ELSEVIER

European Journal of Pharmacology 300 (1996) 197–202

ejp

Antidystonic effects of L-type Ca^{2+} channel antagonists in a hamster model of idiopathic dystonia

Angelika Richter *, Wolfgang Löscher

Department of Pharmacology, Toxicology and Pharmacy, School of Veterinary Medicine, Hannover, Germany

Received 19 October 1995; revised 18 December 1995; accepted 22 December 1995

Abstract

The effects of selective L-type Ca^{2+} channel antagonists on severity of dystonia were investigated in a mutant hamster model of idiopathic generalized dystonia. Nimodipine and diltiazem significantly decreased the severity of dystonia. Nimodipine was more potent in this respect and did not cause any behavioral side effects. The present data therefore suggest that Ca^{2+} channel antagonists could be useful in the treatment of idiopathic dystonia. The antidystonic effect of diltiazem and nimodipine may be based on their antidopaminergic action. However, the lack of significant effects of the L-type channel agonist (±)-BAY k-8644 (1–5 mg/kg; methyl-1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoro-methylphenyl)-pyridine-5-carboxylate)) on severity of dystonia may indicate that voltage-gated Ca^{2+} channels are not critically involved in the pathophysiology of dystonia in mutant hamsters.

Keywords: Ca^{2+} channel antagonist; Dystonia; Dopamine; Movement disorder

1. Introduction

Ca^{2+} channel antagonists, well established for the treatment of cardiovascular diseases, have been suggested to provide a novel therapeutic approach in disorders of the central nervous system (Raeburn and Gonzales, 1988). L-type channel inhibitors both of the dihydropyridine class, such as nimodipine, and diltiazem, a benzothiazepine, can penetrate the blood-brain barrier to a high extent and these agents were found to decrease the activity of striatal dopaminergic neurons (Kerckhoff and Drewes, 1985; Gaggi and Gianni, 1990). Therefore, these compounds might have potential relevance in the treatment of basal ganglia disorders in which enhanced dopaminergic activity is pathophysiologically involved. Several case reports indicate beneficial effects of diltiazem in tardive dyskinesia which was accompanied by (secondary) dystonic symptoms (Ross et al., 1987; Falk et al., 1988, Leys et al., 1988; Pucilowski, 1992). However, to our knowledge there are no clinical or preclinical data on L-type Ca^{2+} channel blockers in idiopathic dystonia.

Pharmacological treatment of dystonia, i.e. a neurological syndrome of sustained muscle contractions resulting in twisting movements of abnormal postures, is unpredictable and often disappointing (McGeer and McGeer, 1988). The pathomechanisms of idiopathic dystonia are largely unknown, but beneficial effects of dopamine receptor antagonists suggest dopaminergic overactivity in some forms of dystonia (Lang, 1988). Although dopamine receptor antagonists are often useful in the treatment of dystonia, they bear the risk of adding a tardive dyskinesia to the dystonia (Marsden and Quinn, 1990). Neuroleptic-induced dyskinesia is attributed to development of postsynaptic dopamine receptor supersensitivity. In contrast to neuroleptics which additionally increase dopamine turnover, Ca^{2+} channel antagonists of the dihydropyridine and benzothiazepine class were found to reduce the striatal dopamine turnover in rats (Fadda et al., 1989; Gaggi and Gianni, 1990), a fact which may explain the antidyskinetic efficacy of Ca^{2+} channel inhibitors. Compared to neuroleptics, L-type Ca^{2+} channel antagonists may therefore provide advances in the treatment of dystonia.

This prompted us to examine the effects of nimodipine and diltiazem on the severity of dystonia in the mutant hamster model of idiopathic dystonia which was recently found to be sensitive to acute treatment with neuroleptics (Löscher and Fredow, 1992; Richter and Löscher, 1993). Furthermore, previous studies have shown antidystonic efficacy of NMDA receptor antagonists in mutant hamsters

* Corresponding author. Department of Pharmacology, Toxicology and Pharmacy, School of Veterinary Medicine, Bünteweg 17, D-30559 Hannover, Germany. Tel.: +49-511-9538723,; fax: +49-511-9538581.

SSDI 0014-2999(95)00878-0

(Richter et al., 1991). The NMDA receptor is distinct from voltage-sensitive channels, but drugs which block this receptor-gated channel (e.g. MK-801) lead to decreased membrane depolarisation and subsequent inactivation of voltage-sensitive Ca^{2+} channels (Skeen et al., 1993). Thus, indirect inhibition of voltage-operated Ca^{2+} channels may contribute to the antidystonic effect of NMDA receptor antagonists in mutant hamsters. In order to examine the pathophysiological role of voltage-gated Ca^{2+} channels, the L-type Ca^{2+} channel agonist (±)-BAY k-8644 (methyl-1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)-pyridine-5-carboxylate) was included in the present study.

2. Materials and methods

The experiments were carried out in 7 groups of 7–14 male and female mutant dystonic hamsters (genetic symbol dt^{sz}) which were obtained by selective breeding (for detailed description see Fredow and Löscher, 1991). Dystonic attacks in dt^{sz} mutant hamsters, characterized by generalized twisting movements and abnormal postures of limbs and trunk, can be induced by handling and mild environmental stimuli. The severity of dystonia is age-dependent with maximum severity between the 30th and 40th day of life ('max period', suitable to study antidystonic effects of drugs). Thereafter, the severity of dystonia slowly declines ('post-max period', suitable to examine prodystonic drug effects). Similar to idiopathic dystonia in humans, dystonia in mutant hamsters occurs in the absence of morphological alterations in the brain or spinal cord (Wahnschaffe et al., 1990).

In the present study, the dystonic attacks were induced by the procedure of triple stimulation (Fredow and Löscher, 1991), i.e. (1) taking the animal from its home cage and placing it on a balance, (2) i.p. injection of vehicle (pre- and post-drug control) or of the drug (in the present study: diltiazem, nimodipine or (±)-BAY k-8644, respectively), (3) placement of the hamster in a clean and empty plastic cage (one animal per cage). The severity of dystonia was rated by the following score system (Löscher et al., 1989): stage 1, flattened ears and flattened posture; stage 2, facial contortions, rearing with forelimbs crossing, disturbed gait with retarded setting of the forepaws; stage 3, stiffened hindlimbs so that the animals appear to walk on tiptoe in a dysmetric hypergait; stage 4, twisting movements and loss of balance; stage 5, hindlimbs hyperextended caudally; stage 6, immobilisation in a twisted, hunched posture with hind- and forelimbs tonically extended forward, Straub tail, alternating unilateral forelimb elevation, opisthotonus, copious red eye mucus and salivation. After reaching the individual maximum stage the hamsters usually recover within 2–5 h. The individual maximum stage of dystonia is usually reached within 3 h after the hamsters were placed in the new cage. Therefore the hamsters were observed for 3 h. During this period the severity of dystonia, the latencies to the different stages and, in case of drug trials, the side effects were noted. Pre- and post-drug control trials were undertaken 2 days before and 2 days after drug testing. The following doses of drugs were administered intraperitoneally: diltiazem at doses of 20, 40 and 100 mg/kg; nimodipine at 10, 20 and 50 mg/kg and (±)-BAY k-8644 at 1, 3 and 5 mg/kg. Diltiazem was freshly dissolved in distilled water and nimodipine was suspended (under dark conditions) in 10% cremophore EL prior to the experiments. In additional experiments, (±)-BAY k-8644 was used in order to examine if this L-type Ca^{2+} channel agonist exerts opposite effects on severity of dystonia compared to the antagonists. The adverse effects of (±)-BAY k-8644 were also investigated in a group of 5 age-matched non-dystonic control hamsters of an outbred

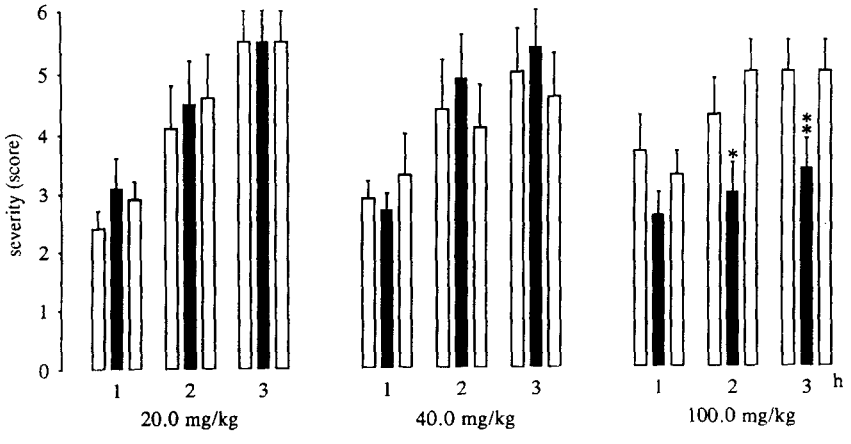

Fig. 1. Effect of diltiazem on severity of dystonia in mutant hamsters at the age of maximum severity ('max period'). The figure shows the average of the maximum individual severity scores of dystonia reached within the 1st, 2nd and 3rd hour after i.p. administration of 20.0, 40.0 or 100.0 mg/kg. Control recordings were undertaken 2 days before (pre-drug control) and 2 days after (post-drug control) the drug trial. Asterisks indicate significant reduction of severity in comparison to the pre- and post-drug control (* $P < 0.05$; ** $P < 0.01$). Data are shown as means + S.E. of 8 (20.0 mg/kg), 7 (40.0 mg/kg) or 11 (100.0 mg/kg) dystonic hamsters. Open bars: pre- and post-treatment control scores; black bars: scores under treatment.

Table 1
Effect of diltiazem, nimodipine and (±)-BAY k-8644 on latency to onset of dystonic attacks in mutant dystonic hamsters

Dose (mg/kg)	Age (days) at drug trial	Latency (min)			n
		Pre-drug trial	Drug trial	Post-drug trial	
Diltiazem					
20.0	38	10.9 ± 1.2	10.0 ± 1.5	8.9 ± 1.9	8
40.0	37	8.3 ± 1.0	13.6 ± 1.0	9.7 ± 2.1	7
100.0	33	7.6 ± 0.7	14.4 ± 1.2 [b]	6.7 ± 0.9	11
Nimodipine					
10.0	34	10.6 ± 1.6	12.9 ± 1.6	10.9 ± 2.0	8
20.0	36	12.4 ± 1.4	11.7 ± 1.4	8.8 ± 1.4	9
50.0	40	8.6 ± 1.5	15.6 ± 1.9 [a]	9.3 ± 1.1	8
(±)-BAY k-8644					
3.0	38	11.3 ± 1.0	7.9 ± 0.9 [(a)]	11.0 ± 1.1	14
1.0	49	11.9 ± 1.4	10.7 ± 0.7	14.5 ± 1.2	13
3.0	50	10.0 ± 1.3	9.0 ± 1.0	12.0 ± 2.1	7
5.0	52	12.0 ± 0.8	7.4 ± 0.9 [(a)]	13.8 ± 1.4	10

Latency was determined as the time to the first unequivocal signs of the dystonic attacks (stage 2). Data are shown as means ± S.E. of the number of hamsters indicated. Significances to pre-drug and post-drug controls are marked by [a] ($P < 0.05$) and [b] ($P < 0.01$). Significant decreases of the latency to onset by (±)-BAY k-8644 ([(a)]) may merely be simulated by behavioral side effects.

line. (±)-BAY k-8644, kindly provided from Tropon (Cologne, Germany), was freshly dissolved in 10% cremophore under dark conditions. Injection volume was 5 ml/kg. For control recordings, the hamsters received the same volume of vehicle. The significance of differences in severity of dystonia and the latency to onset of dystonia between pre- and post-drug control trials and drug trial was calculated by the Wilcoxon signed rank test for paired replicates.

3. Results

As shown in Fig. 1, diltiazem significantly reduced the severity of dystonia in mutant hamsters at the dose of 100 mg/kg during the 2nd and 3rd hour of observation. The latency to onset of dystonic symptoms was significantly increased ($P < 0.01$) from 7.6 ± 0.7 (pre-drug) or 6.7 ± 0.9 (post-drug) to 14.4 ± 1.2 min (Table 1). At 20 or 40 mg/kg, no significant effects on severity or latency to onset of dystonia were recorded. Adverse effects of diltiazem observed at 100 mg/kg were reduction of spontaneous locomotion, moderate sedation and ataxia during the 1st hour after injection.

Nimodipine exerted similar antidystonic effects as diltiazem, but was more potent in this respect. At a dose of 10 mg/kg nimodipine already tended to decrease the severity of dystonia (Fig. 2). At higher dosages of 20 and 50 mg/kg the severity of dystonia was significantly reduced during the 1st and 2nd hour after administration. At 50 mg/kg, the latency to onset of dystonia was increased ($P < 0.05$) from 8.6 ± 1.5 (pre-drug) or 9.3 ± 1.1 (post-

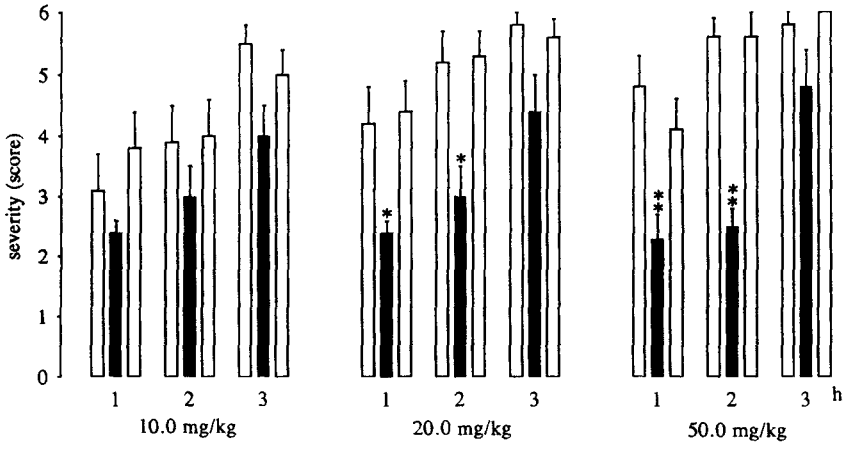

Fig. 2. Effect of nimodipine on severity of dystonia in mutant hamsters at the age of maximum severity ('max period'). The figure shows the average of the maximum individual severity scores of dystonia reached within the 1st, 2nd and 3rd hour after i.p. administration of 10.0, 20.0 or 50.0 mg/kg. Control recordings were taken 2 days before (pre-drug control) and 2 days after (post-drug control) the drug trial. Asterisks indicate significant reduction of severity in comparison to the pre-drug and post-drug control (* $P < 0.05$; ** $P < 0.01$). Data are shown as means + S.E. of 8 (10.0 and 50.0 mg/kg) or 9 (20.0 mg/kg) dystonic hamsters. Open bars: pre- and post-treatment control scores; black bars: scores under treatment.

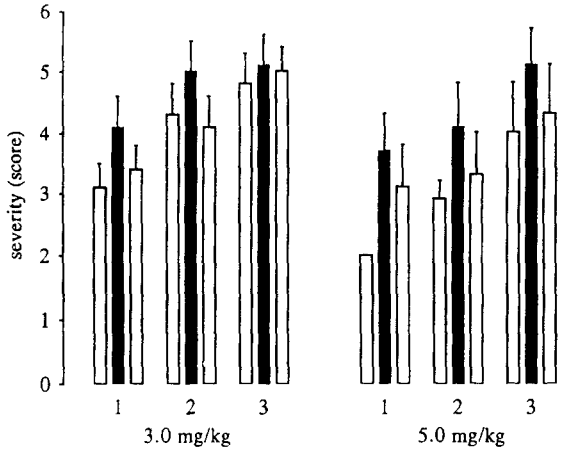

Fig. 3. Effect of (±)-BAY k-8644 on severity of dystonia in mutant hamsters at the age of maximum severity of dystonia ('max period'). The figure shows the average of the maximum individual severity scores of dystonia reached within the 1st, 2nd and 3rd hour after i.p. administration of 3.0 or 5.0 mg/kg. Control recordings were taken 2 days before (pre-drug control) and 2 days after (post-drug control) the drug trial. Data are shown as means + S.E. of 14 (3.0 mg/kg) or 7 (5.0 mg/kg) dystonic hamsters. Open bars: pre- and post-treatment control scores; black bars: scores under treatment.

drug) to 15.6 ± 1.9 min (Table 1). The slow development of higher stages of dystonia during the 2nd and 3rd hour (20 mg/kg) or 3rd hour (50 mg/kg) of observation indicates that the duration of action of nimodipine in hamsters was not long enough to suppress the development of higher stages of dystonia over the whole period of observation. At all doses, nimodipine did not cause any behavioural adverse effects.

The L-type Ca^{2+} channel agonist (±)-BAY k-8644 examined at doses of 3 and 5 mg/kg in mutant hamsters at the age of maximum severity of dystonia ('max period') did not exert significant effects on the severity of dystonia (Fig. 3). However, at a dose of 3 mg/kg the latency to onset of dystonia appeared to be significantly decreased (Table 1). At the dose of 3 mg/kg, marked facial contortions were observed 5–10 min after injection in both dystonic hamsters and in control hamsters. At a dose of 5 mg/kg, (±)-BAY k-8644 caused marked side effects during the 1st hour after administration. Similar to behavioural adverse effects in mice (Bolger et al., 1985; Palmer et al., 1993), Straub tail, facial contortions, limb clonus and tonus, sitting position with rearing and decreased motor activity lasting 30 min were followed by grooming and licking. Since these adverse effects already appeared 5 min after administration, the latency to onset of dystonia could not adequately be determined. (±)-BAY k-8644 (3.0 and 5.0 mg/kg) exerted comparable adverse effects in age-matched non-dystonic control hamsters.

(±)-BAY k-8644 was additionally examined in dystonic hamsters at the age of 49–52 days, at which the severity is decreased ('post-max'). The data shown in Fig. 4 clearly demonstrate the lack of any effects of (±)-BAY k-8644 (1.0, 3.0 and 5.0 mg/kg) on the severity of dystonia. At the dose of 5 mg/kg, the latency to onset of dystonia was significantly reduced (Table 1). No behavioural adverse effects were observed at the dose of 1 and 3 mg and the adverse effects induced by 5 mg (±)-BAY k-8644 were less marked than at the age of maximum severity both in mutant dystonic hamsters and in non-dystonic controls. Thus, at a dose of 5 mg the behavioural adverse effects of (±)-BAY k-8644 were limited to facial contortions, rearing, grooming and licking, which occurred 5 min after administration with a duration of about 10 min.

Since one of the first unequivocal signs of dystonia in mutant hamsters (stage 2) are facial contortions and rearing, the significant decrease of latency to onset found after

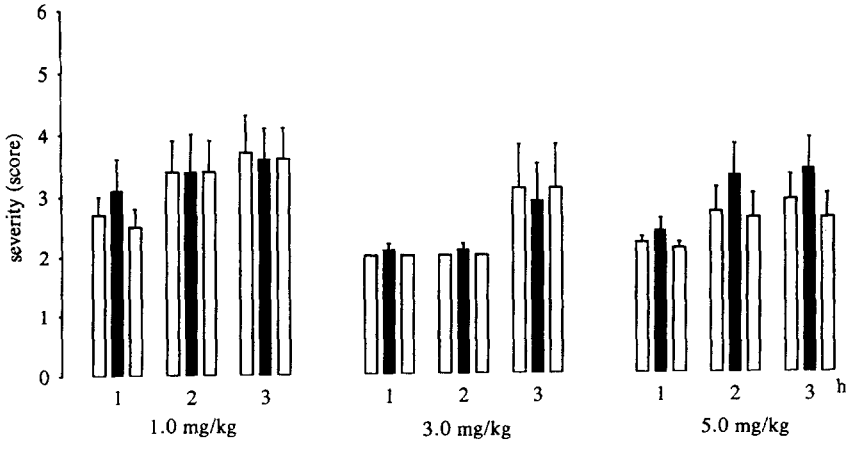

Fig. 4. Effect of (±)-BAY k-8644 on severity of dystonia in mutant hamsters aged 49–52 days, at which the severity of dystonia is decreased ('post-max period'). The figure shows the average of the maximum individual severity scores of dystonia reached within the 1st, 2nd and 3rd hour after i.p. administration of 1.0, 3.0 or 5.0 mg/kg. Control recordings were taken 2 days before (pre-drug control) and 2 days after (post-drug control) the drug trial. Data are shown as means + S.E. of 13 (1.0 mg/kg), 7 (3.0 mg/kg) or 10 (5.0 mg/kg) dystonic hamsters. Open bars: pre- and post-treatment control scores; black bars: scores under treatment.

administration of (±)-BAY k-8644 (Table 1) at doses of 3 ('max period') and 5 mg ('post-max period') seems merely to be due to the adverse effects of (±)-BAY k-8644.

4. Discussion

The present data provide the first experimental evidence that the selective L-type Ca^{2+} channel antagonists nimodipine and diltiazem may exert antidystonic effects in idiopathic dystonia. This finding could be clinically relevant, but the mechanism responsible for the antidystonic action of these Ca^{2+} channel inhibitors remains unclear. Since the L-type Ca^{2+} channel agonist (±)-BAY k-8644, even at high doses which induced convulsions, failed to increase the severity of dystonia in mutant hamsters, a primary pathogenetical role of voltage-operated L-type Ca^{2+} channels seems to be unlikely.

Several reports indicate that the dihydropyridine (e.g. nimodipine) and non-dihydropyridine (e.g. diltiazem) Ca^{2+} channel antagonists possess antidopaminergic properties which may essentially contribute to their therapeutic usefulness in the treatment of a variety of central nervous system disorders (Pucilowski, 1992). This effect of Ca^{2+} antagonists might be relevant for their antidystonic activity found in the present study, since recent pharmacological and neurochemical experiments indicated that an overactivity of the dopaminergic system may be involved in dystonia in mutant hamsters (Löscher and Fredow, 1992; Richter and Löscher, 1993; Nobrega et al., 1995). The decrease in dopamine turnover by nimodipine and diltiazem is restricted to the striatum (Gaggi and Gianni, 1990; Gaggi et al., 1992), whereas the opposite effect of (±)-BAY k-8644 on dopamine turnover seems not to be limited to basal ganglia (Pucilowski, 1992). Such differences may explain that (±)-BAY k-8644 did not aggravate dystonia in mutant hamsters but induced convulsions.

In addition to the antidopaminergic action, dihydropyridine Ca^{2+} channel blockers can inhibit NMDA receptor-mediated responses by other mechanisms than inhibition of L-type Ca^{2+} channels (Chaudieu et al., 1992). With regard to previous finding of antidystonic effects of NMDA receptor antagonists in mutant hamsters (Richter et al., 1991), this effect may contribute to the antidystonic efficacy of nimodipine. Furthermore, the effects of Ca^{2+} channel inhibitors might be, at least partially, related to their anticholinergic properties that were demonstrated both at receptor and functional level (Pucilowski, 1992). As shown by previous pharmacological studies, anticholinergics exert weak antidystonic effects in mutant hamsters (Fredow and Löscher, 1991).

Besides anticholinergics (administered at high doses), antidopaminergic drugs have been found to be the most effective therapeutics in terms of percentage of dystonic patients who receive moderate to marked benefit (Fahn, 1987). However, chronic treatment with neuroleptics bears the risk of inducing tardive dyskinesia and dopamine depleting agents, such as tetrabenazine, may cause depression (Marsden and Quinn, 1990). In this regard Ca^{2+} channel antagonists may provide advances in the treatment of dystonia because they possess antidyskinetic and antidepressant properties (Pucilowski, 1992). However, it is important to note that flunarizine, a non-selective Ca^{2+} channel blocker, exerts opposite effects, i.e. this compound was found to cause tardive dyskinesia and depression (Chouza et al., 1986). In contrast to selective L-type Ca^{2+} channel antagonists, flunarizine increases the striatal dopamine turnover (Fadda et al., 1989; Gaggi and Gianni, 1990), which supports the hypothesis that beneficial effects of diltiazem and nimodipine are based on their antidopaminergic action.

As shown by the present study, at antidystonic effective doses nimodipine did not induce any behavioural adverse effects, whereas diltiazem caused a reduction in spontaneous motor activity and ataxia in dystonic hamsters. A similar dose-dependency of central adverse effects of nimodipine and diltiazem was found in mice (Palmer et al., 1993). Nimodipine might be therefore more useful in the treatment of dystonia than diltiazem, which has been reported to be beneficial in secondary dystonia (Pucilowski, 1992). Ca^{2+} channel inhibitors may certainly cause vasodilatation, but also the common treatment with anticholinergics and neuroleptics is complicated by peripheral side effects (Fahn, 1987). At least, in view of the central side effects, Ca^{2+} channel antagonists may be acutely better tolerated than neuroleptics. Recent pharmacological studies in mutant hamsters have shown that neuroleptics reduced the spontaneous motor activity at antidystonic effective doses (Löscher and Fredow, 1992). Further preclinical and clinical studies are needed in order to examine the chronic efficacy and side effects of Ca^{2+} channel blockers in comparison to neuroleptics in dystonia.

In conclusion, the present study provides evidence that Ca^{2+} channel antagonists might be beneficial in idiopathic dystonia. The antidystonic efficacy of nimodipine and diltiazem could be related to their antidopaminergic activity. Therefore, Ca^{2+} channel antagonist may represent an effective alternative in the treatment of dystonic patients who response to neuroleptics or dopamine depleting agents.

Acknowledgements

We thank Dr. T. Glaser (Tropon, Cologne) for providing (±)-BAY k-8644 and we thank Mrs. C. Bartling for technical assistance. This study was supported by a grant from the Deutsche Forschungsgemeinschaft (Lo 274/4-2).

References

Bolger, G., B.A. Weissman and P. Skolnick, 1985, The behavioral effects of the calcium agonist BAY K 8644 in the mouse: antagonism by the

calcium antagonist nifedipine, Naunyn-Schmied. Arch. Pharmacol. 328, 373.

Chaudieu, I., R. Alonso, H. Mount, R. Quirion and P. Boksa, 1992, Effects of L- and N-type Ca^{2+} channel antagonists on excitatory amino acid-evoked dopamine release, Eur. J. Pharmacol. 220, 203.

Chouza, C., J.L. Caamano, R. Aljanati, A. Scaramelli, O. De Medina and S. Romero, 1986, Parkinsonism, tardive dyskinesia, akathisia, and depression induced by flunarizine, Lancet i, 1303.

Fadda, F., G.L. Gessa, E. Mosca and E. Stefanini, 1989, Different effects of the calcium antagonists nimodipine and flunarizine on dopamine metabolism in the rat brain, J. Neural Transm. 75, 195.

Fahn, S., 1987, Systemic therapy of dystonia, Can. J. Neurol. Sci. 14, 528.

Falk, W.E., J.D. Wojick and A.J. Gelenberg, 1988, Diltiazem for tardive dyskinesia and tardive dystonia, Lancet i, 824.

Fredow, G. and W. Löscher, 1991, Effects of pharmacological manipulation of GABAergic neurotransmission in a new mutant hamster model of paroxysmal dystonia, Eur. J. Pharmacol. 192, 207.

Gaggi, R. and A.M. Gianni, 1990, Effects of calcium antagonists on biogenic amines in discrete brain areas, Eur. J. Pharmacol. 181, 187.

Gaggi, R., A.M. Gianni, L. Chirivi and P. Roncada, 1992, Effects of nimodipine on biogenic amines in discrete brain areas, Pharmacology 44, 237.

Kerckhoff, W. and L.R. Drewes, 1985, Transfer of the Ca^{2+}-antagonists nifidipine and nimodipine across the blood-brain barrier and their regional distribution in vivo, J. Cereb. Blood Flow Metab. 5 (Suppl. 1), 459.

Lang, A.E., 1988, Dopamine agonists and antagonists in the treatment of idiopathic dystonia, in: Dystonia 2, eds. S. Fahn, C.D. Marsden and D.B. Calne (Raven Press, New York) p. 561.

Leys, D., P. Vermersch, T. Danel, S. Comayras, M. Goudemand, J. Caron and H. Petit, 1988, Diltiazem for tardive dyskinesia, Lancet i, 250.

Löscher, W. and G. Fredow, 1992, Effects of pharmacological manipulation of dopaminergic and cholinergic neurotransmission in genetically dystonic hamsters, Eur. J. Pharmacol. 213, 31.

Löscher, W., J.E. Fisher Jr., D. Schmidt, G. Fredow, D. Hönack and W.B. Iturrian, 1989, The *sz* mutant hamster: a genetic model of epilepsy or of paroxysmal dystonia?, Movement Dis. 4, 219.

Marsden, C.D. and N.P. Quinn, 1990, The dystonias, Br. Med. J. 300, 139.

McGeer, E.G. and P.L. McGeer, 1988, The dystonias, Can. J. Neurol. Sci. 15, 447.

Nobrega, J.N., A. Richter, N. Tozman, D. Jiwa and W. Löscher, 1995, Quantitative autoradiography reveals regionally selective changes in dopamine D_1 and D_2 receptor binding in the genetically dystonic hamster, Neuroscience (in press).

Palmer, G.C., M.L. Stagnitto, R.K. Ray, M.A. Knowles, R. Harvey and G.E. Garske, 1993, Anticonvulsant properties of calcium channel blockers in mice: *N*-methyl-D-,L-aspartate- and BAY K 8644-induced convulsions are potently blocked by the dihydropyridines, Epilepsia 34, 372.

Pucilowski, O., 1992, Psychopharmacological properties of calcium channel inhibitors, Psychopharmacology 109, 12.

Raeburn, D. and R.A. Gonzales, 1988, CNS disorders and calcium antagonists, Trends Pharmacol. Sci. 9, 117.

Richter, A. and W. Löscher, 1993, The atypical neuroleptic, clozapine, exerts antidystonic activity in a mutant hamster model. Comparison with haloperidol, Eur. J. Pharmacol. 242, 309.

Richter, A., G. Fredow and W. Löscher, 1991, Antidystonic effects of the NMDA receptor antagonists memantine, MK-801 and CGP 37849 in a hamster model of paroxysmal dystonia, Neurosci. Lett. 133, 57.

Ross, J.L., T.B. Mackenzie, D.R. Hanson and C.R. Charles, 1987, Diltiazem for tardive dyskinesia, Lancet i, 268.

Skeen, G.A., R.E. Twyman and H.S. White, 1993, The dihydropyridine nitrendipine modulates *N*-methyl-D-aspartate receptor channel function in mammalian neurons, Mol. Pharmacol. 44, 443.

Wahnschaffe, U., G. Fredow, P. Heintz and W. Löscher, 1990, Neuropathological studies in a mutant hamster model of paroxysmal dystonia, Movement Dis. 5, 286.