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Effects of 5-HT_{5A} receptor blockade on amnesia or forgetting

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ABSTRACT

Previously the effects (0.01-3.0 mg/kg) of post-training SB-699551 (a 5-HT_{5A} receptor antagonist) were reported in the associative learning task of autoshaping, showing that SB-699551 (0.1 mg/kg) decreased lever-press conditioned responses (CR) during short-term (STM; 1.5-h) or (3.0 mg/kg) long-term memory (LTM; 24-h); relative to the vehicle animals. Moreover, as pro-cognitive efficacy of SB-699551 was reported in the ketamine-model of schizophrenia. Hence, firstly aiming improving performance (conditioned response, CR), in this work autoshaping lever-press vs. nose-poke response was compared; secondly, new set of animals were randomly assigned to SB-699551 plus forgetting or amnesia protocols. Results show that the nose-poke operandum reduced inter-individual variance, increased CR and produced a progressive CR until 48-h. After one week of no training/testing sessions (i.e., interruption of 216 h), the forgetting was observed; i.e., the CR% of control-saline group significantly decreased. In contrast, SB-699551 at 0.3 and 3.0 mg/kg prevents forgetting. Additionally, as previously reported the non-competitive NMDA receptor antagonist dizocilpine (0.2 mg/kg) or the non-selective cholinergic antagonist scopolamine (0.3 mg/kg) decreased CR in STM. SB-699551 (0.3 mg/kg) alone also produced amnesia-like effect. Co-administration of SB-699551-dizocilpine or SB-699551-scopolamine reversed the SB-699551 induced-amnesic effects in LTM (24-h). Nose-poke seems to be a reliable operandum. The anti-amnesic and anti-forgetting mechanisms of amnesic SB-699551-dose remain unclear. The present findings are consistent with the notion that low doses of 5-HT_{5A} receptor antagonists might be useful for reversing memory deficits associated to forgetting and amnesia. Of course, further experiments are necessary.

1. Introduction

Accumulating evidence indicates that diverse serotonin (5-hydroxytrptamine, 5-HT) receptors are involved in learning and memory, including 5-HT_5 (e.g., 11), which have been divided into 5-HT_{5A} and 5-HT_{5B} (e.g., [8]). In a previou-3.0 s work, we reported the effects of SB-699551 (0.01–3.0 mg/kg), a 5-HT_{5A} receptor antagonist. As we have seen before [7] post-training treatment with SB-699551 decreased short- (STM; 1.5-h; at 0.1 mg/kg) and long-term memories (LTM; 24 h; at 3.0mg/kg) as evaluated on an associative learning task of autoshaping. In contrast, Nikiforuk et al. [13] recently reported pro-cognitive efficacy of SB-699551, reversing a delay-induced deficit (i.e., forgetting) in object recognition. SB-699551 was also effective against ketamine-induced social withdrawal, a model of negative-like symptoms of schizophrenia [13]; Nikiforuk et al. [13] conclude that the blockade of 5-HT_{5A} receptor may represent a therapeutic approach for age-related dementia or AD. Moreover, implementation of new instruments for measuring memory in behavioral tasks assists in gaining deeper insight into learning and memory processes. Indeed, of behavioral memory tasks available (e.g., 19; 22; 24; 25), autoshaping presents notable advances, including automatization (e.g., 16) and more importantly, bridging translational testing in mice and humans (23) as well as measuring memory, neural markers (see 17; 21); pharmacological effects (e.g., 21; [11]), and several behavioral/environmental controls groups (e.g., 29). Another aspect that should be taken into consideration when changing from lever press to nose-pokes is that in this later operandum is not necessary the continuous adjustment of force required for the lever-press responses (see 27; 28). Hence, in this work the effects of SB-699551 were separately investigated in the forgetting (30; 27; 28) and amnesia protocols (21). Both protocols have been proved to be useful on detecting pharmacological and neurobiological changes (21), allowing separately the study of amnesia and forgetting; which are, in pharmacological and neuroanatomical terms, different processes (e.g., 27; 28). We also should note that amnesia is an abnormal event and forgetting is a physiological normal process and whose mechanisms have been little explored [11]; [30]. Forgetting is featured by loss of information, its study covers from theories to experimental design and procedures and it is the result of retrieval failure, interrupted consolidation, interference and passive decay (see e.g., 27; 28). Herein, we are using a decay information protocol.

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2. Methods

2.1. Subjects

Adult male Wistar rats were housed collectively in a temperature- and light-controlled room under a 12-:12-h light-dark cycle (light on at 7:00 h). Water and food were provided ad-libitumfor a week. After that period, body weights were gradually reduced to 85% reducing the food intake during 7 days. The experimental protocols were revised and approved by Institutional Review Committee (CICUAL Project No. 0006-12) for the use of animal subjects in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985). Amnesia and forgetting experiments were replicated twice. Experimenters were blind to group assignment and outcome assessment. For each experiment (1–3) new set of animals were used.

2.2. Magazine training

Each rat was placed in an experimental chamber and allowed to habituate to the experimental environment and food-magazine until the animal found and ate 50 food pellets (each pellet 45 mg). Immediately afterwards, pretraining autoshaping sessions occurred (Fig. 1). Animals showing progressive learning were randomly assigned for the following phase (e.g., forgetting or amnesia protocols).

2.3. Autoshaping training

The autoshaping program had been previously reported (20; 2013; 2014a; see also youtube video, phrasing: learning, memory and autoshaping; both lever-press and nose-poke versions). Briefly following the food magazine training autoshaping training/testing sessions occurred and consisted in discrete trials.

2.4. Autoshaping task

A trial begun with the operandum illumination for 8 s with either the presentation of a illuminated retractable lever for 8 s (CS) or a illuminated standard nose-poke response well followed by a 45 mg food-pellet (unconditioned stimulus; US) delivery with an inter-trial interval time (ITI) of 60 s. When the animal pressed the lever or inserted the nose into the CS, it was considered a conditioned response (CR), which shortened the duration of the trial; the light into the lever or the nose-poke was turned off, and a US was delivered. The CR increment or decrement was considered an index for enhancement or impairment of memory formation, respectively.

3. Experiments

3.1. Pretraining phase

For all three experiments, following the magazine training there were 2 consecutive training sessions. The magazine training was followed by 10 trials, and two subsequent (1.5 and 24-h later) autoshaping training/testing sessions of 20 trials. Animals showing progressive performance ranging between 20–30% of CRs or more were included.

3.1.1. Lever-press and nose-poke responses

Following the training autoshaping phase there were further training/testing sessions at 1.5-, 24- and 48-h later.

3.2. Pharmacological experiments

For the forgetting and amnesia protocols (Fig. 1) only the nose-poke was used. For both protocols there were three consecutive pretraining autoshaping sessions and then animals were exposed to their respective protocol.

3.2.1. Forgetting protocol

Following pretraining phase, there were four additional training/testing autoshaping sessions (see Fig. 1, upper), the first three sessions (10 and 20 trials, respectively) were used to determine the maximum level of retention and the fourth session (20 trials) for the forgetting, which occurred following the interruption period (216-h later). SB699551 was injected following the third training/testing session and the final autoshaping testing session occurred following the interruption period.

3.2.2. Amnesia protocol

Following magazine pretraining phase (10 and 20 trials, respectively), three further autoshaping sessions (10 and 20 trials, respectively) occurred used to determine short- and long-term memory as well

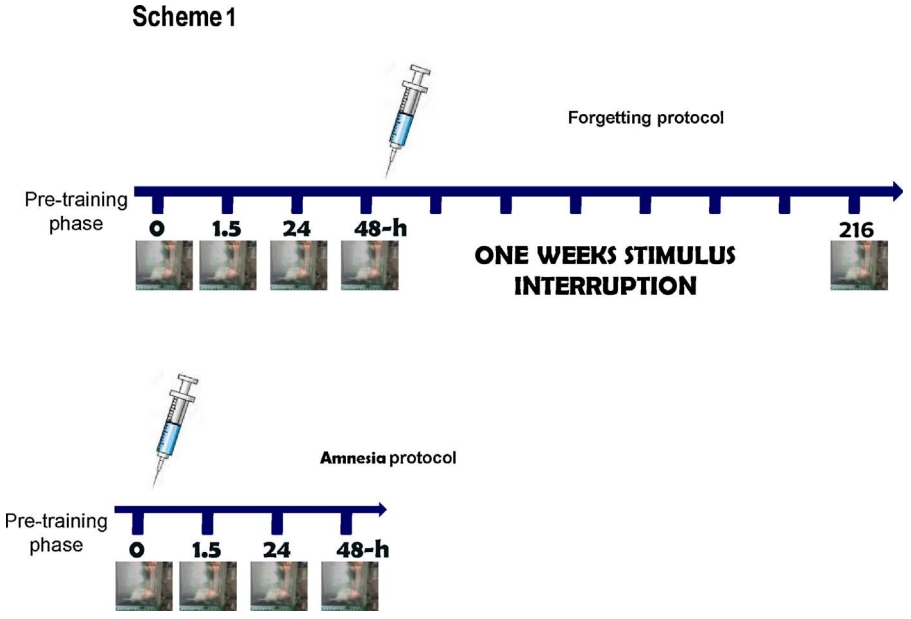

Fig. 1. Scheme representing the forgetting and amnesia protocols.

as amnesia (see Fig. 1, bottom). All compounds were injected immediately following this first training autoshaping session and then the testing sessions were performed 1.5- 24-h later. Animals were given vehicle or SB-6999551 (0.3 mg/kg) immediately after the training autoshaping session and, 10 min later, the animals received dizocilpine (0.2 mg/kg) or scopolamine (0.3 mg/kg) and 1.5- each 24-h later the subsequent testing sessions. It should be noted that both scopolamine and dizocilpine (or MK-801) are well-known amnesic drugs (see [1]; [13])

3.3. Equipment

Operant chambers (Coulbourn Instruments, Lehigh Valley, PA, USA) for rats with standard sound-attenuation were used. Chambers were 25-cm wide, 29-cm long, and 25-cm high. For experiment 1, a retractable and illuminated lever or nose-poke was mounted 4 cm above the floor and 10 cm from the right and left walls, with a 2.54- cm-diameter entrance hole located in the front center panel (conditioned stimulus; CS); in both cases. A food magazine for rat pellets (Bio Serv, Flemington, NJ, USA) was located 5 cm to the right of the lever and 3 cm above the floor. A house light was located in the right top corner. Computer programming equipment was used for control and recording (Coulbourn Instruments, Holliston, MA, USA). For experiments 2–3, only the nose-poke operandum was used.

3.4. Drugs used

All from Tocris: SB-699551 (3-cyclopentyl-*N*-[2-(dimethylamino) thyl]-*N*-[(4{[(2-phenylethyl) amino] methyl}-4-biphenylyl) methyl] propanamide dihydrochloride), scopolamine and dizocilpine (MK-801). Drugs were injected subcutaneously (SC) in a volume of 1 ml/kg. SB-699551 (0.3 mg/kg) was dissolved in dimethylsulfoxide, scopolamine hydrobromide (0.3 mg/kg) cholinergic antagonist and dizocilpine (MK-801; 0.2 mg/kg), a non-competitive antagonist of NMDA receptors were used as amnesics, which were dissolved in saline solution or methylcellulose in a volume of 1 ml/kg.

3.5. Animals assignation, data acquisition and statistical analysis

Animals were randomly assigned to the following protocols: (1) lever-press vs nose-poke experiment; (2) forgetting control vehicle or SB-699551; and (3) amnesia control vehicle, SB-699551, dizocilpine, or scopolamine. As in previous works responses (conditioned responses, CR) in the CS presence were divided by the trials in session, expressed as a percentage of the total trials (Meneses et al., 2015). Student t-test was used for used for retractable lever vs nose-poke experiment (1). For subsequent experiments (2–3) analysis of variance (ANOVA) was used followed by additional post-hoc comparisons and Tukey test. In the case of forgetting protocol, as the levels of retention are different among groups, then the maximum of retention showed at 48-h is transformed in percentage of maximum retention and compared with the respective level showed 216-h later (see 27; 28). In all comparisons, $P < 0.05$ was used as criterion for significance. The n was either 7 (experiment 1) or 8–11 (experiments 2-3) per group, and animals were used only once. Statistical power was calculated using G*Power 3.1.9.2 (15).

4. Results

4.1. Lever-press vs nose-poke responses

One-way analysis of variance showed significant effects [$F(1,5) = 91.26$; $p < 0.0001$) between animals trained and tested with the lever-press vs nose-poke responses in STM (1.5-h) and LTM (either 24- & 48-h; *t*-test depicted significant ($p < 0.05$) changes, showing in STM 7 ± 1 vs 24 ± 2, LTM 12 ± 1 vs 37 ± 2 and LTM 19 ± 2 vs 49 ± 2 of CR trained animals (Fig. 2).

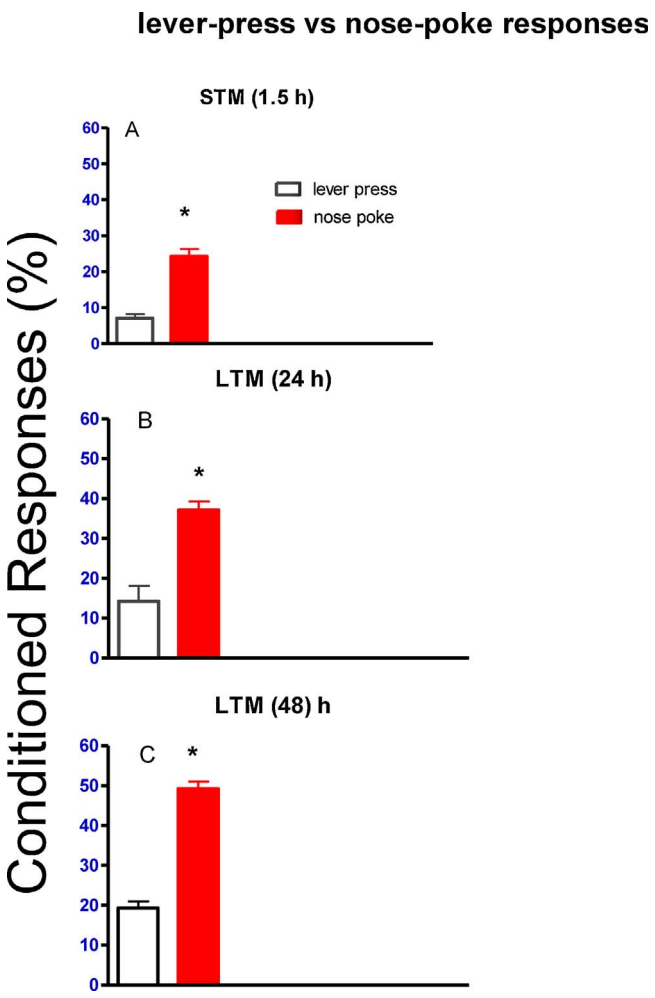

Fig. 2. Comparison between lever-press vs nose-poke conditioned responses (CR ± ES) during short- (STM) and long-term memory (LTM 24- and 48-h) in the autoshaping learning task. The results represent the means ± SEM. ANOVA was followed by Student t-test $p < 0.005$. * Tukey test $p < 0.005$, $n = 7$ animals per group.

4.2. Forgetting protocol

As previously reported (27; 28) control and treated groups shown progressive curves of CR until 48-h. Following drugs administration and 216-h of interruption period, significant [$F(2,1) = 3.5$, $p < 0.036$) differences were observed in treatments and times. Control-saline group significantly ($p < 0.002$] decreased CR (i.e., from 38 ± 6% at 48-h, to 16 ± 6% at 216-h), demonstrating a forgetting effect following one week of interruption of autoshaping training/testing sessions. Moreover, animals treated with SB-699551 showed significant (0.3 mg/kg; $p < 0001$) or slight (3.0 mg/kg; $p < 0.1$) anti-forgetting effect; depicting 114 ± 35% and 82 ± 9% of control-saline group values (Fig. 3).

4.3. Amnesia protocol

Vehicle-control group had 14 ± 4 (STM), 24 ± 4 (LTM 24-h) and 28 ± 4 (LTM 48-h); in contrast, animals treated with dizocilpine (0.2 mg/kg) or scopolamine (0.3) showed significant decrements in CR. Compared to control group dizocilpine significantly (Tukey test $p < 0.05$) decremented CR in STM 4 ± 1% but not in LTM (24- or 48-h) (18 ± 4% or 15 ± 4%; Fig. 4, left). Scopolamine elicited significant (Tukey test $p < 0.05$) changes 3 ± 1% (STM), 14 ± 5% (LTM 24-h) and 37 ± 5% (LTM 48-h) of CR. Those animals treated with SB-699551 (0.3 mg/kg) had significant (Tukey test $p < 0.05$) decrements

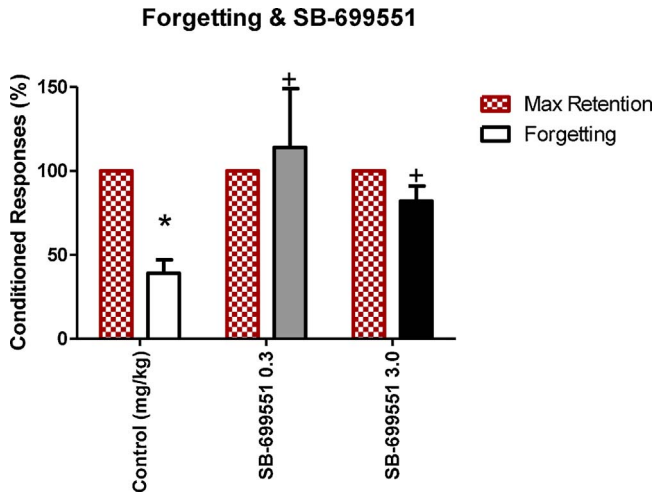

Fig. 3. Groups treated with vehicle SB-699551 in the forgetting protocol (see text) in the autoshaping learning task. Results represent the means ± SEM, were analyzed by Two way ANOVA and * Tukey test $p < 0.005$. n = 9–11 animals per group.

in CR showing 3 ± 2% (STM), 3 ± 2% (LTM 24-h) and 5 ± 3% (LTM 48-h) of CR. Two Way ANOVA of SB-699551-dizocilpine showed significant effects regarding times [$F(2,113) = 8.8$, $p < 0.001$] and treatments [$F(2, 113) = 10.5$, $p < 0.001$]. Similarly SB-699551-scopolamine produced significant effects respect to times [$F(2,86) = 10.4$, $p < 0.001$] and treatments [$F(2,86) = 10.6$, $p < 0.001$]. Co-administration of SB-699551-dizocilpine or SB-699551-scopolamine produced significant (Tukey test, $p < 0.05$) differences compared to SB-699551 alone in LTM (48-h) or STM and LTM (both 24- and 48-h, respectively (Fig. 4).

5. Discussion

The present major results show that relative to lever-press response the nose-poke device increased CR and slightly reduced inter-individual variability (Fig. 2). Moreover, SB-699551 alone produced amnesia-like effect and it reversed forgetting effect (Fig. 3). And co-administration of SB-699551-dizocilpine or SB-699551-scopolamine reversed the SB-699551 induced-amnesic effects in LTM (24-h) or STM and LTM (both 24- and 48-h, respectively (Fig. 4).

Gerhardt and Liebman [2] also reported differential effects in rats

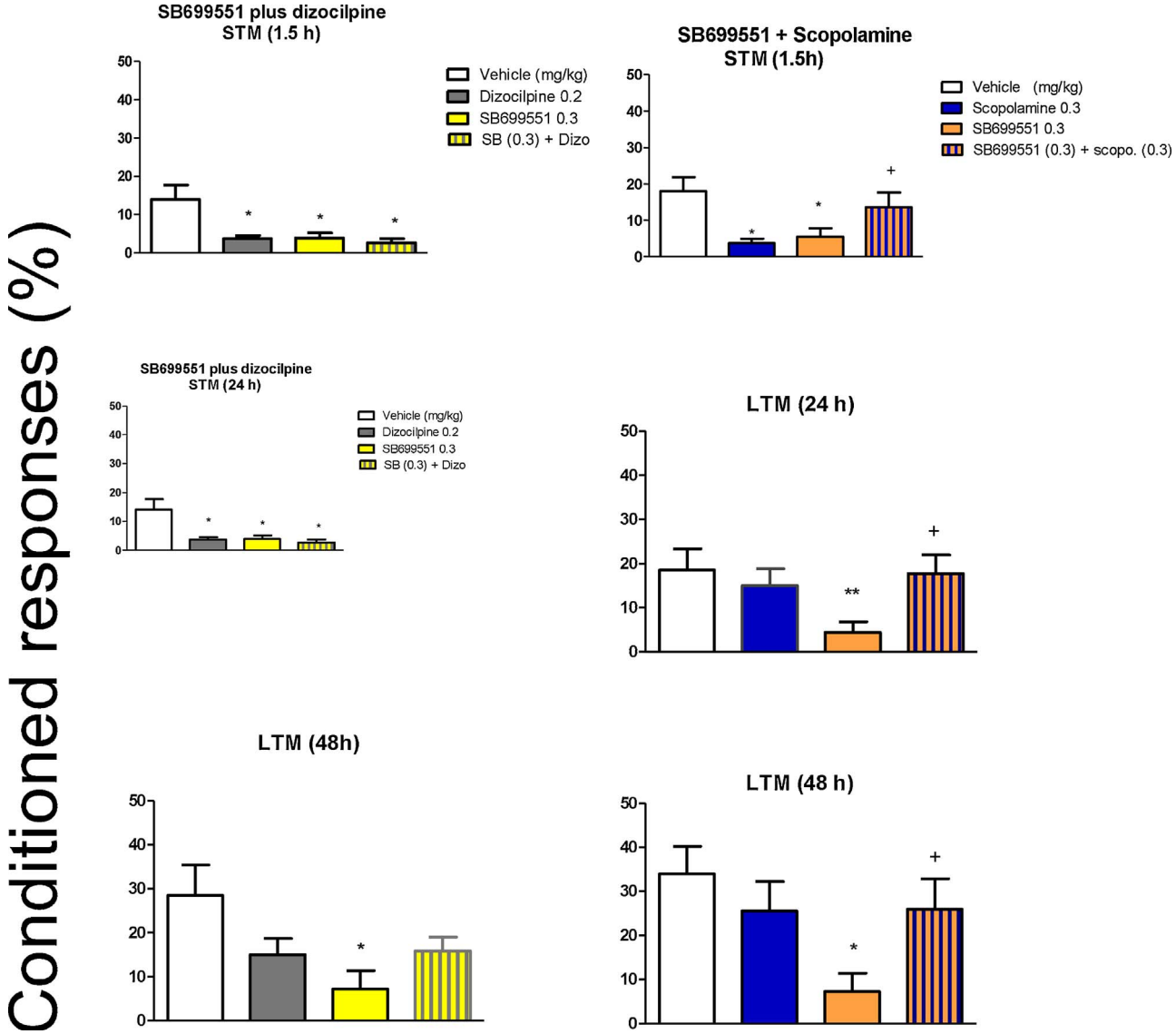

Fig. 4. Groups treated with vehicle and SB-699551 in the amnesia protocol (see text) in the autoshaping learning task. Scopolamine and dizocilpine were used as amnesics and compared with SB-699551. Results represent the means ± SEM and were analyzed by Two way ANOVA followed by Tukey test $p < 0.005$. n = 9–11 animals per group. *control vs treated animals; + SB-699551 alone vs combinations. * Max retention vs interval interruption; + control vs SB-699551.

between nose-poke and bar-press self-stimulation, and suggested that the nose-poke operant appears less vulnerable to drug-induced gross motor impairment and may be more suitable for pharmacological studies of self-stimulation. Moreover, Smith et al. [3] noted that among other results in rats, on a 40-trial midsession reversal, an 80-trial midsession reversal, and a variable-location reversal, the lever-press group acquired the task faster than the nose-poke group, but that both groups reached comparable levels of performance. Also David et al. [12] found no differences between lever-press vs nose-poke operant responding procedures in mice. Notwithstanding the above differences, we should note that while lever-press operandum requires regular adjustments for detecting responses (see e.g., 20), nose-poke responses are, in ethological terms, more compatible with the natural rat behavioral repertoire. In addition, the nose-poke response in transgenic mice allows detecting remarkable preference for the port that triggers optogenetic stimulation of dopamine neurons in ventral tegmental area (VTA) [4]. Even the nose-poke provides a rapid and reliable way for assessing context recognition memory in mice [5].

Moreover, in this work, SB-699551 alone produced amnesia-like effect and it reversed forgetting effect and co-administration of SB-699551-dizocilpine or SB-699551-scopolamine reversed the scopolamine- or SB-699551 induced-amnesic effects in LTM (48-h) or STM and LTM (both 24- and 48-h, respectively. In this connection, Nikiforuk et al. [13] recently reported pro-cognitive efficacy of SB-699551, reversing a delay-induced deficit (i.e., forgetting) in object recognition. SB-699551 was also effective against ketamine-induced social withdrawal, a model of negative-like symptoms of schizophrenia [13]. And these authors (Nikiforuk et al. [13] conclude that the blockade of 5-HT_{5A} receptor may represent a therapeutic approach for age-related dementia or AD and in schizophrenia models. Others also have reported procognitive effects regarding 5-HT_{5A} receptor. For instance, Yamazaki et al. [6] found reported that 5-HT_{5A} receptor antagonists ameliorate scopolamine-induced working memory deficit in mice and reference memory impairment in aged rats.

Although the present findings are consistent with the above anti-amnesic and anti-forgetting effects, we should bear in mind that we are replicating that this 5-HT_{5A} receptor antagonist SB-699551 itself provoked amnesic-like effects in the associative learning task of auto-shaping, showing that post-training injection of SB-699551 impaired (STM; 1.5-h; at 0.1 mg/kg) and LTM (LTM; 24 h; at 3.0 mg/kg) relative to the vehicle animals. Certainly, scopolamine (cholinergic antagonist) and dizocilpine (glutamatergic antagonist) provoked amnesia, and SB-699551 alone produced amnesia-like effect ([7]; this work). Scopolamine and dizocilpine (or MK-801) are well-known amnesic drugs (see e.g., [1]; [13]).

We should note herein that post-training administration of SB-699551 produced a lasting (covering STM and LTM 24- and 48-h) amnesia-like effect, while dizocilpine alone had no effect in LTM (48-h). Notwithstanding, SB-699551-dizocilpine co-administration had significant effect in LTM (48-h), reversing the SB-699551-induced amnesia-like effect. Why? Speculating, probably dizocilpine produced a rebound effect protecting LTM (48-h) against SB-699551 amnesia. Certainly, this is an expected results in the light that SB-699551-scopolamine combination produced greater effects in STM and LTM (both 24- and 48-h), likely reflecting differential interaction among cholinergic, glutamatergic and serotonergic (via 5-HT_{5A} receptor) neurotransmission systems during memory consolidation. This influence might occur both via their primary targets and by indirect interaction either physiological or pharmacological. Firstly, as already mentioned SB-699551 displays affinity for 5-HT_{5A} receptor [8]; secondly, gene expression is strongly influenced by sex hormones in both the frontal cortex and hippocampus, especially Htr5b gene is up-regulated only in male mice [9]; thirdly, we should note that learning and memory might be affected in these mice considering that while both estradiol and testosterone promote memory, the adrenal hormone corticosterone impairs memory (e.g., 18). Hence, 5-HT_5 receptor might be upregulated in the present scopolamine amnesic animals. Thus, 5-HT_5 Cavallaro [10] analyzed deoxyribonucleic acid (DNA) microarrays of hippocampal 5-HT receptors in the behavioral memory tasks of water maze and passive avoidance (for review [11] Cavallaro [10] work showed that apparently, water maze memory requires slight 5-HT_7 receptor expression within 1-h; while, passive avoidance memory involves expression of 5-$HT_{1A\text{-}1F}$, 5-HT_{2A}, and 5-HT_{5A} receptors.

The findings presented in this work showed an anti-amnesic effect of SB 699551, which is in contradiction with the results described by Gonzalez et al [7]. It should bear in mind that though apparently the 5-HT_{5A} receptor antagonist SB-699551 has no affinity for other 5-HT receptors and transporter [8], however in combination with WAY-100635 (selective 5-HT_{1A} receptor antagonist, 0.3 mg/kg, sc) SB-699551 (0.3, 1 or 3 mg/kg, sc) produced a significant increase in extracellular 5-HT levels. We should also note that a similar paradox also was observed regarding 5-HT_{1A} receptor partial agonists (e.g., Meneses, 1999). This kind of compounds (buspirone, tandospirone) produced anti-amnesic effects in schizophrenia-like models. For instance, tandospirone might be useful in the treatment of memory deficits in schizophrenia-like pathophysiology (26) and also has antiamnesic effects or facilitate performance in difficult memory tasks (e.g. 14). Hence 5-HT_{1A} receptor partial agonism is useful in the treatment of dysfunctional memory and hence, the paradoxical effects evidenced in the present work might be, in part related to 5-HT_{1A} and 5-HT_{5A} receptors. Of course, in order to clarify the present and other findings further experiments are necessary. For instance, interaction among multiple 5-HT receptors and other neurotransmission systems (e.g., [11]) is providing new insights. The present evidence indicates that the nose-poke device increased CR and slightly reduced inter-individual variability. On the other hand, SB-699551 itself elicited amnesia-like effect and reversed forgetting effect. SB-699551 plus dizocilpine or -scopolamine reversed the SB-699551-amnesic effect in LTM (48-h) or STM and LTM, respectively

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