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AP-7 into the nucleus accumbens disrupts acquisition but does not affect consolidation in a passive avoidance task

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Abstract

The effect of the blockade of *N*-methyl-D-aspartic acid (NMDA)-type glutamatergic receptors in the nucleus accumbens septi (Acc) during different phases of a passive avoidance task (step-through paradigm, two chambers) of learning was studied in male rats which had been bilaterally cannulated into the Acc. Animals were trained with a punishment procedure (3 s shock of 1 mA) to avoid one of the chambers. The rats received either saline or (±)2-amino-7-phosphonoheptanoic acid (AP-7) solution (1 μg/1 μl) 10 min before training (pretraining schedule) or immediately after the shock (posttraining schedule). In the test phase, the animals were placed back into the white chamber after 1 and 8 days later. In this moment, rats stayed there for 1 min, after which the time elapsed between the removal of the door to the introduction into the dark chamber of the head (Latency 1) and body (Latency 2) and fecal boli expelled were recorded. In the pretraining injection schedule, the drug treatment significantly reduced Latency 2 ($P < .05$) and fecal boli ($P < 0.01$) on Day 1, and all parameters on Day 8 ($P < .05$). The posttraining injection schedule did not modify behavior. We conclude that a preshock NMDA-glutamatergic blockade of the Acc leads to cognitive disturbances during acquisition and a decrease in anxiety levels, but that the consolidation of a learned task is not affected by postshock administration.

Keywords: NMDA-glutamatergic transmission; Accumbens; Cognition; Acquisition; Working memory; Goal-directed behavior; Schizophrenia; Perception

1. Introduction

The nucleus accumbens septi (Acc) of the basal forebrain is a major component of the ventral striatum of the rat [25]. It receives a dopaminergic projection from the ventral tegmental area and of afferents from olfactory and limbic cortex [21]. A glutamatergic pathway from the limbic system reaches the Acc, as a part of the ventral striatum [6], and corresponding receptors are present there [1]. The Acc is also present in birds [44], and evidence that it is involved in cognitive functions has recently been reported [15]. In rats, Acc receives afferents from the amygdala [25], the hippocampus, and the cortical regions. Acc receives dense glutamatergic projections from the hippocampus and the prefrontal cortex [16,31]. Its efferences reach several basal ganglia nuclei, hypothalamic, and limbic areas [31]. Its role as an important interface between the corticolimbic and motor systems has been investigated [25].

The Acc appears to be involved in some cognitive functions: learning [37,38], memory [39,40], spatially mediated behaviors [2,3,34], goal-directed behaviors [20], and several behavioral processes such as locomotion [6], stereotyped behavior patterns [14], motivation [36], reward [21], visual discrimination [15], spatial novelty linked to NMDA neurotransmission [43], and working memory [19], a function closely related to goal-directed behaviors [10].

Posttraining manipulations are interesting tools for examining the involvement of brain structures in mnemonic processing. It is known that NMDA receptors are involved

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in memory storage processes that can be studied using a posttraining systemic drug administration [27]. In systemic administrations, the blockers could reach several brain structures related to memory systems, such as the hippocampus [17,28], the dorsal striatum [28], the entorhinal cortex and amygdala [17].

Diverse structures are activated in different moments of cognitive processing [17]. The aim of the present paper is to examine the action of the blockade of *N*-methyl-D-aspartic (NMDA)-type glutamatergic receptors in the Acc during different phases of a learning process.

2. Methods

2.1. Subjects

Male rats from a Holtzman-derived colony aged 90 days and weighing 240–270 g were used ($n=64$). They were maintained under controlled temperature conditions (22–24 °C) and lighting (lights on 0500–1900 h). Standard rat pellets and water were freely available.

2.2. Surgery

Animals were anesthetized with ether and were stereotaxically implanted with bilateral stainless-steel cannulae into the Acc. Coordinates for cannulae implantation were: anterocaudal: +3.4; lateral: ±2.0; vertical: −4.5, according to the atlas of Pellegrino et al. [29]. The cannulae were double barreled and the set was composed of an outer guiding cannulae stainless-steel tubing (23 gauge, 15 mm in length), provided with a removable stylet (30 gauge, 15 mm in length) to avoid its obstruction. After surgery, rats were housed individually and maintained undisturbed for a week-long recovery period.

2.3. Apparatus and test

A passive avoidance task (step-through paradigm) was used. The apparatus consisted of a brightly illuminated white chamber ($30 \times 30 \times 30$ cm) that led via a vertical slide door to a dimly lit black chamber ($10 \times 10 \times 5$ cm). The latter was fitted with an electric floor grid connected to an electric source.

During the training phase, the animals were placed into the white chamber for 1 min. After 1 min, the door was raised and the animals entered into the dark chamber. Immediately after that, the door was closed and an electric shock was administered to the rats through the electric grid (1 mA, 3 s). The door was opened again, the rats were allowed to return to the white chamber and were removed.

A 30-gauge, 17-mm-long stainless-steel injection cannula (dimensioned to precisely reach 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 1 min to allow for diffusion. The rats bilaterally received either saline or (±)2-amino-7-phosphonoheptanoic acid (AP-7, Resarch Biochemicals International) solution (1 μg/1 μl) 10 min before training (pretraining schedule) or immediately after the shock (posttraining schedule). The injections in the latter schedule were completed within 6 min after the punishment.

During the test phase on Days 1 and 8 (under drug- and saline-free condition), the animals were placed back into the white chamber for a 1-min period, and the door was removed. The time taken between the removal of the door until the introduction of the head into the dark chamber (Latency 1) and the rat placing all four feet onto the grid (Latency 2) was recorded. The number of fecal boli expelled during the test was counted.

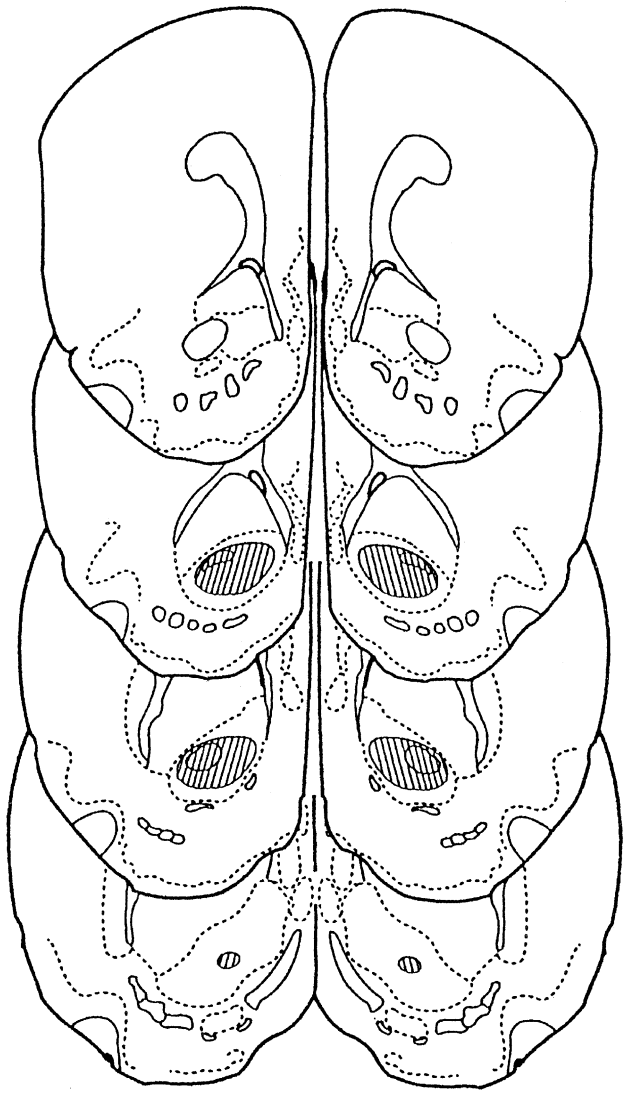

Fig. 1. Frontal brain sections showing the location of the injection site. Schematic representation of histological findings.

2.4. Drugs

Animals were bilaterally injected with AP-7 (Resarch Biochemicals International) dissolved in saline solution (1 μg/1 μl each side) or saline (control group, 1 μl each side).

2.5. Histology

After testing, the rats were sacrificed by an excess of ether. The brains were removed from the skull and fixed in 20% formaline solution. The brains were then 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 selected. Microscopic inspection of these sections served to ascertain the location of these sites. These loci were transferred to standard sections taken from a brain atlas [29] and correct Acc placements were certified (Fig. 1).

2.6. Data analysis

Nonparametric Mann–Whitney tests were used to evaluate significances, and Wilcoxon test was used to compare paired data (Day 1 vs. Day 8 parameters). In all cases, a $P < .05$ (two-tailed) was considered significant. The results reported are medians and interquartile intervals.

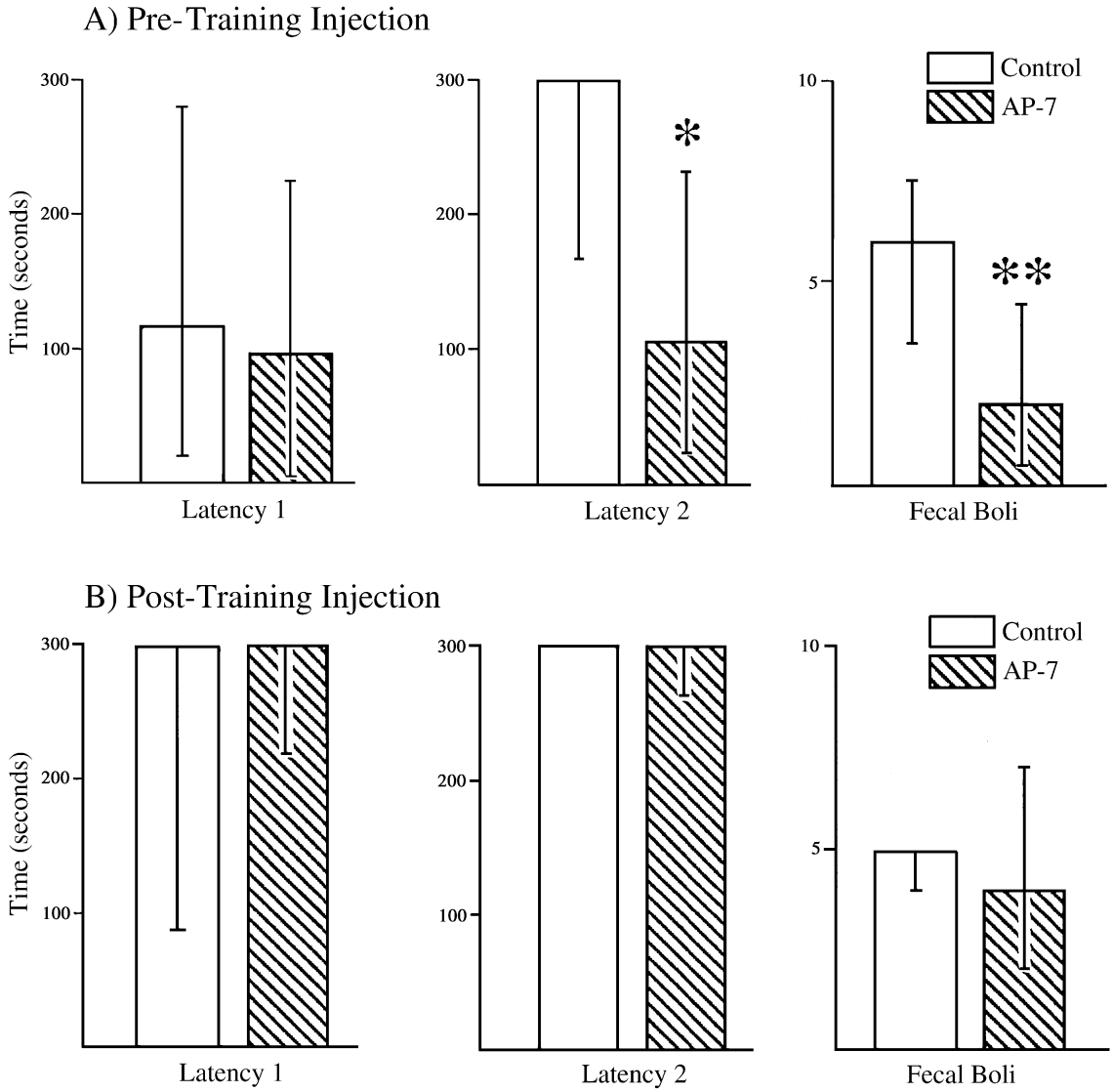

Fig. 2. One day after treatment effects of AP-7 injected into the Acc on Latency 1 (time taken between the removal of the door until the introduction of the head into the dark chamber), Latency 2 (time taken between the removal of the door until the rat placing all four feet onto the grid), and expelled fecal boli in the passive avoidance task (pretraining, top, and posttraining, bottom, injection schedules). Results are reported as medians and interquartile intervals ($n = 15–17$ rats, * $P < .05$; ** $P < .01$).

3. Results

With respect to the pretraining injection schedule (Fig. 2, top), the drug treatment did not modify Latency 1, but significantly reduced Latency 2 ($P<.05$) and fecal boli ($P<.01$) when compared with the saline control group on Day 1 after shock retrieval ($n=17$ each group).

On Day 8 after shock retrieval (Fig. 3, top), Latency 1 was also decreased at a reduced level in the treated group ($P<.05$) when compared with saline. Other parameters (Latency 2 and fecal boli) decreased in a similar way ($P<.05$ in both cases).

The posttraining drug treatment schedule did not lead to any significant difference between saline controls and AP-7-injected rats in the parameters here considered ($n=15$ each group). This was true for both Days 1 and 8 of the after-shock trials (Figs. 2 and 3, bottom).

When a comparison between parameters of Day 1 (Fig. 2, top) and Day 8 (Fig. 3, top) was performed, no differences in the pretraining group were observed, with the exception of a decrease in Latency 2 in the AP-7-treated group ($P<.05$).

When the same temporal comparison (Day 1 vs. Day 8 parameters) was performed in the posttraining treated group, all parameters remain unaffected. In the AP-7-treated group, no differences were evident between Day 1 and Day 8, but, surprisingly, the boli count was still rather high, though no differences were seen when compared with the saline control group.

There were no significant differences between pre- and posttraining administration saline controls on any of the measures. In the Day 1 retrieval, AP-7-treated groups, Latency 1 was clearly decreased in the pretreated group ($P<.01$), as was Latency 2 ($P<.01$). Fecal boli did not yield

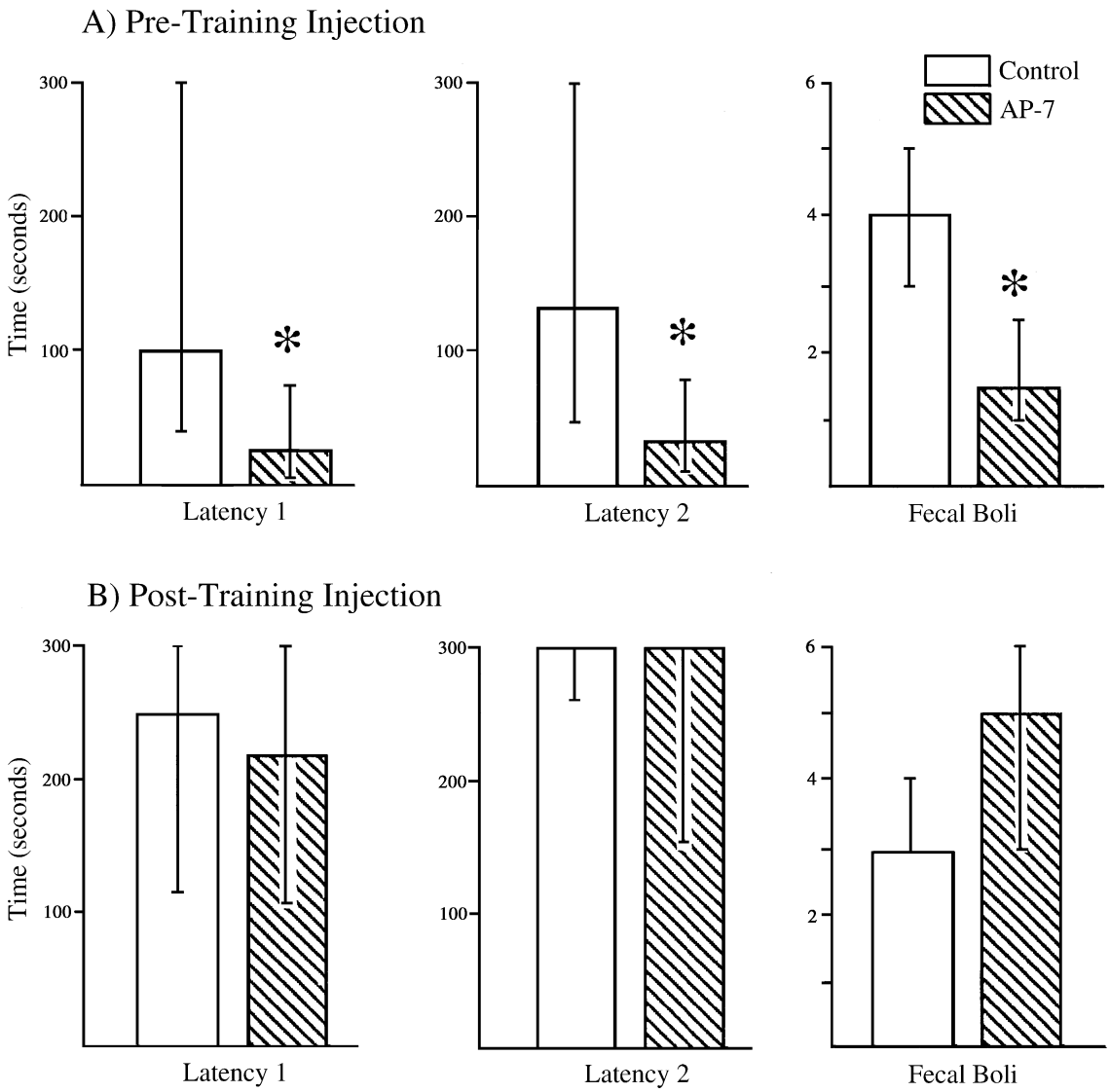

Fig. 3. Eight days after treatment effects of AP-7 injected into the Acc on Latency 1, Latency 2, and expelled fecal boli in the passive avoidance task (pretraining, top, and posttraining, bottom, injection schedules). Results are reported as medians and interquartile intervals ($n=15-17$ rats; $*P<.05$).

significant differences. During the Day 8 retrieval, pretraining administration of AP-7 was effective in modifying all parameters here considered when compared with the posttraining administration. Accordingly, clear differences were seen in Latency 1 ($P < .01$), Latency 2 ($P < 0.01$), and fecal boli ($P < .01$).

4. Discussion

The results show that the acquisition process is interfered with a previous AP-7 administration but the postshock consolidation is not affected by an AP-7-glutamatergic blockade of the Acc region. The fact that Latency 2, but not Latency 1, was affected during the first retrieval test (Fig. 2, top) shows that acquisition was disrupted without interference of exploratory motivation, since the rats were moving, searching the cage in which it has been located and the other cage, introducing its head there, recognizing the environment like the saline-treated group. The fact that during the second retrieval test Latency 1 appears to also be affected in pretraining treated animals (Fig. 3, top) could be explained by a modulatory effect of the first retrieval. Further during the second (8 days) retrieval, parameters remain unaffected in the posttraining injected group when AP-7 administration was compared with saline (Fig. 3, bottom). This is a convincing evidence supporting the absence of any effect on latencies within this postshock schedule. The decrease of fecal boli, linked to aversion [8,26], indicates in the AP-7-pretreated group a possible antiaversive effect of this procedure. Classically, avoidance tasks have been linked to aversion [42], and we can see here a simultaneous interference between aversive levels (fecal boli) and cognitive parameters.

The comparison between 1- and 8-day parameters yielded interesting findings. In the AP-7-pretreated group, cognitive parameters (latencies) showed different results. Latency 1 did not differ significantly from Day 1 to Day 8, suggesting the absence of forgetting or the extinction in this exploratory motivation parameter, though Latency 2, as a cognitive parameter, decreased in a significant manner. Fecal boli remain low on Days 1 and 8, without significant differences, because of the modulatory effect of glutamatergic blockade on aversion during the first experience (training). We can conclude that the facilitation of extinction in the cognitive parameter appears to be linked to the low level of aversion group (AP-7 pretreatment).

In the posttraining injected group, latencies were unaffected from Days 1 to 8. Fecal boli in the AP-7-treated group did not differ from Day 1 to Day 8, and the count remained high, though no differences were seen when compared with the saline control group.

A comparison between the pre- and postinjected groups on Day 1 revealed no differences in the saline-treated animals. In contrast, marked differences were seen in the AP-7-treated groups in Latency 1 and Latency 2 ($P < .01$) as an index of efficacy of AP-7 pretreatment, and an absence of effect in posttreatment conditions. Fecal boli did not differ significantly either in saline control animals or in the AP-7-treated group. When this comparison was made on Day 8, the latency parameters bore the same relationship, with differences in Latencies 1 and 2 between AP-7 pre- and posttraining-treated groups ($P < .01$ in both cases). Fecal boli showed no quantitative differences between pre- and posttraining saline-treated animals, but a significant difference was observed between pre- and posttreated AP-7 rats, with a high number of fecal boli in the posttreated group, which did not significantly differ from posttraining saline-treated group.

The present findings suggest that the glutamatergic transmission in the Acc is subject to a particular temporal pattern during the step-through one-trial learning procedure. Additionally, it is evident that the injection procedure per se did not significantly modify response times since saline controls did not differ between pre- and posttreated groups.

The intraacumbens administration of AP-7 led to a disruption of visual discrimination in pigeons [14], without interference in the mere execution of the task. This fact led us to assume that the blockade affected a more specific process than motivational drive or motor coordination, inducing an attentional impairment [15] as has previously been proposed for the deficits of Acc-lesioned rats performing a complex visual discrimination task [32].

It has been reported that Acc administration of AP-7 produces impairments in a spatial water maze task both during initial training and when the task is well learned [37]. These and other findings [43], which are concurrent with our results, were obtained using the same pharmacological procedure as we have employed. A sustained attention span is probably required for the linkage of visual cues to the position of the platform in these tests. Generally, these effects of glutamatergic blockade could be considered as due to alterations of working memory. In all these instances, the solution of the relevant behavioral tasks can be considered to require an elevated level of attention. Differences between our own and the results of other research groups concerning cognition could be explained by the degree of functional ablation of the Acc induced by lidocaine treatment or ibotenic acid lesions [3,34,38] and tetrodotoxin injections [22]. Here we used a selective pharmacological probe to study the glutamatergic transmission involved in this function, which could involve other systems interfered by the abovementioned treatments. The possibility that a different dose of AP-7 could interfere the function cannot be ruled out. Even so, the dose used to interfere with acquisition was not able to interfere with consolidation.

The role of different brain structures during cognitive processes has been studied extensively. Processes of memory consolidation appear to be related to a sequence of activation of glutamatergic transmission in several brain structures, starting with the amygdala and the hippocampus, and later, the enthorinal cortex [7,17]. Our results suggest

that early consolidation appears not to play a relevant role in the Acc in our conditions, because the postshock treatment did not modify latencies. This structure appears to be involved in the first steps of learning (acquisition, present results) or discrimination tasks [15].

A recent work has pointed the involvement of NMDA-glutamatergic transmission of Acc in consolidation of spatial information processing in a nonassociative task in mice [35]. An important difference with our experimental schedule is that in their study they did not use an aversive stimulus, like in our case. This aversive stimulus could activate projections from the amygdala, instead of afferences from the hippocampus, a brain region classically linked with spatial tasks. Actually, recent findings give support to the idea that a basolateral amygdala complex–nucleus accumbens pathway (BLC–Acc) that runs through the stria terminalis (ST) is involved in glucocorticoid effects on memory consolidation [41], and interacts with hippocampal effects on memory consolidation via this pathway [33]. In our experimental schedule with aversive stimulus, the activation of the BLC–Acc system could be the main pathway involved and it could explain differences with findings in spatial tasks.

Findings in the water maze, injecting a dopaminergic blocker after training, gives support to the idea that another neurotransmitter system could be involved in this moment of learning [40]. However, dopaminergic afferences to Acc are classically related with rewarding properties [45], and by this way could be related to modulation of the previous experience. Glutamatergic afferences are more related to cognitive functions, related to cortical afferences, such as the hippocampus and the prefrontal cortex [16,31].

Glutamatergic blockade has been linked to anticonflict-like effects in other brain areas such as the dorsal periaqueductal gray substance [23]. In the present work, the fact that the fecal boli decreased could be considered an index of the reduction in anxiety levels induced by the aversive stimulus. Decrease in fecal boli is a recognized index of emotionality reduction in rats in the open-field test and increases are related to novelty as an aversive experience [9]. It is reversed by the treatment with antagonists of NMDA-glutamatergic transmission [30]. Additionally, the intraaccumbens blockade of NMDA 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 [18]. A pathway connecting the amygdala and the Acc might be involved in limbic–striatal interactions [4]. Similarly, it has been shown by immunohistochemical staining for *fos*-like immunoreactivity, which maps the functional activation of discrete brain areas, that some anxiogenic situations activate not only the prefrontal cortex and the amygdala, but also the Acc in an intensity-related manner [13].

The Acc receives dense dopaminergic projections as a part of the mesolimbic dopamine system, and it has been related to stress and depression models (see Ref. [5]), and to schizophrenic disorder and the mechanism of action of antipsychotic drugs [24]. Starting from neuropsychological findings in schizophrenic patients [11], we have proposed an animal model of delusional cognition in pigeons [15], consisting of the NMDA-glutamtergic blockade of Acc during a shape discrimination task. In the present study, we have observed a disruption of acquisition with the same pharmacological procedure, probably in conjunction with attention impairment, and an additional affective symptom: decrease of fecal boli. These findings indicating a decrease in aversive components could be linked with the affective flattening seen in schizophrenic patients, among other symptoms. Decrease of glutamatergic transmission has recently been postulated as the underlying mechanism of schizophrenic illness [12]. In these models, glutamatergic blockade could explain positive (delusional mistakes, [15]) and negative symptoms (affective flattening, present results), giving us additional findings to correlate with clinical findings. As mentioned previously, Acc appears to act in instances in which the solution of the relevant behavioral tasks requires an elevated level of attention. At this instant, arousal and anxiety could be elicited together and could be disrupted by glutamatergic blockade of Acc.

We conclude that an NMDA-glutamatergic blockade of the Acc appears to lead to cognitive disturbances, and that this could be due to interference with learning processes, and also the recognition of novel environments, necessary for the acquisition, though not necessarily for the consolidation of a learned task in rats. The relevance of Acc for the emotional background of aversive conditioning was here strongly suggested.

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