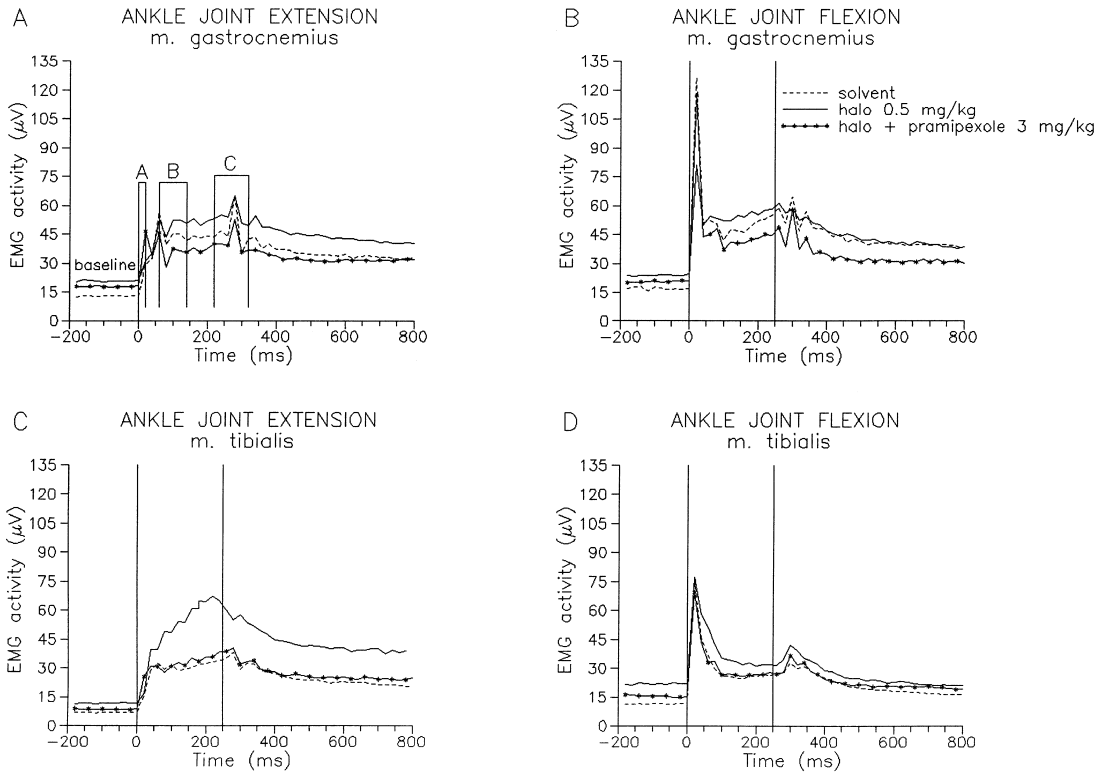

Fig 6. Electromyographic (EMG) activity recorded from the gastrocnemius (A,B) and tibialis anterior (C,D) muscles during ankle joint extension and flexion in control, haloperidol (halo) and haloperidol + pramipexole-treated rats. Haloperidol (0.5 mg/kg, i.p.) was injected 1 h before measurements. EMG activity was recorded 1 h after haloperidol, and 15 min after pramipexole (3 and 5 mg/kg, s.c.) administration. The number of animals in experimental groups — control: $n = 10$; haloperidol: 0.5 mg/kg $n = 10$; pramipexole: 3 mg/kg $n = 9$. For further explanations, see Fig. 3.

nemius muscle, reserpine caused a significant increase in the spontaneous, tonic EMG activity (pre-movement amplitude, EMG baseline; Figs. 3A–B, 4A, 5A), as well as and in long-latency reflex EMG activity (components EMG-B, EMG-C; Figs. 3A–B, 4C–D, 5C–D) in comparison with the control, solvent-treated group. Only the short-latency EMG reflex activity (EMG-A), after reserpine injection showed no significant differences in either muscle examined and movements in comparison with the control, solvent-treated group (Figs. 3A–D, 4B, 5B). Administration of pramipexole (0.5 and 1 mg/kg), a new dopamine D_2/D_3 receptor agonist, significantly decreased both the tonic (EMG baseline) and the reflex EMG activity (EMG-B, EMG-C) in the gastrocnemius muscle during either movement (Figs. 4–5).

In the second experimental group, the dose of haloperidol used (0.5 mg/kg) only slightly enhanced the tonic and the reflex EMG activities; however, the results did not reach statistical significance (Fig. 6). However, higher doses of haloperidol (2.5–10 mg/kg) significantly increased the tonic and reflex EMG activities (Lorenc-Koci et al., 1996) and at the same time completely blocked dopamine receptors. Pramipexole in the doses used (3 and 5 mg/kg) was without effect on the tonic and the early short latency EMG reflex activities (EMG-A) (Fig. 6). However, administration of this compound produced a decreasing tendency to long-latency EMG activity (EMG-B, EMG-C), especially in the gastrocnemius during either movement, and in the tibialis during extension, these effects not being statistically significant (Fig. 6).

4. Discussion

The present results indicated that pramipexole, a new dopamine D_2/D_3 receptor agonist, attenuates the parkinsonian-like muscle rigidity induced by model substances such as reserpine and haloperidol in rats. The drug tested affected muscle rigidity measured as muscle resistance to passive movements in either model. As far as EMG activity, i.e., the second equivalent of muscle tone, is concerned, pramipexole significantly diminished the tonic and the long-latency reflex EMG activities in the reserpine model, whereas, in the haloperidol model of muscle rigidity, only a slight decreasing tendency to long latency EMG activity was observed. A stimulatory action of pramipexole on postsynaptic dopamine receptors seems to be responsible for the above-described effect.

Although the level of muscle rigidity, measured as muscle resistance to passive movements, was fairly similar after both reserpine and haloperidol treatments, the doses of pramipexole were different. The reserpine-induced mus-

cle rigidity was antagonized by postsynaptic doses of pramipexole (0.5 and 1 mg/kg) lower than those used for the haloperidol-enhanced muscle tone (3 and 5 mg/kg). It is well known that reserpine evokes its behavioural effects by depleting dopamine from nigrostratal terminals. The lack of dopamine in the synaptic cleft changes neuronal signalling and leads to an increased sensitivity of dopamine receptors (LaHoste and Marshall, 1994). More sensitive dopamine receptors respond more readily to the dopamine agonist. Therefore, it was possible to use lower doses of pramipexole than that applied in the haloperidol model of muscle rigidity to counteract reserpine-induced muscle rigidity. A similar, more potent stimulating action of pramipexole was also observed by Mierau and Schingnitz (1992) in MPTP-pretreated monkeys, or in rats with a unilateral 6-OHDA lesion of the medial forebrain bundle.

However, in contrast to the reserpine-model of muscle rigidity where the dopamine receptors are free, in the haloperidol model of muscle rigidity these receptors are occupied by haloperidol, which is a potent antagonist of dopamine D_2 receptors (Elliot et al., 1990). It has been postulated that both the catalepsy and the muscle rigidity induced by this drug result from the blockade of dopamine D_2 receptors in the corpus striatum (Ellenbroek et al., 1985; Ossowska et al., 1990). The affinity of haloperidol for striatal dopamine D_2 receptors is considerably higher than the affinity of dopamine and other dopamine agonists (Piercey et al. 1995) for these receptors. Although the dose of 0.5 mg/kg of haloperidol used in the present experiment was the lowest dose which evoked muscle rigidity (Lorenc-Koci et al. 1996), the blockade of dopamine receptors was relatively strong; therefore it was not surprising that high doses of pramipexole (3 and 5 mg/kg) were necessary to compete for dopamine receptors and to antagonize muscle rigidity.

Being an efficient antiparkinsonian drug, pramipexole not only attenuates the muscle rigidity (present data) and allows the performance of movements, but also stimulates locomotor activity, especially at higher doses (Maj et al. 1997). The lack of dose dependence, ascertained both in the reserpine and the haloperidol studies, seems to be due to the fact that higher doses of pramipexole stimulate locomotor activity more potently than do lower ones; thus it is possible that some active movements, which are sometimes difficult to distinguish from passive ones, may enhance a rat's end response to movements.

Besides its stimulatory action on the dopamine D_2 postsynaptic receptor, pramipexole exerts a similar effect on the dopamine D_3 receptor also. However, the latter receptor type has been less thoroughly studied than have classical dopamine $D_1$and D_2 receptors; moreover, it is not clear whether stimulation of this receptor may contribute to the regulation of muscle tone.

Summing up, our present data confirm that pramipexole, which is now commercially available for the treatment of Parkinson's disease, is also a useful and efficacious drug to relieve muscle rigidity of a parkinsonian type. This compound is currently under study in the clinic (Molho et al., 1995; Lieberman et al., 1997; Shannon et al., 1997). The plasma elimination half-life of pramipexole is approximately 7–9 h, which is long enough to make it a drug suitable for oral administration in patients with Parkinson's disease characterized by short-lasting L-DOPA responses (Uitti and Ahlskog 1996). The first clinical experiments with pramipexole also seem to confirm that this compound is likely to produce long-lasting, significant antiparkinsonian effects (Lieberman et al. 1997; Shannon et al. 1997).

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