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Clozapine improves dizocilpine-induced delayed alternation impairment in rats

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Summary. The effects of systemic administration of dizocilpine (0.16 mg/kg, i.p.), clozapine (7.5 mg/kg, s.c.) and coadministration of dizocilpine (0.16 mg/kg, i.p.) and clozapine (7.5 mg/kg, s.c.) on acquisition of delayed alternation in a T-maze were tested in rats (N = 7 per group) on six days with 10 choices per day and animal. Clozapine given alone did not impair delayed alternation learnint, except of the first day. Dizocilpine induced a significant delayed alternation impairment on all days tested. Pretreatment with clozapine significantly improved the dizocilpine-induced impairment. Treatment-induced changes of delayed alternation learning and of locomotor activities showed no correlation. The results demonstrate that clozapine functionally compensated for deficits induced by a blockade of the N-methyl-D-asparatate (NMDA) subtype of glutamate receptors.

Keywords: Clozapine, dizocilpine, glutamate, NMDA receptors, delayed alternation, locomotion, schizophrenia

Introduction

The glutamate hypothesis of schizophrenia proposed by Kim et al. (1980) and Kornhuber and Kornhuber (1986) postulates that a decreased glutamate transmission is involved in the pathophysiology of this disease. In line with this hypothesis are findings that antagonists of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors as phencyclidine (PCP) or dizocilpine induce psychotic reactions in humans resembling those seen in schizophrenia (Allen and Young, 1978; Troupin et al., 1986). Furthermore intake of PCP exacerbate a preexisting psychosis (Luby et al., 1959). Hence, PCP-induced psychosis is regarded to be the best pharmacological model of schizophrenia (Allen and Young, 1978) representing positive as well as negative symptoms (Petersen and Stillman, 1978). The glutamate hypothesis of schizophrenia was further cor-

roborated by observations that parkinsonian patients treated with the anti-parkinson drugs amantadine or memantine which both are noncompetitive NMDA antagonists can develop psychotic side effects (Riederer et al., 1992). In postmortem tissue of patients with schizophrenia, NMDA receptor densities are increased in temporal and parietal cortical areas (Suga et al., 1990) and the putamen (Kornhuber et al., 1989) and glutamate-release is reduced in frontal and temporal cortical tissue (Sherman et al., 1991). In addition, NMDA-associated glycine binding sites are increased in schizophrenic brains (Ishimaru et al., 1992). These findings tentatively support the view of a decreased glutamatergic function and receptor upregulation in schizophrenia.

In rodents NMDA antagonists induce a strong behavioural activation characterized by an increased locomotion, stereotypy (Clineschmidt et al., 1982; Tiedtke et al., 1990; Hoffman, 1992), turning in the Ungerstedt model (Clineschmidt et al., 1982) and cognitive impairments leading to a deficient delayed alternation learning (Schmidt et al., 1988; Hauber and Schmidt, 1990). In addition, prepulse inhibition of the startle response is impaired in rats with systemic injections of dizocilpine or PCP. Prepulse inhibition is also decreased in schizophrenic patients (Mansbach and Geyer, 1989). The behavioural syndrome induced by NMDA antagonists resembles in many respects the behavioural activiation induced by dopamine agonists. However, the psychomotor activation due to blockade of NMDA receptors is still present in animals pretreated with α-methyl-paratyrosine and reserpine as shown by Carlsson and Carlsson (1989).

There is growing evidence for interactions between glutamatergic and dopaminergic systems in the basal ganglia which may be relevant for the symptomatology and the treatment of schizophrenia (see Carlsson and Carlsson, 1990; Schmidt et al., 1992 for review). Intracerebral injection of kynurenic acid, an unselective glutamate antagonist, or AP-5, a competitive NMDA antagonist, into the dorsal striatum induced locomotion and sniffing (Schmidt, 1985, 1986). Local infusion of dizocilpine or SDZ EAA 494 into the dorsal striatum also enhanced sniffing and locomotion (Imperato et al., 1990). Inactivation of striatal neurons bearing NMDA receptors with the excitotoxin quinolinic acid produced a similar behavioural activation (Sanberg et al., 1989; Schmidt et al., 1988). In addition, intrastriatal infusion of AP-5 antagonized neuroleptic-induced catalepsy (Yoshida et al., 1991) and in turn, intrastriatal infusion of NMDA reduced behavioural activities (Schmidt and Bury, 1988). Accordingly, systemically applied NMDA was found to potentiate haloperidol-catalepsy (Mehta and Ticku, 1990).

Clozapine is an atypical antipsychotic drug and the mechanism of action of this compound is largely unknown. Recent studies showed that clozapine antagonized dizocilpine-induced stereotypy (Tiedtke et al., 1990; Hoffman, 1992). Furthermore, stereotypy induced by intrastriatal injection of AP-5 was antagonized by systemic administration of clozapine (Schmidt, 1986). On the basis of the glutamate hypothesis of schizophrenia it was concluded that clozapine may act as a functional glutamate agonist via the NMDA receptor

(Schmidt, 1986, 1991). Interestingly, NMDA was found to share clozapine-like dicrimminative stimulus effects in rats (Schmidt and Volz, 1992).

In the present study we investigated possible glutamate-mimetic effects of clozapine. We examined the effects of dizocilpine and clozapine on delayed alternation learning of rats in a T-maze, because

I) psychomotor stimulation due to blockade of NMDA receptors may be a model of psychosis and

II) the delayed alternation procedure is a sensitive task on integrity of the dorsal striatum (Wikmark et al., 1973) and the prefrontal cortex as well (Fuster, 1981; Markowitsch and Pritzel, 1977). Since pathophysiology of schizophrenia may be related to a frontostriatal dyfunction (see Robbins, 1990 for review) and cortico-striatal glutamatergic neurons are involved in regulation of psychomotor functions (Carlsson and Carlsson, 1989), this task may be especially appropriate.

In our experiments we tested the effects of systemically administered dizocilpine or clozapine and the effect of clozapine in dizocilpine-pretreated animals. Dizocilpine was used in a dose of 0.16 mg/kg which is known to produce a significant impairment in this task (Schmidt et al., 1988). In order to assess a possible effect of treatment-induced locomotor changes on learning data we measured the running times as an index of locomotor activity from all runs in the maze.

If clozapine act as a functional glutamate agonist via NMDA receptors I) it should counteract the impairment in dizocilpine-pretreated animals and II) when given alone it should at least theoretically even improve learning.

Materials and methods

Subjects

Subjects used in this experiment were 28 male Sprague-Dawley rats weighing 250–300 g (Interfauna, Tuttlingen, FRG). Rats were housed in groups of four or five per cage and had free access to water. They received 12 g standard laboratory maintenance diet (Altromin, Lage, FRG) per day and animal. All rats were housed in a colony room maintained at 22 ± 3 °C on a 12 : 12 hours light-dark cycle (lights on 06.00 h).

Apparatus

Delayed alternation was conducted in a T-maze which was made of plastic coated wood with 35 cm high walls and 20 cm wide corridors. The stem was divided by an opaque and manually operated guillotine door into a startbox (length: 30 cm) and a runway (length: 60 cm). At the end of both other arms (length: 70 cm) a food cup was located.

Behavioural procedure

The procedure was designed with reference to the description of Wikmark et al. (1973).

Adaption: The animals were adapted to the maze on four days. On the first day, animals were left into the maze in groups of four and five for 10 min. The next day, food cups in both arms were baited with food pellets (45 mg; Noyes, Lancaster, U.K.), the guillotine door was removed and each rat was left in the maze for 5 min. On day three of adaption,

the guillotine door was introduced and an animal was repeadetly placed into the start box and the door was raised immediatly afterwards. The rats were trained to respond to the opening of the door and to enter one of the arms.

Delayed alternation: Four randomized groups (N = 7 per group) were used receiving injections with either saline, clozapine, dizocilpine or clozapine plus dizocilpine. After the injection a rat was placed back into the home cage for 30 min. Thereafter a rat was tested in one session per day comprising 11 choices. Maze learning was tested on six days. On the initial choice (not scored) both arms were baited. On each of the following choices the animal was rewarded with one food pellet for entering the arm not visited on the previous run, i.e. an arm was baited until the rat responded to it. Errors were defined as successive choices of the same arm and were scored by video observation. The criterion for a scored arm entry was a complete entry in an arm with all four paws. In addition the time from raising the guillotine door up to an animals arrival at the food cup was measured from each choice and was termed here as running time.

Drugs

Dizocilpine ([+]-5-methyl-10,11-dihydro-5 H-dibenzo(a,d)cyclohepten-5,10-imine) (Biotrend, Köln, FRG) was dissolved in physiological saline and administered intraperitoneally. Clozapine (8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e]-[1,4]diazepine) (Sandoz) was dissolved in sesame oil and administered subcutaneously in the neck region. The behavioural procedure was initiated 30 min after injection of either saline (1 ml/kg, i.p.), dizocilpine (0.16 mg/kg, i.p.), clozapine (7.5 mg/kg, s.c.) or coadministration of clozapine and dizocilpine at the given doses.

Data analysis

The data were submitted to an analysis of variance (ANOVA) followed by an appropriate post hoc test for multiple comparisons of means or a T-test. For error data, a two-way ANOVA with days and treatment groups as factors was calculated followed by a Tukey-test. The running time data were submitted to a one-way ANOVA followed by a Tukey-test for multiple comparisons. For simple comparisons a T-test was used. Differences were considered to be significant if the p-value is less then 0.05.

Results

A two-way ANOVA with treatment groups and days as factors revealed a significant effect of treatment $F(3, 126) = 71.1$, $p < 0.0001$, a significant effect of days $F(5, 41) = 6.25$, $p \leqslant 0.0003$ as well as a significant interaction between days and groups $F(15, 108) = 2.32$, $p < 0.0065$. A post hoc Tukey-test showed that dizocilpine-treatment produced on each day a significant increase of errors as compared to saline controls ($p < 0.01$ for each day). Clozapine-treated animals made, except of the first day ($p < 0.05$), not more errors than saline-treated animals. Animals with injections of clozapine plus dizocilpine were, except of the first day ($p < 0.01$), not different from saline-treated animals. A comparison of dizocilpine- and dizocilpine plus clozapine-treatment revealed, that both groups were not different on the first two days, but from the third day on, dizocilpine plus clozapine-treated animals made significantly less errors than dizocilpine-treated animals (Fig. 1). The mean running times from all days were shown for each treatment group in Fig. 2. A one-way ANOVA with

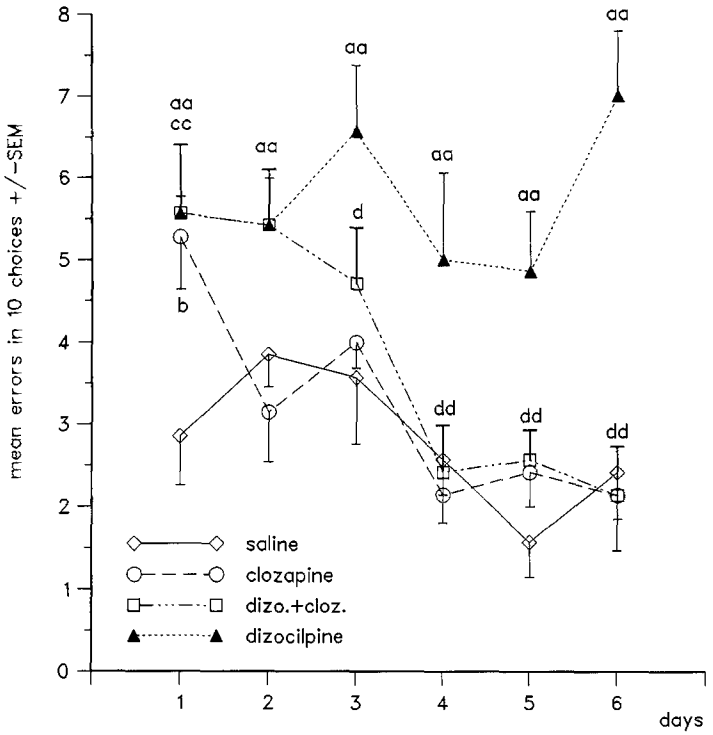

Fig. 1. Mean errors (± SEM) of groups (N = 7 for each group) treated with saline (1 ml/kg, i.p.), clozapine (7.5 mg/kg., s.c.), dizocilpine (0.16 mg/kg, i.p.) and coadministration of clozapine and dizocilpine (at the given doses) tested for six days on acquisition of a delayed alternation task in a T-maze. A: dizocilpine treatment versus saline treatment (aa: $p < 0.01$); b: clozapine treatment versus saline treatment (b: $p < 0.05$); c: dizocilpine plus clozapine treatment versus saline treatment (cc: $p < 0.01$); d: dizocilpine treatment versus dizocilpine plus clozapine treatment (d: $p < 0.05$, dd: $p < 0.01$)(ANOVA followed by Tukey's test)

treatment as factor revealed a significant effect $F(3, 1679) = 60.59$, $p < 0.0001$. A post hoc Tukey-test showed that clozapine-treated animals were signiticantly slower ($p < 0.01$), dizocilpine-and dizocilpine plus clozapine-treated animals significantly faster than saline treated animals ($p < 0.01$ and $p < 0.05$). In addition, dizocilpine coadministration significantly antagonized the clozapine-induced slowing ($p < 0.01$).

In order to reveal a possible relationship between running time and errors we compared the mean running times of all dizocilpine-treated rats from correct and incorrect choices of all days and found no significant differences, $t(417) = -0.44$; $p = 0.97$ (T-test) (Fig. 3). Since this within-group comparison may be confounded by different individual speed preferences of the animals and other factors, we compared the mean running times from each dizocilpine-treated animal in correct and incorrect choices from all days: In none of the dizocilpine-treated animals a significant difference of running times in correct and incorrect choices was found (not shown). We further investigated whether errors in ten choices from each day and animal are a function of the corre-

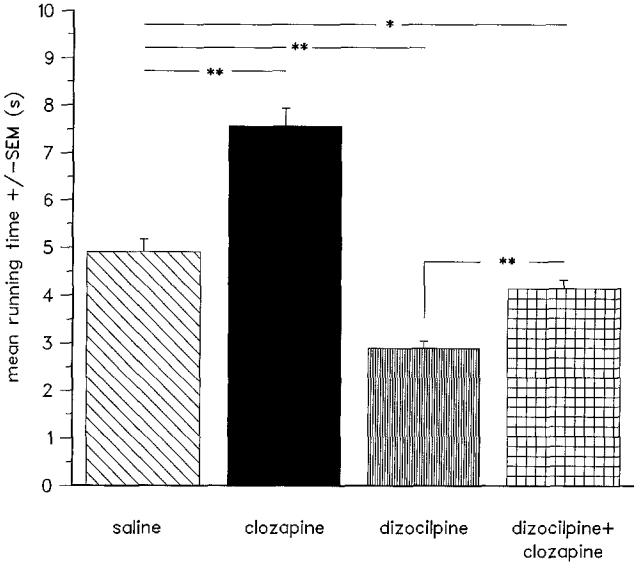

Fig. 2. Mean running times (± SEM) for each treatment group (N = 7, n = 420 for each group) pooled from all days tested. * $p < 0.05$; ** $p < 0.01$ ANOVA followed by Tukey's t-test

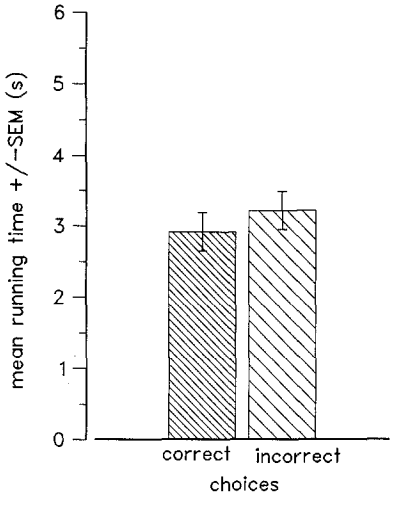

Fig. 3. Mean running times (± SEM) of dizocilpine-treated animals (N = 7) in correct (n = 180) and incorrect (n = 240) choices pooled from all days (p = 0.97, t-test)

sponding mean running times. An analysis comprising the data from all groups with running time as independent and errors as dependent variable revealed no correlation (r = 0.0154). Within-group analysis also revealed no correlations of individual errors and corresponding mean running times on each day for animals with saline (r = 0.135), dizocilpine (r = 0.051), clozapine (r = 0.203) or dizocilpine plus clozapine injections (r = 0.17).

Discussion

Systemic administration of the noncompetitive NMDA antagonist dizocilpine significantly impaired delayed alternation learning in rats on all days tested. Pretreatment with the atypical neuroleptic clozapine significantly improved the dizocilpine-induced impairment on four out of six days. Clozapine when given alone did not alter delayed alternation learning except of the first day.

Furthermore animals with injections of dizocilpine, clozapine and clozapine plus dizocilpine showed differences in their respective locomotor activities: The mean running times from all days were significantly reduced in dizocilpine-treated animals and increased in clozapine-treated animals. Clozapine antagonized reduced running times in dizocilpine-pretreated animals. No correlations were found between treatment-induced errors in delayed alternation learning and changes of running times.

As expected dizocilpine markedly impaired the acquisition of delayed alternation which replicates similar findings in a previous study (Schmidt et al., 1988). This result is also in accordance with studies showing that ketamine, another noncompetitive NMDA antagonist, produced a similar impairment in the same task (Alessandri et al., 1989; Hauber and Schmidt, 1990).

The observation that dizocilpine significantly decreased running times in the maze is also in line with studies showing a dizocilpine-induced increase of spontaneous locomotor activity (Tiedtke et al., 1990; Hoffman, 1992). Regarding the relationship between errors and corresponding running times, both measures seem to be independent regardless of the treatment used here:

I) Dizocilpine-treated animals had the same running times in correct and incorrect choices. Although dizocilpine increased locomotor activity a committed error seems not to be a direct consequence of the increased locomotor activity during the corresponding choice. Thus nonspecific motor effects affecting running time such as ataxia are not causative for the observed increase of errors and this means in turn that clozapine's antagonistic action on errors is not due to a reduction of these effects.

II) neither in dizocilpine- nor in clozapine-, clozapine plus dizocilpine- or saline-treated animals a correlation of running times and errors was found.

Therefore it is concluded that dizocilpine induced a psychomotor activation which is characterized by a increased locomotor activity and a cognitive impairment leading to an impaired delayed alternation learning and both processes seem to be independent. In line with this conclusion is the finding that ketamine selectively impaired acquisition of delayed alternation by naive animals, while retrieval of delayed alternation by ketamine-treated animals trained undrugged to a criterion before was intact. Thus the influence of ketamine-induced nonspecific motor effects on impaired acquisition can be neglected, since retrieval remained intact in ketamine-treated animals (Hauber and Schmidt, 1989).

To the authors knowledge this is the first study using simultaneous measurement of errors and running times in this maze task. Results show that this

could be a simple way to gain more information about drug-induced changes of locomotor behaviour and their possible effects on learning.

Clozapine when given alone did not alter acquisition of delayed alternation, except of the first day on which a significant worsening was observed for unknown reasons. Thus a cognitive enhancing effect of clozapine possibly indicative for a glutamate-agonistic effect of clozapine was not detectable in this task. This may have among others task-related reasons since clozapine mildly improved the finding of a hidden platform in the Morris water task in the same dose used here (Scheel-Krüger and Widy-Tyszkiewicz, 1990).

Clozapine-pretreatment significantly improved dizocilpine-induced delayed alternation impairment. In a pilot study this clozapine-dizocilpine antagonism in delayed alternation was also observed using the same dose of clozapine together with a lower dose (0.12 mg/kg) of dizocilpine (Hauber, 1993). As already discussed, clozapine's action seems not be due to a reduction of non-specific effects, but to a reduction of the dizocilpine-induced psychomotor activition which is characterized by a decreased locomotion and a decrease of errors. However, clozapine was effective not until the third day tested. The reason for this phenomenon is not clear. The results suggest that clozapine may act as a functional glutamate agonist via the NMDA receptor. This view is in accordance with findings on a clozapine-dizocilpine antagonism in studies with spontaneous behaviour and similarities between clozapine and NMDA in a drug discrimmination test (see Introduction). However, Katz and Schmaltz (1981) found that not only the NMDA antagonist amantadine but also the DA agonist apomorphine induced a spatial alternation impairment that is characterized by perseveration reflecting an abnormal attentional process. Since dizocilpine stimulates DA synthesis, release and metabolism (Bubser et al., 1992; Imperato, 1990; Svensson et al., 1992) one may argue that deficient learning of delayed alternation is DA-dependent and clozapine-induced improvement is brought about by its DA receptor blocking properties (see Coward, 1992). However, the DA stimulating effects of dizocilpine in the dose used here are weak (Rao et al., 1990) and behavioural stimulation produced by dizocilpine is still present in monoamine-depleted mice pretreated with haloperidol as shown by Carlsson and Carlsson (1989). Besides haloperidol can lead even in low doses to a significant impairment of spatial learning in the Morris water task (Ploeger et al., 1992). In an 8-arm radial maze task, haloperidol exacerbated impaired learning in dizocilpine-treated animals (Bischoff et al., 1988). Thus the involvement of a DA-dependent-mechanism seems to be unlikely for the dizocilpine-clozapine antagonism in the task used here although in general dizocilpine-induced behavioural stimulation can be mediated through dopamine-dependent and dopamine-independent mechanisms (Carlsson and Carlsson, 1990).

The integrity of the medial part of the striatum and of the prefrontal cortex is a prerequisite for intact acquisition of delayed alternation (Wikmark et al., 1973; Fuster, 1981; Markowitsch and Pritzel, 1977; Pisa and Cyr, 1990). Both structures are anatomically linked by neurons of the prefrontal cortex projecting

to the medial striatum and using most probably glutamate as transmitter (Fonnum, 1984). Furthermore, both structures are part of a cortico-striato-thalamo-cortical functional loop suggested to mediate cognitive functions (Alexander et al., 1986). Blockade of NMDA receptors in the medial striatum by local infusion of the competitive NMDA antagonist AP-5 produced a similar impairment in the same task as used here (Hauber and Schmidt, 1989). These findings suggest that NMDA receptors in the medial striatum are one site of action of systemically administered dizocilpine leading to an impaired acquisition of delayed alternation. If so clozapine may counteract dizocilpine-mediated effects by a modulation of the activity of prefrontal glutamatergic neurons projecting to the medial striatum. This view is in line with the glutamate hypothesis of schizophrenia.

In summary the present finding that clozapine improved dizocilpine-induced impairment of delayed alternation learning suggests that this atypical neuroleptic may act as a functional glutamate agonist via the NMDA receptor. It is speculated that this effect may be brought about by an action within the cognitive cortico-striato-cortical loop.

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