Some central effects of CGP 37849 and CGP 39551, the competitive NMDA receptor antagonists: potential antiparkinsonian activity

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Summary. Two new competitive NMDA receptor antagonists with oral activity CGP 37849 (D,L-E-amino-methyl-phosphono-3-pentenoic acid) and its ethyl ester CGP 39551 were studied in rats. CGP 37849 did not change the locomotor activity or increased it. The hyperactivity induced by CGP 37849 was antagonized by haloperidol but not idazoxan or prazosin. CGP 39551 decreased the locomotor activity. The studied compounds did not increase the locomotion in monoamine-depleted (pretreated with reserpine and α-methyl-p-tyrosine) rats. Clonidine induced antiakinetic effect in monoamine-depleted rats. This effect was more pronounced after joint administration of clonidine and CGP 37849 or CGP 39551. The locomotor hyperactivity induced by joint administration of CGP 37849 and clonidine was inhibited by haloperidol but not prazosin or idazoxan. CGP 37849 but not CGP 39551 also enhanced antiakinetic effect of L-DOPA (given together with benserazide) in monoamine-depleted rats. CGP 37849 antagonized the spiperone- and fluphenazine-induced catalepsy; CGP 39551 had considerably weaker antagonistic effect. The reserpine-induced catalepsy was attenuated by CGP 37849. MK-801, a non-competitive NMDA antagonist inhibited spiperone- but not reserpine-induced catalepsy. The obtained results indicate that CGP 37849 administered alone or in combination with L-DOPA or clonidine may be a potential antiparkinsonian drug.

Keywords: CGP 37849 and CGP 39551, monoamine-depleted rats, locomotor activity, neuroleptic catalepsy.

Introduction

We found previously that MK-801 (dizocilpine), a non-competitive antagonist of NMDA receptors, increases the locomotor activity of rats, most probably via an indirect activation of the dopamine system (Maj et al., 1991). A similar, MK-801-induced locomotor hyperactivity was also described by other authors (e.g. Clineschmidt et al., 1982; Carlsson and
Carlsson, 1989a,b; Hiramatsu et al., 1989). This effect was also observed in monoamine-depleted animals (pretreated with reserpine and α-methyl-tyrosine), in particular when MK-801 was administered jointly with clonidine. MK-801 also induces other effects which suggest involvement of a dopamine mechanism; among others, it potentiates the stimulating effect of L-DOPA and antagonizes catalepsy induced by haloperidol (Klockgether and Turski, 1990; Schmidt and Bubser, 1989).

The present study has been designed to find out whether competitive antagonists of NMDA receptors have an action similar to that of MK-801. To this end we used two new compounds of this type, CGP 37849 (D,L-E-amino-methyl-phosphono-3-pentenoic acid) and its ethyl ester CGP 39551 (Fagg et al., 1990; Pozza et al., 1990; Schmutz et al., 1990; Sills et al., 1991). Both these compounds are well transported into the brain, showing – when administered intravenously, intraperitoneally or perorally – an anticonvulsant activity. Their intraperitoneal administration in our previous experiments produced an antidepressant-like effect in the forced swimming test, which was antagonized by haloperidol (Maj et al., 1992). We studied here the effects of CGP 37849 and CGP 39551 on the locomotor activity of normal and monoamine-depleted rats, the interaction with L-DOPA, and the effect on the catalepsy evoked by neuroleptics. Sparse data on the activity of the compounds studied in some of the above-mentioned tests have already been given (see: Discussion).

Materials and methods

The experiment was carried out on male Wistar rats (220–260 g) housed in group of 10 in normal day-night cycle with free access to food and water.

The substances were dissolved in distilled water (benserazide, CGP 37849, CGP 39551, clonidine, fluphenazine, haloperidol, idazoxan, spiperone) or suspended in 1% aqueous solution of Tween 80 (L-DOPA, α-MT, prazosin). Control animals received vehicle according to the same schedule.

Locomotor activity was measured in photoresistor actometers (two light beams) in which the animals were placed individually.

In preliminary experiments we observed that the stimulation of the locomotor activity (measured as above) appeared 60–120 min after injection of CGP 37849. It lasted at least about 4 h. The ataxia was also present but it was stronger in the first period of time. Therefore the time interval between 3 and 4 h was chosen for further experiments.

In normal rats CGP 37849 and CGP 39551 were given i.p. 3 h before the experiment. The activity counts were recorded for 1 h. Haloperidol (0.25 mg/kg i.p.) was injected 30 min before CGP 37849, 20 or 40 mg/kg i.p.; prazosin (3 mg/kg i.p.) and idazoxan (10 mg/kg i.p.) – 30 min before CGP 37849 20 mg/kg.

Monoamine-depleted rats were treated with reserpin and α-MT in various experimental paradigms (described in literature):

1. According to Kannari and Markstein (1991): reserpine, 5 mg/kg i.p. and α-MT 250 mg/kg, were given 18 h and 0.5 before the test, respectively; CGP 37849 (10, 20, 40 mg/kg) and CGP 39551 (10, 20, 40 mg/kg) were given i.p. and then the rats were immediately placed in the actometers. The activity counts were recorded for 4 h.

2. According to Carlsson and Svensson (1990): reserpin, 10 mg/kg i.p. and α-MT, 250 mg/kg i.p., were injected 20 h and 4 h before the test, respectively. CGP 37849 and CGP 39551 (both at the doses of 5 and 10 mg/kg) were given 3 h, and clonidine