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Effects of selective NMDA and non-NMDA blockade in the nucleus accumbens on the plus-maze test

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Abstract

Effect of blocking *N*-methyl-D-aspartic acid (NMDA) and non-NMDA-glutamatergic receptors on performance in the plus-maze was studied in male rats bilaterally cannulated into the nucleus accumbens (Acc). Rats were divided into seven groups that received either 1 μl injections of saline, (±)2-amino-7-phosphonoheptanoic acid (AP-7, 0.2, 0.5, or 1 μg) or 2,3 dioxo-6-nitro-1,2,3,4,tetrahydrobenzo-(*f*)quinoxaline-7-sulphonamide disodium (NBQX, 0.2, 0.5, or 1 μg) 15 min before testing. Time spent in open arm, time per entry, end arrivals, open, closed, and total arm entries, relationship between open-, closed-, and total arm entries, rearing, face-, head-, and body grooming, and number of fecal boli were recorded. Time spent in the open arm increased under AP-7 (0.5 and 1 μg; $P<.01$) and NBQX (1 μg; $P<.05$) treatment, whereas time per entry was increased only with AP-7 (1 μg; $P<.05$). Open arm entries were increased by the intermediate doses of AP-7 (0.5 μg; $P<.01$) and NBQX (0.5 μg; $P<.05$); *end* arrivals were increased by the intermediate dose of AP-7 (0.5 μg/1 μl, $P<.05$). The frequency of rearing, grooming, and closed arm entries was not affected by the treatment. We conclude that NMDA and non-NMDA-glutamatergic blockade in the Acc lead to a behavioral disinhibition of cortical influences with the median doses, but that at higher doses the blockers have an anxiolytic-like effect.

Keywords: NMDA-glutamatergic transmission; Nucleus accumbens; Anxiety; Plus-maze; Schizophrenia; Affective flatness; Perception

1. Introduction

In recent years, much attention has been paid to the nucleus accumbens septi (Acc) of the basal forebrain. It is a major component of the ventral striatum of the rat [33], and receives dopaminergic projections from the ventral tegmental area and from the olfactory and limbic cortex [27], and a glutamatergic projection from the limbic system, particularly from the amygdala [8,33], hippocampus, and prefrontal cortex [22,35]. Corresponding receptors are found in the Acc [1]. The Acc efferents reach several basal ganglia nuclei, as well as hypothalamic and limbic areas [35], suggesting that the Acc plays a role as an important interface between the corticolimbic and motor systems. [33]. The Acc is also present in birds [48]. This nucleus appears to be involved in several behavioral processes, such as motor activity [8,17], motivation and reward [27,40], and some cognitive functions [2,3,11,19,25,26,39,41,43–45,47]. The role of dopaminergic transmission in the Acc in stress has been studied [49,51].

N-Methyl-D-aspartic acid (NMDA) receptor antagonists have also been shown to be anxiolytic when selective antagonists were given systemically in a wide range of rodent models, such as social interaction, elevated plus-maze, separation-induced vocalization, Vogel test, open field, and conflict procedures [9,10,15,24,36,50]. It has been reported that this effect usually coincides with an increase in locomotor activity, but that the effect on anxiety levels is in some cases independent of motor variables [36]. Additionally, the intraaccumbens blockade of NMDA

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receptors has been reported to have an anxiolytic-like effect in rats in two different models of anxiety, the open field and the Vogel test [23].

The aim of the present report is to compare the action of selective blockers of NMDA and non-NMDA-glutamatergic receptors injected stereotaxically into the Acc on performance in the plus-maze anxiety test, in order to elucidate if there are anxiolytic effects not related to an increase in locomotor activity, under these conditions.

2. Materials and methods

2.1. Subjects

Male rats from a Holtzman-derived colony, aged 90 days and weighing 240–270 g were used ($n = 141$). They were maintained under controlled temperature (22–24 °C) and lighting (0500–1900 h) conditions. Standard rat chow and water were freely available.

2.2. Surgery

Animals were anesthetized with ether and were stereotaxically implanted with bilateral stainless-steel cannuli into the Acc. Coordinates for cannuli implantation were: anterocaudal: +3.4; lateral: ±2.0; vertical: −4.5, according to the Atlas of Pellegrino et al. [34]. The cannuli consisted of an outer guiding cannula stainless-steel tubing (23 gauge, 15 mm in length) and an inner removable stylet (30 gauge, 15 mm in length) to prevent obstruction. After surgery, rats were housed individually and maintained undisturbed for a week-long recovery.

2.3. Apparatus

The plus-maze was made of wood and consisted of two open arms, 50 × 10 cm (length × width), and two enclosed arms, 50 × 10 × 50 cm (length × width × height), arranged such that the arms of each kind were opposite each other. The maze was elevated 50 cm above the floor level. The room was illuminated by a 60-W bulb 1.5 m above the apparatus.

2.4. Procedure

The animals were injected while manually restrained 15 min before testing. A 30-gauge, 17-mm-long stainless-steel injection cannula (dimensioned to reach precisely the Acc) attached to a 10-μl microsyringe (Hamilton) was introduced into the guide cannula. Volumes of 1 μl solution were gradually injected over 2-min periods into both the left and right Acc. The injection cannulae were left in place for an additional minute to allow for diffusion. The rats received bilateral injections of saline or drugs (see below) 15 min before each session.

The rats were placed individually in the center of the plus-maze apparatus, facing the open arm, and allowed 5 min for

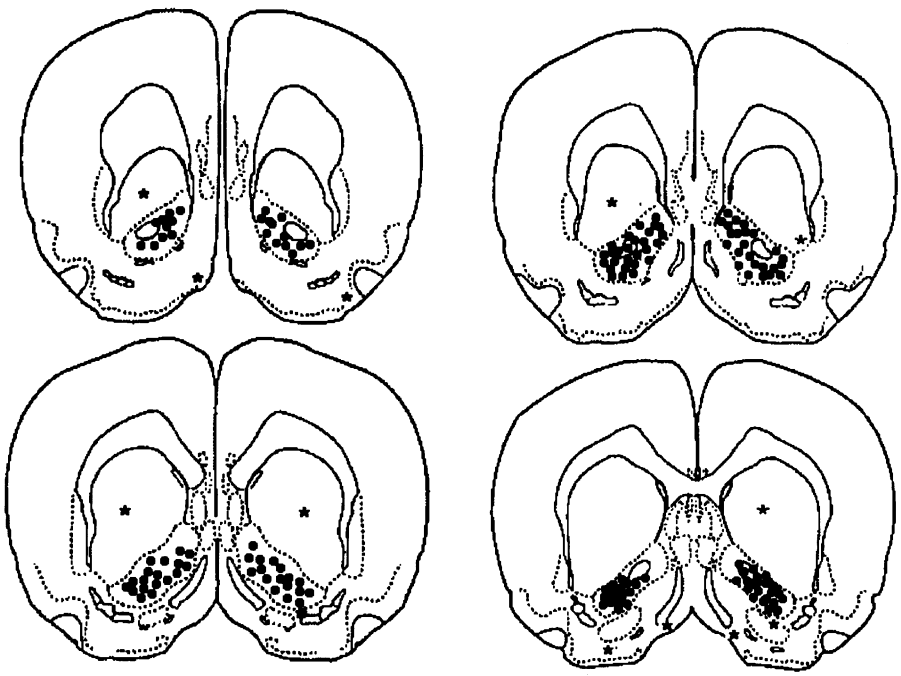

Fig. 1. Frontal brain sections showing the location of the injection site. ●: Correct placements, *: Incorrect placements 1: 3.6 mm, 2: 3.4 mm, 3: 3.4, and 4: 3.0 mm anterior to bregma [34].

free exploration. All the sessions took place between 1700 and 1900 h. Each rat was used only once. Guided by previous findings, we recorded some standard measures and some ethological variables [18,46]. The standard measures were the time spent in the open arm, the time per entry (quotient between the time spent in the open arm and the number of entries into open arms) and closed arm entries (all four paws in a given arm), and the quotient between open and closed arm entries [29].

The ethological items recorded were face grooming, head grooming, rearing, end arrivals, and defecation (number of fecal boli expelled). Face grooming was defined as the washing with the forepaws from the snout to the ears, and head grooming from the ears to the neck. Rearing was defined as a partial or complete standing on the hind limbs. The number of events was recorded to measure grooming and rearing. Extreme arrivals were defined as the number of times the rat reached the end of an open arm.

2.5. Drugs

Seven groups of animals were injected with (±)2-amino-7-phosphonoheptanoic acid (AP-7, Research Biomedical International) solution (0.2, 0.5, and 1 μg/1 μl), 2,3 dioxo-6-nitro-1,2,3,4,tetrahydrobenzo-(*f*)quinoxaline-7-sulphonamide disodium (NBQX disodium salt, Tocris) solution, dissolved in saline (0.2, 0.5, or 1 μg/1 μl), or saline (control group, 1 μl).

2.6. Histology

When the testing was completed, the rats were injected with saturated methylene blue solution (1 μl). Fifteen minutes later they were sacrificed with an excess of ether. The brains were removed from the skull and fixed in 20% formaline solution. Later they were mounted and frozen in a cryotome and cut into 40-μm sections. The block face was examined with a 10× magnifying lens and the sections containing the injection sites were saved. Microscopic inspection of these sections served to ascertain the location of the cannula tips. The locations were transferred to standard sections taken from a brain atlas [34]. We only report data for those rats which had correct Acc cannula placements (Fig. 1).

2.7. Data analysis

The Kolmogorov Smirnov test was used to decide whether the distribution of the data was normal. One-way analysis of variance (ANOVA) followed by Dunnett's test was applied to normally distributed data. A Kruskal–Wallis ANOVA followed by a Dunn's test was applied to non-normally distributed data. In all cases, a $P<.05$ (two-tailed) was considered significant. The results are reported as means ± standard errors ($n=17-22$).

3. Results

3.1. Histology

Nine animals were excluded from the group because of the misplacement of the cannulae.

3.2. Standard measures

Time spent in the open arm was modified by the treatments ($F=7.097$; $df=6,131$; $P<.001$). This measure was increased by both AP-7 (0.5 and 1 μg/1 μl, $P<.01$), and NBQX (1 μg/1 μl, $P<.05$, Fig. 2, top). Time per entry was affected by treatment (KWs = 23.24; $P=.0007$), and increased only by AP-7 (1 μg/1 μl, $P<.05$, Fig. 2, bottom). Total entries were not significantly modified by the experimental conditions (Table 1). The open arm entries were modified by drug treatment ($F=3.135$; $P<.007$), and increased by the median dose of AP-7 (0.5 μg/1 μl, $P<.01$) and NBQX (0.5 μg/1 μl, $P<.05$, Fig. 3, top).

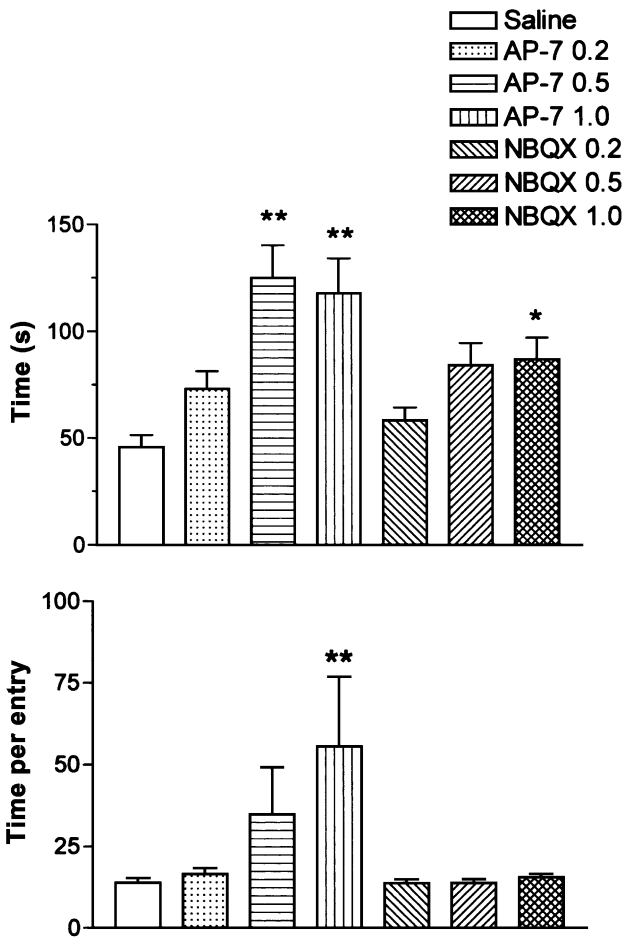

Fig. 2. Top panel: Time spent in the open arm by rats injected into the Acc with saline (1 μl), AP-7 (0.2, 0.5, and 1.0 μg/1 μl), and NBQX solution (0.2, 0.5, or 1 μg/1 μl) 15 min before testing. Bottom panel: Time per entry of the same groups ($n=17-22$ rats; means ± S.E.M.; *$P<.05$; **$P<.01$).

Table 1
Other behavioural parameter

		AP-7			NBQX		
	SAL	0.2	0.5	1.0	0.2	0.5	1.0
Total entries	10.67 ± 0.85	11.37 ± 0.96	12.68 ± 1.36	10.0 ± 1.53	11.45 ± 0.97	13.90 ± 0.82	12.95 ± 0.80
Closed arm entries	7.12 ± 0.77	6.68 ± 0.63	6.37 ± 0.71	6.00 ± 1.18	6.91 ± 0.65	7.63 ± 0.52	7.41 ± 0.56
Open/closed arm quotient	0.59 ± 0.09	0.76 ± 0.08	0.99 ± 0.16	0.94 ± 0.16	0.70 ± 0.07	0.85 ± 0.08	0.79 ± 0.11
Face grooming	14.11 ± 3.34	9.53 ± 3.33	6.89 ± 2.42	7.16 ± 2.53	13.91 ± 3.04	11.79 ± 2.71	8.29 ± 1.89
Head grooming	2.42 ± 0.89	0.47 ± 0.33	1.37 ± 0.52	1.95 ± 1.07	1.68 ± 1.04	1.37 ± 0.52	1.88 ± 0.68
Rearing	9.47 ± 0.63	9.95 ± 1.56	9.26 ± 1.21	11.44 ± 1.64	8.82 ± 1.02	12.89 ± 2.06	10.18 ± 1.64
Fecal boli	1.00 ± 0.24	0.68 ± 0.22	0.95 ± 0.34	1.32 ± 0.40	1.41 ± 0.32	0.47 ± 0.19	0.53 ± 0.23

Closed arm entries and the relationship between open and closed arm entries (Table 1) were not significantly modified by the treatments.

3.3. Ethological measures

The extreme arrivals were modified by drug treatment ($F = 3.777$; $P = .002$) and increased by the intermediate AP-7 dose (0.5 μg/1 μl, $P < .01$, Fig. 3, bottom). Face and head grooming, rearing, and defecation were not modified by the treatments (Table 1).

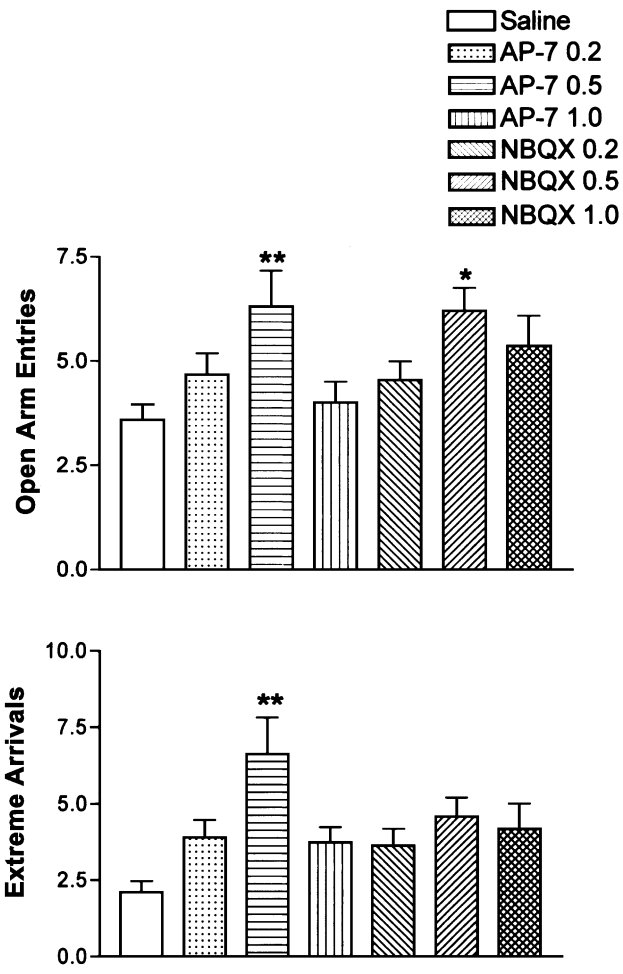

Fig. 3. Top panel: Open arm entries by rats injected in the Acc with saline (1 μl), AP-7 (0.2, 0.5, and 1.0 μg/1 μl), and NBQX solution (0.2, 0.5, or 1 μg/1 μl) 15 min before testing. Bottom panel: Extreme arrivals of the same groups ($n = 17–22$ rats; means ± S.E.M.; $^{*}P < .05$; $^{**}P < .01$).

4. Discussion

The results show that time spent in the open arm was significantly increased by the higher doses of AP-7, and also by the higher dose of NBQX. The time per entry was also significantly increased with the higher dose of AP-7. We suggest that such increases may indicate an anxiolytic effect independent of an unspecific increase in locomotion [29] as the classical indices of general activity (the number of entries to close arms and the total number of entries) were not modified [16].

Other authors using systemically administered glutamatergic antagonists also found that anxiety levels were, in some cases, decreased independently of motor activity [36]. Furthermore, it is known that certain competitive NMDA receptor antagonists with good brain access after peripheral administration [42] are devoid of locomotor stimulatory properties [5,30]. Additionally, the intraaccumbens blockade of NMDA receptors has been reported to have an anxiolytic-like effect in rats in two different tests of anxiety, the open field and the Vogel test [23], the latter not being influenced by locomotor activity (drinking punished test). The combined administration of diazepam and MK-801 increased punished responding, suggesting an enhancement of the anticonflict potency of benzodiazepines by NMDA antagonists [28]. AP-7 was reported to have drug-discriminative properties similar to diazepam [4]. All these support the hypothesis that the effect shown here is not merely due to an increase in locomotor activity. Taken altogether, our results suggest that the higher doses of AP-7 have an anxiolytic effect.

The open arm entries, a possible index of motor disinhibition due to the striatal blockade of cortical inhibitory inputs that are mainly glutamatergic in nature, were increased by the intermediate dose of AP-7 but not by the other doses. The maximal dose used yielded an important increase of time spent per entry, a parameter thought to be a specific sign of anxiolytic action [29].

With NBQX the results are not so clear. The largest dose yielded an increase of time spent in the open arm; with the intermediate dose there was an increase in open arm entries.

However, the time per entry was not modified, even when the maximal dose was used, suggesting that it had no anxiolytic-like effect when injected into the Acc. The increase in the open arm entries might represent a behavioral motor disinhibition related to blockade of cortical inhibitory inputs.

We have previously found that intraacumbens administration of AP-7 lead to a disruption of visual stimuli discrimination in pigeons. As we observed here, the treatment did not interfere with the execution of the task, not being evident disturbances in motor coordination. Therefore, we assumed that the blockade affected a more specific process than mere motivational drive or motor coordination. We suggested that the effect obtained was due to attention impairment [19]. A similar explanation has been proposed for the deficits of Acc-lesioned rats performing a complex visual discrimination task [37]. It may be that the attention needed to evaluate the risks associated with open arms in the present test was similarly curtailed.

Glutamatergic blockade in other brain areas, such as in the amygdala and dorsal periaqueductal gray substance, has been linked with anticonflict-like effects [20,21,31,38]. As remarked previously, the intraaccumbens blockade of NMDA receptors has been reported to have an anxiolytic-like effect in rats exposed to the open field and the Vogel test [23]. A pathway connecting the amygdala with the Acc might be involved in limbic–striatal interactions [6]. Consistent with this, it has been shown with immunohistochemical staining for *fos*-like activity, which maps functional activation of discrete brain areas, that at least two of three anxiogenic situations (foot shocks and an elevated plus-maze) activate not only the prefrontal cortex and amygdala, but also the Acc [14]. The fact that less stressing air puffs did not activate *fos*-like activity in the Acc leads us to assume that this activation is dependent on the intensity of the aversive stimuli. This evidence also supports the idea that Acc has a role in anxiety and emotionality.

The Acc, as part of the mesolimbic dopamine system, has been related to stress and depressive disorders [7], but also to schizophrenic disorders and the action of antipsychotic drugs [32]. We have proposed an animal model of delusional cognition in pigeons [19] based on neuropsychological findings in schizophrenic patients [12]. The test involved a shape discrimination task and the pharmacological treatment was, as here, a blockade of glutamatergic Acc afferents. In the present study with rats, we observed a decrease in anxiety levels with the same pharmacological treatment. We propose that this anxiety reduction could be considered as a partial manifestation of a wider phenomenon, the equivalent of the affective flatness in schizophrenia.

Some current theories postulate that a decrease in glutamatergic transmission underlies the schizophrenic disorder [13]. Our models suggest that a glutamatergic blockade could indeed explain the positive symptoms (the delusional perceptions; [19]) and the negative symptoms (the decrease in anxiety as a singular manifestation of affective flattening, present results) that can be related to clinical descriptions. As mentioned before, the Acc appears to intervene in instances in which the solution of the behavioral tasks at hand require an increased level of attention. A glutamatergic activation of the Acc might normally elicit this attention enhancement through an increase in anxiety.

We conclude that an NMDA-glutamatergic blockade of the Acc apparently leads to decreased emotionality levels. The relevance of the Acc for the emotional background of exposure to the plus-maze test conditions was observed here. Additionally, an anxiolytic effect does not appear to be related to an increase in locomotor activity in these conditions.

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