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Behavioral effects in the elevated plus maze of an NMDA antagonist injected into the dorsal hippocampus: influence of restraint stress

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Abstract

The objective of the study was to investigate the influence of restraint stress on the effects of 2-amino-7-phosphonoheptanoic acid (AP7), an NMDA receptor antagonist, injected into the hippocampus of rats submitted to the elevated plus maze (EPM). Male Wistar rats with cannulas aimed to the dorsal hippocampus were forced immobilized for 2 h. Twenty four hours later they received bilateral injections of saline or AP7 (10 nmol/0.5 μl), and were tested in the EPM. In another experiment the animals received the treatment immediately before or after the restraint period, and were tested in the EPM 24 h later. AP7 had no effect in any anxiety measure in non-stressed rats. In stressed animals the drug increased the percentage of open arm entries when injected before the test in the EPM. When administered immediately after the restraint period, AP7 increased the percentage of time spent in the open arms and tended to do the same with the percentage of entries in these same arms. The results suggest that interference with hippocampal NMDA receptors modify the anxiogenic effect of restraint stress in an EPM.

Keywords: Anxiety; AP7; Glutamate; Antidepressant; Anxiolytic

Exposure to environmental stress is implicated in the etiology of many human disorders such as depression, anxiety or cardiovascular disease [31]. Several long-lasting behavior effects induced by stress, for example, exploratory deficit of new environments, have also been demonstrated in laboratory animals [13,16,22,24,25].

The hippocampus has been implicated in responses to aversive stimuli and in the development of behavioral consequences of stress [11,13]. Corticoid receptors are remarkably located in this region and studies using c-*fos* mRNA detection suggest that it is activated during restraint stress [13,36]. The restraint-induced exploratory deficit is attenuated by hippocampal injection of cycloheximide, a protein synthesis inhibitor [24], or by 5-HT1A receptor agonists [13,25]. Morphological changes in the hippocampus have also been found in chronically stressed animals [23].

Glutamate is involved in physiological and/or pathological processes in the hippocampus such as learning and memory, seizures and neurotoxicity [7,14,17,21,23,28]. It may also be related to behavioral and/or neurochemical consequences of stress. Both the restraint-induced increase in c-*fos* or c-*jun* mRNA expression in the hippocampus and the morphological changes induced by chronic restraint stress are attenuated by treatment with NMDA antagonists [18,23,36]. In addition, although a larger increase is found in the frontal cortex, glutamate extra-cellular concentration also increases in the hippocampus [19,26] after restraint.

Considering these evidences, the objective of the present study was to investigate if restraint stress could modify the effects of 2-amino-7-phosphonoheptanoic acid (AP7), an NMDA receptor antagonist, injected into the dorsal hippocampus of rats submitted to the elevated plus maze (EPM), an animal model of anxiety [9].

1. Methods

1.1. Animals

Male Wistar rats (200–220 g) were housed in pairs in a temperature-controlled room (23 ± 1°C) under standard laboratory conditions with free access to food and water and a

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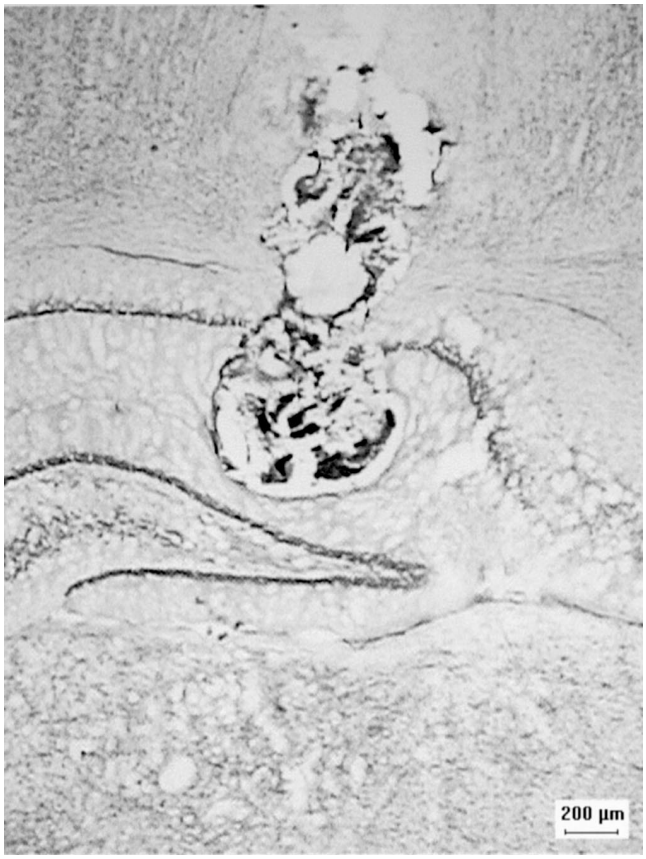

Fig. 1. Photomicrograph of a representative vehicle injection site in the hippocampal formation.

12 h light cycle (lights on at 6:30 a.m.). Procedures were conducted in conformity with the Brazilian Society of Neuroscience and Behavior guidelines for the care and use of laboratory animals, which are in compliance with international laws and policies. All efforts were made to minimize animal suffering.

1.2. Drug

AP7 (Ciba-Geigy) was dissolved in sterile isotonic saline and administered at a dose of 10 nmol. This dose was chosen based on previous studies employing intracerebral injection [2,12]. Moreover, in an initial experiment the dose of 30 nmol induced a significant decrease in the number of enclosed arm entries (5.2 ± 0.6 vs. 2.3 ± 0.6) and ataxia signs.

1.3. Apparatus

Animals were restrained in a wire chamber (6.3×19.3 cm) with an adjustable roof. The wood plus maze consisted of two open and two enclosed arms of equal length and width (50×10 cm). The open arms had a 1 cm high Plexiglas edge while the enclosed arms had 40 cm high wooden sides. The plus maze was elevated 50 cm above the floor. Experiments were carried out in a sound-attenuated, temperature-controlled room, illuminated with two 40-W fluorescent lights placed 1.3 m away from the EPM. The observer stayed 1 m or so away from the maze.

1.4. Stereotaxic surgery

Rats were anesthetized with 2.5% 2,2,2,-tribromoethanol (10 ml/kg i.p.) and fixed in a stereotaxic frame. A stainless steel guide cannula (0.7 mm o.d.) was introduced bilaterally aimed to the dorsal hippocampus (coordinates: A: -4.0mm, L: 2.8 mm, D: 2.1 mm, Paxinos and Watson [30]). The cannula tip was 1.5 mm above the injection site and the cannula was attached to the skull bone with stainless steel screws and acrylic cement. A stiletto inside the cannulas prevented obstruction. The behavioral experiments took place 1 week after surgery.

1.5. EPM test

Immobilization took place from 8:00 to 10:00 a.m. Twenty-four hours later the animals were submitted to the EPM as described previously [12,13]. The following experiments were performed. (1) Previously restrained or controls rats received bilateral intra-hippocampal injection of saline (restraint group, $N=27$, non-restraint group, $N=18$) or AP7 (restraint group, $N=27$, non-restraint group, $N=20$)

Table 1
Number of enclosed arm entries in an EPM

		Saline	AP7 (10 nmol)
Pre-test treatment *	RESTRAINT	6.03 ± 0.8 (27)	3.7 ± 0.6 (27)
	NO-RESTRAINT	4.4 ± 0.7 (18)	2.8 ± 0.5 (20)
Treatment 24 h before the test	POST-RESTRAINT	6.1 ± 1.6 (10)	5.1 ± 0.8 (16)
	PRE-RESTRAINT	5.2 ± 0.7 (31)	4.4 ± 0.6 (32)
	NO-RESTRAINT	5.8 ± 0.9 (9)	5.3 ± 0.8 (12)

Data represent the mean ± SEM of (*n*) animals. Rats received bilateral intra-hippocampal injection of saline or AP7 (10 nmol) 5 min before the test in the EPM. In the first experiment animals were submitted to a 2-h restraint period 24 h before (RESTRAINT). Control animals were not submitted to restraint stress (NO RESTRAINT). In the second experiment the treatments were performed immediately after (POST-RESTRAINT) or before (PRE-RESTRAINT) the immobilization. Control groups (NO-RESTRAINT) received the same treatments but were not submitted to forced immobilization. The test was performed 24 h after injection.

* $P < 0.05$, saline versus AP7-treated groups (ANOVA).

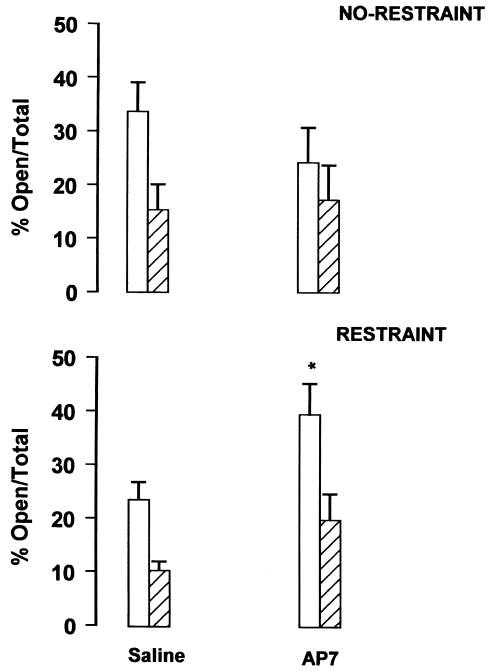

Fig. 2. Effects in the EPM of AP7 (10 nmol) or saline injected bilaterally into the dorsal hippocampus 5 min before the test. The animals were forced immobilized 24 h before the test (RESTRAINT). Control animals were not submitted to restraint stress. Data represent the mean (±SEM) percent of entries (open bars) and time spent (hatched bars) in open arms. $*p<0.05$ compared to saline (*t*-test).

and 5 min later were tested in the EPM. (2) Animals received, immediately after or before the 2 h restraint period, intra-hippocampal injection of saline ($N=10$ and 31, respectively) or AP7 ($N=16$ and 32, respectively), and were tested in the EPM 24 h later. Control, non-stressed animals, received intra-hippocampal injection of saline ($N=9$) or AP7 ($N=12$) and were tested 24 h later.

1.6. Intracerebral injection

A thin dental needle (0.3 o.d.) was introduced through the guide cannula until its tip was 1.5 mm below the cannula end. A polyethylene catheter (PE 10) was interposed between the upper end of the dental needle and the microsyringe. A volume of 0.5 μl was injected in 30 s using a Hamilton (USA) microsyringe. The movement of an air bubble inside the polyethylene catheter confirmed drug flow.

1.7. Histology

After the behavioral tests the rats were sacrificed under deep urethane anesthesia and their brains perfused through the left ventricle of the heart with isotonic saline followed by 10% formalin solution. After a minimum period of 3 days immersed in a 10% formalin solution, 50 μm sections were obtained in a Cryostat (Cryocut 1800). The injection sites were identified with the help of the Paxinos and Watson atlas [30]. Rats that received injections outside the dorsal hippocampus were excluded from analysis.

1.8. Data analysis

The percent entries (100 × open/total entries) and time spent in the open arms (100 × open/open + enclosed) of the EPM was calculated for each rat. These data, together with the number of enclosed arm entries, were analyzed by a two-way ANOVA, the factors being treatment and experimental conditions. In case of significant interaction, post-hoc comparisons were performed with *t*-test or a one-way ANOVA followed by the Duncan test, as appropriate.

2. Results

A representative injection site can be seen in Fig. 1.

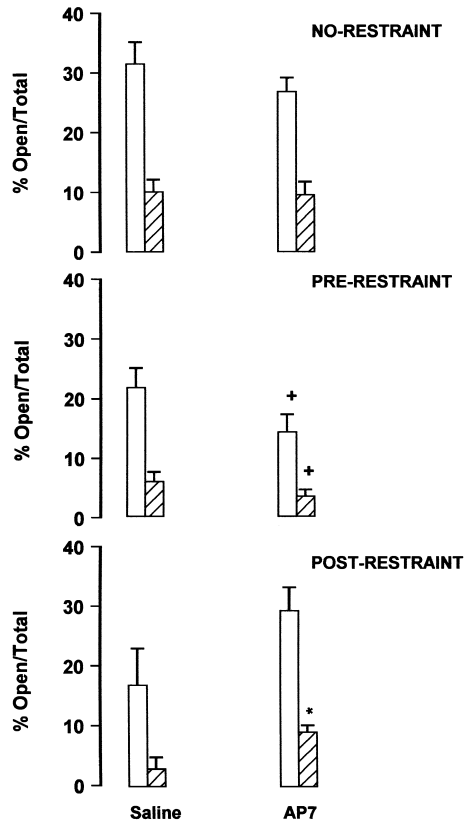

Fig. 3. Effects in the EPM of AP7 (10 nmol) or saline injected bilaterally into the dorsal hippocampus immediately after (POST-RESTRAINT) or before (PRE-RESTRAINT) a 2-h restraint period. Control groups (NO-RESTRAINT) received the same treatments but were not submitted to forced immobilization. The test was performed 24 h after injection. Data represent the mean (±SEM) percent of entries (open bars) and time spent (hatched bars) in open arms. $*p<0.05$ compared to saline (*t*-test), $^{+}p<0.05$ compared to NO-RESTRAINT or POST-RESTRAINT treatments (Duncan test).

2.1. Experiment 1

There was a significant interaction between treatment and experimental conditions ($F_{1,88} = 5.38$, $p = 0.023$) in the percentage of open arm entries. No significant effect was found in the percentage of time spent in the open arms. The drug decreased the number of enclosed arm entries ($F_{1,88} = 8.70$, $p = 0.004$, Table 1). Post-hoc tests showed that the administration of AP7 5 min before the test in stressed rats increased the percentage of open arm entries (t-test ($DF = 52$) = 2.31, $p = 0.025$, Fig. 2). This effect was still significant when the data was submitted to an analysis of covariance using the number of enclosed arm entries as covariate ($F_{1,51} = 6.16$, $p = 0.016$).

2.2. Experiment 2

Restraint stress decreased the percentage of open arm entries ($F_{2,104} = 3.74$, $p = 0.027$), as compared to non-stressed animals. The drug effect was dependent on the time of the administration (treatment × experimental condition interaction, $F_{2,104} = 3.40$, $p = 0.037$, Fig. 3). Similar effects were found in the percentage of time spent in the open arms (experimental condition factor, $F_{2,104} = 3.69$, $p = 0.028$; treatment × experimental condition interaction, $F_{2,104} = 3.25$, $p = 0.043$). No effect was found in the number of enclosed arm entries (Table 1). Post-hoc tests showed that AP7 administered immediately after restraint increased the percentage of time spent in the open arms (t-test ($DF = 24$) = 2.38, $p = 0.026$) and tended to do the same with the percentage of open arm entries (t-test ($DF = 24$) = 1.81, $p = 0.08$), as compared to saline. Open arm exploration of the group that received AP7 before the immobilization was decreased as compared to the other two drug-treated groups (Duncan test, $p < 0.05$).

3. Discussion

Systemic injection of NMDA receptor antagonists, or i.c.v. treatment with an NMDA-R1 antisense oligodeoxynucleotide, produces anxiolytic effects in several animal models [8,40,41,43]. Similar effects have been shown after intracerebral administration of these compounds into the dorsolateral periaqueductal gray [12]. In the hippocampus anxiolytic effects of AP7 were detected in rats submitted to the Vogel's conflict test [15]. However, the present study, employing the EPM, failed to find anxiolytic effects after pre-test intra-hippocampal injection of AP7 in non-stressed rats. The EPM is an animal model of anxiety that has been validated on pharmacological, physiological and behavioral grounds [9]. It is based on the natural preference of rodents for the enclosed arms of the maze, probably because the animals cannot engage in thigmotaxic behavior in the open arms [37], and exploratory indices of open arms are proposed to be inversely related to anxiety [9]. It offers the advantage, in relation to conflict procedures, of not exposing the animals to stressful and painful stimuli such as electrical shocks.

In contrast to the lack of effect in non-stressed animals, pre-test administered AP7 was able to increase the percentage of open arm entries in previously stressed rats, an effect that was still significant after the data was covariated to the number of enclosed arm entries [9]. It also tended to do the same when administered immediately after stress. In this case, it significantly increased the percentage of time spent in the open arms. This suggests an anxiolytic effect when the drug is injected into the dorsal hippocampus immediately or 24 h after a period of restraint stress.

Several groups have shown interference of previous stressful situations in animal models of anxiety. For example, restraint stress or exposure to a predator decrease open and, in some studies, enclosed arms exploration of an EPM [1,13,20,22,24,25]. This suggests that exposure to a previous aversive experience is able to change behavior when the animal is confronted with a new threatening situation, represented by the open arms of the EPM. Although the mechanisms for this phenomenon are unknown, they probably involve plastic changes in the central nervous system [24], perhaps through the induction of immediate early genes expression [18,36]. One brain structure proposed to be involved in such changes is the amygdala [1]. However, although blockade of NMDA receptors in the left basolateral amygdala attenuated the lasting anxiogenic effect of a predator exposure detected in the potentiation of startle amplitude, it failed to do so in the EPM [1]. To explain these results it has been suggested that open-arm exploration requires integration of spatial information about the environment, a process that could also involve the hippocampus [1].

NMDA-mediated neurotransmission in the hippocampus is altered by stress. For example, forced immobilization and other stresses acutely increase glutamate release [3,19] and increase mRNA expression of NMDA receptor subunits in the hippocampus 24 h later [4]. Moreover, an increase in the potency of glycine at the NMDA receptor was also found after forced swim stress [29]. In this test, a commonly used animal model of depression [41], AP7 produces antidepressant effects after systemic administration [38]. So, it is possible that stress-induced changes in hippocampal NMDA-mediated neurotransmission could help to explain the anxiolytic effect of AP7 injected before the test.

The hippocampus is proposed to be a key structure in learning and memory processes and NMDA antagonists block long-term potentiation, a form of synaptic plasticity that has been related to learning mechanisms [5,6]. Post-training interference with NMDA neurotransmission in the hippocampus has significant effects in memory tests [14]. For example, exposure to restraint stress followed by electric foot shocks facilitated classical conditioning and increased reactivity to a new aversive stimulus 24 h later, an effect that was blocked by NMDA antagonism [34]. AP5, an

NMDA receptor antagonist, impaired step-down inhibitory avoidance performance when given into the dorsal hippocampus immediately, but not 30 min post-training. In this study the retention test was performed 24 h after training [42]. Finally, MK-801, a non-competitive NMDA antagonist, impaired performance in a behavioral task when injected up to 2 h after the training session, performed 24 h before the test [32]. So, the possibility remains that the anxiolytic effect of AP7 administered immediately after restraint could involve interference with memories of aversive events.

When AP7 was administered before the immobilization period it significantly decreased the percentage of open arm entries, as compared to drug injections after stress or in non-stressed animals, suggesting an anxiogenic effect. No explanation exists at the moment for this effect. However, Lowy et al. [19] showed that glutamate release was greater at the end of the immobilization period, actually peaking after this period in older rats. So, the influence of glutamate on behavioral consequences of restraint could depend on its action immediately after the stress. Blockade of hippocampal NMDA at the beginning of restraint could have activated feedback control mechanisms that would facilitate glutamate release at the end of the stress period, when the drug concentration was probably smaller or absent.

AP7, when administered before the test, decreased the number of enclosed arm entries, suggesting that the drug interferes with general activity in the maze [9]. Non-specific mechanisms may be involved in this effect. Behavioral changes such as ataxia, stereotyped behavior and impairment of bar-pressing response in a conflict procedure have been described after administration of large doses of NMDA antagonists [33,39].

Stressful stimuli play a substantial role in the development of depressive disorders [10,31] and the hippocampus is proposed to be an important site for the therapeutic effect of antidepressant drugs [10,27]. The present results suggest that hippocampal NMDA receptors could play a role in the development of behavioral changes induced by stress. This may be related in the antidepressant effects showed by NMDA antagonists in animal models [35].

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