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Atypical antipsychotic-like effect of AMPA receptor antagonists in the rat

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Summary. Systemic administration of two chemically different AMPA receptor antagonists, GYKI52466, 20 mg/kg, and LY326325, 18 mg/kg, given subcutaneously, caused a selective suppression of conditioned avoidance response in the rat with preservation of escape behavior. The number of intertrial crosses was not affected and no catalepsy was observed. These experimental results indicate, in principle, an antipsychotic effect of AMPA receptor antagonists with a low liability for extrapyramidal side effects and, consequently, a pharmacological profile consonant with atypical antipsychotic drugs.

Keywords: Amino acids – Conditioned avoidance response – AMPA – Kainate – Behavior – Antipsychotic

Introduction

Psychotomimetic, non-competitive NMDA receptor antagonists, e.g. phencyclidine, may elicit a psychosis in healthy individuals that may appear indistinguishable from acute schizophrenia and may also aggravate pre-existing schizophrenic symptoms in patients, including both positive and negative symptoms as well as the cognitive impairment (see Javitt and Zukin, 1991). Thus, the psychotomimetic properties of NMDA receptor antagonists offer a pharmacological model of psychotic states for studies in experimental animals. In analyzing this model we previously observed that systemic administration of dizocilpine (MK-801), a specific, non-competitive NMDA receptor antagonist, potently activates dopamine (DA) neurons in the ventral tegmental area (VTA), in particular cells located in the paranigral subnucleus which essentially project subcortically (Murase et al., 1993). In parallel, systemic MK-801 also evoked an increase in metabolism and release of DA in the nucleus accumbens (NAC; see Bubser et al., 1992; Mathé et al., 1996, 1998). The concurrent locomotor stimulation seems directly related to the augmented mesolimbic DA output and recent data indicate that it may be

specifically caused by indirect activation of AMPA and/or kainate receptors in the VTA, probably due to enhanced glutamatergic input (Mathé et al., 1998; Svensson et al., 1998a). Accordingly, both systemic and intra-VTA administration of AMPA receptor antagonists have been shown to effectively antagonize the behavioral, i.e. locomotor stimulation caused by systemic MK-801 as well as the associated increase in DA metabolism and release in the NAC (Bubser et al., 1995; Mathé et al., 1998).

Previously, many antipsychotics have been shown to antagonize the locomotor stimulation evoked by low doses of D-amphetamine as well as psychotomimetic NMDA receptor antagonists, behavioral effects that largely but not exclusively seem to depend on increased mesolimbic DA release (see Ögren, 1996). However, the selective suppression of the conditioned avoidance response (CAR), i.e. without inhibition of escape behavior has previously been found to be a more specific behavioral effect of antipsychotic drugs (see Courvoisier, 1957; Cook and Weidley, 1957; Verhave et al., 1958; Mopurgo, 1965; Janssen et al., 1965; Costall and Naylor, 1980; Arnt, 1982), and potencies in the CAR test have been found to be highly correlated with, and to specifically predict, therapeutic efficacy in schizophrenia (Janssen et al., 1965; Arnt, 1982). Therefore, we subsequently studied the effects of two chemically different AMPA receptor antagonists, GYKI52466 and LY326325, on CAR performance in the rat (see Svensson et al., 1998b; Mathé et al., 1999).

Materials and methods

Male Bkl:SD rats (Bantin & Kingman Universal AB, Sollentuna, Sweden) were maintained on a reversed light:dark cycle (lights on at 18:00) and given R34 rat chow and water ad libitum. A shuttle-box (530 × 250 × 225 mm) divided into two compartments by a partition was used (see Wadenberg et al., 1990). Upon presentation of a conditioned stimulus (CS; 80 dB white noise) the animals had 10 s to move into the adjacent compartment of the shuttle-box. If the rat remained in the same compartment for longer than 10 s, the unconditioned stimulus (UCS) was presented, i.e. an intermittent electric shock in the floor grid (4 shocks per 10 s, duration 0.5 s, approximately 0.2 mA), until an escape response was performed, i.e. moving into the other compartment. Avoidance was recorded as a response to the CS within 10 s, escape as response to CS and UCS, i.e. > 10 s, and intertrial crosses, i.e. movement between compartments between trials. The animals were trained for three consecutive days and were initially habituated to the shuttle-box for 5 min, and subsequently trained. Each training session consisted of 20 trials randomly distributed over 15 min. Experimental trials were preceded by a pre-test to reaffirm the rats' maintenance of CS responding ($\geq$80% avoidance). All pre-tests and experimental trials consisted of 10 trials randomly distributed over 7.5 min. Test sessions were conducted 20, 90 and 240 minutes after systemic administration of drug or vehicle. Animals were subjected to repeated observations using a change-over design (Li, 1964) with a one week inter-trial delay period. For assessment of catalepsy scores, animals were placed on an 60° inclined grid and, excluding the first 30 s, the time the rat remained in the same position was measured, for a maximum of 2.5 min. Catalepsy was scored from 0–5 according to the (square root transformation) immobility time (min): $0 = 0 - 0.08$, $1 = 0.09 - 0.35$, $2 = 0.36 - 0.80$, $3 = 0.81 - 1.42$, $4 = 1.42 - 2.24$, $5 \geq 2.25$. GYKI52466 (Research Biochemicals Inc.; 10 and 20 mg/kg) and LY326325 (LY293558 monohydrate; a generous gift from Eli Lilly and Company; 6 and 18 mg/kg) were dissolved in deionized

water. Vehicle injections refer to deionized water. The treatments were administered subcutaneously (s.c.) at a volume of 2 ml/kg. The data for CAR and intertrial crosses were statistically analysed using Friedman's analysis of variance (ANOVA) followed by the Wilcoxon's signed ranks test. Catalepsy scores were analysed using the Kruskal-Wallis ANOVA followed by the Mann-Whitney U-test (Ahlenius and Hillegaart, 1986). A p value < 0.05 was considered significant.

Results and discussion

Systemic administration of GYKI52466 significantly suppressed the CAR at 20 min following injection at a dose of 20 mg/kg s.c. ($p < 0.05$). LY326325 was also found to attenuate CAR performance at 90 min after injection when administered systemically at a dose of 18 mg/kg s.c. ($P < 0.05$). For both drugs, escape responses increased correspondingly, and no response failures were observed. Administration of the drugs at lower doses failed to affect CAR behavior significantly, as did administration of vehicle. No significant changes in inter-trial crosses were obtained following administration of the drugs in any of the doses tested, or vehicle. Some mild sedation or tranquillity was observed in rats for a short period of time immediately following treatment with GYKI52466 or LY326325. However, this effect was not strong enough to cause any reduction of the number of intertrial crosses in the present experiments, at any of the doses tested. In addition, although some minor and short lasting ataxia was observed at gross inspection, neither the CAR performance nor the intertrial crosses were significantly attenuated.

Systemic administration of GYKI52466 (10 and 20 mg/kg s.c.) or LY326325 (6 or 18 mg/kg s.c.) did not significantly affect catalepsy scores throughout the four hour catalepsy rating session when compared to control animals.

The finding that systemic administration of both the non-competitive AMPA receptor antagonist GYKI52466 and the competitive AMPA receptor antagonist LY326325 in the rat causes a significant suppression of the avoidance response without any inhibition of escape behavior is, in principle, indicative of an antipsychotic effect of these compounds. Moreover, the attenuation of CAR was achieved at doses of the AMPA receptor antagonists that are well in agreement with the doses previously found to attenuate the locomotor stimulation evoked by D-amphetamine or MK-801 in mice (Bubser et al., 1995; Vanover, 1998) as mentioned above.

Previous experiments also revealed an apparent sedation or tranquility as well as ataxia in rats reated with AMPA receptor antagonists (Vanover, 1998). However, since these effects of GYKI52466 and LY326325 were not strong enough to cause any reduction of the number of intertrial crosses, as shown by the present experiments, the suppression of CAR by the AMPA receptor antagonists appears unrelated to any generally sedative action of the drugs or to impaired motor performance *per se*.

The mechanism of action for the suppression of CAR by the AMPA receptor antagonists remains to be elucidated. Available evidence demonstrates that blockade of mesolimbic DA receptors is of major importance for

the inhibitory effect of classical antipsychotic drugs on CAR (Wadenberg et al., 1990), but previous data indicate that systemic administration of GYKI52466 does not affect basal DA metabolism when given alone (Bubser et al., 1995). Interestingly, during the actual performance of the CAR brain DA activity seems to increase (S. Ahlenius, personal communication) and, consequently, the demonstrated capability of AMPA receptor antagonists to prevent evoked mesolimbic DA activity (Mathé et al., 1998) may well contribute to suppress the CAR performance.

Since the present study did not reveal any significant catalepsy during the four hours of observation after administration of GYKI52466 or LY326325 in the same doses that caused significant suppression of CAR, our results suggest that AMPA receptor antagonists may not cause extrapyramidal side effects, in similarity with atypical antipsychotic drugs such as clozapine.

Previously, clozapine has been shown to attenuate the behavioral effects of psychotomimetic NMDA receptor antagonists more effectively than classical antipsychotic drugs (Tiedtke et al., 1990; Hoffman, 1992; Hauber, 1993). Therefore, the potent antagonistic effect of AMPA receptor antagonists on the locomotor stimulation caused by MK-801 (Bubser et al., 1995; Vanover, 1998) is indeed consonant with an antipsychotic profile of AMPA receptor antagonists as directly indicated by our results with GYKI52466 and LY326325 within the CAR paradigm. Recently, AMPA and kainate receptor antagonists have been reported to ameliorate also cognitive deficits in rats induced by systemically administered ketamine, another psychotomimetic NMDA receptor antagonist (Moghaddam et al., 1997). Hence, the putative antipsychotic effect of AMPA receptor antagonists may include also cognitive symptoms. This may of particular importance since an amelioration of cognitive functions has been linked to a significantly improved long-term social rehabilitation of schizophrenic patients (see e.g. Lindström, 1994). Taken together, these results suggest that AMPA receptor antagonists may represent a novel type of antipsychotic compounds with a clinical profile more similar to that of atypical antipsychotic drugs such as clozapine than that classical neuroleptics.

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