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1*S*,3*R*-ACPD has cataleptogenic effects and reverses MK-801- and less pronounced, D,L-amphetamine-induced locomotion

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Abstract

The purpose of this study was to examine the motor effects of (1*S*,3*R*)-1-amino-cyclopentane-1,3-dicarboxylic acid (1*S*,3*R*-ACPD), an agonist at metabotropic glutamate receptors, its interaction with dizocilpine (MK-801), a NMDA receptor antagonist, and with D,L-amphetamine, an indirect dopamine receptor agonist. 1*S*,3*R*-ACPD (20, 30, 40, 80 μg) evoked prominent locomotor and exploratory deficits in an open-field hole-board test and a moderate akinesia and rigidity in a catalepsy test (30, 40, 80 μg). MK-801 (0.08, 0.16, 0.32 mg/kg i.p.) as well as D,L-amphetamine (1.0, 2.0, 3.0 mg/kg i.p.) potently reversed 1*S*,3*R*-ACPD-induced (80 μg) catalepsy. MK-801 and D,L-amphetamine, administred alone, induced motor stimulation. 1*S*,3*R*-ACPD (80 μg) reversed the effects of the two lower doses of MK-801. 1*S*,3*R*-ACPD reversed D,L-amphetamine-induced motor stimulation to a minor extent than that of MK-801. Thus motor deficits induced by 1*S*,3*R*-ACPD were reversed by both, NMDA receptor blockade and dopamine receptor activation. 1*S*,3*R*-ACPD reversed motor stimulation, induced by NMDA receptor blockade and, however less pronounced, that by dopamine receptor activation.

Keywords: Metabotropic glutamate receptors; D,L-Amphetamine; MK-801; Basal ganglia; Open-field; Catalepsy

1. Introduction

The overwhelming majority of excitatory synapses in the central nervous system uses glutamate as their neurotransmitter (Fonnum, 1984). In the past, research on the glutamatergic system focused on ionotropic receptors: NMDA, AMPA and kainate receptors (Monaghan et al., 1989). Meanwhile a second family of glutamate receptors has been characterised: The metabotropic glutamate (mGlu) receptors, which are G-protein coupled receptors acting via second messenger systems (Pin and Duvoisin, 1995). With respect to their sequence homology, functional coupling and pharmacology, mGlu receptors can be classified in three groups (Schoepp and Conn, 1993): Group I (mGlu receptor 1 and 5, with respective splice variants) increasing phosphatidylinositol turnover (Schoepp and Conn, 1993), group II (mGlu receptor 2 and 3) and group III (mGlu receptor 4, 6, 7 and 8) decreasing forskolin-induced cyclic AMP turnover (Tanabe et al., 1992; Tanabe et al., 1993).

Glutamatergic afferents from cortical areas and dopaminergic afferents from midbrain areas converge within the striatum and nucleus accumbens and are crucially involved in the control of motor behaviour. The functional role of ionotropic glutamate receptors and their interaction with dopamine receptors has been addressed in numerous studies (for review see Schmidt et al. (1992)). Regarding glutamate receptors, especially those of the NMDA subtype have a prominent function in controlling motor behaviour, as NMDA receptor antagonists have anti-cataleptic effects and enhance sniffing in rats (Maj et al., 1974; Schmidt and Bubser, 1989; Kretschmer and Schmidt, 1996). Non-competitive NMDA receptor blockade by dizocilpine (MK-801) or memantine additionally induces a prominent motor stimulation (Carlsson and Carlsson, 1989; Tiedtke et al., 1990; Bubser et al., 1992). It is well known that dopamine receptor activation stimulates locomotion and that NMDA receptor antagonists and dopamine receptor agonists have qualitative similar effects (Carlsson and Carlsson, 1989; Schmidt et al., 1992).

mGlu receptors, which are widely distributed in the basal ganglia of adult rats (Testa et al., 1994), are known for a decade (Sladeczek et al., 1985). The striatum, as the input structure of the basal ganglia, possesses one of the

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highest densities of mGlu receptor binding sites in the brain (Young and Fagg, 1990; Wright et al., 1994). In addition mGlu receptors have a specific pattern of expression: mGlu receptors 5 are expressed presumably on striatal enkephalinergic output neurons and mGlu receptors 2 on striatal cholinergic interneurons (Testa et al., 1994; Testa et al., 1995). Both neuron populations co-express ionotropic glutamate and dopamine receptors and numerous studies report intense interaction between these receptors. Nevertheless only few studies investigated the functional role of mGlu receptors on their own and on their possible interaction with ionotropic glutamate or dopamine receptors (Colwell and Levine, 1994; O'Connor et al., 1994; Ambrosini et al., 1995; Kaatz and Albin, 1995). However mGlu receptors are not confined to the basal ganglia. They are expressed in afferent structures as well (e.g. amygdala, hippocampus etc.) and several earlier studies examined behavioural effects following local infusions of mGlu receptor ligands in these structures (Koch, 1993; Keele et al., 1995; Riedel et al., 1995).

It is not clear whether currently available mGlu receptor ligands can cross the blood–brain barrier, thus they can not be administered systemically. We characterised effects of 1*S*,3*R*-ACPD infusion into the lateral ventricle of rats on motor behaviour in an open-field with hole-board and in a catalepsy test. 1*S*,3*R*-ACPD is one of the most selective and most frequently used mGlu receptor ligands, activating group I and group II mGlu receptors (Pin and Duvoisin, 1995). In order to get further insight into the role of mGlu receptors and their interaction with ionotropic glutamate and dopamine receptors, with respect to motor behaviour, we combined NMDA receptor blockade by MK-801 and indirect activation of dopamine receptors by D,L-amphetamine with activation of group I and group II receptors by 1*S*,3*R*-ACPD.

2. Material and methods

2.1. Animals

Subjects were 61 male Sprague–Dawley rats (Interfauna, Tuttlingen) weighing 215–280 g from the surgery until the end of the experiment, housed in groups of five to seven in standard macrolon cages. Animals were fed with 12 g/day/animal standard rat chow following the behavioural testing, water was available ad libitum. Housing conditions were a constant 12 h light–dark cycle, light on at 6 a.m. and temperature of 22 ± 3°C.

2.2. Cannula implantation and i.c.v. infusion

Stainless steel guide cannulas (outer diameter 0.8 mm, length 15.0 mm) were implanted under chloralhydrate anaesthesia (400 mg/kg i.p.). Coordinates for the implantation relative to bregma were: AP = −0.8 mm, L = 1.4 mm and DV = −2.8 mm according to a stereotactic atlas (Paxinos and Watson, 1986). Guide cannulas were firmly closed with stainless steel stylets of the same length. Following the surgery animals were allowed to recover for 3–5 days before behavioural testing. I.c.v. infusion was executed by infusion needles extending 0.8 mm over the tip of the guide cannulas. Infusion volume of 4 μl was applied over a period of 2 min, infusion needles were left in place for 1 min to allow diffusion.

2.3. Drugs and solutions

1*S*,3*R*-ACPD (Tocris, Bristol) was dissolved in sterile 0.2 M phosphate-buffer, adjusted to pH 7.4 with 0.1 M NaOH. Chloralhydrate (E. Merck, Darmstadt), MK-801, (RBI, Biotrend, Köln) and D,L-amphetamine sulphate (Geyer, Stuttgart) were dissolved in sterile saline and injected i.p.. Injection volume of chloralhydrate was 10 ml/kg, the injection volume of MK-801 and D,L-amphetamine was 1 ml/kg. Control animals received the respective vehicle. Animals were randomly assigned to groups receiving 0.0, 20, 30, 40, 80 μg 1*S*,3*R*-ACPD, 0.08, 0.16, 0.32 mg/kg MK-801, 1.0, 2.0, 3.0 mg/kg D,L-amphetamine and respective combinations with 80 μg 1*S*,3*R*-ACPD $n = 8–12$/group.

2.4. Behavioural quantification

Preliminary studies indicated an immediate effect on locomotor activity and catalepsy after i.c.v. infusions of 1*S*,3*R*-ACPD. This effect gradually declined within 60 min following the infusion and was completely absent 300 min following the infusion, when tested again. Thus we decided to test behavioural effect 15 min and to control recovery 300 min following the infusion.

15 min following i.c.v. infusion of 20–80 μg 1*S*,3*R*-ACPD or vehicle, animals were gently placed in an open-field for 8 min; animals treated with 30–80 μg 1*S*,3*R*-ACPD and their vehicle groups were gently placed in the same open-field for a 2nd trial (8 min) 300 min following the infusion. In the case of combined applications MK-801, D,L-amphetamine or vehicle were injected i.p. 30 min and 1*S*,3*R*-ACPD or vehicle were infused i.c.v. 15 min before gently placing the animals for 8 min in the open-field. By this way, the effects of combined application were tested at the same time point as after single 1*S*,3*R*-ACPD infusion.

The open-field (69 × 69 cm) was equipped with a hole-board, divided into 16 equal-sized squares with 16 holes (diameter 4 cm), each located in the centre of each field. Open-field was placed inside a wooden box and illuminated with four red bulbs (20 W), providing non-aversive conditions. Background noise was masked by a fan. Behaviour was recorded on video tape; the number of line-crossings as a measure of locomotor activity, the number of head-dips as a measure of exploratory activity

and the duration of sitting without visible motor activity were analysed manually afterwards supported by a PC.

Induction and disappearance of cataleptogenic effects of 30–80 μg 1*S*,3*R*-ACPD were tested 23 min and 308 min following i.c.v. infusion, by hanging the animals on a vertical grid and measuring descent latency (time until first movement of an extremity). Cut-off value was 3 min; in this case animals were regarded as maximal cataleptic. For combined applications MK-801, D,L-amphetamine or vehicle were injected i.p. 38 min before testing, 1*S*,3*R*-ACPD and vehicle were infused i.c.v. 23 min before testing. This way the effects of combined application were tested at the same time point as after single 1*S*,3*R*-ACPD infusion.

2.5. Histological verification

At the end of the experiments location of the guide cannulas was verified histologically. 35 μm slices were stained with a standard cresyl violet staining technique. Animals exhibiting incorrect cannula placement or tissue damage were excluded from statistical analysis.

2.6. Statistical analysis

For open-field data one-way factorial analysis of variance (ANOVA) was used to detect significant ($P \leq 0.05$) group differences, followed by Fisher's Least Significant Difference (Protected *t*) Test. For catalepsy data Kruskal–Wallis one-way ANOVA was used to detect significant ($P \leq 0.05$) group differences, followed by Mann–Whitney U-Test.

3. Results

3.1. Effects of i.c.v. infusions of 1S,3R-ACPD on locomotor activity and catalepsy

Infusion of 1*S*,3*R*-ACPD (20, 40, 80 μg) into the lateral ventricle of rats reduced the number of line-crossings 15 min following the infusion in a dose-dependent fashion (Fig. 1) and 30, 40, 80 μg increased the duration of sitting without motor activity (Table 1). 1*S*,3*R*-ACPD

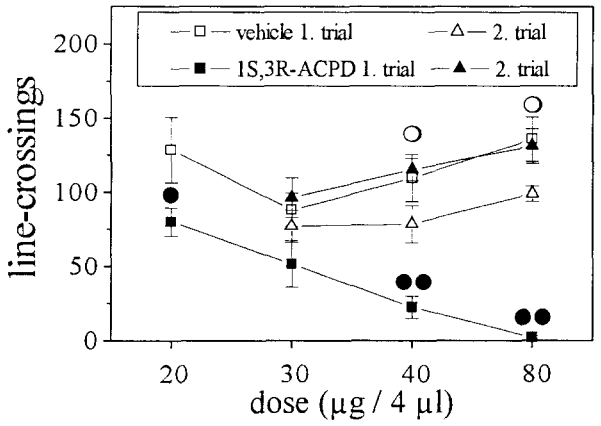

Fig. 1. Inhibition of locomotor activity during 1st trial (15 min following the infusion) and recovery during the 2nd trial (300 min following the infusion) by i.c.v. infusion of 1*S*,3*R*-ACPD. (●) $P \leq 0.05$, (●●) $P \leq 0.01$ versus vehicle group (1st trial), (○) $P \leq 0.05$ versus vehicle group (2nd trial) (data are the mean ± S.E.M. of vehicle $n = 8–10$ and 1*S*,3*R*-ACPD $n = 10–12$).

application also reduced the number of head-dips (Table 1). In animals (30, 40, 80 μg) placed 300 min following the infusion in the same open-field for a 2nd trial, the number of line-crossings (Fig. 1) and head-dips (Table 1) of 1*S*,3*R*-ACPD treated groups was higher than in the 1st trial and about at the level of vehicle groups in their 1st trial. The vehicle groups showed habituation in this 2nd trial.

1*S*,3*R*-ACPD (40 and 80 g) induced catalepsy, as shown by the increased descent latency in the 1st trial, but not in the 2nd trial (Fig. 2).

3.2. Effects of combined MK-801 and 1S,3R-ACPD application on locomotor activity and catalepsy

As shown in Fig. 3, 0.16 and 0.32 mg/kg (i.p.) of MK-801 alone increased the number of line-crossings, whereas this variable was reduced by 80 μg 1*S*,3*R*-ACPD alone (see above). Comparing the difference between the effects of MK-801 alone and of combined application of

Table 1
The effect of i.c.v. infusion of 1*S*,3*R*-ACPD on the duration of sitting and number of head-dips during the 1st and 2nd trial

Dose 1*S*,3*R*-ACPD (μg)	Duration sitting (s)				Head-dip (No.)			
	20.0	30.0	40.0	80.0	20.0	30.0	40.0	80.0
1*S*,3*R*-ACPD treated group (1st trial)	0.0	187.0 ± 48.38 ●●	263.8 ± 49.58 ●●	390.6 ± 35.36 ●●	12.7 ± 2.04	4.64 ± 1.19	3.36 ± 1.16 ●	0.7 ± 0.41 ●
Respective vehicle group (1st trial)	0.0	11.3 ± 6.40	25 ± 22.09	0.4 ± 0.4	17.8 ± 3.48	10.8 ± 2.04	10.7 ± 1.79	19.5 ± 4.39
1*S*,3*R*-ACPD treated group (2nd trial)	n.t.	0.09 ± 0.09	0.0	0.0	n.t.	8.63 ± 1.60	13.09 ± 2.01	28.82 ± 4.03 ●●
Respective vehicle group (2nd trial)	n.t.	8.67 ± 5.95	11.70 ± 8.88	0.0	n.t.	9.89 ± 1.62	9.1 ± 1.59	19.0 ± 3.31

(●) Indicates a significant difference of $P \leq 0.05$, (●●) of $P \leq 0.01$ from vehicle group, n.t. = not tested. (Data are mean ± S.E.M. of vehicle $n = 8–10$, 1*S*,3*R*-ACPD $n = 10–12$.)

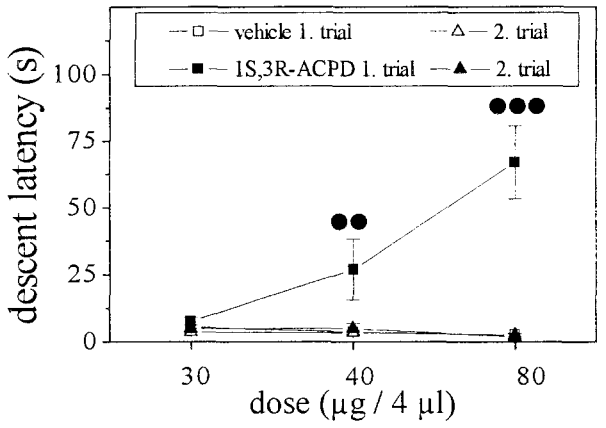

Fig. 2. Increased descent latency from the vertical grid during the 1st trial (23 min following the infusion) by i.c.v. 1*S*,3*R*-ACPD infusion and recovery at the timepoint of the 2nd trial (308 min following the infusion). (●●) $P \leq 0.01$, (●●●) $P \leq 0.001$ as compared to vehicle group (1st trial) (data are the mean ± S.E.M. of vehicle $n = 8$–10 and 1*S*,3*R*-ACPD $n = 10$–12).

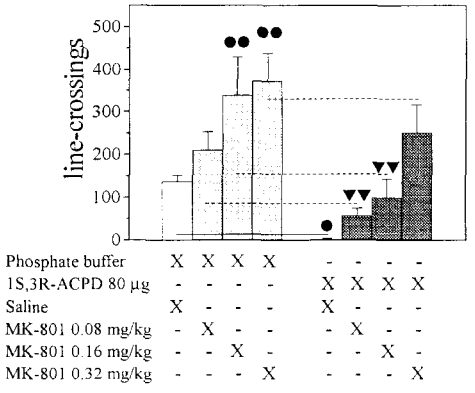

Fig. 3. The effect of 1*S*,3*R*-ACPD, MK-801 and their combined application on locomotor activity in an open-field. (●) $P \leq 0.05$, (●●) $P \leq 0.01$ versus vehicle group; (▼▼) $P \leq 0.01$ as compared to respective MK-801 group (data are mean + S.E.M. of saline $n = 10$, MK-801 or 1*S*,3*R*-ACPD $n = 8$–11, MK-801 plus 1*S*,3*R*-ACPD $n = 10$–11).

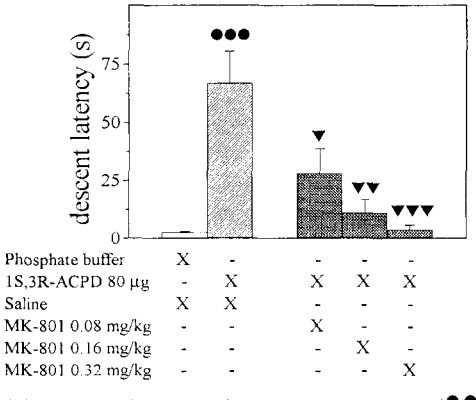

Fig. 4. MK-801 reversed 1*S*,3*R*-ACPD-induced catalepsy. (●●●) $P \leq 0.001$ as compared to vehicle group; (▼) $P \leq 0.05$, (▼▼) $P \leq 0.01$, (▼▼▼) $P \leq 0.001$ as compared 1*S*,3*R*-ACPD group (data are mean + S.E.M. of saline $n = 10$, 1*S*,3*R*-ACPD $n = 11$, 1*S*,3*R*-ACPD plus MK-801 $n = 10$–11).

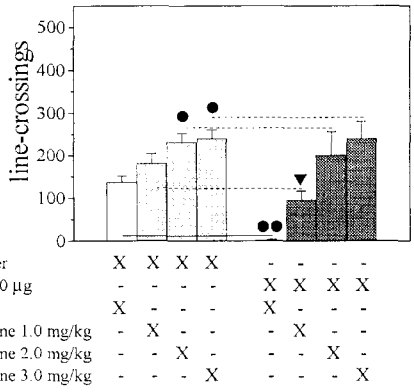

Fig. 5. Effect of 1*S*,3*R*-ACPD on D,L-amphetamine-induced line-crossings. (●) $P \leq 0.05$, (●●) $P \leq 0.01$ versus vehicle group; (▼) $P \leq 0.05$ as compared to respective D,L-amphetamine group (data are mean + S.E.M. of saline $n = 10$, D,L-amphetamine or 1*S*,3*R*-ACPD $n = 9$–11, D,L-amphetamine plus 1*S*,3*R*-ACPD $n = 10$).

1*S*,3*R*-ACPD plus MK-801, 80 µg 1*S*,3*R*-ACPD reversed the effects of 0.08 and 0.16 mg/kg of MK-801, but not of 0.32 mg/kg MK-801 (Fig. 3).

Catalepsy induced by 80 µg 1*S*,3*R*-ACPD was potently reversed by prior application of 0.08–0.32 mg/kg of MK-801 (Fig. 4).

3.3. Effects of combined D,L-amphetamine and 1S,3R-ACPD application on locomotor activity and catalepsy

2.0 and 3.0 mg/kg of D,L-amphetamine induced a small but significant increase in the number of line-crossings. Comparing the difference between the effects of D,L-amphetamine alone and that of the combined application of 1*S*,3*R*-ACPD plus D,L-amphetamine, 80 µg 1*S*,3*R*-ACPD reversed the small and not significant effect of 1.0 mg/kg D,L-amphetamine (Fig. 5). Concerning the increased number of line-crossings by 2.0 or 3.0 mg/kg

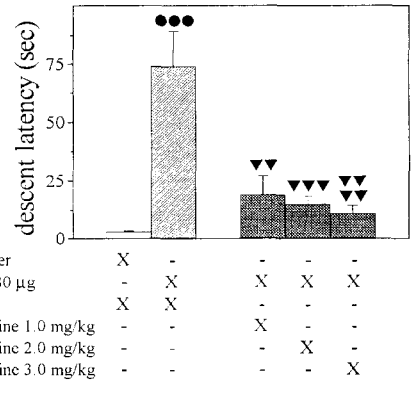

Fig. 6. D,L-amphetamine reversed 1*S*,3*R*-ACPD-induced catalepsy. (●●●) $P \leq 0.001$ as compared to vehicle group; (▼▼) $P \leq 0.01$, (▼▼▼) $P \leq 0.001$, (▼▼▼▼) $P \leq 0.0001$, as compared 1*S*,3*R*-ACPD group (data are mean + S.E.M. of saline $n = 10$, 1*S*,3*R*-ACPD $n = 11$, 1*S*,3*R*-ACPD plus D,L-amphetamine $n = 10$).

D,L-amphetamine, 80 μg 1*S*,3*R*-ACPD-mediated reversal was less pronounced, compared to the reduction of MK-801-induced locomotion, and not significant.

Fig. 6 shows, that similar to MK-801, D,L-amphetamine (1.0, 2.0, 3.0 mg/kg i.p.) was able to potently reverse catalepsy evoked by 80 μg 1*S*,3*R*-ACPD.

4. Discussion

These data show that i.c.v. infusion of the highly selective mGlu receptor agonist 1*S*,3*R*-ACPD immediately induced a robust and prominent akinesia in rats, as shown by the decreased number of line-crossings (Fig. 1) and head-dips, the increased duration of sitting (Table 1) and descent latency in the catalepsy test (Fig. 2). When the effects of 1*S*,3*R*-ACPD were tested in a 2nd trial 300 min following the infusion, an increase of locomotion was found, when compared to habituated vehicle groups but not when compared to vehicle groups tested for the 1st time (Fig. 1).

Until now, only studies investigating the role of mGlu receptors in cognitive behaviour (Riedel et al., 1995) or epileptogenic processes (Tizzano et al., 1995) were published. The present study is one of the first addressing the role of mGlu receptors in motor functions, which shows behavioural depressant effects of 1*S*,3*R*-ACPD. In an earlier study of Sacaan et al. (1992a), 1*S*,3*R*-ACPD was reported to enhance turning behaviour after 1 h with a plateau after 3–6 h, when it was infused unilaterally into the striatum. Although we observed stimulatory effects of 1*S*,3*R*-ACPD in the same time range, our interpretation is not in line with that of Sacaan et al. (1992a). In our study, rats treated with 1*S*,3*R*-ACPD showed during the 2nd trial a very similar level of locomotor activity as rats treated with vehicle and tested for the first time in the open-field. Therefore it seems more likely, that due to reduced exploratory and locomotor activity of the 1*S*,3*R*-ACPD treated rats (e.g., reduced number of head-dips and line-crossings) during the 1st trial, the exploratory and locomotor activity during the 2nd trial is higher than in vehicle groups. The latter one had the possibility to explore during the 1st trial and show a habituated response during the 2nd one. The view of a habituated response of vehicle groups is supported by several studies, demonstrating that repeated exposure of animals to an open-field reduces exploratory activities (Cador et al., 1989; Kelley, 1993). Besides this, there are some further methodological differences between the study of Sacaan et al. (1992a) and our study, which may explain the different outcome. They infused 1*S*,3*R*-ACPD intrastriatally in anaesthetised animals, while we used awake animals with chronically implanted guide cannulas, making it feasible to observe effects occurring immediately following infusions and excluding acute interactions with anaesthetics. With respect to anaesthesia, microdialysis studies showed, that transmitter release and thus the effects of drugs are clearly different in awake and anaesthesied rats (Osborne et al., 1990; Stahle et al., 1990). Furthermore in contrast to striatal 1*S*,3*R*-ACPD infusions, where effects are probably restricted to the infusion area, i.c.v. infusions of 1*S*,3*R*-ACPD result in activation of mGlu receptors in many periventricular areas, thus closely resembling systemic administrations.

Thus, one can only speculate about the site of action of 1*S*,3*R*-ACPD. The density of mGlu receptors is differentially distributed in the rat brain and hippocampal areas express one of the highest mGlu receptor densities in the brain (Young and Fagg, 1990; Wright et al., 1994). Thus these areas may contribute to the locomotor deficit observed in this study. This would be in line with the following facts: (1) 1*S*,3*R*-ACPD application reduces inhibitory postsynaptic currents of hippocampal neurons (Poncer et al., 1995); (2) 1*S*,3*R*-ACPD facilitates glutamate release of hippocampal nerve terminals (Vázquez et al., 1994); (3) 1*S*,3*R*-ACPD and a selective group I agonist provoke epileptic seizures, by activation of hippocampal and thalamic mGlu receptors respectively (Sacaan and Schoepp, 1992b; Tizzano et al., 1995) and (4) projections from hippocampal areas terminate on basal ganglia input structures (Brog et al., 1993). In detail, the anatomical studies show, that the ventral and dorsal subiculum project to the medial (shell) and lateral parts (core) of the nucleus accumbens, respectively, whereas the entorhinal cortex projects to the striatum (Aylward and Totterdell, 1993; Burns et al., 1993; Finch et al., 1995). The entorhino-striatal projection however is much less marked than the subiculo-accumbal projections. Efferences from the subiculum are glutamatergic and an increased activation of glutamate receptors of the NMDA subtype in the nucleus accumbens reduces motor activity (Kretschmer and Schmidt, 1996), whereas hippocampal lesions, reducing the glutamate release, induce spontaneous hyperactivity (Hannigan et al., 1984; Save et al., 1992; Mittleman et al., 1993). Thus the 1*S*,3*R*-ACPD-induced locomotor deficit might be attributed to the increased glutamate release from these hippocampal efferences.

The catalepsy induced by 1*S*,3*R*-ACPD may be due to an action of 1*S*,3*R*-ACPD at striatal mGlu receptors: (1) mGlu receptor density within the striatum is very high, as shown in binding assays (Young and Fagg, 1990; Wright et al., 1994), (2) intense fos-like immunoreactivity has been observed in striatal neurons following striatal application of 1*S*,3*R*-ACPD (Kaatz and Albin, 1995), (3) 1*S*,3*R*-ACPD causes a direct excitatory action on striatal neurons in a slice preparation (Calabresi et al., 1992) and (4) striatal perfusion with 1*S*,3*R*-ACPD via a microdialysis probe increases glutamate concentrations within the striatum (Liu and Moghaddam, 1995). Thus, it is tempting to speculate that 1*S*,3*R*-ACPD via mGlu receptor 5 presumably located on striatal enkephalinergic output neurons or via mGlu receptor 2 located on intrastriatal cholinergic interneurons (Testa et al., 1994; Testa et al., 1995) may

contribute to the akinesia, since the enhanced activation of glutamate receptors by infusion of agonists, has been shown to reduce behavioural activity (Schmidt and Bury, 1988; Svensson et al., 1994) and enhance catalepsy (Metha and Ticku, 1990).

In some studies neuronal damage with intracerebral infusions of 1*S*,3*R*-ACPD was observed (Sacaan and Schoepp, 1992b; Tizzano et al., 1995). In our study 1*S*,3*R*-ACPD induced a significant akinesia already at the lowest dose infused, which is approximately 77% below the lowest toxic dose and approximately 89% below the dose recently infused locally for behavioural studies (Sacaan et al., 1992a; Kaatz and Albin, 1995). Furthermore toxic effects of 1*S*,3*R*-ACPD were observed only when 1*S*,3*R*-ACPD was infused directly into brain nuclei, whereas we infused it i.c.v., reducing concentration due to dilution and diffusion. In addition it is reported that DCG-IV, which is as 1*S*,3*R*-ACPD a group II agonist (Pin and Duvoisin, 1995), protects against excitotoxic neuronal death (Bruno et al., 1994). Furthermore, motor deficits were reported for mice lacking mGlu receptor 1 (Conquet et al., 1994), supporting a non-toxic involvement of mGlu receptor in motor behaviour.

MK-801 and D,L-amphetamine stimulated locomotor activity in a dose-dependent fashion (Fig. 3 and Fig. 5). The effects of 0.08 mg/kg and 0.16 mg/kg of MK-801 could be reversed by 80 μg 1*S*,3*R*-ACPD. At the highest dose of MK-801 (0.32 mg/kg), 80 μg 1*S*,3*R*-ACPD failed to reverse stimulated locomotion. Similar to this, 80 μg 1*S*,3*R*-ACPD reversed the motor stimulation achieved with 2.0 and 3.0 mg/kg of D,L-amphetamine but to a much lesser extent and not significantly. Only the minor effects of 1.0 mg/kg D,L-amphetamine were reversed by 80 μg 1*S*,3*R*-ACPD.

As agonists of mGlu receptor 5 and NMDA receptors increase activity of enkephalinergic striatal output neurons, their inhibition by NMDA receptor blockade might be counteracted by activation of mGlu receptor 5, thus reversing motor stimulation induced by NMDA receptor blockade. In addition 1*S*,3*R*-ACPD increases glutamate concentrations within the striatum (Liu and Moghaddam, 1995); by this way 1*S*,3*R*-ACPD may also indirectly reduce the effects of NMDA receptor antagonists by increasing glutamate transmission.

In the case of non-competitive NMDA receptor blockade by high doses of MK-801 however, a dopaminergic component can not be precluded, as neurochemical and electrophysiological studies demonstrated activation of dopaminergic neurons (French and Ceci, 1990; Liljequist et al., 1991; Bubser et al., 1992; French et al., 1993). The dopamine release may be the reason why 1*S*,3*R*-ACPD failed to reverse motor stimulation induced by 0.32 mg/kg MK-801, in a similar way as 1*S*,3*R*-ACPD failed to reverse motor stimulation induced by 2.0 and 3.0 mg/kg D,L-amphetamine. However, because of opposite effects of dopamine via inhibitory D2 receptors and 1*S*,3*R*-ACPD via excitatory mGlu receptors 5 on the activity of basal ganglia enkephalinergic output neurons, one might have expected much more pronounced antagonistic effects.

For analysis of the motor deficits induced by 1*S*,3*R*-ACPD, which were observed in the open field as reduced number of line-crossings, a catalepsy test was used. At doses at which classical neuroleptics block locomotor activity of rats to a similar degree as observed with 80 μg 1*S*,3*R*-ACPD in this study, marked catalepsy was demonstrated in the same test as used in this study (Ouagazzal et al., 1993; Kretschmer, 1994; Kretschmer et al., 1994). In contrast to classical neuroleptics, 1*S*,3*R*-ACPD failed to induce such marked akinisia and rigidity, as we observed only very mild catalepsy. This mild catalepsy was potently reversed by both, MK-801 as well as D,L-amphetamine. This result is in line with the data from the open-field experiments, where the locomotor deficit was dose-dependently antagonised by both NMDA receptor blockade and dopamine receptor activation.

Catalepsy and locomotor activity however are mediated by different structures, the dorsal striatum mediates catalepsy, whereas the nucleus accumbens mainly mediates locomotor behaviour (Kelly et al., 1975; Koob et al., 1978; Kretschmer and Schmidt, 1996). This functioanatomical dichotomy may underlie the result, that both D,L-amphetamine and MK-801 reversed 1*S*,3*R*-ACPD-induced catalepsy, while 1*S*,3*R*-ACPD mediated reversal of locomotor stimulation was more pronounced in the case of MK-801 than in the case of D,L-amphetamine.

In summary, (1) 1*S*,3*R*-ACPD induced a moderate catalepsy, which was reversed by MK-801 and D,L-amphetamine and (2) 1*S*,3*R*-ACPD reversed MK-801-induced motor stimulation, similar to classical neuroleptics, while reversal of D,L-amphetamine-induced motor stimulation by 1*S*,3*R*-ACPD was not pronounced.

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