# The non-NMDA glutamate receptor antagonist GYKI 52466 counteracts locomotor stimulation and anticataleptic activity induced by the NMDA antagonist dizocilpine

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**Summary.** The effects of the non-NMDA glutamate receptor antagonist GYKI 52466 (2.4 and 4.8 mg/kg, i.p.) on spontaneous locomotor activity and haloperidol-induced catalepsy (0.5 mg/kg, i.p.) were assessed in naive rats and in rats pretreated with the NMDA antagonist dizocilpine (0.08 mg/kg, i.p.). GYKI 52466 given alone did not alter locomotor activity and haloperidol-induced catalepsy, but significantly antagonized the dizocilpine-induced locomotor stimulation and counteracted the anti-cataleptic effects of dizocilpine on haloperidol-induced catalepsy. Thus blockade of non-NMDA glutamate receptors antagonized the behavioural stimulant effects of a NMDA receptor blockade.

## Introduction

The synaptic responses elicited by excitatory amino acids (EAA) are mediated by different receptor subtypes distinguished according to their preferential agonists as N-methyl-D-aspartate (NMDA)-, kainate (KA)-, α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA)-preferring receptors and the metabotropic 1-amino-cyclopentane-transdicarboxylate (ACPD) receptor (Monaghan et al. 1989). The behavioural pharmacology of AMPA and KA subtypes of glutamate receptors, termed here collectively as non-NMDA receptors, is rarely investigated at present. Furthermore little is known about the interactions of non-NMDA receptors with NMDA receptors or other transmitter systems, e.g. the dopaminergic system, in behavioural models. The quinoxalinedione NBQX (2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)-quionoxaline) (Honoré et al. 1988) and the 2,3-benzodiazepine GYKI 52466 (Tarnawa et al. 1989) are selective

antagonists of non-NMDA receptors (Honoré 1991; Tarnawa et al. 1990; Quardouz and Durand 1991). Systemic administration of NBQX to drug-naive rats had no or even a weak suppressive effect on spontaneous motor behaviour (Klockgether et al. 1991). In animal models or Parkinson's disease (PD), NBQX potentiated the antiparkinson activity of L-DOPA but had no effect or even increased hypoactivity when given alone (Klockgether et al. 1991; Löschmann et al. 1991). By contrast, systemic administration of NMDA antagonists produced a marked behavioural stimulation in drug-naive rats (Bubser et al. 1992; Hoffman 1992; Tiedtke et al. 1990) and reversed parkinsonian symptoms in rodent models of PD (Carlsson and Carlsson 1989; Schmidt and Bubser 1989; Hauber and Schmidt 1990). The effects of NMDA and non-NMDA antagonists are mediated by complex actions within the basal ganglia as shown by studies using local drug administration (see Schmidt et al. 1992 for review). On the basis of these findings a blockade of NMDA receptors (Carlsson and Carlsson 1989; Schmidt and Bubser 1989) or AMPA receptors (Klockgether et al. 1991; Löschmann et al. 1991) was suggested to provide a new strategy for the treatment of PD.

In the present study we investigated the effects of a blockade of non-NMDA receptors on spontaneous locomotor activity and on haloperidol-induced catalepsy in rats. Neuroleptic-induced catalepsy may be considered as a model of PD because of similarities with the parkinsonian symptoms akinesia and rigidity (Sanberg et al. 1988). We further examined the effects of a simultaneous blockade of NMDA and non-NMDA receptors in these behavioural tests. The non-NMDA antagonist GYKI 52466 and dizocilpine, a potent noncompetitive NMDA antagonist, were used to investigate the contribution of these glutamate receptor subtypes to the expression of motor behaviour.

## Materials and methods

*Animals.* Male Sprague-Dawley rats (Interfauna, Tuttlingen, Germany) were used weighing 235–250 g at the start of the experiment. They were

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housed in groups of four or five per cage with free access to water. Food was restricted to 12 g standard laboratory maintenance diet (Altromin, Lage, Germany) per animal and day. Rats were housed in a colony room maintained at $22\pm3\,°C$ on a 12:12 light-dark cycle (lights on 06.00 h).

*Behavioural procedure.* Spontaneous locomotor activity was assessed in an open field (69×69 cm) divided by lines in 9 squares of equal size. The open field box was opaque and illuminated by 4 red light bulbs (20 W); back ground noise was masked by a fan. An animal was placed individually for 10 min into the open field. Locomotor activity was monitored by video recording and evaluated by counting the number of line crossings during the observation period.

Catalepsy was measured 30 and 60 min after injection of haloperidol in three different tests performed in the following order (Scheel-Krüger 1983):

I. Bar: both forelegs were placed on a horizontal bar (9 cm above the surface); II. Podium: one foreleg was placed on a podium (3 cm high); III. Grid: an animal was clinged to a vertical wire grid.

The latency from paw placement until the first movement of one of the respective paws (termed here as descent latency) was measured (cut-off: 180 s).

*Drugs.* Dizocilpine ([+]-5-methyl-10,11-dihydro-5H-dibenzo(a,d)cyclo-hepten-5,10-imine) (Biotrend, Köln, Germany) and haloperidol (Janssen, Neuss, Germany) were dissolved in physiological saline, respectively. GYKI 52466 (1-(4-aminophenyl)-4-methyl-7,8-methylendi-oxy-5H-2,3-benzodiazepine HCl) obtained from Dr. I. Tarnawa (Inst. Drug Research, Hungary) was dissolved in destilled water. Dizocilpine (0.08 mg/kg, i.p.), GYKI 52466 (2.4 and 4.8 mg/kg, i.p.) and haloperidol (0.5 mg/kg, i.p.) were administered alone or in combination in a maximum volume of 1 ml 30 min before the individual onset of the behavioral test. Controls in the open field and catalepsy experiment received intraperitoneal injections of saline (1 ml/kg).

*Statistical analysis.* Data are presented as means with standard errors of the means (±SEM). The open field data were submitted to an analysis of variance (ANOVA) with treatment as factor followed by a Tukey-test for comparing means of treatment groups. The catalepsy data were submitted to a Mann-Whitney U-test (two-tailed). Differences were considered to be significant if the P-value is less then 0.05.

## Results

### Open field

A one-way ANOVA with treatment as factor followed by a Tukey protected $t$-test revealed that dizocilpine (0.08 mg/kg, i.p.) given alone induced a significant increase of spontaneous locomotor activity (ANOVA: $P<0.0005$; dizocilpine versus saline: $t = -4.01$; $P<0.01$). Administration of GYKI (2.4 and 4.8 mg/kg, i.p.) did not significantly alter spontaneous locomotor activity (Fig. 1).

Administration of GYKI 52466 (2.4 and 4.8 mg/kg, i.p.) to animals pretreated with dizocilpine (0.08 mg/kg, i.p.) significantly antagonized dizocilpine-induced locomotor hyperactivity as shown in Fig. 1 (ANOVA $P<0.0001$; dizocilpine versus dizocilpine+GYKI 52466 2.4 mg/kg: $t = 5.3$, $P<0.01$; dizocilpine versus dizocilpine plus GYKI 4.8 mg/kg: $t = 3.8$, $P<0.01$). Line crossings of all treatment groups are significantly different from the saline group (saline versus dizocilpine: $t = -8.1$; $P<0.01$; saline versus dizocilpine plus GYKI 52466 2.4 mg/kg: $t = -2.7$; $P<0.05$; saline versus dizocilpine plus GYKI 52466 4.8 mg/kg: $t = -4.3$; $P<0.01$).
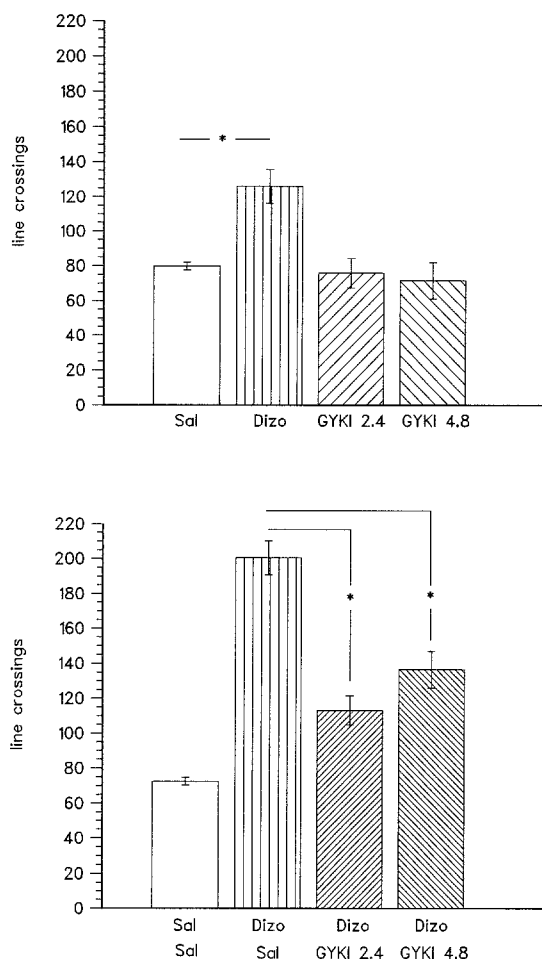


Fig. 1. Mean number of line crossings (±SEM) in an open field. Treatment groups received intraperitoneal injections of saline (1 ml/kg; $n = 6$), dizocilpine (0.08 mg/kg, $n = 6$) or GYKI 52466 (2.4 mg/kg, $n = 6$ and 4.8 mg/kg, $n = 6$) (*top*) or intraperitoneal coinjections of dizocilpine (0.8 mg/kg) plus saline (1 ml/kg, $n = 6$) or dizocilpine (0.08 mg/kg) plus GYKI 52466 (2.4 mg/kg, $n = 6$ and 4.8 mg/kg, $n = 6$). Rats with saline injections (1 ml/kg, $n = 6$) served as controls (*bottom*). $*P<0.01$ (ANOVA followed by Tukey's test)

### Catalepsy

Dizocilpine (0.08 mg/kg, i.p.) given alone exerted a significant anti-cataleptic effect (haloperidol versus haloperidol plus dizocilpine: $P<0.007$ for each test and measurement).

As shown in Fig. 2 the anti-cataleptic activity of dizocilpine was completely reversed by coadministration of GYKI 52466 (2.4 mg/kg) (haloperidol plus dizocilpine versus haloperidol plus dizocilpine plus GYKI: $P<0.01$ for each test and measurement). Results obtained in animals treated with haloperidol plus dizocilpine plus GYKI were not statistically different from animals treated only with haloperidol ($P>0.05$ for each test and measurement). The higher dose of GYKI (4.8 mg/kg, i.p.) in combination with haloperidol and dizocilpine exerted a strong muscle relaxant effect. In more then 50% of the animals it was impossible to perform the grid and bar test because animals slipped away due to muscle relaxation. In the remaining animals there was a clear tendency for a reversal of the anti-cataleptic activity of dizocilpine (da-
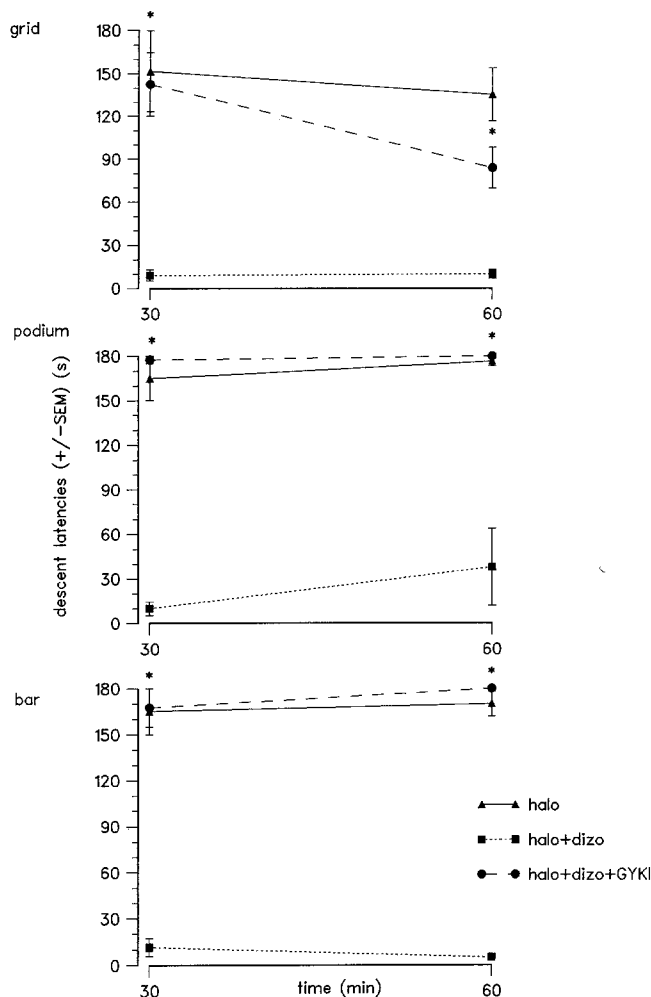
grid

podium

descent latencies (+/−SEM) (s)

bar

▲——▲ halo

■····■ halo+dizo

●— ● halo+dizo+GYKI

time (min)

**Fig. 2.** Mean descent latencies (±SEM) in the catalepsy test. Treatment groups received intraperitoneal injections of haloperidol (0.5 mg/kg) plus saline (1 ml/kg, $n = 6$), haloperidol (0.5 mg/kg) plus dizocilpine (0.08 mg/kg) plus saline (1 ml/kg, $n = 6$) or haloperidol (0.5 mg/kg) plus dizocilpine (0.08 mg/kg) plus GYKI 52466 (2.4 mg/kg, $n = 5$) *$P<0.01$ haloperidol plus dizocipline versus haloperidol plus dizocilpine plus GYKI (Mann-Whitney U-test, two-tailed)

ta not shown). GYKI 52466 given alone in a dose shown to potently reverse dizocilpine-induced anticataleptic effect did not alter the degree of haloperidol-induced catalepsy: Mean descent latencies of animals ($n = 6$) with injections of GYKI 52466 (2.4 mg/kg, i.p.) plus haloperidol (0.5 mg/kg, i.p.) and of animals ($n = 5$) with injections of saline (1 mg/kg, i.p.) plus haloperidol (0.5 mg/kg, i.p.) were not different 30 and 60 min after drug administration ($P>0.05$ for each test and measurement, Mann-Whitney U-test (data not shown).

## Discussion

Systemic administration of the non-NMDA antagonist GYKI 52466 in doses shown to be anticonvulsant and without adverse effects in rodent models of epilepsy (Smith et al. 1991) had not effect on spontaneous locomotor activity. Furthermore GYKI 52466 given alone did not alter the degree of haloperidol-induced catalepsy.

However, coadministration of GYKI 52466 significantly antagonized dizocilpine-induced locomotor hyperactivity. In addition, coadministration of GYKI 52466 significantly reversed the anti-cataleptic effect of dizocilpine.

Thus a blockade of non-NMDA receptors potently reversed the stimulating motor effects induced by a noncompetitive blockade of NMDA receptors, but did not significantly change motor activity when given alone.

The finding that administration of a non-NMDA antagonist did not change spontaneous motor activity confirms previous studies showing that NBQX had no effect on or reduced the locomotor activity in drug-naive rats (Klockgether et al. 1991) and did not affect motor behaviour in normal monkeys (Greenamyre 1992). In rats with unilateral nigral 6-hydroxydopamine lesions or MPTP-treated monkeys, systemic administration of NBQX reduced rotational behaviour and locomotor activity (Löschmann et al. 1991). In addition, NBQX did not improve akinesia, but suppressed muscular rigidity in monoamine-depleted rats (Klockgether et al. 1991) and did not antagonize raclopride-induced catalepsy (Papa et al. 1993). These findings are congruent with the present data showing that GYKI given alone did not antagonize haloperidol-induced catalepsy.

The effects of NBQX in monoamine-depleted rats, in rats with nigral 6-hydroxydopamine lesions and in MPTP-treated monkeys and the present findings on GYKI 52466 in the haloperidol-induced catalepsy argue against the view that non-NMDA antagonists given alone are useful in the treatment of PD.

Why systemically administered non-NMDA antagonists did − in contrast to local infusion into basal ganglia nuclei- not alter motor activity remains unclear and cannot be determined by the present study using systemic administrations. Local administration of non-NMDA antagonists into basal ganglia output nuclei produced marked anti-akinetic effects in animals with parkinsonian symptoms (Brotchie et al. 1991, 1992; Graham et al. 1990; Klockgether et al. 1991). It was suggested that these effects are brought about by a blockade of non-NMDA receptors in basal ganglia output nuclei which are overactive in this condition. On the other hand, the density of glutamate receptor subtypes is relatively low in non-striatal basal ganglia nuclei. For this reason the efficacy of modifying the activity of non-striatal basal ganglia nuclei by systemic administration of EAA antagonists appears to be limited (Albin et al. 1992). Studies on the role of non-NMDA receptors in basal ganglia nuclei with high AMPA/KA receptors densities, i.e. the caudate-putamen and the nucleus accumbens showed that local infusion of kainate or quisqualate into these structures induced a behavioural stimulation (Imperato et al. 1990). In addition, local infusion of NBQX into the dorsal striatum did not antagonize akinesia in reserpinized rats (Klockgether et al. 1991). Therefore non-NMDA receptors in the striatum and the nucleus accumbens seem to mediate opposite behavioural effects as non-NMDA receptors in basal ganglia output nuclei which is difficult to explain with regard to the proposed basal ganglia pathways. Thus the contribution of non-NMDA receptors in relevant basal ganglia nuclei to the behavioural effects of systemically

administered non-NMDA antagonists remain obscure at present. The present study further revealed that the non-NMDA antagonist GYKI 52466 significantly antagonized the locomotor stimulation induced by the noncompetitive NMDA antagonist dizocilpine and abolished the anticataleptic activity of dizocilpine. The findings on dizocilpine-induced locomotor stimulation and anticataleptic activity replicate similar observations in a number of previous reports (e.g. Hauber and Schmidt 1990; Hoffman 1992; Schmidt and Bubser 1989; Tiedtke et al. 1990). The dizocilpine-induced anti-cataleptic activity was potently antagonized by the lower dose of GYKI 52466, while the higher dose of GYKI exerted in this test a strong muscle relaxant activity. Although GYKI 52466 was found to have central muscle relaxant properties (Tarnawa et al. 1989, 1990), no muscle relaxation was observed when GYKI 52466 had been given alone in the doses used here. Thus muscle relaxation seen in the catalepsy test seems to be due to the combined administration of the high dose of GYKI 52466 together with dizocilpine and haloperidol.

Again the mechanisms and sites of action in the basal ganglia through which a non-NMDA receptor antagonist can inhibit the motor stimulating effects of a NMDA receptor blockade are unknown. The striatum is the main input structure of the basal ganglia and receives glutamatergic inputs from the neocortex. These cortical inputs are transmitted via a direct and an indirect striato-thalamic route back to the cortex. The direct pathway encompasses neurons from the striatum to the output nuclei of the basal ganglia, namely the substantia nigra and the entopeduncular nucleus (the rat homologue of the medial pallidal segment). The indirect pathway encompasses neurons from the striatum to the globus pallidus (the rat homologue of the lateral pallidal segment) and via the subthalamic nucleus to the basal ganglia output nuclei (see Albin et al. 1989 for review). It was recently proposed that the direct and indirect pathway are distinct with regard to the tonicity of their respective glutamatergic inputs (Svensson et al. 1992). According to this hypothesis the direct pathway which is behaviourally activating receives a low glutamatergic input from cortical-striatal neurons. By contrast the indirect loop is behaviourally suppressive. Glutamatergic cortical neurons impinging on striatal neurons of the indirect pathway were suggested to have a higher activity as compared to cortico-striatal neurons impinging on the direct pathway (Svensson et al. 1992). Thus dizocilpine preferentially blocks striatal neurons which are part of the indirect pathway because the higher glutamatergic tonicity enhances the binding probability of the open channel blocker dizocilpine. The dizocilpine binding site is within the NMDA receptor associated ion channel and therefore binding of dizocilpine depends on channel activation by NMDA receptor stimulation (see Chen et al. 1992 for references). The dizocilpine-induced selective blockade of the behavioural suppressive indirect pathway leads then to motor stimulation (Svensson et al. 1992). Thus a decreased glutamatergic tonicity in the indirect pathway would reduce use-dependent binding and behavioural effects of the noncompetitive NMDA antagonist dizocilpine. Indeed

GYKI 52466 was found to reduce extracellular glutamate in the striatum and cortex induced by ischemia in rats. This effect is probably due to an inhibition of glutamate release via presynaptic kainate receptors (Arvin et al. 1992). A decreased glutamate release could explain why GYKI 52466 reversed dizocilpine-induced effects. However it is not known whether GYKI 52466 also reduces glutamate release in non-ischemic conditions. Furthermore a GYKI 52466-induced reduction of glutamate release should counteract haloperidol-induced catalepsy in a similar way as shown for frontal decortication (Yoshida et al. 1991). This was, however, not observed when GYKI 52466 was given alone, thus making this mechanism unlikely.

An alternative explanation is that GYKI 52466 blocks postsynaptic non-NMDA receptors on striatal neurons which are part of the indirect loop. A blockade of non-NMDA receptors reduces depolarisation which is in turn a prerequisite for the voltage-sensitive activation of NMDA receptor associated channels and binding of dizocilpine (see Headley and Grillner 1991 for review). Furthermore, interactions of NMDA and non-NMDA receptors in the indirect pathway downstream of the striatum may contribute the GYKI 52466-induced reversal of the dizocilpine effects. However, the contribution of non-striatal EAA receptor subtypes appears to be limited due to the low receptor density in non-striatal basal ganglia nuclei (see above).

In summary, systemic administration of a non-NMDA antagonist reversed the stimulating motor effects induced by a noncompetitive NMDA antagonist. This interaction is likely to take place within the basal ganglia by mechanisms which remain to be detected by studies with local drug administration. The present study does not support the view of a therapeutic potential for non-NMDA antagonists in the treatment of PD when given alone.

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