Behavioural Brain Research 252 (2013) 246–251

Contents lists available at SciVerse ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Short communication

Role of 5-HT$_{5A}$ receptors in the consolidation of memory

Roberto Gonzalez [a], Karla Chávez-Pascacio [b], Alfredo Meneses [a,*]

[a] Dept Pharmacobiol CINVESTAV-IPN, México City, 14330, México
[b] National School of biological Sciences, Mexico City, Mexico

HIGHLIGHTS

- 5-HT$_5$ receptor occurs in brain areas implicated in learning and memory.
- Blockade of 5-HT$_{5A}$ receptor impaired memory consolidation.
- 5-HT$_{5A}$ receptor stimulation might facilitate it.

ARTICLE INFO

Article history:
Received 1 April 2013
Received in revised form 23 May 2013
Accepted 27 May 2013
Available online 2 June 2013

Keywords:
Autoshaping
5-HT Receptors
Learning rat

ABSTRACT

5-HT$_5$ receptor occurs in brain areas implicated in learning and memory. Hence, the effects (0.01–3.0 mg/kg) of SB-6995516 (a 5-HT$_{5A}$ receptor antagonist) in the associative learning task of autoshaping were studied. The results showed that post-training injection of SB-699551 decreased conditioned responses (CR) during short-term (STM; 1.5 h; at 0.1 mg/kg) and long-term memory (LTM; 24 h; at 3.0 mg/kg) relative to the vehicle animals. Moreover, considering that there are no selective 5-HT$_{5A}$ receptor agonists, next, diverse doses of the serotonin precursor l-tryptophan were studied during STM and LTM, showing that l-tryptophan (5–100 mg/kg) facilitated performance, particularly at 50 mg/kg. In interactions experiments, l-tryptophan (50 mg/kg) attenuated the impairment effect induced by SB-699551 (either 0.3 or 3.0 mg/kg). All together this evidence suggests that the blockade of 5-HT$_{5A}$ receptor appear to be able to impair STM and LTM (24 h), while its stimulation might facilitate it. Of course further investigation is necessary, meanly with selective 5-HT$_{5A}$ compounds are necessary.

1. Introduction

Using receptor binding profiles, common secondary messenger coupling and functional activity ligands, seven families of 5-hydroxytryptamine receptors (5-HT$_1$ to 5-HT$_7$) have been identified [1]. And the investigation of 5-HT systems has been benefited from the identification, classification and cloning of multiple receptors for this monoamine [2]. For instance, the administration of 5-HT drugs with diverse mode of action has been used to study the basic mechanisms of learning and memory under physiological and pathophysiological conditions (e.g., pharmacological models of amnesia), aimed them as therapeutic treatments for cognitive dysfunctions (see, Meneses 1999, 2003 for a review).

Hence, it is not a surprise that growing evidence indicates that 5-HT systems are involved in the mechanisms of physiological, pathophysiological and/or therapeutic aspects of cognitive processes (see e.g., [3]; Meneses, 2003; [2]; [4]) and diverse 5-HT mechanisms could useful in the treatment of learning and memory dysfunctions (Meneses, 1999; [2]). In spite this encourage information, it is not clear what role some 5-HT systems play in cognitive processes [2]. For instance, in the case of 5-HT$_5$ receptor occurs in hippocampus, cerebral cortex, amyloid nuclei and raphe nuclei [5,6], brain areas involved in learning and memory processes (e.g., [7,8]). The 5-HT$_5$ receptor class is 1 of 7 major subtypes of 5-HT receptor [6]. Two 5-HT$_5$ receptor subtypes, 5-HT$_{5A}$ and 5-HT$_{5B}$, have been identified in both mouse (for review [6]; Volk, 2010). The 5-HT$_{5A}$ receptor has also recently been cloned from guinea pig [27], but It has not yet been established whether the 5-HT$_{5B}$ receptor is functionally expressed in the guinea pig, as in mouse and rat, or, is a pseudogene, as in human [6].

According with Thomas [6], findings from 5-ht$_{5A}$ receptor mRNA localization and immunolabelling studies have revealed widespread expression in the CNS, and have provided pointers to the potential functional role(s) of the receptor. The expression of the 5-ht5A receptor in raphe nuclei and in other brain areas, such as the cerebral cortex and hippocampus, suggests a potential autoreceptor function. This information provides further support to the contention that: (1) 5-HT pathways and receptors show a regional distribution in brain areas implicated in learning and memory, and (2) significant changes occur in brain 5-HT systems functions

* Corresponding author. Tel.: +52 55 54832869; fax: +52 55 54832863.
E-mail address: ameneses@msn.com (A. Meneses).

0166-4328/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.bbr.2013.05.051

as results of aging, memory formation, amnesia and effects anti-amnesic (for review see Meneses, 2003; [4]).

Certainly, the 5-HT_5 receptor might play an inhibitory role (see review [6]), inasmuch as 5-HT currents were suppressed by the 5-HT_{5A} antagonist [9], SB-699551, and these findings were not observed in 5-HT_{5A} receptor knock-out mice [10]. Goodfellow et al. observed that genetic deletion of the inhibitory 5-HT_{5A} receptor results in an unexpected, large increase in the inhibitory 5-HT_{1A} receptor currents. According with these same authors, the presence of functional prefrontal 5-HT_{5A} receptors in normal rodents along with compensatory plasticity in 5-HT_{5A} receptor knock-out mice testifies to the significance of this receptor in the healthy prefrontal cortex [10]. Prefrontal cortex, among others brain areas, is important for memory function and forgetting (e.g., [11]). Hence, the role of 5-HT_{5A} receptors in memory formation was investigated, by testing the effects of the selective 5-HT_5 receptor antagonist SB-69955 (3-cyclopentyl-N-[2-(dimethylamino) ethyl]-N-[(4′-{[(2-phenylethyl) amino] methyl}-4-biphenylyl) methyl] propanamide dihydrochloride) [9] in an autoshaping associative learning task. Autoshaping task produces modest changes on learning and memory performance; however, it had been useful to study the effects of diverse selective 5-HT agonist and antagonist and drugs for other neurotransmitter systems (Meneses, 2003, [11,12,29]). Importantly similar results had been reported in other behavioral tasks (see e.g., [13]).

Then, the effects of SB-699551 (0.3–3.0) mg/kg) were studied during short- (STM) and long-term memory (LTM; [11]). The doses used were based in Thomas et al. [9], which produced a significant increase in extracellular 5-HT levels. And as both STM and LTM recruit different behavioral, neural and cognitive demand (Tellez et al., 2010); hence, these cognitive processes were selected. Next, diverse doses (5–100 mg/kg) of the serotonin precursor (see e.g., [14]), l-tryptophan were also studied during STM and LTM. While, l-tryptophan depletion had been implicated in memory deficits (see e.g., [15]), l-tryptophan administration had depicted benefic effects on learning and memory consolidation (see e.g., Haider et al., 2007) even in humans (see [16]). As there are no available selective 5-HT_5 receptor agonists, as mentioned above the serotonin precursor l-tryptophan might be useful for the stimulation of 5-HT_5 receptor. Hence, l-tryptophan (50 mg/kg) plus SB-699551 (0.1 or 3.0 mg/kg) were tested.

An autoshaping learning task combines the action of classical and instrumental conditionings, modeling behavioral situations requiring integration of information derived from sign- and goal- tracking settings (Meneses and Pérez-García, 2007; [17]). Autoshaping tasks (Pavlovian or instrumental; see e.g. [18], Stahl et al., 2010 and Pavlovian/instrumental [12]) produce variable and/or initial modest levels of conditioned response (CR). However, memory formation in Pavlovian/instrumental is accompanied by neural markers, including serotonin, glutamate, dopamine and GABA transporters expression [11], 5-HT receptors expression and cAMP production (see for references [2]). Notably, similar results of those reported in an autoshaping had been found in other behavioral tasks (e.g., Carli et al., 2001; see also [12] for further references); as well as neurobiological changes (e.g., [19]; [20]; Marcos et al., 2008).

2. Subjects

Male Wistar rats (12 weeks-old) were collectively housed in a temperature and light–controlled room under a 12:12 h light:dark cycle (light beginning at 7:00 A.M.) with water and food provided ad libitum for a week. After that period, their body weights (ad libitum) were reduced to 85% by gradually decreasing the food intake during seven days. All experiments were performed in accordance with the 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).

3. Experimental protocol

3.1. Apparatus

Autoshaping task STM and LTM protocols have been previously described [12,21,22]. In short, the autoshaping learning task apparatus (Coulbourn Instruments, LehighValley, PA) included a standard attenuation system, with the following inner dimensions: 25 cm × 29 cm × 25 cm (width × length × height) and consisted of a metal frame and transparent Perspex and aluminum walls and a bars floor. A computer program (Coulbourn Instruments) was used for control and recording. An acrylic retractable lever was mounted 4 cm above the floor and 10 cm from the right and left walls. The lever micro-switch was adjusted to require 8.4 g force for operation. A food magazine for rat pellets was located 5 cm to the right of the lever and 3 cm above the floor. A photocell was mounted with the food magazine to measure head-pokes during the presence of conditioned stimulus (CS) and was defined as head-pokes/CS [11]. A house light was located in the right top corner and maintained being turned on during session period.

3.2. Food-magazine training

For habituation period (circa 5 min) each rat was placed in an experimental chamber and had access to 50 food-pellets (45 mg each previously place into the food-magazine); once the animal presented 150 head-pokes (measured by a photocell into the food-magazine), the autoshaping program was initiated.

3.3. Autoshaping Training

Each rat was placed in an experimental chamber and allowed to habituate to the experimental environment until the animal found and ate 50 food pellets (45 mg each pellet) and presented 150 head-pokes into the food-magazine. Immediately afterwards, the program began. This consisted in the presentation of an illuminated and retractable lever for 8 sec (conditioned stimulus, CS), followed by the delivery of a food pellet (unconditioned stimulus, US) every 60 s. When the animal pressed the CS, the lever was retracted, the light was turned off, and a food pellet (US) was delivered immediately; this was considered a conditioned response (CR). As previously [11,12] reported, the increment or decrement in percentage of CR was considered as an enhancement or impairment in memory, respectively. The first session consisted of 10 trials and the subsequent sessions of 20. All compounds were injected immediately after the first autoshaping session (protocol of STM and LTM); then, the trial was repeated (1.5, 24 and 48 h) later.

3.4. STM and LTM

Immediately after the first autoshaping training/testing session, the animals received vehicle (DSM or saline), SB-699551 or l-tryptophan. They were then placed in their home cages until the autoshaping training/testing sessions were performed 1.5, 24 and 48 h later.

3.5. Interaction experiments

3.5.1. 5-HT_{5A} receptor and l-tryptophan

Other animals were given SB-699551 immediately after the autoshaping training/testing session and 5 min after that they

received l-tryptophan. After 1.5, 24 and 48 h, the training/testing sessions were performed.

The drugs used in the present study were: SB-69955 (3-cyclopentyl-N-[2-(dimethylamino) ethyl]-N-[(4′-{[(2-phenylethyl) amino] methyl}-4-biphenylyl) methyl] propanamide dihydrochloride) (Tocris) and l-tryptophan (Sigma). All drugs were injected subcutaneously (SC) in a volume of 1 ml/kg. SB-699551 was dissolved in dimethylsulfoxide or l-tryptophan in physiological saline.

3.5.2. Statistics

Multiple group comparisons were made using a one way ANOVA followed by Tukey test, comparing memory control vs. SB-699551 or l-tryptophan treatments and the combination of them during STM, LTM (24 h) and LTM 48 h). The total head-pokes and head-pokes during the CS were computed by means of statistical ANOVA, post hoc Tukey test (data no shown). Behavioral measures had normal distribution and equal variance [11]. In all statistical comparisons, $p < 0.05$ was used as criterion for significance. The n per group was 8 and the same animals were used for STM and LTM.

4. Results

4.1. SB-699551 and l-tryptophan

The percentage of CR in the saline groups during the autoshaping STM and LTM testing sessions (Figs. 1 and 2) varied according to the doses of SB-699551 and l-tryptophan as well as times (STM, LTM 24 and LTM 48 h), showing the following values: (STM 1.5 h) 15 ± 3, 6 ± 2, 4 ± 3, 5 ± 3 and 9 ± 3; LTM (24 h) 13 ± 3, 7 ± 2, 4 ± 2, 5 ± 2, 6 ± 2, 6 ± 2 and LTM (48 h) 12 ± 4, 6 ± 3, 7 ± 4, 8 ± 4 and 8 ± 2 of CR; respectively. The vehicle animals had a progressive performance and significantly higher %CR [$F(4,39) = 3.1$; $P < 0.05$]; [$F(4,39) = 3.5$; $p < 0.05$] and [$F(4,39) = 4.1$; $p < 0.05$] than that those groups treated with SB-699551. Tukey test revealed that respect to control animals SB-699551 at 0.3 mg/kg significantly decreased %CR during STM and LTM (24 h); while at 1.0 and 3.0 mg/kg significantly decreased performance during LTM (24 h) (Fig. 1). It should be noted that the free-operant level of CR is around 0.6 ± 0.2 to zero and/or spontaneous lever-pressing responses in naïve rats are almost zero (for references see [12]).

4.2. L-Tryptophan and STM-LTM

As depicted in Fig. 2, the post-training injection of l-tryptophan produced significant effects during STM [$F(4,39) = 3.9$; $P < 0.05$], both LTM (24 and 48 h) [$F(4,39) = 3.6.$; $P < 0.05$] and [$F(4,39) = 3.7$; $P < 0.05$] relative to the control animals; Tukey test showed significant effects of l-tryptophan at 50 mg/kg, which increased %CR relative to control group.

4.3. Interaction experiments

4.3.1. L-tryptophan plus SB-699551

The impairment-effect on %CR induced by SB-699551 (at 0.3 or 3.0 mg/kg) during STM and LTM (24 h) or only LTM (24 h) was significantly [$F(4,39) = 4.3$; $P < 0.05$] or [$F(4,39) = 4.0$; $P < 0.05$] attenuated by L-tryptophan (50 mg/kg) (Table 1), Tukey test revealed not significant differences respect to control group or regarding control and SB-699551 alone.

5. Discussion

The main results showed that post-training injection of SB-699551 at 0.3 decreased performance during STM (1.5 h and LTM (24 h) or at 1.0 and 3.0 mg/kg impaired LTM (24 h) relative to the vehicle animals. L-Tryptophan (50.0 mg/kg) facilitated performance; and in the interactions experiments, it attenuated the impairment effect induced by SB-699551 (either 0.1 or 3.0 mg/kg). Why, these doses of SB-699551 or l-tryptophan selectively altered specific phases of memory? We should keep in that mind that many agents have 'inverted U' dose–response curves in behavioral and mechanistic procedures of memory tasks, thus biphasic dose–response curves imply a 'set point' for optimal (or worst) performance, such that under- or overactivation of the drug target has a deleterious (or improvement) effect [23]. In addition, pharmacological manipulation of 5-HT systems [21] evidenced serial and parallel function between STM and LTM. For instance, the '5-HT tone via 5-HT_{1B} receptors' function in a serial manner from STM to LTM, whereas working in parallel using 5-HT_{1A}, 5-HT_{2A}, 5-$HT_{2B/2C}$, 5-HT_4, or 5-HT_6 receptors [22]. Hence, we might assume that the function of 5-HT_{5A} receptor (as antagonized by SB-699551) during STM and LTM is parallel and serial; which was dependent of the dose; while l-tryptophan (at 50.0 mg/kg) allowed STM and LTM (24 h) functioned in serial manner. Thus, l-tryptophan attenuated the SB-induced impairment effect in both STM and LTM. Of course, future studies should clarify issues like e.g., why l-tryptophan at 100 mg/kg had no effects? Part of the answer might be the above mentioned by Millan et al. [23]. Moreover, systematic studies of other drugs stimulating 5-HT receptors revealed that except for DOI (agonist for 5-$HT2_{A/2C}$ receptors) dose-dependently impaired STM and, at 10.0 mg/kg only impaired LTM; other 5-HT receptor agonists did not (e.g., dual 5-$HT_{1A/7}$ receptor, 5-HT_{1B}, 5-HT_3, 5-HT_4, and 5-HT_7) [21].

It should be noted that inasmuch as that SB-699551 at the dose of 0.1 or 3 mg/kg has not effect on LTM (48 h), then how explaining the decrease of the beneficial effect of L-tryptophan (50 mg/kg) (∞ 20% of CR, Fig. 2) on LTM memory (48 h) when it was administered with SB-699551 at the dose of 3.0 mg/kg ($CR = 9 \pm 2\%$)? An alternative is that at this time and l-tryptophan dose might be stimulating not only 5-HT_{5A} receptor but also others whose stimulation impaired LTM (e.g., 5-HT_3 receptor) [21]. It is not possible to exclude the interaction of other neurotransmission systems and convergent cell signaling.

5.1. Autoshaping task

Taking advantage of the fact that the 5-HT systems count with a wide variety of drugs, displaying multiple modes of action (e.g. agonists, antagonists, depleters, etc.), in a set series of experiments we have been studying the modulatory effects induced by 5-HT drugs and other neurotransmitter systems on learning and memory consolidation in the autoshaping learning task (see [12] for further details).

Certainly, considering the modest and variable response in autoshaping tasks, new instruments aiming to measure CR in mice [18] and reducing its variability in pigeons (e.g., [24]) or mice and rats [25] had been reported. Herein the reduction (8.4 g) of the force required for the lever-press response, show a progressive performance in control animals (see also [11]). Notably, this same situation was present in control saline and treated animals, notwithstanding differential drugs effects were detected in the latter. This conclusion is supported by the behavioral parameters of saline and treated groups [11]. In contrast, for instance, Papachristos and Gallistel [26] using mice, head-poke responses and feeding stations, reported that in autoshaping experiments, the acquisition of anticipatory head poking in individual mice. In most mice, upward changes in the amount of anticipatory poking per trial were abrupt, and tended to occur at session boundaries, suggesting that the session is as significant a unit of experience as the trial. There were large individual differences in the latency to the onset of

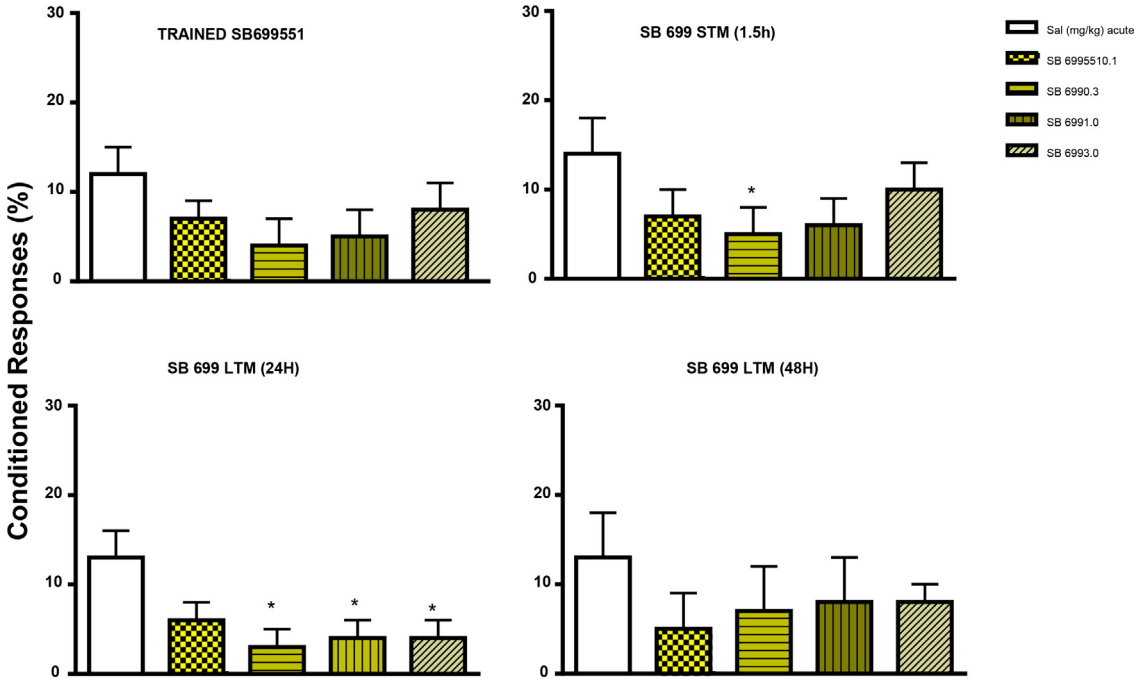

Fig. 1. The effects of post–training sc administration of SB-699551 on the autoshaping task in fasted animals. Data are plotted as percentage of conditioned responses (CR%). Values represent the mean "S.E.M. of 8 different animals. *Tukey test, $p < 0.05$ vs vehicle–treated rats.

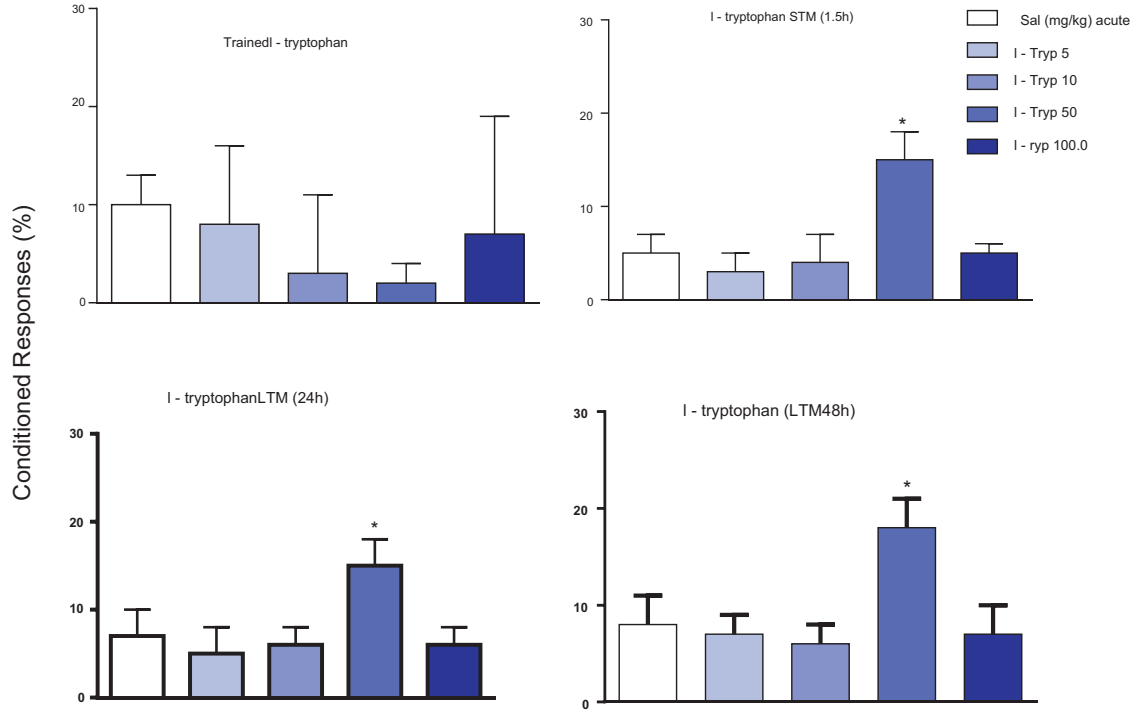

Fig. 2. The effects of post–training sc. administration of SB-699551 plus l-tryptophan in fasted animals. Data are plotted as percentage of conditioned responses (CR%). Values represent the mean "S.E.M. of 8 different animals. *Tukey test, $p < 0.05$ vs vehicle–treated rats.

Table 1
Effects of SB-699551 (0.1 or 3.0 mg/kg) plus L-tryptophan (50.0 mg/kg on the percentage of conditioned response (CR) (mean ± SE) in the autoshaping learning test.

Treatment (Dose: mg/kg)	Training	STM (1.5 h)	LTM (24 h)	LTM (48 h)
Control	4 ± 2	10 ± 2	10 ± 3	10 ± 3
SB-699551 (0.3)	3 ± 2	4 ± 2*	6 ± 3	12 ± 6
SB-699551 (3.0)	4 ± 2	8 ± 3	4 ± 2*	9 ± 2
l-tryptophan (50) + SB-699551 (0.3)	3 ± 2	10 ± 3*+	8 ± 3	27 ± 6*+
l-tryptophan (50) + SB-699551 (3.0)	4 ± 2	8 ± 3	8 ± 2*+	9 ± 2

*Values are significantly different from the respective control (vehicle) or +SB.699551 alone (<0.05, Tukey test).

vigorous responding. "Asymptotic" performance was unstable; large, bidirectional, and relatively enduring changes were common [26], concluding that given the characteristics of the individual learning curves, it is unlikely that physiologically meaningful estimates of rate of learning can be extracted from group-average learning curves [26]. Importantly, methodological differences exist respect to other authors using autoshaping and the present and other works [11], including food-magazine training, behavioral response, operandum device, extent of training/testing sessions and species used.

5.2. 5-HT systems and memory

Considering that other serotonin receptors have been widely studied in recent decades (especially 5-HT_{1A}, 5-HT_4, 5-HT_6 and 5-HT_7), and their putative roles in memory have been demonstrated. Then what is the value of studying another subtype of serotonin receptors such as 5-HT_{5A} receptors? Even more, why a neurotransmission system requires multiple receptors? Firstly, growing evidence indicates that multiple receptors, is common feature among neurotransmission systems. Secondly, the study multiple receptors (in this case in memory) had produced new insights about functions, cell signaling associated and therapeutic applications. Thirdly, the identification of new receptors had provided renewed impulses, allowing new insights and novel developments. Certainly as memory alterations is not only about amnesia and/or forgetting, e.g., post traumatic stress disorder (see e.g., Millan et al. 2012); then determining the effects of drugs in different phases of memory and/or diverse neurotransmission systems is crucial.

5.3. 5-HT_5 receptor and memory

How explaining the few studies evaluating the involvement of 5-HT_5 receptors, even though selective antagonist for this receptor are available for about a decade? Volk et al. [27] suggested that since the 5-HT_{5B} receptor is not expressed in humans, no serious efforts have been undertaken to develop selective ligands for this receptor subtype. In addition, serotonergic systems in memory investigation remained little explored in the first years of 1990s in spite of availability multiple pharmacological tools; however, at the present growing number of publications have being published. For instance, 5-HT_6 and 5-HT_7 receptors represent a growing scientific interest.

Hence, it seems timely to highlight that the present data are consistent with the notion that 5-HT_{5A} receptor might have a role in memory [27]. 5-HT_5 receptor might play an inhibitory role (see review [6]; Goodfellows et al., 2012). Inasmuch as genetic deletion of the inhibitory 5-HT_{5A} receptor results in an unexpected, large increase in the inhibitory 5-HT_{1A} receptor currents Goodfellow et al. [10], suggesting that the presence of functional prefrontal 5-HT_{5A} receptors in normal rodents along with compensatory plasticity in 5-HT_{5A} receptor knock-out mice testifies to the significance of this receptor in the healthy prefrontal cortex [10]. Of course, herein we used systemic administration and considering that prefrontal cortex, among others brain areas, are important for memory function and forgetting (e.g., [11]). Hence, intracerebral administration of SB-699551 might reveal important insights about the function of 5-HT_{5A} receptor for memory and other functions. Even within this context, the finding that SB699551-l-tryptophan combination revealed the functional importance of this receptor.

Thus, with the classification of multiple 5-HT receptors [1], it has been become clear that the stimulation or blockade of 5-HT receptors modulate memory formation (e.g., Terry et al., 2008; 2011). It should be noted that Curtin et al [30] recently reported that 5-HT_{5A} regulates cell excitability by modulation of a membrane conductance in the goldenfish, which in turn influences the magnitude of sensorimotor gating and prepulse inhibition. In consequence, it is not surprise that the 5-HT_5 receptor blockade affected STM and LTM (24 h). As already mentioned, 5-HT_5 receptor occurs in hippocampus, cerebral cortex, amyloid nuclei and raphe nuclei [5,6], brain areas involved in learning and memory processes (e.g., [7,8]). This information provides further support to the contention that: I) 5-HT pathways and receptors show a regional distribution in brain areas implicated in learning and memory, 2) significant changes occur in brain 5-HT systems functions as results of AD, aging, memory formation, amnesia and effects anti-amnesic (for review see [17]) and 3) 5-HT compounds modulate memory formation; in the present context, SB-699551 impaired STM and LTM. Inasmuch as this compound displays affinity for 5-HT_{5A} receptor [9], blockade of this receptor impaired these cognitive processes and as l-tryptophan attenuated this SB-699551 effect; hence, then a serotonergic mechanism is implicated. An interesting and heuristic possibility it is the investigation of 5-HT_{5A} receptor agonists.

Concluding, the role of 5-HT_{5A} receptor in cognitive processes might be critical. Of course, it remains to be determined many other aspects. For instance, further studies with selective 5-HT_5 receptor agonists and other antagonists and using other behavioral tasks are needed.

References

[1] Hannon J, Hoyer D. Molecular biology of 5-HT receptors. Behav Brain Res 2008;195(1):198–213.
[2] Meneses A, Liy-Salmeron G. Serotonin and emotion, learning and memory. Rev Neurosci 2012;23(5–6):543–53.
[3] Lesch KP, Waider J. Serotonin in the modulation of neural plasticity and networks: implications for neurodevelopmental disorders. Neuron 2012;76(1):175–91.
[4] Rodríguez JJ, Noristani HN, Verkhratsky A. The serotonergic system in ageing and Alzheimer's disease. Prog Neurobiol 2012;99(1):15–41.
[5] Kassai F, Schlumberger C, Kedves R, Pietraszek M, Jatzke C, Lendvai B, Gyertyán I, Danysz W. Effect of 5-HT5A antagonists in animal models of schizophrenia, anxiety and depression. Behav Pharmacol 2012;23(4):397–406.
[6] Thomas DR. 5-ht_{5A} receptors as a therapeutic target. Pharmacol Ther 2006;111(3):707–14.
[7] Hampel H, Prvulovic D, Teipel SJ, Bokde AL. Recent developments of functional magnetic resonance imaging research for drug development in Alzheimer's disease. Prog Neurobiol 2011;95(4):570–8.
[8] Molinuevo JL, Sánchez-Valle R, Lladó A, Fortea J, Bartrés-Faz D, Rami L. Identifying earlier Alzheimer's disease: insights from the preclinical and prodromal phases. Neurodegener Dis 2012;10(1-4):158–60.
[9] Thomas DR, Soffin EM, Roberts C, Kew JN, de la Flor RM, Dawson LA, Fry VA, Coggon SA, Faedo S, Hayes PD, Corbett DF, Davies CH, Hagan JJ. SB-699551-A (3-cyclopentyl-N-[2-(dimethylamino)ethyl]-N-[(4'-{[(2-phenylethyl)amino]methyl}-4-biphenylyl)methyl]propanamide dihydrochloride), a novel 5-ht_{5A} receptor-selective antagonist, enhances 5-HT neuronal function: evidence for an autoreceptor role for the 5-ht5A receptor in guinea pig brain. Neuropharmacology 2006;51(3):566–77.
[10] Goodfellow NM, Bailey CD, Lambe EK. The native serotonin 5-HT_{5A} receptor: electrophysiological characterization in rodent cortex and 5-HT_{1A}-mediated compensatory plasticity in the knock-out mouse. J Neurosci 2012;32(17):5804–9.
[11] Tellez R, Gómez-Viquez L, Liy-Salmeron G, Meneses A. GABA, glutamate, dopamine and serotonin transporters expression on forgetting. Neurobiol Learn Mem 2012;98(1):66–77.
[12] Meneses A, Perez-Garcia G, Liy-Salmeron G, Ponce-Lopez T, Tellez R, Flores-Galvez D. Associative learning, memory and serotonin: a neurobiological pharmacological analysis. In: Rocha Arrieta LL, Granados-Soto V, editors. Models of Neuropharmacology. Trivandrum: Transworld Research Network; 2009. p. 169–82, 978-81-7895-383-0.
[13] Zhang G, Ásgeirsdóttir HN, Cohen SJ, Munchow AH, Barrera MP, Stackman Jr RW. Stimulation of serotonin 2A receptors facilitates consolidation and extinction of fear memory in C57BL/6J mice. Neuropharmacology 2013;64(January):403–13, http://dx.doi.org/10.1016/j.neuropharm.2012.06.007. Epub 2012 Jun 18.
[14] Riedel WJ, Sobczak S, Schmitt JA. Tryptophan modulation and cognition. Adv Exp Med Biol 2003;527:207–13.
[15] Mendelsohn D, Riedel WJ, Sambeth A. Effects of acute tryptophan depletion on memory, attention and executive functions: a systematic review. Neurosci Biobehav Rev 2009;33(6):926–52.
[16] Harrison BJ, Olver JS, Norman TR, Burrows GD, Wesnes KA, Nathan PJ. Selective effects of acute serotonin and catecholamine depletion on memory in healthy women. J Psychopharmacol 2004;18(1):32–40.

[17] Meneses A, Perez-Garcia G, Ponce-Lopez T, Castillo C. 5-HT_6 receptor memory and amnesia: behavioral pharmacology–learning and memory processes. Int Rev Neurobiol 2011;96:27–47.
[18] Tomie A, Lincks M, Nadarajah SD, Pohorecky LA, Yu L. Pairings of lever and food induce Pavlovian conditioned approach of sign-tracking and goal-tracking in C57BL/6 mice. Behav Brain Res 2012;226(2):571–8.
[19] de Silva Costa-Aze V, Quiedeville A, Boulouard M, Dauphin F. 5-HT_6 receptor blockade differentially affects scopolamine-induced deficits of working memory, recognition memory and aversive learning in mice. Psychopharmacology (Berl) 2012;222(1):99–115.
[20] Haahr ME, Fisher P, Holst K, Madsen K, Jensen CG, Marner L, Lehel S, Baaré W, Knudsen G, Hasselbalch S. The 5-HT4 receptor levels in hippocampus correlates inversely with memory test performance in humans. Hum Brain Mapp 2012;(June), http://dx.doi.org/10.1002/hbm.22123 [Epub ahead of print].
[21] Meneses A. Stimulation of 5-HT_{1A}, 5-HT_{1B}, 5-$HT_{2A/2C}$, 5-HT_3 and 5-HT_4 receptors or 5-HT uptake inhibition: short- and long-term memory. Behav Brain Res 2007;184(1):81–90.
[22] Meneses A. Do serotonin(1-7) receptors modulate short and long-term memory? Neurobiol Learn Mem 2007;87(4):561–72.
[23] Millan MJ, Agid Y, Brüne M, Bullmore ET, Carter CS, Clayton NS, Connor R, Davis S, Deakin B, DeRubeis RJ, Dubois B, Geyer MA, Goodwin GM, Gorwood P, Jay TM, Joëls M, Mansuy IM, Meyer-Lindenberg A, Murphy D, Rolls E, Saletu B, Spedding M, Sweeney J, Whittington M, Young LJ. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. Nat Rev Drug Discov 2012;11(2):141–68.
[24] Stahlman WD, Young ME, Blaisdell AP. Response variability in pigeons in a Pavlovian task. Learn Behav 2010 May;38(2):111–8.
[25] Bussey TJ, Holmes A, Lyon L, Mar AC, McAllister KA, Nithianantharajah J, Oomen CA, Saksida LM. New translational assays for preclinical modelling of cognition in schizophrenia: the touchscreen testing method for mice and rats. Neuropharmacology 2012;62(3):1191–203.
[26] Papachristos EB, Gallistel CR. Autoshaped head poking in the mouse: a quantitative analysis of the learning curve. J Exp Anal Behav 2006;85(3):293–308.
[27] Volk B, Nagy BJ, Vas S, Kostyalik D, Simig G, Bagdy G. Medicinal chemistry of 5-HT_{5A} receptor ligands: a receptor subtype with unique therapeutical potential. Curr Top Med Chem 2010;10(5):554–78.
[28] Terry Jr AV, Callahan PM, Hall B, Webster SJ. Alzheimer's disease and age-related memory decline (preclinical). Pharmacol Biochem Behav 2011 Aug;99(2):190–210.
[29] Vanover KE, Barrett JE. An automated learning and memory model in mice: pharmacological and behavioral evaluation of an autoshaped responses. Behav Pharmacol 1998;9:273–83.
[30] Curtin PCP, Medan V, Neumeister H, Bronson DR, Preuss T. The 5-HT_{5A} receptor regulates excitability in the auditory startle circuit: functional implications for sensorimotor gating. J Neurosci 2013;33(24):10011–20.