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Research report

Serotonergic modulation of septo-hippocampal and septo-mammillary theta activity during spatial learning, in the rat

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HIGHLIGHTS

- Septal serotonin depletion (5HT-D) facilitates the acquisition of spatial learning.
- 5HT-D increases the hippocampal theta frequency during the spatial learning.
- 5HT-D results in higher septo-hippocampal theta coherence during the learning.
- 5HT-D results in higher septo-mammillary theta coherence during the learning.
- Serotonin, acting on the medial septum, modulates hippocampal theta activity and spatial learning.

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ABSTRACT

Theta activity has been related to the processing of spatial information and the formation of hippocampus-dependent memory. The medial septum (MS) plays an important role in the control and coordination of theta activity, as well as in the modulation of learning. It has been established that increased serotonergic activity may desynchronize theta activity, while reduced serotonergic activity produces continuous and persistent theta activity in the hippocampus. We investigate whether serotonin acting on the medial septum could modify spatial learning and the functional relationship between septo-hippocampal and septo-mammillary theta activity. The serotonin was depleted (5HT-D) from the medial septum by the injection of 5,7 DHT (5,7- dihydroxytryptamine). Theta activity was recorded in the dorsal hippocampus, MS and mammillary nuclei (SUM, MM) of Sprague-Dawley male rats during spatial learning in the Morris water maze. Spatial learning was facilitated, and the frequency of the hippocampal theta activity during the first days of training increased (to 8.5 Hz) in the 5HT-D group, unlike the vehicle group. Additionally, the coherence between the MS-hippocampus and the MS-mammillary nuclei was higher during the second day of the test compared to the vehicle group. We demonstrated that septal serotonin depletion facilitates the acquisition of spatial information in association with a higher functional coupling of the medial septum with the hippocampus and mammillary nuclei. Serotonin, acting in the medial septum, modulates hippocampal theta activity and spatial learning.

1. Introduction

Hippocampal theta activity is a regular electroencephalographic oscillation from 4 to 12 Hz that can also be recorded in other mesencephalic and diencepahlic structures that are part of the ascending synchronising system [19,112,101,117]. Hippocampal theta activity has been associated with a functional role in the representation and processing of spatial information in memory and other cognitive processes [44,21,8,54,90]. In particular, changes in efficiency in place learning tasks had been related to changes in the power and frequency of hippocampal theta activity [96,91,93,20,104,124]. As part of the ascending synchronising system, the medial septum and diagonal band of Broca (hereafter known as the medial septum, MS) is a critical information relay station in the circuit

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connecting the hippocampus and other subcortical limbic regions, such as the median mammillary and supramammillary nuclei (MM and SUM, respectively) [50,97]. SUM has been implicated in hippocampal theta frequency encoding [59,81,62] and spatial learning [105,96,107,40] while the MM has neurons that fire rhythmically in phase with the hippocampal theta, which are driven by descending projections from the hippocampus [10,64]. The MS is considered the pacemaker of the theta rhythm, as it has a determining role in the temporal coordination of the hippocampus information flow and in the generation of the theta rhythm [36,4,58,123]. The inhibition of the MS cell activity with lidocaine abolishes theta oscillations in the hippocampus and entorhinal cortex [4,74,68] and results in severe deficits in spatial learning [75,124]. Thus, the MS regulates spatial hippocampal representation [77]. Selective medial septal lesions on GABAergic and/or cholinergic cells impair spatial learning in the Morris water-maze [18,29,98], reduce the power of hippocampal theta activity and result in the loss of rhythmic firing of septo-hippocampal neurons [69,6,43,110].

In parallel with the ascending synchronising system, there is a serotonergic system that originates from the dorsal and medial raphe nuclei; the median raphe nucleus (MR) has extensive projections to the MS and hippocampus that express different types of receptors to serotonin [72,83,115,79]. This system has been proposed to be directly involved in hippocampal EEG desynchronization or the non-theta state [122,117,71,121]. Based on experiments in anesthetized and freely moving rats, electrical stimulation of the MR has been shown to inhibit the firing of hippocampal pyramidal cells [106], to disrupt the bursting discharge of septal pacemaker cells [7,119], to decrease theta expression in the medial septal area and to desynchronize the hippocampal EEG [60,119]. In addition, the selective systemic administration of 5HT2C receptor agonist inhibits theta oscillations of the MS and theta activity in the hippocampus [42]. In contrast, continuous and persistent hippocampal theta activity has been shown after the inhibition, temporal inactivation (with lidocaine or procaine) or selective application of 5HT1A serotonin receptor agonist to the MR in anesthetized rats and awake rabbits [114,60,116].

In relation to the functional role of serotonin as a desynchronizer of hippocampal theta activity, it has been proposed that information arriving in the absence of theta (desynchronization) is not encoded [117]; therefore, serotonin could block or temporally suspend memory processes in the hippocampus and, to a certain extent, is responsible for the ability to ignore non-significant environmental events [120]. In addition, it was proposed that a high serotonergic tone in the medial septum could prevent coding information, while a low tone could facilitate the encoding and consolidation of information [53]. However, these hypotheses have not been simultaneously tested in experiments during information processing related to spatial learning and memory, with records of the underlying theta activity.

The participation of serotonin in the modulation of hippocampal theta activity in relation to information processing has been demonstrated in the hippocampus and supramammillary nucleus [94,39,40,47]. However, because of the important role of the MS on the theta activity and spatial learning and the participation of serotonin as possible desynchronizer of hippocampal theta activity, it is important to know the functional role of serotonin on the medial septum and its impact on theta activity of the septo-hippocampal and septo-mammillary circuit, especially during behaviour involving the encoding and retrieval of information, such as learning and memory. We selectively depleted serotonin in the medial septum, and the EEG was simultaneously recorded in the hippocampus, medial septum and mammillary nuclei during place learning in the rat.

2. Materials and methods

2.1. Animals

A total of 29 male Sprague Dawley rats weighing between 400 and 460 g were used in this study. The rats were maintained under a normal light/dark cycle (12 h/12 h) at a temperature of 22 °C with free access to water and food. In the room colony, four rats were housed per cage, after the surgery one rat was housed per cage until the end of the experiments. Eight rats were assigned to the experimental group in which the serotonin was depleted (5HT-D) from the medial septum by the injection of 5,7-DHT and eight rats were assigned to the vehicle group. The remaining rats did not meet the inclusion criteria (serotonin reduction greater than 50% compared to the vehicle group, the proper position of the electrodes in each recording site) and were discarded. The order in which the rats started the behavioural test was counterbalanced. All experiments were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publication No. 80-23) and for the "Norma Oficial Mexicana" for the use of experimental animals (NOM-062-ZOO-1999). All the experiments were approved by the Research Ethics Committee of the Instituto Mexicano del Seguro Social.

2.2. Surgery

The rats were deeply anesthetized with Ketamine (60 mg/kg i.m.) and sodium pentobarbital (14 mg/kg i.p.) before stereotaxic surgery. The rats were depleted of serotonin through the micro-infusion of 5,7-dihydroxytriptamine (5,7-DHT) into the MS according to the Atlas of [99], (coordinates: same as the recording electrode) (1.5 μg dissolved in 0.1 μl of 0.1% ascorbic acid in a saline solution) at an infusion rate of 0.1 μl/min for 5 min using a Hamilton 10-μl syringe located on an infusion pump. Thirty minutes before the infusion of 5,7-DHT, the rats received pargyline (30 mg/kg, i.p.) in order to protect the noradrenergic terminals [14,15,95,28]. The other rats received the vehicle solution infusion (vehicle group), in a similar volume and rate as the 5HT-D group. In the same surgery, the rats were chronically implanted with bipolar concentric electrodes in the MS (coordinates: 0.6 mm anterior from the bregma,1.5 mm right to the midline,15° from vertical and 6.8 mm dorsoventral from the cranial surface or DVC); the dentate gyrus (DG, coordinates: 3.5 mm posterior to the bregma or PB, 1.5 mm lateral from the midline and 3.6 mm DVC), CA1 (coordinates: 4.5 mm PB, 2.4 mm lateral from the midline and 2.6 mm DVC) from the hippocampus; the SUM (coordinates: 4.6 mm PB, 0-0.2 mm lateral from the midline and 8.24 DVC) and MM (coordinates: 4.6 mm PB, 1.3 mm lateral left from the midline, 13° from vertical and 9.2 DVC). The electrodes were made of nichrome wire (60 μm) located in a stainless steel #30 calibre cannula isolated with epoxy resin with a small surface exposed on the tip. The electrodes were fixed to the skull with dental acrylic, and one screw was placed in the frontal bone for grounding. After the surgery, a combination of antibiotics, analgesics, antipyretics and expectorants was administered (Respivet Senosiain 0.1 ml/kg i.m). After a 15-day recovery period, the behavioural test began.

2.3. Behavioural test

To evaluate spatial learning, the Morris water maze was used, which consisted of a circular pool (150 cm in diameter) filled with water maintained at 27 +–1 °C and dyed dark blue by the addition of gentian violet. The pool contained a circular platform that was 10 cm in diameter, and the surface was placed 2 cm under the water level in a fixed position in one quadrant. Stimuli were located around the maze in the room.