ELSEVIER

European Journal of Pharmacology 369 (1999) 335–338

ejp

Short communication

Gabapentin decreases the severity of dystonia at low doses in a genetic animal model of paroxysmal dystonic choreoathetosis

Angelika Richter *, Wolfgang Löscher

Department of Pharmacology, Toxicology and Pharmacy, School of Veterinary Medicine, Bünteweg 17, D-30559 Hannover, Germany

Received 10 December 1998; revised 9 February 1999; accepted 12 February 1999

Abstract

The effects of the γ-aminobutyric acid (GABA)-potentiating drug gabapentin (1-(aminomethyl) cyclohexaneacetic acid) on severity of dystonia were examined in a hamster model of idiopathic paroxysmal dystonic choreoathetosis. In the genetically dystonic hamster (*dt*^{sz}) recent pharmacological and neurochemical studies suggested that disturbed GABAergic inhibition is involved in the pathogenesis. In line with a case report of beneficial effects in human paroxysmal dystonic choreoathetosis, gabapentin reduced the severity of dystonia in mutant hamsters at doses of 5 and 10 mg kg^{-1} i.p. At higher doses (20 and 100 mg kg^{-1}), gabapentin, however, failed to exert antidystonic effects. The GABApotentiating activity of gabapentin could explain the antidystonic effects of low doses, while the loss of efficacy at higher doses may be due to other mechanisms of gabapentin.

Keywords: Dystonia; Dyskinesia; GABA (γ-aminobutyric acid); Movement disorder

1. Introduction

Gabapentin (1-(aminomethyl)cyclohexaneacetic acid) is a novel anticonvulsant drug which is generally well-tolerated (Ramsey, 1995). Although classical antiepileptic drugs are not effective in idiopathic paroxysmal dystonic choreoathetosis, a subtype of dystonia in which episodes of dystonic and choreoathetotic movements precipitated by stress may last up to several hours, gabapentin has been reported to exert beneficial effects (Chudnow et al., 1997b). The pathophysiology of idiopathic paroxysmal dystonic choreoathetosis in humans is unknown, but previous pharmacological and neurochemical findings in mutant dystonic hamsters (gene symbol *dt*^{sz}), an animal model which shows all characteristics of paroxysmal dystonic choreoathetosis, indicated that dysfunction of the γ-aminobutyric acid (GABA)-ergic system plays a critical role in the pathogenesis (Richter and Löscher, 1998).

Although gabapentin was designed as a structural analog of GABA, it does not modulate GABA receptor function, i.e., the drug actions are distinct from those of several other GABApotentiating drugs such as benzodiazepines which are known to be effective in human paroxysmal dystonic choreoathetosis (Demirkiran and Jankovic, 1995) and to reduce the severity of dystonia in *dt*^{sz} hamsters (Richter and Löscher, 1998). Gabapentin was found to elevate brain GABA levels probably by enhanced GABA synthesis (Löscher et al., 1991) and also decreases brain glutamate concentrations (Taylor et al., 1998). In dystonic hamsters, neurochemical studies suggested that the GABA synthesis is reduced in the striatum, and drugs such as aminooxyacetic acid which increase brain GABA levels exerted antidystonic effects in the hamster model (Richter and Löscher, 1998). Furthermore, glutamate receptor antagonists decreased the severity of dystonia in *dt*^{sz} mutant hamsters (Richter et al., 1991, 1993). With regard to the effects of gabapentin on inhibitory and excitatory amino acids, we examined in the present study if gabapentin reduces the severity of dystonia in mutant hamsters, as observed in a patient with paroxysmal dystonic choreoathetosis (Chudnow et al., 1997b).

2. Materials and methods

The mutant dystonic hamsters (genetic symbol *dt*^{sz}) used for the present study were obtained by selective breeding (for detailed description see Richter and Löscher,

* Corresponding author. Tel.: +49-511-9538723; Fax: +49-511-9538581; E-mail: arichter@pharma.tiho-hannover.de

0014-2999/99/$ - see front matter
PII: S0014-2999(99)00104-1

1998). The experiments were carried out in four groups of 9–11 mutant dystonic hamsters with an age of 30–40 days, at which the age-dependent dystonia reaches maximum severity. In dt^{sz} hamsters dystonic attacks can be provoked by mild stress. In the present study, the dystonic attacks were induced by the procedure of triple stimulation (Löscher et al., 1989), 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 gabapentin, (3) placement of the hamster in a clean and empty plastic cage (one animal per cage). Since the dystonic syndrome consists of a sequence of abnormal movements, the severity of dystonia can be rated by following score-system (Löscher et al., 1989; Richter and Löscher, 1998): 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 tiptoes in a dysmetric hypergait; stage 4, twisting, choreoathetotic 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 and other signs, such as alternating unilateral forelimb elevation and opisthotonos. 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 noticed. Pre- and post-drug control trials were undertaken 2 days before and 2 days after drug testing.

Gabapentin was administered intraperitoneally at doses of 5, 10, 20 and 100 mg kg^{-1}. Gabapentin was freshly dissolved in distilled water. The injection volume was 5 ml kg^{-1}. 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, gabapentin decreased the individual maximum severity of dystonia in mutant hamsters at a dose of 5.0 mg kg^{-1} in comparison to the pre- and post-drug controls. At a dose of 10.0 mg kg^{-1}, the antidystonic effect became already evident during the second hour of observation. At both doses, the severity of dystonia was not reduced during the first hour after administration and no significant effects could be observed on the latency to onset of unequivocal dystonic symptoms (stage 2), indicating a delay in the onset of gabapentin's antidystonic effect. The antidystonic effective doses did not cause any side effects.

At higher doses of 20.0 and 100 mg kg^{-1}, gabapentin did not exert any significant effects on the severity of dystonic choreoathetosis (Fig. 1). The symptoms of the different stages appeared to be more marked after administration of 100 mg kg^{-1} gabapentin compared to the vehicle controls, and the latency to stage 6 tended to be decreased from 84.7 ± 9.7 (pre-drug) or 81.3 ± 13.3 (post-drug control) to 56.0 ± 7.6 min ($P < 0.05$ vs. pre-

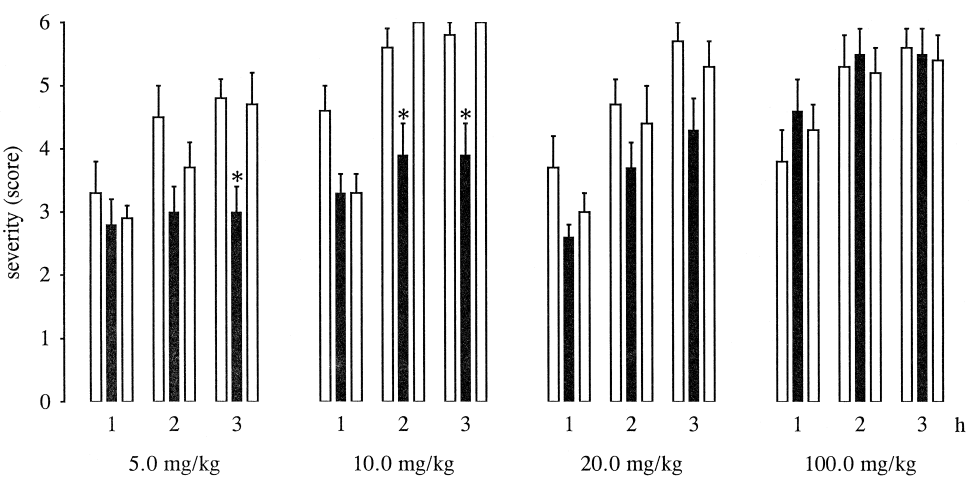

Fig. 1. Effect of gabapentin on severity of dystonia in mutant hamsters. Usually, the individual maximum severity of dystonia is reached within 3 h after induction of dystonia by triple stimulation including the i.p. injection 5, 10, 20 or 100 mg kg^{-1} gabapentin (black bars) or vehicle for pre- and post-drug controls (open bars). 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, reflecting the progression of dystonia in mutant hamsters after treatment with the compounds and without drug-treatment (vehicle controls). Control recordings were undertaken 2 days before (pre-drug control) and 2 days after (post-drug control) the drug trial. Data are shown as means + S.E. of 11 (5.0 mg kg^{-1}), 9 (10.0 mg kg^{-1}) or 10 (20.0 and 100 mg kg^{-1}) dystonic hamsters. Asterisks indicate significant reduction of severity in comparison to the pre-drug and post-drug control ($^{*}P < 0.05$).

drug, not significant vs. post-drug), indicating a tendency to prodystonic effects. A dose of 20 mg kg^{-1} caused moderate hyperlocomotion lasting from 30 to 100 min after injection. Twenty minutes after administration of 100 mg kg^{-1} gabapentin, the hamsters exhibited marked hyperactivity (hyperlocomotion and biting) and ataxia during the 3-h observation period.

4. Discussion

The present finding of antidystonic efficacy of low doses of gabapentin in mutant hamsters confirms the dt^{sz} hamster as a suitable animal model for drug testing because the data are in line with a case report of human paroxysmal dystonic choreoathetosis in which gabapentin (10 mg kg^{-1} day^{-1}) exerted benefit (Chudnow et al., 1997b). These observations seem to support the suggestion of Fouad et al. (1996) that GABAergic dysfunctions deserve attention in human paroxysmal dystonic choreoathetosis. Although the cellular mechanisms of pharmacological actions of gabapentin are not completely known, several lines of evidence indicate that gabapentin increases GABA synthesis (Löscher et al., 1991; Taylor et al., 1998). Furthermore, gabapentin inhibits the striatal dopamine release and the synthesis of glutamate (Reimann, 1983; Taylor et al., 1998). These mechanisms of action may be relevant for its antidystonic efficacy in mutant hamsters. As indicated by recent pharmacological and neurochemical studies in dt^{sz} hamsters, disturbed GABAergic function and enhanced striatal dopaminergic activity play a critical role in the dystonic syndrome, and glutamatergic overactivity may contribute to the manifestation of dystonia (Rehders et al., 1998; Richter and Löscher, 1998). Furthermore, gabapentin seems to exert calcium channel antagonistic properties (Taylor et al., 1998). Although there is no evidence that calcium channel function is disturbed in mutant hamsters, antidystonic effects of calcium channel blockers which decrease dopamine release were observed in recent studies (Richter and Löscher, 1996).

However, the antidystonic effects of 5 and 10 mg kg^{-1} gabapentin were not very marked in dystonic hamsters, probably due to delayed onset of action of gabapentin. Delayed onset, also observed for the anticonvulsant properties, has been explained by delayed distribution of gabapentin to the brain compartment and biochemical events, such as elevation of extracellular GABA levels (Welty et al., 1997; Taylor et al., 1998).

The lack of antidystonic effects of gabapentin at higher doses of 20 and 100 mg kg^{-1} in mutant hamsters was an unexpected finding. Since recent studies have shown prodystonic effects of Na^+ channel blockers in mutant hamsters (Richter et al., 1994, 1997), it should be considered that gabapentin decreases sustained firing of Na^+-dependent action potentials during long incubation periods in vitro (Wamill and McLean, 1994). In humans, various Na^+ channel inhibitors have been reported to may cause dystonic and choreoathetotic movements (Corey and Koller, 1983; Frost et al., 1996). Chudnow et al. (1997a) described two epileptic patients with choreoathetotic reactions after treatment with high doses of gabapentin (>20 mg kg^{-1}). Tentatively, the loss of antidystonic efficacy at higher doses, and a tendency of aggravation of dystonia observed after administration of 100 mg kg^{-1} gabapentin in mutant hamsters, may be related to effects on voltage-dependent Na^+ channels. From the present data in mutant hamsters and case reports in humans, it may be concluded that gabapentin could represent an interesting candidate for the treatment of paroxysmal dystonic choreoathetosis at low well-tolerated doses, but the administration of higher doses of gabapentin may rather bear the risk to aggravate dystonia.

Acknowledgements

This study was supported by a grant from the Deutsche Forschungsgemeinschaft (Lo 274/4-3).

References

Chudnow, R.S., Dewey, R.B., Lawson, C.R., 1997a. Choreoathetosis as a side effect of gabapentin therapy in severely neurologically impaired patients. Arch. Neurol. 54, 910–912.

Chudnow, R.S., Mimbela, R.A., Owen, D.B., Roach, E.S., 1997b. Gabapentin for familial paroxysmal dystonia choreoathetosis. Neurology 49, 1441–1442.

Corey, A., Koller, W., 1983. Phenytoin-induced dystonia. Ann. Neurol. 14, 92, Letter.

Demirkiran, M., Jankovic, J., 1995. Paroxysmal diskinesias: clinical features and classification. Ann. Neurol. 38, 571–579.

Fouad, G., Servidei, S., Durcan, S., Bertini, E., Ptacek, L.J., 1996. A gene for familial paroxysmal dyskinesia (FPD1) maps to chromosome 2q. Am. J. Hum. Genet. 59, 135–139.

Frost, M.D., Ritter, F.J., Hoskin, C., Mims, J., Espe-Lillo, J., 1996. Movement disorder associated with lamotrigine treatment in children and adolescents. Epilepsia 37 (5), 112, Suppl.

Löscher, W., Fisher, J.E. Jr., Schmidt, D., Fredow, G., Hönack, D., Iturrian, W.B., 1989. The sz mutant hamster: a genetic model of epilepsy or of paroxysmal dystonia?. Mov. Dis. 4, 219–232.

Löscher, W., Hönack, D., Taylor, C.P., 1991. Gabapentin increases aminooxyacetic acid-induced GABA accumulation in several brain regions of rat brain. Neurosci. Lett. 128, 150–154.

Ramsey, R.E., 1995. Gabapentin: toxicity. In: Levy, R.H., Mattson, R.H., Meldrum, B.S. (Eds.), Antiepileptic Drugs. Raven Press, New York, pp. 857–860.

Rehders, J.H., Löscher, W., Richter, A., 1998. The mutant dystonic (dt^{sz}) hamster: evidence for enhanced striatal dopaminergic activity found by pharmacological manipulations. Soc. Neurosci. Abstr. 24, 660.

Reimann, W., 1983. Inhibition by GABA, baclofen and gabapentin of dopamine release from rabbit caudate nucleus: are there common or different sites of action?. Eur. J. Pharmacol. 94, 341–344.

Richter, A., Löscher, W., 1996. Antidystonic effects of L-type Ca^{2+}

channel antagonists in a hamster model of idiopathic dystonia. Eur. J. Pharmacol. 300, 197–202.

Richter, A., Löscher, W., 1998. Pathophysiology of idiopathic dystonia: findings from genetic animal models. Prog. Neurobiol. 54, 633–677.

Richter, A., Fredow, G., Löscher, W., 1991. Antidystonic effects of the NMDA receptor antagonists memantine, MK-801 and CGP 37849 in a hamster model of paroxysmal dystonia. Neurosci. Lett. 133, 57–60.

Richter, A., Löscher, W., Löschmann, P.-A., 1993. The AMPA receptor antagonist NBQX exerts antidystonic effects in an animal model of idiopathic dystonia. Eur. J. Pharmacol. 231, 287–291.

Richter, A., Löschmann, P.-A., Löscher, W., 1994. The novel antiepileptic drug lamotrigine exerts prodystonic effects in a mutant hamster model of generalized dystonia. Eur. J. Pharmacol. 264, 345–351.

Richter, A., Gernert, M., Löscher, W., 1997. Prodystonic effects of riluzole in an animal model of idiopathic dystonia related to decreased total power in the red nucleus?. Eur. J. Pharmacol. 332, 133–142.

Taylor, C.P., Gee, N.S., Su, T.Z., Kocsis, J.D., Welty, D.F., Brown, J.P., Dooley, D.J., Boden, P., Singh, L., 1998. A summary of mechanistic hypotheses of gabapentin pharmacology. Epilepsy Res. 29, 233–249.

Wamill, A.W., McLean, M.J., 1994. Limitation by gabapentin of high frequency action potential firing by mouse central neurons in cell culture. Epilepsy Res. 17, 1–11.

Welty, D.F., Wang, Y., Busch, J.A., Taylor, C.P., Vartanian, M.G., Radulovic, L.L., 1997. Pharmacokinetics and pharmacodynamics of CI-1008 (pregabalin) and gabapentin in rats using maximal electroshock. Epilepsia 38, 35–36, abstract.