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The competitive NMDA receptor antagonist SDZ 220-581 reverses haloperidol-induced catalepsy in rats

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Abstract

The present studies investigated whether SDZ 220-581 ((*S*)-α-amino-2′-chloro-5-(phosphonomethyl)[1,1′-biphenyl]-3-propanoic acid), a potent, competitive antagonist at the NMDA glutamate receptor subtype, reversed haloperidol-induced catalepsy in rats, a widely used model of Parkinson's disease. SDZ 220-581 (0.32–3.2 mg/kg i.p.) dose- and time-dependently reduced the time spent in an abnormal position induced by haloperidol (1.0 mg/kg s.c.). Compared to other NMDA receptor antagonists the rank order of potency was MK-801 ((+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine) > SDZ 220-581 > SDZ EAA 494 (D-CPPene: (*S*)-(*E*)-4-(3-phosphonoprop-2-enyl)-piperazine-2-carboxylic acid) > SDZ EAB 515 ((*S*)-α-amino-5-(phosphonomethyl)[1,1′-biphenyl]-3-propanoic acid). Since it has been demonstrated that SDZ 220-581 counters the effects of L-dihydroxyphenylalanine (L-DOPA) on the motor disturbances of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-pre-treated primates, the results suggest that the reversal of haloperidol-induced catalepsy by competitive NMDA receptor antagonists may not be predictive of efficacy in other models of Parkinson's disease.

Keywords: NMDA receptor antagonist; Haloperidol; Catalepsy; (Rat); Parkinson's disease

1. Introduction

The motor impairments induced in man by typical neuroleptics, such as haloperidol, are considered to model aspects of the movement disturbances seen in Parkinson's disease (Hornykiewicz, 1973). The reversal of neuroleptic-induced catalepsy in rats by competitive and non-competitive NMDA receptor antagonists has often been cited as evidence of these compounds having potential therapeutic utility in Parkinson's disease (Schmidt and Bubser, 1989; Mehta and Ticku, 1990; Schmidt et al., 1991; Moore et al., 1993; Papa et al., 1993). The validity of the neuroleptic-induced catalepsy model for predicting antiparkinsonian effects of competitive NMDA receptor antagonists is supported by the demonstration that 4-(3-phosphonopropyl)piperazine-2-carboxylic acid (CPP) and the unsaturated analogue SDZ EAA 494 (D-CPPene) augment the actions of direct and indirect dopamine agonists in reserpinized mice (Svensson et al., 1992), 6-hydroxydopamine-lesioned rats, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-pre-treated primates (Löschmann et al., 1991). This is consistent with the hypothesis that glutamate antagonists would synergise with dopamine agonists in reversing the motor disturbances seen after dopamine depletion by blocking the resulting overactive glutamatergic pathways (Klockgether and Turski, 1989; Greenamyre, 1993).

Recently, the pharmacology of SDZ 220-581, a biphenyl derivative of 2-amino-7-phosphonoheptanoic acid (AP-7), and potent, competitive antagonist at the NMDA receptor, has been described (Fig. 1; Urwyler et al., 1996a,b). Contrary to expectation, SDZ 220-581 was found to antagonise the effects of L-dihydroxyphenylalanine (L-DOPA) in the MPTP-pre-treated primate model of Parkinson's disease (Urwyler et al., 1996b). It was therefore investigated whether SDZ 220-581 would reverse haloperidol-induced catalepsy. The effects were compared to those of the non-competitive NMDA receptor antagonist MK-801; the competitive receptor antagonist SDZ EAA 494 (D-CP-

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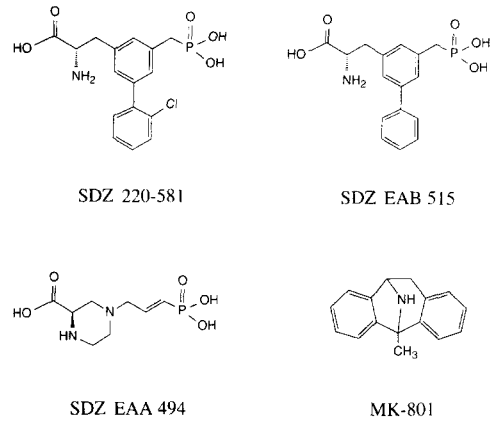

Fig. 1. Chemical structures of SDZ 220-581, SDZ EAA 494, SDZ EAB 515 and MK-801.

Pene); and the unsubstituted derivative of SDZ 220-581, SDZ EAB 515 (Fig. 1).

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (Interfauna, Germany) weighing 140–170 g were used. The animals were collected from the Animal Facility on the day of the experiment. Food (NAFAG) and water were available ad libitum.

2.2. Procedure

The experiments were conducted in a quiet room. 1.0 mg/kg haloperidol was administered s.c. to the animals 90 min before the test compounds. SDZ 220-581 (0.32, 1.0 and 3.2 mg/kg), MK-801 (0.032, 0.1 and 0.32 mg/kg), SDZ EAA 494 (1.0, 3.2 and 10.0 mg/kg) and SDZ EAB 515 (3.2, 10.0 and 32.0 mg/kg) were administered i.p. ($n = 8$). Catalepsy was determined 1, 2, 3 and 4 h after administration of the test substances by carefully positioning the animals with their forepaws resting on a 7-cm high wooden block. With minimal disturbance by the experimenter, the time taken for the animal to move both paws to the lab bench (i.e. time spent by the animals in an abnormal position or catalepsy time) was measured with a cut-off time of 60 s.

2.3. Drugs

SDZ 220-581 ((*S*)-α-amino-2′-chloro-5-(phosphonomethyl)[1,1′-biphenyl]-3-propanoic acid, Müller et al., 1995), SDZ EAA 494 (D-CPPene: (*S*)-(*E*)-4-(3-phosphonoprop-2-enyl)-piperazine-2-carboxylic acid; Aebischer et al., 1989), SDZ EAB 515 ((*S*)-α-amino-5-(phosphonomethyl)[1,1′-biphenyl]-3-propanoic acid; Müller et al., 1992) and MK-801 ((+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine; Wong et al., 1986) were dissolved in 0.9% saline and administered in a volume of 10 ml/kg. 5 mg/ml concentrations of haloperidol (Janssen) were diluted with saline. All doses were calculated as the base of the compound.

2.4. Statistical analysis

Since the data did not meet the assumptions of parametric statistics, non-parametric statistical analyses were employed. The Kruskal-Wallis *H*-test was used to investigate treatment effects at each time point (Siegel, 1956). Significant effects were investigated using Mann-Whitney *U*-tests comparing treatment groups with controls. The significance level was set at 5% ($P < 0.05$).

3. Results

The time spent in the abnormal position on the wood block by animals administered haloperidol and the NMDA receptor antagonists are shown in Figs. 2–5. SDZ 220-581 (Fig. 2) dose-dependently and statistically significantly reduced the median catalepsy time at each time point (1 h: $H = 11.1$, $P = 0.011$; 2 h: $H = 16.1$, $P < 0.001$; 3 h: $H = 16.6$, $P < 0.001$; 4 h: $H = 9.4$, $P = 0.02$). The reduction in catalepsy time in those animals administered the 3.2 mg/kg dose was significant throughout the experiment although it can be seen that the effect was attenuating over time. 3 h after administration the effect observed in the 1.0 mg/kg group was also significant.

MK-801 (Fig. 3) dose-dependently reduced the time in the abnormal position at each time point with a reduction in efficacy over the test period (1 h: $H = 14.7$, $P = 0.002$; 2 h: $H = 18.1$, $P < 0.001$; 3 h: $H = 19.0$, $P < 0.001$; 4 h: $H = 11.9$, $P = 0.008$). Statistically significant reductions

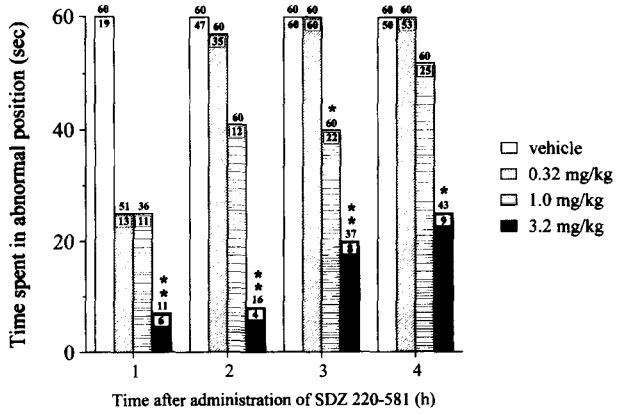

Fig. 2. The effects of SDZ 220-581 upon the time spent in the abnormal position induced by 1 mg/kg haloperidol (s.c.) in rats ($n = 8$) at various doses 1, 2, 3 and 4 h following the administration of the NMDA antagonist. The data are expressed as medians with upper quartile (above top of bar) and lower quartile (below top of bar). * $P < 0.05$, ** $P < 0.01$ compared to vehicle, Mann-Whitney *U*-test.

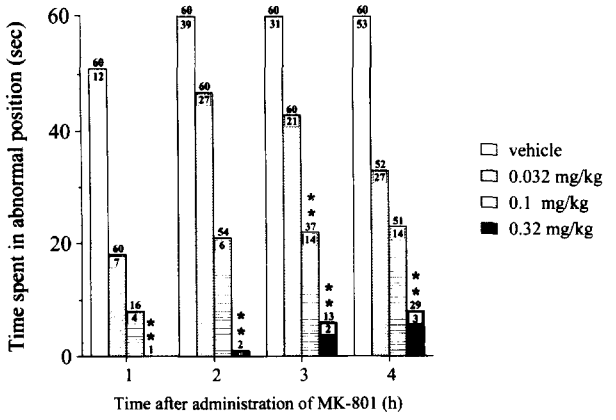

Fig. 3. The effects of MK-801 upon the time spent in the abnormal position induced by haloperidol. See legend to Fig. 2 for further details.

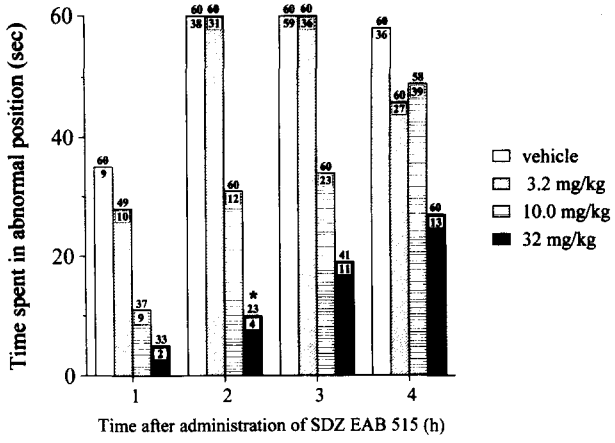

Fig. 5. The effects of SDZ EAA 515 upon the time spent in the abnormal position induced by haloperidol. See legend to Fig. 2 for further details.

were observed in those animals given 0.1 mg/kg at the 3-h time point and in those animals given 0.32 mg/kg at each time point.

SDZ EAA 494 (Fig. 4) also reduced the catalepsy time over the first 3 h following administration (1 h: $H = 9.35$, $P = 0.025$; 2 h: $H = 10.3$, $P = 0.016$; 3 h: $H = 10.9$, $P = 0.01$). The effects, however, were not dose-dependent. 1 h post-administration those animals given 1 and 3 mg/kg showed significant reductions in the time spent in the abnormal position. 2 and 3 h post-administration those animals given 10 mg/kg showed significant differences from controls. A significant effect was recorded in the 1 mg/kg treatment group at the 2-h time point.

SDZ EAB 515 (Fig. 5) dose-dependently reduced the catalepsy time although the dose-response curve was quite flat. It should be noted that at the 1-h time point, the median time spent in the abnormal position by the controls was lower than in the other experiments. A statistically significant effect was recorded at the 2-h time point (2 h: $H = 8.2$, $P = 0.041$) with the effect 3 h post-administration approaching significance (3 h: $H = 6.55$, $P = 0.087$). Paired comparisons revealed significant differences between controls and the 32 mg/kg treatment group only, at the 2-h time point.

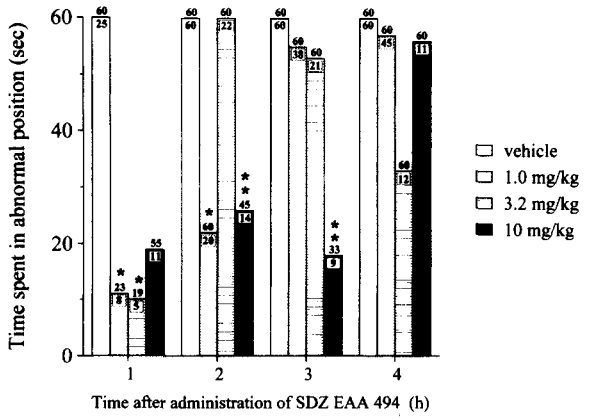

Fig. 4. The effects of SDZ EAA 494 upon the time spent in the abnormal position induced by haloperidol. See legend to Fig. 2 for further details.

4. Discussion

All four compounds reduced the time spent by the animals in the abnormal position following haloperidol administration. These results parallel the previous reports of the reversal of haloperidol-induced catalepsy by both competitive and non-competitive NMDA receptor antagonists (Schmidt and Bubser, 1989; Mehta and Ticku, 1990; Schmidt et al., 1991; Moore et al., 1993; Papa et al., 1993). The effects of SDZ 220-581, MK-801 and SDZ EAB 515 were dose- and time-dependent. Consistent antagonism of haloperidol by SDZ EAA 494 was seen at the highest dose only. The rank order of potency was MK-801 > SDZ 220-581 > SDZ EAA 494 > SDZ EAB 515. The superior potency of SDZ 220-581 over SDZ EAA 494 and SDZ EAB 515 is consistent with the high binding affinity to the NMDA receptor, potent functional NMDA receptor antagonism, and good bioavailability (Urwyler et al., 1996a,b).

In the present model of Parkinson's disease, SDZ 220-581 reversed the motor disturbances due to dopamine D_2 receptor blockade. When co-administered with L-DOPA to MPTP-pre-treated marmosets, however, SDZ 220-581 significantly reversed the locomotor stimulation provided by L-DOPA and countered the L-DOPA-induced amelioration of the disability scores (Urwyler et al., 1996b). Similar results to SDZ 220-581 have been obtained with MK-801: counteraction of the reversal of motor disturbances in reserpinized mice and 6-OHDA-lesioned rats by dopamine D_2 receptor agonists (Svensson et al., 1992; Morelli and Di Chiara, 1990), and reversal of the effects of L-DOPA in MPTP-pre-treated primates (Close et al., 1990; Rupniak et al., 1992). On the other hand, SDZ EAA 494 potentiates the effects of dopamine D_2 receptor agonists in reserpinized mice (Svensson et al., 1992), and CPP synergises

with L-DOPA to induce movement in 6-OHDA-lesioned rats and MPTP-pre-treated monkeys (Löschmann et al., 1991). It would therefore appear that reversal of haloperidol-induced catalepsy by competitive as well as non-competitive NMDA receptor antagonists may not be predictive of efficacy in either rodent or primate dopamine-depletion models of Parkinson's disease. The lack of predictability also extends to non-NMDA receptor antagonists: 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(f)quinoxaline (NBQX), an antagonist of the α-amino-3-hydroxy-5-methylisoxazole acid (AMPA) subtype of glutamate receptors, does not reverse catalepsy induced by dopamine D_1 or D_2 receptor antagonists (Papa et al., 1993) but is effective in potentiating the effects of dopamine agonists in 6-hydroxydopamine-lesioned rats and MPTP-pre-treated primates (Löschmann et al., 1991).

There are two possible explanations for the discrepancy between different NMDA receptor antagonists and between the various Parkinson's disease models. First, that there is variation in the effects of the compounds upon the basal ganglia. For instance, while SDZ EAA 494 spares cholinergic and γ-aminobutyric acid (GABA)-ergic neurones from lesioning after intra-striatally injected quinolinic acid to a similar extent, SDZ 220-581 protects cholinergic neurones more than GABAergic neurones (Urwyler et al., 1996b). This difference, together with the superior potency with which SDZ 220-581 changes 2-deoxyglucose uptake in the caudate putamen and globus pallidus compared to SDZ EAA 494 (Urwyler et al., 1996b), may be expressed in those Parkinson's disease models employing dopamine depletion rather than simply dopamine D_2 receptor blockade. Indeed, it has been demonstrated that NMDA receptor-mediated mechanisms may interact differently with dopamine D_1 and D_2 receptors (Morelli and Di Chiara, 1990; Svensson et al., 1992). A second explanation is that the NMDA receptor antagonists produce muscle relaxation which counters the rigidity produced by haloperidol and has a confounding influence on the test read-out. Although SDZ 220-581 and SDZ EAA 494 do not produce motor incoordination or ataxia until high doses are administered (Lowe et al., 1994; Urwyler et al., 1996b), and that chlordiazepoxide is ineffective in reducing haloperidol-induced catalepsy (32 mg/kg i.p., results not shown; see also Moore et al., 1993), changes in muscle tone via mechanisms different from that of benzodiazepines may confound the apparent reduction in the time spent by the animals in the abnormal position.

In conclusion, the competitive NMDA receptor antagonist SDZ 220-581, in common with other competitive and non-competitive antagonists, reverses haloperidol-induced catalepsy. However, since the compound counters the effects of L-DOPA on the motor disturbances of MPTP-pre-treated primates, the results suggest that the reversal of haloperidol-induced catalepsy by some competitive NMDA receptor antagonists may not be predictive of efficacy in other animal models of Parkinson's disease.

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