The Effects of Centrally Acting Muscle Relaxants on the Intrathecal Noradrenaline-Induced Facilitation of the Flexor Reflex Mediated by Group II Afferent Fibers in Rats

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Received June 14, 1993 Accepted August 16, 1993

ABSTRACT—The effects of centrally acting muscle relaxants on the flexor reflex mediated by group II afferent fibers (group II flexor reflex) in anesthetized intact rats and on the intrathecal noradrenaline-HCl-induced facilitation of the group II flexor reflex in anesthetized spinal rats were investigated. In anesthetized intact rats, mephenesin, tolperisone-HCl, chlorpromazine-HCl and baclofen inhibited the group II flexor reflex dose-dependently, whereas the inhibitory effect of tizanidine-HCl was bell-shaped. The effect of diazepam tended to be saturated. In anesthetized spinal rats, mephenesin, tolperisone-HCl, chlorpromazine-HCl, diazepam and baclofen also depressed the group II flexor reflex, but tizanidine-HCl slightly increased it. The intrathecal noradrenaline-HCl-induced facilitation of the group II flexor reflex was not affected by mephenesin or diazepam, but was inhibited by tizanidine-HCl, tolperisone-HCl, chlorpromazine-HCl and baclofen. These results suggest that compounds with centrally acting muscle relaxant activity depress the group II flexor reflex in different manners, and the inhibition of descending noradrenergic tonic facilitation within the spinal cord participates in the depressant action of the group II flexor reflex produced by tolperisone-HCl, tizanidine-HCl, chlorpromazine-HCl and baclofen.

Keywords: Centrally acting muscle relaxant, Flexor reflex, Afferent fiber (group II), Noradrenaline

Noradrenergic neurons arising from the nucleus locus ceruleus and the subjacent subcoeruleus/medial parabrachial nuclear complex innervate the ventral horns of the spinal cord (1) and exert tonic facilitatory effects via $\alpha_2$-receptors on the motor mechanisms (including spinal reflexes) (2). Centrally acting muscle relaxants (CAMRs), used for the treatment of spasticity, are known to inhibit the spinal reflexes. Tizanidine, a CAMR, was suggested to depress the spinal reflex due to its $\alpha_2$-autoinhibitory action at the level of the locus coeruleus, resulting in the suppression of the descending noradrenergic tonic facilitation (DNTF) of the spinal reflexes (3). Chlorpromazine, which has CAMR activity, has been reported to exhibit an $\alpha$-blocking action within the spinal cord (4–6) which causes a blockade of the DNTF and inhibition of the spinal reflexes. The above results suggest the possibility that the inhibitory effects of CAMRs on the spinal reflexes are exerted, at least in part, through their depressive action on the DNTF. For as CAMRs other than tizanidine and chlorpromazine, supraspinal actions (7–9), an $\alpha$-blocking action (10) or relationships with catecholamines (11, 12) have been reported, but few studies have been performed concerning the effects on the DNTF. In this study, the effects of CAMRs on the DNTF within the spinal cord were studied by using the polysynaptic flexor reflex mediated by group II afferent fibers (group II flexor reflex) (13) which was facilitated by intrathecal administration of noradrenaline (NA) via $\alpha_2$-adrenoceptors as in the previous study (14). As a first step, the effects of CAMRs on the group II flexor reflex was substantiated in anesthetized intact rats. Next, the effects of CAMRs on the intrathecal NA-HCl-induced facilitation of the group II flexor reflex were investigated in anesthetized spinal rats.

MATERIALS AND METHODS

Recording of the group II flexor reflex

Male Wistar rats (246–610 g) were used. The group II flexor reflex was recorded using the phasic electromyogram (EMG) component evoked in the muscle tibialis anterior by stimulation of the ipsilateral tibial nerve according to a previous report (13). In brief, animals were
anesthetized by intraperitoneal injection of urethane (400 mg/kg) and α-chloralose (50 mg/kg) which were supplemented as required. The left sciatic nerve was exposed, and all branches were cut except for the common peroneal nerve. The tibial nerve was placed on bipolar electrodes for stimulation (0.2 Hz, 0.05 msec, supramaximal, MSE-3 or SEN-7103; Nihon Kohden, Tokyo). A silver ball electrode was placed on the ipsilateral muscle tibialis anterior to record the group II flexor reflex. An indifferent needle electrode was inserted in the skin. The group II flexor reflex was displayed on a memory-oscilloscope (VC-10, Nihon Kohden), averaged 6 times by an averaging computer (DAT-1100, Nihon Kohden) and recorded on a recorder (RJG-4124, Nihon Kohden). The height of the initial negative wave of the group II flexor reflex was measured. A skin pouch was formed and the exposed tissues were covered with warm liquid paraffin. The rectal temperature was monitored and maintained at 37 ± 1°C with a heat lamp.

Effects of CAMRs on the intrathecal NA-HCl-induced facilitation of the group II flexor reflex in anesthetized spinal rats

The spinal cord was transected at the level of Th 8–9 more than 2 hr prior to recording the group II flexor reflex. Laminectomy was performed from Th13 to L2. An intrathecal (i.t.) catheter (PE10) was inserted through a small slit in the dura at L1 and its tip was positioned on the left ventral aspect of the spinal cord at L2. As previously described (14), NA-HCl exerts an α₂-adrenoceptor-mediating inhibition as well as an α₁-adrenoceptor-mediating facilitation of the group II flexor reflex, so yohimbine-HCl, a selective α₂-antagonist, was given before treatment with NA-HCl to exclude any α₂-adrenoceptor-mediated effect. NA-HCl and yohimbine-HCl were administered via the intrathecal catheter in a volume of 10 μl followed by 5 μl of saline. The pretreatment time of the CAMRs was chosen to allow their maximal effects on the group II flexor reflex in anesthetized intact rats with a maximum of the intrathecal NA-HCl-induced facilitation. Namely, CAMRs except for baclofen and mephenesin were administered 10 min before treatment with NA-HCl, and baclofen was given 30 min before the NA-HCl administration. Yohimbine-HCl was administered 5 min before treatment with NA-HCl. Mephenesin and yohimbine-HCl were given successively, followed 2 min later by NA-HCl.

Drugs

The drugs used were urethane and α-chloralose (Tokyo Kasei, Tokyo); yohimbine-HCl, norepinephrine-HCl and mephenesin (Sigma, St. Louis, MO, USA); tolperisone-HCl (Nippon Kayaku, Tokyo); baclofen and tizanidine-HCl (extracted by Nippon Kayaku); diazepam (Horizon injectable; Yamanouchi, Tokyo); and chlorpromazine-HCl (Nihon Sieber Hegner, Tokyo). All drugs except for diazepam and mephenesin were dissolved in saline. Mephenesin was dissolved in 20% propylene glycol. Diazepam was prepared by diluting the commercial preparation with 20% propylene glycol. CAMRs were administered via the right femoral vein at a volume of 0.1 ml/100 g body weight (1 ml/min).

Statistics

Comparison of groups of data to evaluate significance was performed by Dunnett's test.

![Figure 1](image-url)

**Fig. 1.** Effect of mephenesin (A) and diazepam (B) on the group II flexor reflex in anesthetized intact rats. Ordinate: mean amplitudes of the initial negative waves of the group II flexor reflex, as percentages of the value just prior to drug administration, with S.E.M. indicated (n=4-6). Abscissa: time in min after drug administration. ○: 20% propylene glycol; (A) mephenesin, 40 (●) or 80 (△) mg/kg; (B) diazepam, 1.3 (●) or 2.5 mg/kg (△). *P<0.05, **P<0.01: statistical significance of the difference from the 20% propylene glycol-treated group (Dunnett's test).
RESULTS

Effects of CAMRs on the group II flexor reflex in anesthetized intact rats

Mephenesin inhibited the group II flexor reflex dose-dependently, and the inhibition reached a peak of approximately 50% at 2 min after treatment with a dose of 40 mg/kg. At a dose of 80 mg/kg, the group II flexor reflex almost disappeared, and significant inhibition was observed within 50 min (Fig. 1A). Diazepam also inhibited the group II flexor reflex. The inhibitory effects reached a maximum within 5 min; however, it was saturated at a dose of 2.5 mg/kg; the maximal inhibition was about 50% (Fig. 1B). Tizanidine depressed the group II flexor reflex in a bell-shaped manner. At a dose of 0.3 mg/kg, the depression reached its maximum of approximately 70% at 5 min after administration, and significant depression was observed within 30 min; however, no significant change was observed at a dose of 1 mg/kg within 60 min (Fig. 2A). Tolperisone, chlorpromazine and baclofen showed dose-dependent inhibitory effects on the group II flexor reflex. The inhibition by tolperisone at doses of 5 and 10 mg/kg reached peaks of about 50 and 75%, respectively, at 2 min after administration. Significant inhibition was observed within 30 min (Fig. 2B). The effects of chlorpromazine at doses of 0.2 and 0.6 mg/kg reached peaks of approximately 50 and 80%, respectively, at 5 min after administration. Significant inhibition was observed within 40 min (Fig. 2C). Baclofen reduced the group II flexor reflex by approximately 50, 60 and 85% at the dose of 0.6, 1.3 and 2.5 mg/kg, respectively. The effects reached a maximum within 40 min (Fig. 2D).

Effects of CAMRs on the group II flexor reflex and on the intrathecal NA-induced facilitation of the group II flexor reflex in anesthetized spinal rats

NA (0.1 μmol, i.t.) facilitated the group II flexor reflex remarkably in the presence of yohimbine (0.1 μmol, i.t.).

Fig. 2. Effects of tizanidine-HCl (A), tolperisone-HCl (B), chlorpromazine-HCl (C) and baclofen (D) on the group II flexor reflex in anesthetized intact rats. Ordinates: mean amplitudes of the initial negative waves of the group II flexor reflex, as percentages of the value just prior to drug administration, with S.E.M. indicated (n=3–6). Abscissae: time in min after drug administration. ○: saline; (A) tizanidine-HCl, 0.1 (○), 0.3 (●) or 1.0 (▲) mg/kg; (B) tolperisone-HCl, 2.5 (●), 5.0 (▲) or 10 (▲) mg/kg; (C) chlorpromazine-HCl, 0.2 (○) or 0.6 (▲) mg/kg; (D) baclofen, 0.6 (○), 1.3 (▲) or 2.5 (▲) mg/kg. *P<0.05, **P<0.01: statistical significance of the difference from the saline-treated group (Dunnett’s test).
The facilitation reached a peak of more than 800% at 5–10 min after the administration of NA, which corresponded with the previous report (14).

Mephenesin depressed the group II flexor reflex in a dose-dependent manner, and the depression was 28.7 ± 24.9 and 67.4 ± 3.0% (n=3) at doses of 40 and 80 mg/kg, respectively, at 2 min after administration. The NA-induced facilitation of the group II flexor reflex was not affected by mephenesin (Fig. 3A). Diazepam at a dose of 2.5 mg/kg produced a slight inhibition (30.8 ± 19.0%; n=3) at 5 min after administration without affecting the NA-induced facilitation of the group II flexor reflex (Fig. 3B). Tizanidine facilitated the group II flexor reflex slightly (22.6 ± 20%; n=3) at 5 min after treatment with a dose of 0.3 mg/kg. Pretreatment with tizanidine markedly depressed the NA-induced facilitation of the group II flexor reflex; the maximal facilitation was about one-quarter of that observed in saline-treated rats (Fig. 4A). Tolperisone inhibited the group II flexor reflex dose-dependently and the inhibition was 44.3 ± 9.6 and 58.7 ± 17.7% (n=4 and 3) at doses of 5 and 10 mg/kg, respectively, at 5 min after administration. The NA-induced facilitation of the group II flexor reflex was also inhibited in a dose-dependent manner. At a dose of 10 mg/kg, the facilitation was about half of that observed in the saline-treated rats (P<0.1, Fig. 4B). Chlorpromazine slightly depressed the
group II flexor reflex; and at a dose of 0.6 mg/kg, the inhibition was 13.5 ± 18.3% (n = 4) at 5 min after administration. Significant inhibition of the NA-induced facilitation of the group II flexor reflex was observed at a dose of 0.6 mg/kg; the maximal facilitation of the reflex was about one-fifth of that observed in the saline-treated rats (Fig. 4C). Baclofen inhibited the group II flexor reflex dose-dependently, and the inhibition at 25 min after administration was 17.7 ± 8.8 and 23.5 ± 26.5% (n = 4) at the doses of 0.6 and 1.3 mg/kg, respectively. The NA-induced facilitation of the group II flexor reflex was also inhibited dose-dependently. At a dose of 1.3 mg/kg, the maximal facilitation was approximately one-fifth of that observed in the saline-treated rats (Fig. 5).
The patterns of the effects of CAMRs on the group II flexor reflex in anesthetized intact and spinal rats and on the intrathecal NA-induced facilitation of the group II flexor reflex are summarized in Table 1.

**DISCUSSION**

The group II flexor reflex is a polysynaptic reflex with more than one interneuron (15), which receives a DNTF via α1-receptors (14). In this study, the effects of CAMRs on the DNTF within the spinal cord were investigated.

Mephenesin, tolperisone, tizanidine, baclofen and diazepam have been reported to have no effect on the contraction of the muscle tibialis anterior induced by stimulation of the ipsilateral sciatic nerve (16–19). Chlorpromazine at a dose of 0.6 mg/kg did not affect the EMG evoked in the muscle tibialis anterior by stimulation of the ipsilateral common peroneal nerve (K. Sakitama, unpublished data). These results indicate that the peripheral actions of the CAMRs used can be ruled out.

Mephenesin and tolperisone, whose site of action is mainly within the spinal cord (9, 20), dose-dependently inhibited the group II flexor reflex similarly in anesthetized spinal rats and intact rats. Ono et al. (20) suggested the participation of a membrane stabilizing action in spinal reflex inhibition produced by tolperisone as well as mephenesin and classified both compounds in the same category, "mephenesin-type muscle relaxants". The present results that the NA-induced facilitation was not affected by mephenesin but inhibited by tolperisone show that only tolperisone has an inhibitory effect on the DNTF within the spinal cord. The fact that tolperisone exerts an α-blocking effect on the vasculature (10) might show that an α-blocking action is also produced within the spinal cord.

Marked inhibition of the NA-induced facilitation of the group II flexor reflex induced by chlorpromazine and baclofen suggests that the suppression of the DNTF...
within the spinal cord contributes to the reflex inhibition. Taken together with the fact that chlorpromazine depresses the monosynaptic reflex potential via an α-blocking action within the spinal cord (4–6), an α-blocking action is considered to also be involved in the depression of the polysynaptic group II flexor reflex. The present results concerning baclofen might be consistent with the suggestions reported by Fukuda et al. (11) that catecholamines were involved in the inhibitory effects of baclofen on the spinal reflexes. Ito et al. (21) reported little contribution of monoamines to the effects of baclofen on the polysynaptic extensor reflex evoked by the phasic EMG component evoked in the muscle gastrocnemius, the antagonistic muscle of the muscle tibialis anterior, by stimulation of the ipsilateral common peroneal nerve. Collectively, there might be a difference in the contribution of catecholamines to the inhibitory effects of baclofen on the flexor and on the extensor reflex.

The results that the inhibitory effects of diazepam on the group II flexor reflex tended to be saturated at a dose of 2.5 mg/kg, a higher dose than that which caused a perfect inhibition of the flexor reflex recorded by the contraction of the flexor muscle (8), might indicate that the group II flexor reflex is a component of the polysynaptic reflexes which are resistant to the benzodiazepines as suggested by Farkas et al. (22) and Schlosser (23). The effects of diazepam in anesthetized spinal rats were reduced in comparison with those in intact rats, which is in agreement with the results of other investigators (9, 24), but diazepam did not affect the NA-induced facilitation of the group II flexor reflex. These results suggest the mechanisms of the effects of diazepam are other than those on the DNTF within the spinal cord.

Tizanidine, which has both α₁- and α₂-agonistic properties (25, 26), depressed the group II flexor reflex in anesthetized intact rats not in a dose-dependent manner, but in a bell-shaped one, whereas a slight facilitation of the reflex was observed in anesthetized spinal rats. Chen et al. (25) reported that tizanidine dose-dependently depressed the flexor reflex recorded by an EMG component with a latency of more than 60 msec which was considered to be mediated by group III or IV afferent fibers in intact rats, while facilitatory effects on this reflex via α₁-adrenoceptors were produced in spinal rats. Taken together, these results might show that the effects of tizanidine are different depending on the types of afferent fibers mediating the flexor reflex in intact animals, but the facilitatory effects in spinal animals are exhibited via α₁-adrenoceptors independently of the afferent fiber types. There might be a possibility that the inhibitory effects of tizanidine on the turnover of 5-hydroxytryptamine (19) which also facilitates the flexor reflex (27) relate to the depressant effects on the NA-induced facilitation of the group II flexor reflex; however, the underlying mechanisms are unknown.

Although the relationships between the mechanisms underlying the induction of spasticity and the changes in the group II flexor reflex are not understood, the group II flexor reflex may be involved in the control of movement during locomotion in man (28, 29). The inhibition of the group II flexor reflex induced by CAMRs, the mechanisms of which are different, might be a factor in ameliorating the dysfunction of extremities movement or gait disturbance in spasticity (30–32).

In summary, it was found that compounds with CAMR activity depress the flexor reflex mediated by group II afferent fibers, and participation of the inhibition of the DNTF within the spinal cord in the depressant action of the group II flexor reflex produced by tolperisone, tizanidine, chlorpromazine and baclofen.

Acknowledgment
The author thanks Professor H. Fukuda, Department of Pharmacology, College of Pharmacy, Nihon University, Funabashi, Japan, for critical reading of the manuscript.

REFERENCES

1 Björklund, A. and Skagerberg, G.: Descending monoaminergic projections to the spinal cord. In Brain Stem Control of Spinal Mechanisms, Edited by Sjörlund, B. and Björklund, A., pp. 55–88, Elsevier Biochemical Press, Amsterdam (1982)
2 Fukuda, H. and Ono, H.: Control of spinal motor system by descending noradrenergic neuron. Folia Pharmacol. Japon. 96, 1–9 (1990) (Abs. in English)
3 Palmeri, A. and Wiesendanger, M.: Concomitant depression of locus coeruleus neurons and of flexor reflexes by an α₂-adrenergic agonist in rats: a possible mechanism for an α₂-mediated muscle relaxation. Neuroscience 34, 177–187 (1990)
4 Hino, M., Ono, H. and Fukuda, H.: Supraspinal tonic influence on spinal reflexes and involvement in the effect of chlorpromazine. Gen. Pharmacol. 15, 155–158 (1984)
5 Hino, M., Ono, H. and Fukuda, H.: Involvement of noradrenergic systems in the effects of the lower brain stem on the lumbar spinal reflex in rats. Gen. Pharmacol. 18, 41–45 (1987)
6 Strahlendorf, J.C., Strahlendorf, H.K., Kingsley, R.E., Gintautas, J. and Barnes, C.D.: Facilitation of the lumbar monosynaptic reflexes by locus coeruleus stimulation. Neuropharmacology 19, 225–230 (1980)
7 Kaneko, T., Ozo, H. and Fukuda, H.: Simultaneous evaluation of drug effects on both the spinal cord and the descending pathways in rats. Arch. Int. Pharmacodyn. Ther. 287, 203–210 (1987)
8 Polc, P., Möhler, H. and Haefely, W.: The effect of diazepam on spinal cord activities: possible sites and mechanisms of action. Naunyn Schmiedebergs Arch. Pharmacol. 284, 319–337 (1974)
9 Ochiai, T. and Ishida, R.: Pharmacological studies on 6-amino-2-fluoromethyl-3-(o-tolyl)-4(3H)-quinazolinone (afloqualone), a new centrally acting muscle relaxant (1). Japan. J. Pharmacol. 31, 491–501 (1981)
10 Furuta, Y. and Yoshikawa, A.: Reversible adrenergic \( \alpha \)-receptor blocking action of 2,4'-dimethyl-3-piperidino-propiophenone (tolperisone). Japan. J. Pharmacol. 26, 543–550 (1976)

11 Fukuda, H., Kudo, Y. and Ono, H.: Effects of \( \beta \)-(p-chlorophenyl)-GABA (baclofen) on spinal synaptic activity. Eur. J. Pharmacol. 44, 17–24 (1977)

12 Sawynok, J.: Monoamines as mediators of the antinociceptive effect of baclofen. Naunyn Schmiedebergs Arch. Pharmacol. 323, 54–57 (1983)

13 Sakitama, K. and Ishikawa, M.: The flexor reflex mediated by group II afferent fibers: effects of morphine-HCI and mephenesin. Japan. J. Pharmacol. 60, 127–131 (1992)

14 Sakitama, K.: Intrathecal noradrenaline facilitates and inhibits the flexor reflex mediated by group II afferent fibers via \( \alpha_1 \)- and \( \alpha_2 \)-receptors, respectively. Japan. J. Pharmacol. 62, 131–136 (1993)

15 Eccles, R.M. and Lundberg, A.: Synaptic actions in motoneurons by afferents which may evoke the flexion reflex. Arch. Ital. Biol. 97, 199–221 (1959)

16 Fukuda, H., Kudo, Y., Ono, H. and Kokubo, M.: Pharmacological study on a centrally acting muscle relaxant (chlorphenesin carbamate) with special reference to the effects on motor systems. Folia Pharmacol. Japon. 70, 341–358 (1974) (Abs. in English)

17 Fujii, Y., Ishii, Y., Suzuki, T. and Murayama, S.: Neuropharmacological studies on tolperisone hydrochloride. Folia Pharmacol. Japon. 75, 655–668 (1979) (Abs. in English)

18 Sypniewska, M.: The effect of baclofen on the hind limb flexor reflex of the spinal rats. Pol. J. Pharmacol. 31, 493–501 (1979)

19 Sayers, A.C., Burki, H.R. and Eichenberger, E.: The pharmacology of 5-chloro-4-(2-imidazolin-2-yl-amino)-2,1,3-benzothiadiazole (DS 103-282), a novel myotonolytic agent. Arzneimittelforschung 30, 793–803 (1980)

20 Ono, H., Fukuda, H. and Kudo, Y.: Mechanisms of depressant action of muscle relaxants on spinal reflexes: participation of membrane stabilizing action. J. Pharmacobiodyn. 7, 171–176 (1984)

21 Ito, T., Furukawa, K., Karasawa, T., Kadokawa, T. and Shimizu, M.: Effects of chlorpromazine, imipramine and baclofen on the spinal polysynaptic reflex in acute, chronic and 6-hydroxydopamine-treated spinal rats. Japan. J. Pharmacol. 32, 1125–1133 (1982)

22 Farkas, S., Tarnawa, I. and Berzenyi, P.: Effects of some centrally acting muscle relaxants on spinal root potentials: a comparative study. Neuropharmacology 28, 161–173 (1989)

23 Schlosser, W.: Action of diazepam on the spinal cord. Arch. Int. Pharmacodyn. Ther. 194, 93–102 (1971)

24 Ngai, S.H., Tseng, D.T.C. and Wang, C.: Effects of diazepam and other central nervous system depressants on spinal reflexes in cats: a study of site of action. J. Pharmacol. Exp. Ther. 153, 344–351 (1966)

25 Chen, D.F., Blanchetti, M. and Wiesendanger, M.: The adrenergic agonist tizanidine has differential effects on flexor reflexes of intact and spinalized rat. Neuroscience 23, 641–647 (1987)

26 Takayanagi, I. and Konno, F.: Pharmacological actions of tizanidine, a centrally acting muscle relaxant on various smooth muscle organs. Pharmacometrics 29, 493–500 (1985) (Abs. in English)

27 Bell, J.A. and Matsumiya, T.: Inhibitory effects of dorsal horn and excitant effects of ventral horn intraspinal microinjections of norepinephrine and serotonin in the cat. Life Sci. 29, 1507–1514 (1981)

28 Dietz, V., Quinter, J. and Berger, W.: Afferent control of human stance and gait: evidence for blocking of group I afferents during gait. Exp. Brain Res. 61, 153–163 (1985)

29 Dietz, V., Quinter, J. and Sillen, M.: Stumbling reactions in man: significance of proprioceptive and pre-programmed mechanisms. J. Physiol. (Lond.) 386, 149–163 (1987)

30 Meinck, H.M., Benecke, R. and Conrad, B.: Spasticity and the flexor reflex. In Clinical Neurophysiology in Spasticity, Edited by Delwaide, P.J. and Young, R.R., pp. 41–54, Elsevier, Amsterdam (1985)

31 Kuroiwa, Y., Sobue, I., Tazaki, Y., Nakanishi, T., Ohtomo, E. and Itahara, K.: Effects of E-0646 on cases of spasticity: A double blind comparison using tolperisone hydrochloride. Clin. Eval. 9, 391–419 (1981) (Abs. in English)

32 Kaurimsky, Z.F. and Fassbender, H.M.: Tizanidine (DS 103-282) in the treatment of acute paravertebral muscle spasm: A controlled trial comparing tizanidine and diazepam. J. Int. Med. Res. 9, 501–505 (1981)