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Short communication

The AMPA receptor antagonist GYKI 52466 reverses the anti-cataleptic effects of the competitive NMDA receptor antagonist CGP 37849

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Abstract

The effects of the AMPA receptor antagonist GYKI 52466 (1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine HCl) on haloperidol-induced catalepsy were tested in drug-naive rats and in rats pretreated with the competitive NMDA receptor antagonist CGP 37849 (DL-(*E*)-2-amino-4-methyl-5-phosphono-3-pentenoic acid). CGP 37849 (4 mg/kg i.p.) given alone significantly reversed haloperidol-induced catalepsy (0.5 mg/kg i.p.) while GYKI 52466 (4.8 mg/kg i.p.) given alone was without effect. Administration of GYKI 52466 to rats pretreated with CGP 37849 abolished the anticataleptic effects of the competitive NMDA receptor antagonist seen following single administration. Thus the AMPA receptor antagonist prevents behavioural effects induced by a NMDA receptor antagonist in this behavioural model.

Key words: Haloperidol-induced catalepsy; GYKI 52466 (1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine HCl); CGP 37849 (DL-(*E*)-2-amino-4-methyl-5-phosphono-3-pentenoic acid); AMPA receptor; NMDA receptor; (Rat)

1. Introduction

Glutamate is the main excitatory transmitter in the mammalian brain and its effects are mediated through distinct receptor subtypes termed as AMPA, NMDA and kainate receptors which are ionotropic and metabotropic receptors which are activated by *trans*-1-aminocyclopentane-1,3-dicarboxylate (Monaghan et al., 1989). The behavioural pharmacology of AMPA receptors, their interactions with NMDA and dopamine receptors is rarely investigated at present. In recent studies it was shown that AMPA receptor antagonists did not reverse neuroleptic-induced catalepsy in rats (Papa et al., 1993; Zadow and Schmidt, 1994; Hauber and Andersen, 1993) and parkinsonian symptoms in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated primates (Luquin et al., 1993). Furthermore coadministration of AMPA receptor antagonists to rats pretreated with dizocilpine or L-3,4-dihydroxyphenylalanine (L-DOPA) abolished the anticataleptic effects of dizocilpine and weakened the anticataleptic effects of L-DOPA (Zadow and Schmidt, 1994; Hauber and Andersen, 1993).

In order to further investigate the effects of a combined AMPA/NMDA receptor blockade on haloperidol-induced catalepsy we tested in the present study whether or not the selective AMPA receptor antagonist GYKI 52466 (Tarnawa et al., 1989) is able to reverse the well-documented anticataleptic effects of the competitive NMDA receptor antagonist CGP 37849 (Kretschmer et al., 1992).

2. Materials and methods

2.1. Drugs

Male Sprague-Dawley rats (235–270 g) (Interfauna, Tuttlingen, Germany) were tested for the effects of single or combined administration of behaviourally active doses of GYKI 52466 (1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine

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HCl) (4.8 mg/kg i.p.) (Hauber and Andersen, 1993; Zadow and Schmidt, 1994; Smith et al., 1991) and CGP 37849 (DL-(*E*)-2-amino-4-methyl-5-phosphono-3-pentenoic acid) (4 mg/kg i.p.) (Kretschmer et al., 1992) on haloperidol-induced catalepsy (0.5 mg/kg i.p.). GYKI 52466 (Dr. I. Tarnava, Inst. Drug Res., Budapest, Hungary) was dissolved in distilled water, haloperidol (Janssen, Neuss, Germany) and CGP 37849 (Ciba-Geigy, Basel, Switzerland) were dissolved in physiological saline. All drugs were given 30 min before the onset of the catalepsy test.

2.2. Behavioural procedure

The degree of catalepsy was measured as previously described (Hauber and Schmidt, 1993) in three subtests performed in the following order. (1) Bar: both forelegs were placed on a horizontal bar (9 cm above the surface). (2) Podium: one foreleg was placed on a podium (3 cm high). (3) Grid: an animal was clinged to a vertical wire grid. In all subtests the latency from paw placement until the complete removal of one paw from the support ('descent latency') was measured (cut-off: 180 s).

2.3. Statistics

The data are presented as mean descent latencies and standard errors of the mean (S.E.M.) for each subtest and treatment group. The data were subjected to a Mann-Whitney *U*-test (two-tailed). Differences were considered to be significant if the *P* value was less than 0.05.

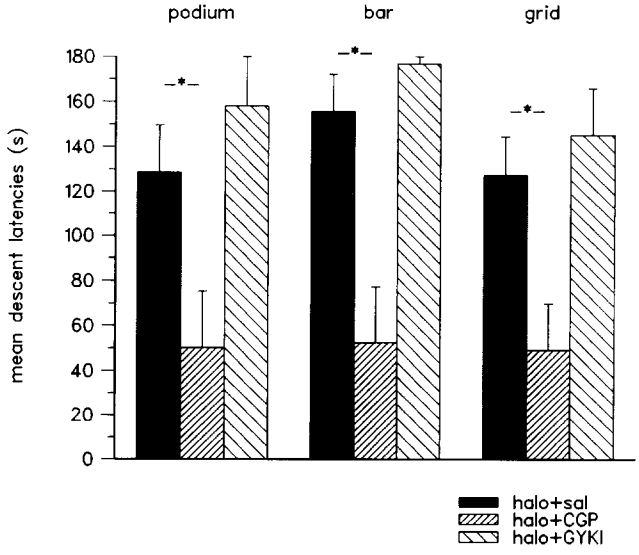

Fig. 1. Mean descent latencies (±S.E.M.) in the catalepsy test 30 min after drug administration. Treatment groups received intraperitoneal injections of haloperidol (0.5 mg/kg) plus saline (1 ml/kg, $n = 8$), CGP 37849 (4 mg/kg, $n = 9$) or GYKI 52466 (4.8 mg/kg, $n = 6$). * $P < 0.05$, Mann-Whitney *U*-test (two-tailed).

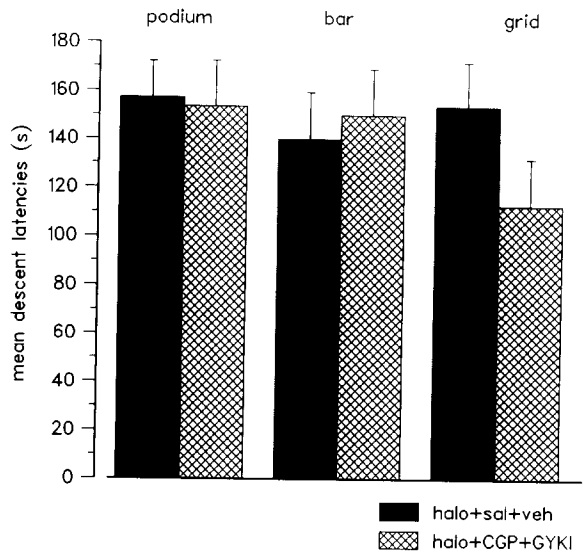

Fig. 2. Mean descent latencies (±S.E.M.) in the catalepsy test 30 min after drug administration. Treatment groups received combined injections of haloperidol (0.5 mg/kg i.p.) plus CGP 37849 (4 mg/kg i.p.) and GYKI 52466 (4.8 mg/kg i.p., $n = 7$) or plus saline/vehicle (1 ml/kg i.p., $n = 7$).

3. Results

Haloperidol-induced catalepsy was significantly reversed by administration of CGP 37849 (4 mg/kg i.p.) in all three subtests (podium: $U = 13$, $P < 0.034$; bar: $U = 11$, $P < 0.021$; grid: $U = 10.5$, $P < 0.018$). By contrast, administration of GYKI 52466 (4.8 mg/kg i.p.) did not reverse haloperidol-induced catalepsy ($P > 0.05$ in all subtests), but even induced a small increase of the cataleptic response (Fig. 1).

Administration of GYKI 52466 abolished the anticataleptic effect of CGP 37849: the cataleptic response of animals with combined administration of CGP 37849 (4 mg/kg i.p.) and GYKI 52466 (4.8 mg/kg i.p.) was not different from animals which received haloperidol alone ($P > 0.05$ in each subtest) (Fig. 2).

4. Discussion

In confirmation of previous studies the NMDA receptor antagonist CGP 37849 was found to reverse neuroleptic-induced catalepsy (Kretschmer et al., 1992), while GYKI 52466 did not alter but even slightly enhanced the cataleptic response in haloperidol-treated

animals (Papa et al., 1993; Zadow and Schmidt, 1994; Hauber and Andersen, 1993). In addition coadministration of GYKI 52466 was found to abolish the anticataleptic effect of the competitive NMDA receptor antagonist CGP 37849. Since GYKI 52466 also reduced locomotor stimulant (Hauber and Schmidt, 1993) and abolished anticataleptic effects of the noncompetitive NMDA receptor antagonist dizocilpine (Zadow and Schmidt, 1994; Hauber and Andersen, 1993) the AMPA receptor antagonist seems to counteract behavioural stimulant effects of competitive and noncompetitive NMDA receptor antagonists. This result is difficult to explain for several reasons. First the contribution of NMDA and AMPA receptors in different basal ganglia pathways to the motor effects of systemically applied NMDA and AMPA receptor antagonists is not very well characterized (see Schmidt et al., 1992 for discussion). With regard to the known NMDA/AMPA receptor interactions and localization of glutamate receptor subtypes in the basal ganglia pathways which are involved in the expression of catalepsy, one would predict synergistic rather than antagonistic effects of a combined NMDA/AMPA receptor blockade on motor behaviour. Second, although competitive and noncompetitive NMDA receptor antagonists reverse neuroleptic-induced catalepsy they differ not only in their mode of action at the NMDA receptor complex but also in their neurochemical and electrophysiological effects (see Schmidt et al., 1992 for references). Thus the GYKI 52466-induced reversal of the anticataleptic effects of competitive and noncompetitive NMDA receptor antagonists does not necessarily involve the same mechanisms. However, excitatory inputs to efferents of the motor cortex are mediated through non-NMDA, but not through NMDA receptors (Castro-Alamancos and Borell, 1993). Therefore a blockade of non-NMDA receptors downstream of the basal ganglia in this cortical motor output structure may in part account for the suppressive effects of the AMPA receptor antagonists on motor stimulation induced by NMDA receptor antagonists.

In rodent or primate models of Parkinson's disease the AMPA receptor antagonist NBQX potentiated the antiparkinson activity of L-DOPA, while being ineffective when given alone (Klockgether et al., 1991; Löschmann et al., 1991). Due to their ability to reverse parkinsonian symptoms in respective models, therefore not only NMDA receptor antagonists (Schmidt and Bubser, 1989; Carlsson and Carlsson, 1989) but also AMPA receptor antagonists (Klockgether et al., 1991; Löschmann et al., 1991) were suggested to have a therapeutic potential in the treatment of this disease. The present results do not support the suggested therapeutic potential of AMPA receptor antagonists in the treatment of Parkinson's disease, because they do not reverse neuroleptic-induced catalepsy which may constitute an animal model of pharmacologically induced parkinsonism and even abolish anticataleptic effects of NMDA receptor antagonists. In line with this view the AMPA receptor antagonist NBQX did not reverse parkinsonism in MPTP-treated monkeys (Luquin et al., 1993).

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