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Artigo de Pesquisa

Anxiolytic-like effects of Atenolol injected into the nucleus accumbens septi in rats after restrain stress in the elevated plus maze test

Efeitos ansiolíticos do Atenolol injetado no núcleo accumbens septi em ratos após restrição de estresse no teste do labirinto em cruz elevado

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Abstract

Objetives: Previously, we observed that the injection of glutamate antagonists injected within the Nucleus Accumbens Septi (NAS) produced an anxiolytic-like effect in the elevated plus maze (EPM) test in basal non-disturbed state rats. The effect of metoprolol, a specific Beta-1 Adrenoreceptor antagonist in the EPM, was studied previously in a resting condition in male rats bilaterally cannulated in the NAS. Methods: Rats were previously submitted to restrain stress and divided into four groups. They received bilaterally 1 µl injections of saline (n=13) or atenolol in different doses within the NAS: 0.75 (n=15), 1 (n=13) and 2 µg/1 µl (n=13), 15 min before testing. Rats were maintained under restrain between injection and test. Results: Time Spent in the Open Arm (TSOA) was modified by treatment ($F = 4.239$, $p = 0.0096$, $df = 3$) and increased by the medium dose group when it was compared with the saline group ($p<0.05$) and the lowest dose group ($p<0.01$). Open arms entries (OAE) were modified by treatment ($F = 3.461$, $p = 0.0231$, $df = 3$). This parameter was increased by the medium dose of atenolol ($p<0.05$) when compared to saline and the lowest dose. No significant differences were observed in other parameters studied. Conclusion: We conclude that atenolol beta-1 receptor blockade within the NAS after restraint leads to an anxiolytic-like effect related to an increase in the Time Spent in the Open Arm (TSOA), and behavioural disinhibition, evidenced in the increase in the Open Arm Entries (OAE), showing a specific behavioural pattern.

Keywords: Atenolol; Plus-maze; Glutamate; Accumbens; Anxiety; Schizophrenia.

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Resumo

Objetivos: Anteriormente, observamos que a injeção de antagonistas de glutamato injetados dentro do Nucleus Accumbens Septi (NAS) produziu um efeito ansiolítico no teste do labirinto em cruz elevado (LCE) em ratos em estado basal não perturbado. O efeito do metoprolol, um antagonista específico do receptor beta-1 adrenérgico no LCE, foi estudado anteriormente em condição de repouso em ratos machos canulados bilateralmente no NAS. Métodos: Os ratos foram previamente submetidos ao estresse de contenção e divididos em quatro grupos. Eles receberam injeções bilaterais de 1 µl de solução salina (n=13) ou atenolol em diferentes doses dentro do NAS: 0,75 (n=15), 1 (n=13) e 2 µg/1 µl (n=13), 15 min antes do teste. Os ratos foram mantidos sob controle entre a injeção e o teste. Resultados: O tempo gasto no braço aberto (TSOA) foi modificado pelo tratamento ($F = 4,239$, $p = 0,0096$, $df = 3$) e aumentado pelo grupo de dose média quando comparado com o grupo de solução salina ($p<0,05$) e o grupo de dose média e grupo de dose mais baixa ($p<0,01$). As entradas de braços abertos (EOA) foram modificadas pelo tratamento ($F = 3,461$, $p = 0,0231$, $gl = 3$). Esse parâmetro foi aumentado pela dose média de atenolol ($p<0,05$) quando comparado ao soro fisiológico e à dose mais baixa. Não foram observadas diferenças significativas nos demais parâmetros estudados. Conclusão: Concluímos que o bloqueio do receptor beta-1 pelo atenolol dentro do NAS após a contenção leva a um efeito do tipo ansiolítico relacionado ao aumento do Tempo Passado no Braço Aberto (TSOA), e à desinibição comportamental, evidenciada no aumento de Entradas de Braço Aberto (EOA), mostrando um padrão comportamental específico.

Palavras-chave: Atenolol; Labirinto em cruz elevado; Glutamato; Accumbens; Ansiedade; Esquizofrenia.

INTRODUÇÃO

Nucleus Accumbens Septi (NAS) of the basal forebrain is considered an essential component of the ventral striatum. The first descriptions were made by Meynert, Ganser, and Zuckerkandl. Finally, Ziehen gave the present name to this nucleus (Chronister and DeFrance, 1981). NAS has been described in mammals as a brain site with multiple connections (Groenewegen *et al.,* 1987) and a complex zone connected to a relevant number of brain regions, in which functional assemblies have been described (Pennartz *et al.,* 1984).

Initially, its function was reduced to an interface linking the limbic system to locomotion (Mogenson *et al.,* 1980; Kelley *et al.,* 2003). After it, its role in drug reinforcement and addiction was studied (Koob, 1992; Salamone, 1994). The presence of dopaminergic terminals coming from the ventral tegmental area constitutes the mesolimbic pathway, related to schizophrenia and antipsychotic drugs mechanism of action (Koob, 1992; Gargiulo and Gargiulo, 2014).

NAS receives a critical number of glutamatergic projections from amygdala, hippocampus and prefrontal cortex. An imbalance of these corticostriatal glutamatergic pathways has been postulated as the main pathophysiological disturbance underlying schizophrenia (Gargiulo and Gargiulo, 2014; Gargiulo *et al.,* 1998; Grace, 2000; Grace *et al.,* 2007). An initial glutamatergic dysfunction within NAS was previously postulated by us based on perceptual disorders of schizophrenia, suggesting that dopamine antagonists modify the conditions therapeutically, but were not related to the origin of the illness (Gargiulo *et al.,* 1998). This nucleus is also present in birds (Veenman *et al.,* 1995; Bruce *et al.,* 2016). In fact, some of our studies were realized in pigeons' NAS involving perceptual integration (Gargiulo *et al.,* 1998; Acerbo *et al.,* 2002; Gargiulo *et al.,*

2005). Once again, the NAS appears integrating all these projections, assuming a coordination role of complex functions.

Following this evidence, we have observed that glutamate blockade induces relevant behavioural modifications that should be considered valid animal models of homologous schizophrenia signs or symptoms (see Gargiulo and Gargiulo, 2014). In these studies, we observed, according with previous findings (Jessa *et al.,* 1996), that glutamate antagonists injected in this nucleus have an anxiolytic-like effect. We suggested in this context that this phenomenon may be considered equivalent or compatible with a phenomenon of schizophrenic affective flattening (Martínez *et al.,* 2002a; Martínez *et al.,* 2002b).

We proposed it considering the role of NAS as an integrative structure (see previously). This pharmacological antagonism of glutamatergic transmission has been related to anxiolytic but also antiaversive effects (Salamone, 1994; Gargiulo and Gargiulo, 2014; Martínez *et al.,* 2002a; Martínez *et al.,* 2002b; Gargiulo *et al.,* 2018). However, these glutamate antagonists may not be clinically used without risks due to its potential phencyclidine-like psychotogenic effect (Allen and Young, 1978).

As an alternative strategy, antagonism of secondary neurons activated by glutamate could be attempted. We have previously shown that noradrenergic blockade antagonizes some effects of glutamatergic stimulation on behavioural and endocrine parameters (Landa *et al.,* 2006; Landa *et al.,* 2009). It allows thinking that noradrenergic antagonism may mimic the anxiolytic effect of glutamate antagonists. Some findings have been recently related to the fact that beta noradrenergic transmission action is related to anxiety in rats and mice (Van Bockstaele *et al.,* 2006; Schank *et al.,* 2008; Rudoy *et al.,* 2009). We have previously observed an anxiolytic-like effect injecting atenolol within the NAS under resting conditions (Llano López *et al.,* 2020). Consequently, the aim of this study is to search for the acute effect of atenolol on anxiety injected within NAS in a stress condition on the behavioural patterns displayed in the Elevated Plus Maze (EPM).

METHODS

Subjects

Male rats from a Holtzman-derived colony (90 days old, 240 to 290g, n=54) were used in the present experiments. The conditions of controlled temperature (22-24 ºC) and lighting (lights on at 07:00 and 19:00) were constant and controlled in the maintenance of rats. All tests were

performed under the light cycle. Animals received free standard rat food and water available throughout breading and during experiments.

Surgery

Surgery was realized maintaining the animals under ether anesthesia. Surgical intervention consisted of a stereotaxic implant of a double-barreled bilateral stainless-steel cannula into the NAS. Each set was composed of two elements: an outer guiding cannula stainless steel tubing (23 gauge, 15mm in length) and a removable stylet (30 gauge, 15mm in length). The stylet was used to avoid the cannula obstruction. After surgery, all rats were housed individually. They were maintained under care, in control conditions and undisturbed for a week's recovery period.

Apparatus

The elevated plus-maze (EPM) is a wooden apparatus. It consisted of two open arms, 50 X 10 cm (length per wide), perpendicularly disposed to two closed arms 50 X 10 X 50 cm (length per wide per height). The two arms of each type are opposite to each other. The EPM is elevated to a height of 50cm. A 60W bulb 1.5m above the apparatus illuminated the apparatus and the room.

The restrain apparatus was a plexiglass cylinder of 7cm (diameter) and 17cm long. The rats were unable to escape by a square stop, also made of plexiglass (8cm high and 7cm wide) introduced perpendicularly in the cylinder.

Experimental Design

15 min before testing rats were injected (manual restraint). A stainless steel injection cannula (30 gauge, 17mm long, dimensioned to reach in a precise manner the goal area) attached to a 10µl microsyringe (Hamilton) was introduced into the guide cannula. Volumes of 1 µl solution were injected gradually over 1 min period. This procedure was executed into both the left and right brain structures, leaving the injection cannula positioned in place for an additional 1 minute allowing diffusion. After injection, rats were maintained under restrained conditions for 15 minutes in the plexiglass tube as a stressor.

At the beginning of the behavioral experiment, rats were placed individually in the center of the plus-maze apparatus. They were introduced facing the open arm and allowed 5 min for free exploration. The experiments were performed between 08.00 to 12.00 h (light cycle).

Parameters and methods of our previous studies were maintained (Martínez *et al.,* 2002a; Gargiulo *et al.,* 2018; Gargiulo and Donoso, 1989; 1996; Laconi *et al.,* 2001; Llano López *et al.,* 2012; 2013; Gargiulo *et al.,* 2020). We measured classical parameters of our lab, according to our previous studies. They were: Time Spent in the Open Arm (TSOA), time per entry (defined as the quotient between time spent in the open arm divided by the number of entries to open arms), Open and Closed Arm Entries (the arm entry was defined as all four paws located into the arm, OAE, CAE), the relationship between the open and the closed arm entries, and extreme arrivals. Extreme arrivals were defined as the times number that the rat reaches the end part of the open arm (distal third of the open arm).

Drugs

Rats were manually injected bilaterally into the NAS with either saline (1µl, n=13) or Atenolol (Research Biochemical Industries, RBI) 0.75 (n=15), 1 (n=13) and 2 µg/1µl (n=13).

Histology

After the experiments, the rats were intracerebrally injected with saturated methylene blue solution (1 µl) aiming to assert placement of the cannula. Five minutes later, they were sacrificed using ether excess, and brains removed from the skull and fixed in 20 % formalin solution. One week later, brains were sectioned and observed with a 10 x magnifying lens. Injection sites were verified, and they were transferred to graphic papers of standard sections inspired and copied from a brain atlas (Pellegrino *et al.,* 1979). Microscopic inspection of these sections led to ascertaining the location of the end of the injection cannula. We report here only data from those rats in which a correct placement of the cannula was verified (Figure 1).

Data analysis

The parametric distribution of data was ascertained using the Kolmogorov Smirnov test. After it, one way ANOVA followed by Newman-Kewls Multiple Comparison Test were used. In all cases, the value of $p<0.05$ (two-tailed) was considered significant. The results are presented as means ± Standard Error of the Mean (SEM, n=13-15).

Statement of Ethics

Bioethical and legal dispositions were considered in animal's care. Housing and experimental

procedures were carried on according to rules of the project approval criteria of the National University of Cuyo, and following the guidelines set by European Community Council (Directive 86/609/EEC).

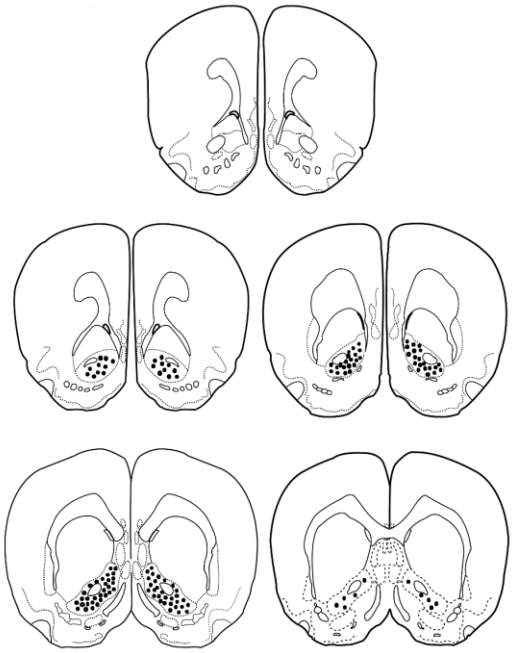

Figure 1 - Histology of rats used in the plus maze test with the injection of Atenolol within NAS. Present frontal brain sections shows schematically the histological findings regarding location of the injection site. ●: Injection cannula placement. 1: 5.4 mm; 2: 5.6 mm; 3: 5.8 mm; 4: 6.0 mm; 5: 6.2 mm and 6: 6.4 mm anterior to bregma (Pellegrino et al., 1979).

RESULTS

Time Spent in the Open Arm was modified by treatment (F=4.239, p=0.0096, df=3). It was increased by the medium dose group when it was compared with the saline group (p<0.05) and the lowest dose group (p<0.01, Figure 2).

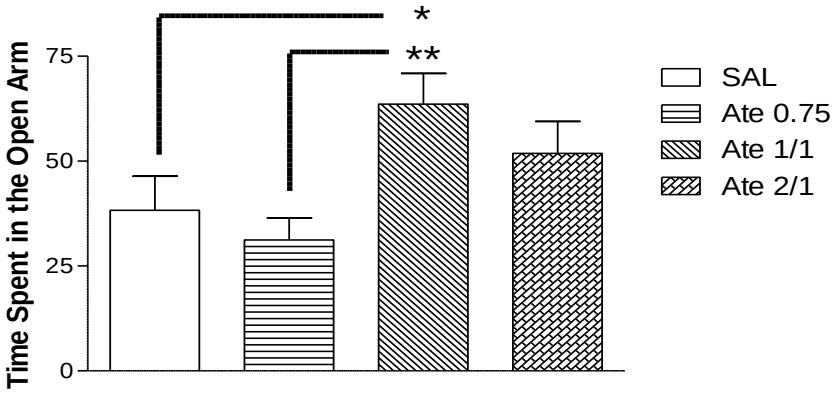

Figure 2 - Time Spent in the Open Arm (TSOA) observed in the elevated plus maze (EPM) test with the injection of Atenolol within the NAS. Rat groups received injection of saline (1 μl, n=15 rats), and Atenolol (0.75, 1.0 and 2.0 μg/1 μl) solution 15 min before testing. Results are reported as mean ± Standard Error of the Mean (SEM) (n=13-15 rats, *=p<0.05, **=p<0.01).

Open arm entries were modified by treatment (F=3.461, p=0.0231, df=3). This parameter was increased by the medium dose of atenolol (p<0.05, Figure 3) when compared to saline and the lowest dose.

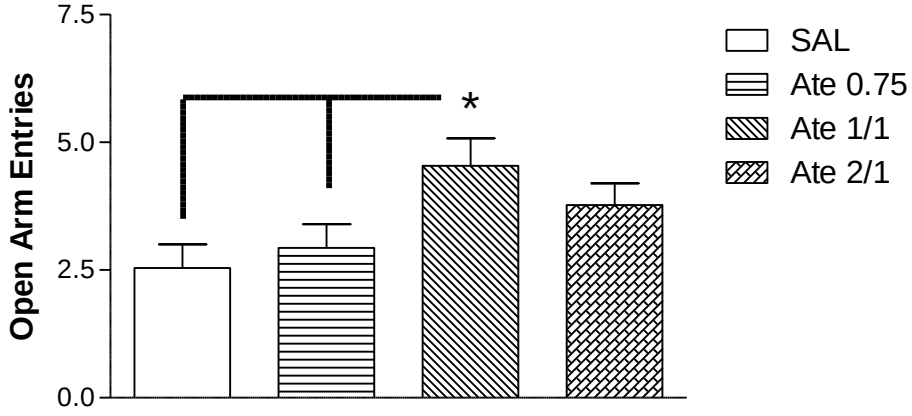

Figure 3 - Open Arm Entries (OAE) observed in the elevated plus maze (EPM) test with the injection of Atenolol within the NAS. Rat groups received injection of saline (1 μl, n=15 rats), and Atenolol (0.75, 1.0 and 2.0 μg/1 μl) solution 15 min before testing. Results are reported as mean ± Standard Error of the Mean (SEM) (n=13-15 rats, *=p<0.05, **=p<0.01).

No significant differences were observed in other parameters studied (Table 1).

Table 1 - Values of Extreme Arrivals, Time per entry, Closed Arm Entries and Open/Closed Arm Quotient obtained with Saline and Atenolol (0.75, 1 and 2 μg/μl) injected within the NAS

	SALINE	**ATENOLOL**		
	n=13	**0.75 μg / 1 μl** n=15	**1.00 μg / 1 μl** n=13	**2.00 μg / 1 μl** n=13
Extreme Arrivals	1.62 ± 0.45	1.53 ± 0.38	2.62 ± 0.35	2.31 ± 0.44
Time per Entry	13.11 ± 2.54	8.92 ± 1.31	14.53 ± 1.17	13.71 ± 1.14
Closed Arm Entries	6.15 ± 0.72	5.93 ± 0.92	7.15 ± 0.69	5.69 ± 0.72
Open/Closed Arm Quotient	0.43 ± 0.09	0.71 ± 0.19	0.70 ± 0.09	0.76 ± 0.11

DISCUSSION

Positive and negative results were evident. TSOA was significantly modified by treatment, and this was increased by the medium dose group experimenting a significant increase when compared with the saline group ($p<0.05$) and the lowest dose group ($p<0.01$, Figure 1). OAE was modified by treatment, and the dose of atenolol significantly increased this parameter ($p<0.05$ vs. saline and the lowest dose, Figure 2). The other parameters did not show significant modifications (Table 1).

The TSOA is considered the most classical and indicative parameter of an anxiolytic-like effect in EPM test (Gargiulo and Donoso, 1989; Jessa *et al.,* 1996; Laconi *et al.,* 2001; Gargiulo *et al.,* 2018; Llano López *et al.,* 2012). Rats' behavior exhibited here a clear anxiolytic like effect induced by the injection of atenolol, involving beta-1 adrenergic receptors in this state. The time spent in the open arm, a parameter traditionally associated with anxiolytic behavior was modified only by 1 µg dose, with significant differences when compared to saline ($p<0.05$, Figure 2) and 0.75 µg dose ($p<0.01$, Figure 2). The 1 µg dose induced a maximal effect, decreasing slightly with 2 µg dose. This anxiolytic like effect vanished with the maximal dose (2 µg), suggesting a weak sedative incipient state. The phenomenon appears to conform to an inverted "U" shape curve. We have not here a classical dose response curve that is a sign of specific action on the receptor (Allen and Young, 1978; Gargiulo *et al.,* 2018; Llano López *et al.,* 2012). However, increasing the dose we had some relationship between the dose increase and the response.

OAE was modified by treatment, and the medium dose of atenolol increased significantly this parameter versus saline controls ($p<0.05$, Figure 3). Significant differences were also observed between atenolol 1 µg/1 µl versus saline and 0.75 µg ($p<0.05$, Figure 3). No differences were observed versus 2 µg. Like in TSOA, the effect vanished when increasing the dose, suggesting an early sedative effect. The increase obtained with the medium dose may be indicating behavioural disinhibition and not an increase in locomotor activity. CAE but not OAE is considered an index of increased locomotor activity in the EPM test (Llano López *et al.,* 2013). In this case, CAE did not exhibit modifications and therefore cannot be interpreted as a motor modification (Table 1). OAE may be better considered as behavioral disinhibition.

Consequently, treatment induces here a significant decrease in anxiety, represented by the increase in TSOA, and behavioral disinhibition, exposed by the presence of an increase in OAE. From present results, we may deduce that the submaximal dose exerted the most evident effect on

both mentioned parameters. TSOA was increased by the submaximal dose, allowing to sustain that an actual anxiolytic effect was observed with this drug in these conditions. This effect was accompanied by behavioral disinhibition evidenced in the increase in OAE. It is interesting to note that the structure here involved is NAS. Once again, evidence point this structure as related to anxiety modulation. This modulation has been described previously manipulating glutamate receptors, but also dopaminergic pathways interact with these receptors within this structure (Kelley *et al.,* 2003).

In some states linked to high levels of anxiety, such as abstinence, the role of noradrenergic receptors has been signaled. For example, betaxolol, a beta-1 blocker, antagonizes the increases in the expression of adrenergic beta-1 receptors in the amygdala when initiating early cocaine withdrawal. This pharmacological treatment led to a decrease in anxiety levels during abstinence. These facts are closely related to a decrease in corticotropin-releasing factor gene expression in the amygdala (Van Bockstaele et al*.,* 2006; Schank et al*.,* 2008; Rudoy *et al.,* 2009; Gargiulo *et al.,* 2020). These groups have proposed that the amygdala is a relevant neural substrate in the processes of interaction between β-1 adrenergic receptor and corticotropin-releasing factor and its corresponding gene expression (Van Bockstaele *et al.,* 2006; Rudoy *et al.,* 2009). Furthermore, it was shown that betaxolol neutralizes, during early cocaine withdrawal, the increase of CRH gene expression in amygdala. β-1 receptors have been observed in CRH amygdala immunoreactive neurons. It may be postulated that they may affect CRH expression (Rudoy *et al.,* 2009). The role of Corticotropin Releasing Hormone (CRH) is relevant in anxiety mediation. We have shown that intracerebroventricular injection of this peptide induces an increase in anxiety levels in the EPM, and significant increases in some specific patterns of grooming behavior (Gargiulo and Donoso, 1989; 1996).

All these findings led to consider that noradrenergic β-1 signaling has a critical role in the expression of the anxiety states induced by cocaine withdrawal (24). It is congruent with this evidence set that the cute injection of betaxolol in the NAS abolished aversion (Schank *et al.,* 2008). Additional interactions appear to take place in NAS. In this sense, the injection of a classical and selective noradrenaline uptake inhibitor like reboxetine, induces an increase of noradrenaline efflux but also a dopamine one within the NAS. It demonstrates new interactions in this structure (Mizoguchi *et al.,* 2008).

The conditions of abstinence studies have here some similarities and some differences with our present experimental schedule. Restrain is acting as an anxiogenic-like state inducing stress.

However, we have here an acute, non-genomic effect. Rats were injected with the beta antagonist 15 minutes before the test. Drug withdrawal experiments realized by other groups were carried out 24 and 48 hours after the drug suppression (Rudoy *et al.,* 2009). We may consider that our present results are evidencing a non-genomic effect, and, consequently, not involving CRH transcription mechanisms.

It is important to note that we tried to approximate our experimental conditions to the anxiogenic states, like those induced by cocaine abstinence. They were tested under stress conditions. In this schedule, an anxiolytic-like effect was induced injecting the atenolol acutely in the NAS, giving additional evidence of its role in anxiety modulation, as we have previously postulated (Gargiulo *et al.,* 2018; Kelley *et al.,* 2003; Martínez at el, 2002a, 2002b; Gargiulo and Landa de Gargiulo, 2004; Llano López *et al.,* 2012, 2013; Gargiulo *et al.,* 2020).

Another interesting point that is here illuminated is the common biological subjacent mechanisms of anxiety and depressive disorders. It may allow to explain that anxiety and depressive disorders have clear overlapping in diverse symptoms. The coexistence of these disorders may be considered as a comorbid condition. However, it could be thought that it may be reflecting a closely related underlying pathophysiology for both pathologies. An important fact that gives support to this hypothesis is that antidepressants exert their action on anxiety but also on the comorbid anxiety of depressive disorders (Feighner, 1999). The more accepted mechanism of action proposed for antidepressants is downregulation of beta-1 adrenergic, serotonin 5HT2 and 5HT1A receptors in the central nervous system (Stahl, 1992). In the same way, it has been postulated a correlation between the clinical efficacy of antidepressants and its desensitizing ability on cortical beta 1-adrenergic receptors (Baiardi *et al.,* 2007). If beta-1 receptors mediate anxiety, as is here observed, it may be understood that its blockade exerts anxiolysis. Additionally, the reversal of beta-1 receptor brain hyperfunction in depression leads to disappearance of depressive disorder and also to anxiety decrease.

Present findings evidenced here that it may be concluded that atenolol exerts an acute anxiolytic-like effect when injected within NAS in rats under stress conditions. It reinforces the concept of the role of the beta-1 noradrenergic receptors modulating anxiety within this structure.

In our previous study under resting conditions, atenolol induced an increase4 in time spent in the open arm and in the time per entry. This second parameter is classically linked to a specific anxiolytic effect (Laconi *et al.,* 2001). In the present study, submitting the rats to previous restraint, it appears to be that the anxiolytic effect is present, and it may be observed in the increase in the

time spent in the open arm (Figure 2). However, the disinhibitory effect after restraint prevails, inducing disinhibitory conditions represented by an increase in open arm entries (Figure 2).

This evidence may lead to new approaches to anxiety treatment. The NAS shows here, once again, its role in modulating anxiety. These findings increase and enriches our previous findings of NAS function (Gargiulo, 1996, 2003; Gargiulo and Landa de Gargiulo, 2004, 2014; Baiardi *et al.,* 2007). An additional goal of the present study is related to the role of NAS and the specific behavioural profile in anxiety under stress conditions.

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