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.

© 2013 Elsevier B.V. All rights reserved.

## 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

Download English Version:

https://daneshyari.com/en/article/4312640

Download Persian Version:

https://daneshyari.com/article/4312640

Daneshyari.com