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Acute lecozotan administration increases learning and memory in rats without affecting anxiety or behavioral depression

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ABSTRACT

Lecozotan is a selective serotonergic 5-HT$_{1A}$ receptor antagonist previously shown to enhance task performance efficiency in aged rhesus monkeys. In the present report we tested the ability of this drug to modify memory and learning in rats during a modified passive avoidance response test, and also tested its effect on anxiety with the elevated plus maze, and behavioral depression in the inescapable swim test. Lecozotan enhanced memory in a dose-dependent manner (0, 0.3, 0.5, 1 and 2 mg/kg; s.c.), or prevented memory impairment previously induced with scopolamine-HCl. No significant changes in anxiety and behavioral depression were detected in animals treated with different doses of lecozotan (0, 0.3, 1 and 2 mg/kg; s.c.) compared to control animals. These results suggest that lecozotan could enhance learning and memory in animals without affecting anxiety or behavioral depression scores and that it could be a viable alternative in the treatment of patients with cognitive deficits such as the Alzheimer's disease.

1. Introduction

The serotonergic receptor 5-Hydroxytryptamine 1A (5-HT$_{1A}$) is a member of a superfamily of receptors associated to protein Go/Gi that hyperpolarizes neurons (Kowal et al., 2002; Tada et al., 1999). It can be located both in the presynaptic (autoreceptors) and postsynaptic (heteroreceptors) terminals within the central nervous system (CNS) (Hoyer et al., 2002). Serotonin binding to 5HT$_{1A}$ autoreceptors reduces the firing rate of serotonergic neurons and decreases 5-Hydroxytryptamine (5-HT) release from the nerve terminals (Blier and de Montigny, 1990). Heteroreceptors are fundamentally localized on glutamatergic and cholinergic neurons from the hippocampus, amygdala, septum, entorhinal and frontal cortex (Pompeiano et al., 1992). Agonists binding to 5-HT$_{1A}$ heteroreceptors induce hyperpolarisation of non-serotonergic neurons (Blier and de Montigny, 1990), while antagonists prevent the inhibitory effect of 5-HT (Forster et al., 1995). This suggests that the serotonergic system through 5HT$_{1A}$ heteroreceptors could act as a negative modulator of glutamatergic and cholinergic neurons (Czyrak et al., 2003; Chessell et al., 1993), and probably affecting cognitive process, with particular emphasis on learning and memory (Meneses, 2003; Schechter et al., 2002; Steckler and Sahgal, 1995).

5-HT$_{1A}$ receptor antagonists have been employed in several works and have allowed to increase our knowledge on the role of this receptor in cognitive behaviors and memory (Fletcher et al., 1993; Forster et al., 1995; Hirst et al., 2008; Johansson et al., 1997; Schechter et al., 2002); and in non-cognitive behaviors such as feeding, innate fear, sexual activity, pain perception, sleep and temperature regulation (Barnes and Sharp, 1999; Hoyer et al., 2002; Shields and King, 2008).

Anxiety and behavioral depression are other pathophysiological processes linked to the 5-HT$_{1A}$ receptor functions (Overstreet et al., 2003). There are few and controversial evidences in relation to the use of 5-HT$_{1A}$ receptor drugs in the treatment of anxiety or depression. Several studies have found that 5-HT$_{1A}$ agonists act as anxiolytic and antidepressant agents (Koek et al., 1998; Van Reeth et al., 1999). The transient overexpression of the 5-HT$_{1A}$ receptor in mice has showed to be capable to reduce anxiety-related behaviors (Kusserow et al., 2004). While different strains of the 5-HT$_{1A}$ receptor knockout mice showed an increased anxiety-related behavior (Heisler et al., 1998; Parks et al., 1998; Ramboz et al., 1998), others noted that this phenotype only appears in a specific period of time during development (Gross et al., 2002). In contrast, several studies have suggested that the use of 5-HT$_{1A}$ antagonists alone or in a combination with antidepressant drugs could be anxiolytic or enhance their antidepressive effect in patients and animal models (Cao and Rodgers, 1997a,b,c; Hjorth, 1993; Kinney et al., 2000; Rasmussen et al., 2000; Tatarczynska et al., 2002).

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Alzheimer's disease (AD) is a neurodegenerative disorder that compromises neurotransmission in CNS. AD patients manifest a memory deficit probably due to a hypofunction of the cholinergic and glutamatergic systems in cerebral regions linked to learning and mnemonic processes (Bowen, 1990; Hardy et al., 1987). Additionally, several authors have demonstrated the involvement of the serotonergic system in AD. An abnormally high prolactin release after fenfluramine administration has been reported as an evidence of the hyperresponsivity of central serotonergic neurons in AD patients (McLoughlin et al., 1994), and this could in turn inhibit the cholinergic and glutamatergic functions, worsening the cognitive impairment. Others have recently found a decrease in the 5-HT_{1A} receptor expression and binding in AD patients (Kepe et al., 2006; Lai et al., 2003; Lanctot et al., 2007; Meltzer et al., 1998; Meneses, 1999). This mechanism of downregulation of the 5-HT_{1A} receptor could be a compensatory process due to an excessive 5-HT release after a serotonergic challenge (such as fenfluramine administration), and suggests that a 5-HT hyperfunction could be deleterious to AD patients. Other report has proposed that AD-related loss of function of the serotonergic system is due to a neuronal and glial regression to immature states (Meneses, 1999). That could explain the abnormal response of the 5-HT release and downregulated 5-HT_{1A} receptor function and expression in brain areas related to learning and memory. Additionally, an abnormal serotonergic system also could trigger other neuropsychiatric disorders such as anxiety and behavioral depression (Meltzer et al., 1998). Owed to the importance of the 5-HT_{1A} receptor over the regulation of neurotransmission linked to cognitive behaviors, Bert et al. (2008) have proposed that drugs with a postsynaptic 5-HT_{1A} antagonist action or presynaptic 5-HT_{1A} agonist action could ameliorate learning and cognitive impairments associated to cholinergic dysfunction, as it seems to happen in AD patients.

Lecozotan (4-ciano-*N*-{2*R*-[4-(2,3-dihidrobenzo[1,4]-dioxin-5-il)-piperazina-1-il]propil}-*N*-piridina-2-il-benzamida HCl) is a new selective, and high affinity drug with a full antagonist and with no agonist/partial agonist activity on 5-HT_{1A} receptors. This drug does not alter the sensitivity of 5-HT_{1A} receptors when it is chronically administered, and increases extracellular levels of glutamate and acetylcholine (ACh) in the hippocampus of rats when administered in the presence of an infusion of K^+ (Schechter et al., 2005). Additionally, it can improve task performance efficiency in aged rhesus monkeys that naturally show impaired learning and memory parameters (Schechter et al., 2005). In support to these findings, another 5-HT_{1A} antagonist, WAY-100635 has been capable to prevent memory deficits induced by the blockade of the glutamatergic and cholinergic systems in rats and monkeys (Carli et al., 1997; Harder and Ridley, 2000). Thus, it is possible that a 5-HT_{1A} receptor antagonist such as lecozotan may have a potential use in the treatment of AD patients (Seabrook et al., 2007).

In the present report, we evaluated the potential of lecozotan at different acute doses to modulate learning and memory parameters, using a modified version of the passive avoidance test in rats. In separate experiments, different acute doses of lecozotan were tested on depressive and anxiety states using the inescapable swimming test and elevated plus maze respectively.

2. Materials and methods

2.1. Subjects

Male Sprague–Dawley rats weighing between 250 and 400 g purchased at the Central Vivarium of the University Centroccidental Lisandro Alvarado were used. Animals were housed in pairs with food and water *ad libitum*, at room temperature and 12–12 h light–dark cycle. A new different group of rats were employed in each behavioral test. All the experiments were carried out according to the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals.

2.2. Drugs

Lecozotan was obtained from Wyeth-Ayerst Research (Princeton, NJ) and was dissolved in sterile water for subcutaneous (s.c.) injection. Scopolamine hydrochloride was obtained from Sigma-Aldrich (St. Louis, MO) and dissolved in sterile isotonic saline for intraperitoneal (i.p.) injection.

2.3. Passive avoidance response test

A modified passive avoidance response test was examined in the step-down situation to study the parameters of learning and memory in rats as previously described (Cumin et al., 1982; Ogasawara et al., 1999). All rats were tested on two consecutive days. The first day rats were trained to remain on a rubber platform ($15 \times 15 \times 0.5$ cm) placed at a corner of a wooden box ($25 \times 30 \times 33$ cm) that was equipped with an electrified grid floor. When the rats moved away from the safety zone (rubber platform), they received electric shocks (60 Hz, 0.5 ms, 0.8 mA) from the grid floor. The training session consisted of five consecutive trials (1 min each). Rats learned to step back onto the rubber platform to avoid shocks, and never stepped down onto the grid floor after the third trial. During the second day (test session, 24 h later) the grid floor electric current was turned off. Animals were placed again over the rubber platform and the time spent over it, before stepping down onto the grid floor (at least 3 limbs) was measured (latency time, LT). Experiments were performed between 1600 and 2100 h. A closed circuit camera system was used during the training session (day-1) and test session (day-2) to avoid any external influence. An observer, blind to the conditions, measured LT in all experimental and control groups. LT between group differences were interpreted as changes in learning and memory; considering raised LT measures as improved learning and memory, and reduced LT measures as impaired learning and memory.

2.4. Effect of lecozotan on learning and memory

30 min before the training session (day-1), each group of rats received a dose of lecozotan (0, 0.3, 0.5, 0.8, 1 and 2 mg/kg s.c.) (Schechter et al., 2005) followed 15 min later by an i.p. injection of either scopolamine hydrochloride (0.3 mg/kg) or saline. LT was measured the next day (day-2).

2.5. Inescapable swim test

We followed the modified inescapable swim test protocol to induce a behavioral depression on a different group of rats (Rada et al., 2006). Tests were conducted between 800 and 1200 h. On day-1, each rat was placed in an opaque cylindrical water tank (27 cm of diameter; 42 cm of height; 33 cm of water depth at 25 °C and changed for each rat) for 10 min. During the second day (24 h later; day-2), rats were placed again in the water tank for 10 min. For day-1 and day-2, the length of time that rats spent swimming and no swimming (immobility) was measured. "Swimming" was defined by escape behaviors (i.e. diving, rigorous paddling with all four legs, circling the tank, and climbing at the tank walls). "Immobility" was scored as floating and treading water just enough to keep the nose above water. All experimental groups were carried out employing a closed circuit camera system to avoid external influences and an observer, blind to the treatment, measured the swimming time at day-1 and day-2. Normally, rats decrease the percentage of swimming time at day-2 with respect to day-1; and an increase in the percentage of swimming time at day-2 is interpreted as an antidepressant activity, while the opposite is interpreted as pro-depressant activity.

2.6. Effect of lecozotan over behavioral depression

Lecozotan was administered at 0, 0.3, 1 or 2 mg/kg dose, 30 min before day-1 of the inescapable swim test. Swimming times were measured in each case for the two days and day-2 data were normalized, considering day-1 data as 100% (Rada et al., 2006; Schechter et al., 2005).

2.7. Elevated plus maze

This protocol has been previously employed to measure changes in anxiety state on rats (Car and Wisniewska, 2006). A separate group of animals to perform this behavioral test was employed. The elevated plus maze (black opaque wooden planks) consisted of four arms (two open and two closed), each 50 cm long and 10 cm wide, positioned to form a square cross around a 10 cm central square. The closed arms had 40 cm high walls, and they were opposite to the open arms. The maze was illuminated by a 60 W light and elevated 50 cm from the floor. Before the test, every animal was handled daily for 5 min and at least during 5 consecutive days to avoid handle anxiety. Experiments were performed between 800 and 1200 h. During the test day, the subjects were placed in a pre-test arena ($45\times45\times35$ cm) for 30 min, allowing exploratory behaviors, and then immediately placed in the center of the elevated plus maze facing one of the open arms. Every animal was placed 5 min in the maze and the number of entries to every arm, total time spent in closed arms, open arms and center of the plus maze were video monitored and measured by an observer blind to the conditions. The maze was cleaned with a 70% v/v of ethanol/water solution between every rat. An increase in the percentage of the time spent in open arms indicates an anxiolitic-like activity, as rats naturally prefer closed arms.

2.8. Effect of lecozotan over anxiety state

Lecozotan was administered at 0, 0.3, 1 or 2 mg/kg dose, 30 min before placing the animals on the elevated plus maze. The total time spent in closed arms, open arms and center of the maze were measured and the percentage of time in closed and open arms with respect to the total time of the test (5 min) was calculated for each group.

2.9. Statistical analysis

Results of each group are shown as mean ± SEM. Two-tailed *t* test for unpaired measures was used to compare LT of trained-rats vs. not trained-rats and to compare trained-rats vs. scopolamine-treated rats. One-way ANOVA and Dunnett's post-hoc test were employed to compare LT over lecozotan and/or scopolamine treatment and to determine the optimal lecozotan dose in animals in relation to the control group (saline). One-way ANOVA and Dunnett's post-hoc test were used to compare the percentage of swimming time and to compare the percentage of closed/open arms spent time in elevated plus maze in animals treated with different doses of lecozotan. Data were analyzed using Prism version 4.0 for Windows (GraphPad Software, San Diego, CA, USA). In all cases, $p<0.05$ indicated a significant difference.

3. Results

3.1. Passive avoidance response test

The amount of time (LT) spent on the insulated platform was dependent on training. LT in trained-rats was 350 ± 71 s ($n=10$) compared to 6 ± 1 s ($n=10$) in non-trained rats ($t(18)=4.86$, $p<0.0001$) (see Fig. 1).

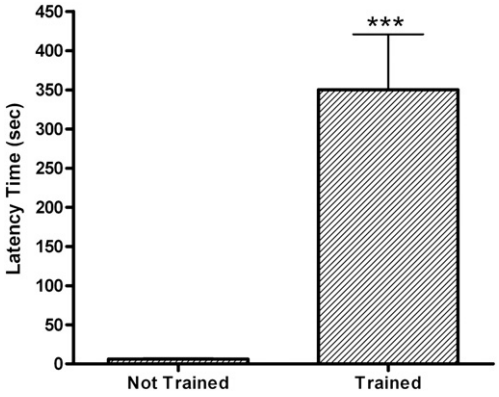

Fig. 1. Bars represent LT as mean ± SEM of non-trained animals (6 ± 1 s, $n=10$) vs. trained animals (350 ± 70.8 s, $n=10$) on the passive avoidance response test ($t(18)=4.86$, $^{***}p<0.0001$).

3.2. Effect of lecozotan on memory and learning

Lecozotan alone significantly and dose-dependently increased LT ($F(5,61)=12.34$, $p<0.001$) (Fig. 2 left, Table 1). The best effect was found with injection of 1 mg/kg of lecozotan increasing LT up to 1962 ± 316 s compared to 350 ± 71 s in rats receiving vehicle (dose 0) (Table 1). A significant reduction of LT to 38 ± 28 s was observed in rats receiving water (lecozotan vehicle, dose 0) followed by 0.3 mg/kg of scopolamine, compared to control subjects (without drugs) ($t(17)=3.923$, $p<0.005$). Lecozotan was capable of blocking dose-dependently the amnesic effect produced by scopolamine. Injection of 1 mg/kg of lecozotan increased LT from 38 ± 28 s (scopolamine effect) to 396 ± 110 s ($F(5,51)=3.125$, $p<0.0001$) (Fig. 2 right; Table 1), which is similar to the control level in the previous experiment.

3.3. Effect of lecozotan over behavioral depression

All animals showed a reduction of swimming times on the second day of the forced swim test but lecozotan treated rats consistently swam more the second day. Control animals swam 80.2 ± 3.2% compared to day-1 ($n=12$). Rats treated with 0.3, 1 and 2 mg of lecozotan swam 85.3 ± 2.7% ($n=9$); 87.7 ± 8.5% ($n=10$); and 90.4 ± 5.9% ($n=9$), respectively. These percentage differences were not statistically significant.

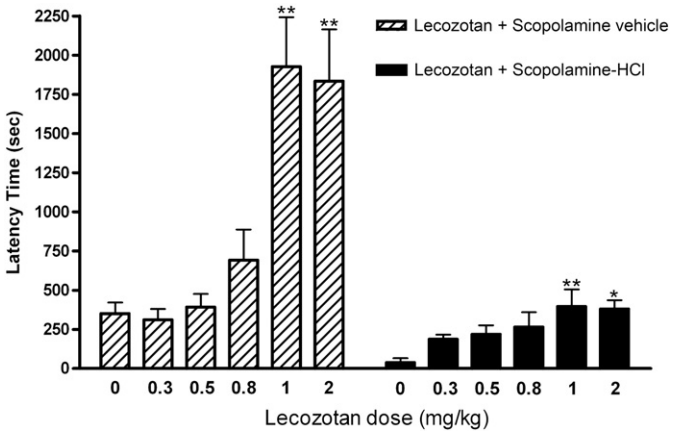

Fig. 2. Effect of increasing doses of lecozotan (0, 0.3, 0.5, 0.8, 1 and 2 mg/kg)(s.c.) over LT (presented as mean ± SEM) of animals trained on the passive avoidance response test. Lined bars represent animals treated with lecozotan + scopolamine vehicle; $F(5,61)=12.34$, $p<0.0001$. Filled bars represent animals treated with lecozotan + scopolamine-HCl; $F(5,51)=3.125$, $p<0.0001$. Dunnet's post-hoc $^{*}p<0.05$; $^{**}p<0.01$.

Table 1
Latency times (LT) of animals treated with different doses of lecozotan + scopolamine vehicle or + scopolamine (0.3 mg/kg, i.p.). Dunnet's post-hoc: $^{*}p<0.05$; $^{**}p<0.01$.

Dose of lecozotan (mg/kg)	Without scopolamine			With scopolamine		
	Mean(s)	SEM	*n*	Mean(s)	SEM	*n*
0	350.1	70.8	10	38.1	28.4	9
0.3	310.3	69.2	10	187.7	29.0	9
0.5	392.8	83.2	12	218.9	55.8	9
0.8	691.4	195.2	17	264.5	95.7	10
1	1926.2*	315.6	9	395.7**	110.1	11
2	1834.8*	330.3	9	379.9*	55.9	9
	$F(5,61)=12.34$, $p<0.0001$			$F(5,51)=3.125$, $p<0.0001$		

3.4. Effect of lecozotan over anxiety

Treatment with lecozotan did not produce any statistical differences at any dose on anxiety levels in animals assayed in the elevated plus maze. Percentages of the time spent in closed and open arms for control animals were respectively $68.9\pm3.0\%$ and $5.0\pm2.1\%$ ($n=7$). Lecozotan administered at a dose of 0.3 mg/kg spent $61.5\pm3.9\%$ in the closed arms and $7.0\pm1.3\%$ ($n=7$) in the open arms. In addition 1 mg/kg and 2 mg/kg of lecozotan induced $62.2\pm4.7\%$ and $6.6\pm2.0\%$ ($n=7$), and $56.9\pm5.0\%$ and $5.4\pm1.5\%$ ($n=7$) in the closed and open arms respectively.

4. Discussion

The present report showed that lecozotan improved memory in rats during a passive avoidance test and prevents the amnesic effect of scopolamine. This effect was dose-dependent and no changes were observed in anxiety or depression scores. Thus this further supports the previous evidence that 5-HT_{1A} antagonists, such as lecozotan, are procognitive enhancers (Schechter et al., 2005).

The passive avoidance response test has been shown to be a quick and easy method of detecting changes in learning and memory (Ogasawara et al., 1999) and has been used before to determine memory disturbance produced by the competitive non-selective cholinergic antagonist scopolamine (Frey et al., 1992). However, it is important to note that this behavioral model cannot differentiate other behavioral processes such as pain perception, motivation and locomotor activity, which can alter this test and could be misinterpreted as changes in learning and memory (Sarter et al., 1992). In our case, rats did not present any significant differences in the locomotor activity on the elevated plus maze test when lecozotan was administered at different doses (data not shown). Our results and the finding by others (Luttgen et al., 2005; Madjid et al., 2006; Misane and Ogren, 2003) suggest that lecozotan improves memory and learning but caution should be taken since in our work we did not discard possible confounding issues like pain perception or motivation.

Lecozotan increased LT in the passive avoidance test. This supports the previous reports that show that other fully 5-HT_{1A} receptor antagonists improve learning and memory in various behavioral animal models (Boast et al., 1999; Harder et al., 1996; Harder and Ridley, 2000; Hirst et al., 2008; Madjid et al., 2006; Misane and Ogren, 2003; Pitsikas et al., 2003; Schiapparelli et al., 2006). Contrarily, several studies have found that the use of the 5-HT_{1A} receptor antagonist, intraventricularly injected, produces a dose-dependent amnesic effect (Galeotti et al., 2000; Herremans et al., 1995). With the employment of the 5-HT_{1A} agonist also occurs an apparent contradiction. A classical 5-HT_{1A} receptor agonist 8-hydroxi-2-dipropylaminotetralin (8-OH-DPAT) was generally found to cause memory impairment at high doses (Egashira et al., 2006; Madjid et al., 2006; Misane et al., 1998). However, the administration of lower doses of 8-OH-DPAT has reported to enhance cognition (Carli et al., 2001; Madjid et al., 2006; Micheau and Van Marrewijk, 1999). This apparent contradiction could be related to the 5-HT_{1A} functioning as an autoreceptor (Ago et al., 2003; Blier and de Montigny, 1990). When 5-HT_{1A} antagonists are locally injected in the brain they probably disinhibit serotonin neurons in the dorsal raphe increasing their firing and release rate (Bert et al., 2008; Galeotti et al., 2000), and thus inhibit ACh and glutamate neurons in the hippocampus and worsen memory loss. In favor of this hypothesis is that direct stimulation of 5-HT_{1A} receptors in the dorsal raphe reverts the scopolamine-induced amnesia (Carli et al., 1998). This report behaviorally suggests that systemic administered lecozotan primarily acts on the heteroreceptor located in the hippocampus, and it would increase the release of ACh and glutamate (Schechter et al., 2005); which in turn could be responsible for the increase of learning and memory parameters (LT) observed in rats.

Scopolamine has been employed to impair learning and memory in rats (Buresova et al., 1986; Rush, 1988), and it has been useful as an animal model of the memory deficit seen in patients with neurodegenerative disorders like AD (Christensen et al., 1992; Ebert and Kirch, 1998; Patel and Tariot, 1991). We treated rats with scopolamine and corroborated that it significantly reduced LT in rats subjected to passive avoidance test which would validate our paradigm as an effective measurement of learning and memory in rats. Considering that AD is a neurodegenerative process that reduces the number of cholinergic and glutamatergic neurons in several brain areas related to learning and memory, various animal models of AD aim to block these neurotransmitter systems (Bowen, 1990; Hardy et al., 1987). It is important to note that in the present report we did not block the glutamatergic system to cause memory deficit in rats. Future works will be necessary to corroborate if this model is sensitive to glutamatergic as well as to cholinergic deficits.

5-HT_{1A} antagonists are known to enhance cognitive responses in rats and reverse the cognitive impairment induced by different drugs or lesions (Harder et al., 1996; Hirst et al., 2008; Misane and Ogren, 2003; Pitsikas et al., 2003). In our hands, lecozotan dose-dependently prevented the memory impairment produced by scopolamine. This suggests that lecozotan could become a potential tool in the treatment of cognitive disorders and could also be a useful drug to attenuate memory impairment in patients with AD (Seabrook et al., 2007).

AD and other neurodegenerative disorders are comorbid with depression and anxiety presumably through the serotonergic system (Hattori, 2008; Lavretsky et al., 2009; Meltzer et al., 1998), and the employment of antagonists to this receptor could in turn modify anxiety, behavioral depression and memory (Cao and Rodgers, 1997c; Fornal et al., 1996; Hirst et al., 2008; Hjorth, 1993; Kinney et al., 2000; Misane and Ogren, 2003; Tatarczynska et al., 2002). A drug for the treatment of memory impairment in AD that does not worsen, or better yet, improves these symptoms is ideal. In our work, acute lecozotan administration did not modify significantly the swimming times in the forced swim test; however, a tendency to increase swimming time on the second day was seen. Several reports have found that high doses of the 5-HT_{1A} receptor antagonists WAY-100635 and LY426965 increase extracellular levels of 5-HT in the dorsal raphe nucleus and hypothalamus, suggesting an antidepressant effect (Fornal et al., 1996; Rasmussen et al., 2000). Moreover, LY426965 potentiates the therapeutical effect of the antidepressant fluoxetine, a selective serotonin reuptake inhibitor (SSRI), when they are co-administered together to rats (Rasmussen et al., 2000); however, other report has failed to demonstrate that WAY-100635 has any antidepressive effect (Tatarczynska et al., 2002). Furthermore, lecozotan administered at 3 mg/kg (s.c.) did not change the hippocampal extracellular levels of 5-HT (Schechter et al., 2005). This suggests that the low doses used in the present report did not modify behavioral depression scores because they did not change 5-HT extracellular levels. However, it is possible that lecozotan works in a similar way than LY42696 or WAY-100635 when they are administered alone. Further studies employing increased doses of lecozotan (>3 mg/kg)

should be done. Also it is possible that lecozotan could work as an enhancer of SSRIs when they are co-administered to rats, and future work will be necessary to verify it. Additionally, with respect to the tendency of rats to increase swimming times, a previous report has indicated that this phenomenon could be due to a serotonergic component, associated to swimming behaviors, or due to a noradrenergic component, associated with climbing behaviors (Cryan et al., 2005). In any case, further studies should clarify which component is responsible of this observed situation when rats are treated with lecozotan.

Finally, lecozotan did not modify anxiety scores in animals subjected to the elevated plus maze paradigm. We expected that the administration of lecozotan alone to animals would be anxiolytic but this was not observed at any dose of lecozotan. Previous works have suggested that 5-HT_{1A} antagonists could act as anxiolytics (Cao and Rodgers, 1997a, b, c; Griebel et al., 2000). However, other works have failed to demonstrate this phenomenon (Madjid et al., 2006; Tatarczynska et al., 2002). In support, the employment of 8-OH-DPAT has showed to be anxiogenic on animals (Micheau and Van Marrewijk, 1999). In our studies, acute treatment with lecozotan did not produce any anxiolytic effect on animals, but future work will be necessary to demonstrate if chronic treatment with lecozotan alone or co-administration with classic anxiolytic drugs can potentiate the antidepressive effect.

In summary, the new $5HT_{1A}$ antagonist lecozotan improves memory in rats subjected to a modified passive avoidance test, while showing no effects on anxiety or depression parameters under the conditions tested and it is capable of preventing the amnesic effect induced by scopolamine, which corroborates the data that 5-HT_{1A} antagonists can increase memory scores under multiple paradigms. Taken together this study further suggests that lecozotan could have potential as an alternative treatment of memory loss in AD patients.

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