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Septal serotonin depletion in rats facilitates working memory in the radial arm maze and increases hippocampal high-frequency theta activity



Miguel Ángel López-Vázquez^{a,b}, Elisa López-Loeza^b, Naima Lajud Ávila^c, Blanca Erika Gutiérrez-Guzmán^d, J. Jesús Hernández-Pérez^d, Yoana Estrada Reyes^a, María Esther Olvera-Cortés^{d,*}

^a Laboratorio de Neuroplasticidad de los Procesos Cognitivos, Centro de Investigación Biomédica de Michoacán, Instituto Mexicano del Seguro Social, Mexico

^b Laboratorio de Biofísica, Instituto de Física y Matemáticas, Universidad Michoacana de San Nicolás de Hidalgo, Mexico

^c Laboratorio de Neuroendocrinología, Centro de Investigación Biomédica de Michoacán, Instituto Mexicano del Seguro Social, Mexico

^d Laboratorio de Neurofisiología Experimental, Centro de Investigación Biomédica de Michoacán, Instituto Mexicano del Seguro Social, Camino de la arboleda 300, Exhacienda de san José de la Huerta, Morelia, Mich C.P. 58341, Mexico

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ABSTRACT

Hippocampal theta activity, which is strongly modulated by the septal medial/Broca's diagonal band neurons, has been linked to information processing of the hippocampus. Serotonin from the medial raphe nuclei desynchronises hippocampal theta activity, whereas inactivation or a lesion of this nucleus induces continuous and persistent theta activity in the hippocampus. Hippocampal serotonin depletion produces an increased expression of high-frequency theta activity concurrent with the facilitation of place learning in the Morris maze. The medial septum–diagonal band of Broca complex (MS/DBB) has been proposed as a key structure in the serotonin modulation of theta activity. We addressed whether serotonin depletion of the MS/DBB induces changes in the characteristics of hippocampal theta activity and whether the depletion is associated with learning in a working memory spatial task in the radial arm maze. Sprague Dawley rats were depleted of 5HT with the infusion of 5,7-dihydroxytryptamine (5,7-DHT) in MS/DBB and were subsequently trained in the standard test (win-shift) in the radial arm, while the CA1 EEG activity was simultaneously recorded through telemetry. The MS/DBB serotonin depletion induced a low level of expression of low-frequency (4.5–6.5 Hz) and a higher expression of high-frequency (6.5–9.5 Hz) theta activity concomitant to a minor number of errors committed by rats on the working memory test. Thus, the depletion of serotonin in the MS/DBB caused a facilitator effect on working memory and a predominance of high-frequency theta activity.

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1. Introduction

Hippocampal theta activity is a sinusoidal-like slow oscillation that ranges from 4 to 12 Hz and is prominent in the rat hippocampus during voluntary behaviour (Vanderwolf, 1969; Whishaw and Vanderwolf, 1973) and during the display of behaviours related to the acquisition of environmental information (Eichenbaum et al., 1992; Vinogradova, 1995). The expression and characteristics of the hippocampal theta activity have been linked to place learning ability in humans and rats (Cornwell et al., 2008; Watrous et al., 2011; Olvera-Cortés et al., 2002, 2004). Conversely, a relationship has been observed between decreases in theta frequency and place

learning impairments (Maho et al., 1988; Pan and McNaughton, 1997).

The medial septum–diagonal band of Broca complex (MS/DBB) acts as a pacemaker for the hippocampal theta activity (Ford et al., 1989; Hangya et al., 2009; Petsche et al., 1962) as it sends projections to the hippocampus from cholinergic, GABAergic, and glutamatergic neurons (Amaral and Kurz, 1985; Colom et al., 2005; Freund, 1989), all of which appear to be important in the regulation of hippocampal theta activity (Hangya et al., 2009; Manns et al., 2002; Monmaur et al., 1993; Sotty et al., 2003). Lesions or inactivation of the medial septum disrupts hippocampal theta activity and causes learning deficits in both reference and working memory tasks (Givens and Olton, 1994; McNaughton et al., 2006; Mitchell et al., 1982; Mizumori et al., 1990; Rawlins et al., 1979). The septal area is an important structure in the control of hippocampal theta activity (Rawlins et al., 1979; Vertes and

* Corresponding author. Tel./fax: +52 44 33 22 26 00.

Kocsis, 1997), and it is also crucial in the processing of information that is related to hippocampal function (Mitchell et al., 1982). While serotonin has been proposed as the only neurotransmitter that desynchronises hippocampal theta activity, the cerebral depletion of serotonin induces persistent and continuous theta activity in the hippocampus (Maru et al., 1979; Vertes, 1986; Vertes and Kocsis, 1997; Vinogradova et al., 1999), an effect that is mediated principally in the SM (Crooks et al., 2012). In view of the relevant role of theta oscillations in the processing of information by the hippocampus, it is reasonable to postulate that the regulation of theta activity by the 5-HT could assume a modulator role in the processing of information by the hippocampus, a premise that has received scant attention to date. Stimulation of the median raphe nucleus (MR), the main input of serotonin to the hippocampus, desynchronises the hippocampal EEG signal (Kitchigina et al., 1999; Maru et al., 1979; Vertes and Martin, 1988), and lesions of the MR result in the presence of persistent and continuous trains of theta activity (Maru et al., 1979; Vertes, 1986; Vinogradova et al., 1999). Septal neuronal activity is modulated by serotonin acting on cholinergic, GABAergic (Acsady et al., 1996; Jeltsch-David et al., 2008), and possibly glutamatergic neurons through different receptors, such as 5-HT_{1A} and 5-HT_{2A} (expressed on cholinergic and GABAergic septo-hippocampal neurons) (Luttgen et al., 2004, 2005).

As serotonergic fibres target parvalbumin-expressing GABAergic neurons in MD/DBB, these cells synapse on hippocampal GABAergic basket and chandelier cells. Accordingly, it has been proposed that this arrangement can generate rhythmic disinhibition and produce a powerful inhibition of hippocampal interneurons (Freund, 1989; Freund and Antal, 1988; Leranath and Vertes, 1999). Serotonin also inhibits cholinergic and non-cholinergic neurons on MS (Alreja, 1996). Additionally, it has been proposed that the serotonergic fibres that innervate the medial septum could exert an inhibitory influence on the rhythmic firing of septal cells (Assaf and Miller, 1978).

Serotonin also modulates learning and memory processes, although its role is unclear. In rats, enhanced learning in spatial discrimination has been reported after cerebral and hippocampal serotonin depletion (Altman et al., 1990; Normile et al., 1990), and improvement in working memory performance has been detected after prefrontal serotonin depletion (Perez-Vega et al., 2000). Recently, improvement in place learning concurrent with increased high-frequency theta activity during the search for the platform in the Morris maze was reported after hippocampal serotonin depletion (Gutiérrez-Guzmán et al., 2011), while deficient learning associated with a reduced expression of hippocampal high-frequency theta activity after serotonin depletion in the supramammillary nucleus and posterior hypothalamus (SUM/PH) was observed in rats (Gutiérrez-Guzmán et al., 2012).

Thus, the effects of serotonin on theta activity may be strongly mediated through MS/DBB, which is the pacemaker of hippocampal theta activity and is related to learning and memory processes. The aim of this study was to evaluate the effect of serotonin MS/DBB reduction in the modulation of working memory and theta-related activity.

2. Materials and methods

2.1. Animals

Forty Sprague Dawley male rats weighing between 350 and 450 g were used. The experiments were performed in accordance with the National Institute of Health guide regarding the care and use of laboratory animals (NIH Publications no. 80-23) and with the "Norma Oficial Mexicana para el uso de animales de

laboratorio" (NOM-062-ZOO-1999). Furthermore, the experiments were approved by the research ethics committee of the Instituto Mexicano del Seguro Social. All rats were maintained under standard housing conditions in the animal facility. The rats were assigned to one of two groups, the 5,7-DHT group ($n=15$) or the vehicle group ($n=15$).

2.2. Surgery

Under pentobarbital anaesthesia (30 mg/kg ip), the 5,7-DHT rats received microinjections of 5,7-dihydroxytryptamine (5,7-DHT) into the MS (0.6 mm anterior from the bregma, 1.5 mm right of the midline, 15° from the vertical and 6.8 mm dorsoventral from the cranial surface) and into the DBB (0.6 mm anterior from the bregma, 0.5 mm bilateral of the midline and 7.8 mm dorsoventral from the cranial surface). The rats subsequently received 30 mg/kg of desipramine (ip) to protect noradrenergic terminals 30 min before the 5,7-DHT injections. The dose administered was 1 µg of 5,7-DHT freebase in 0.1 µl of saline solution with ascorbic acid (0.1%). The volume injected into the MS was 0.5 µl, whereas 0.4 µl were bilaterally infused into the DBB. The rate of infusion was 0.1 µl/min using a Hamilton syringe of 25 gauge infusion stainless steel. During the same operation, a sub-group of eight rats was implanted with a chronic monopolar electrode in the hippocampal CA1 area, specifically 4.0 mm posterior from the bregma, 2.2 mm right of the midline, and 3.7 mm dorsoventral from the cranial surface. All coordinates reference the Watson and Paxinos atlas (Paxinos and Watson, 1996). The recording electrode was constructed of 25-gauge stainless steel insulated with epoxy resin and containing a small recording surface in the tip. The electrode was soldered to a telemetry transmitter that was placed under the skin of the neck of the rat. The vehicle group rats received the infusion of the vehicle solution in the coordinates and volumes as previously described for the 5,7-DHT group. Eight rats from the vehicle group were also implanted with the recording electrode as described for the 5,7-DHT group rats.

After the surgery, the rats were subjected to food restriction (80% of their normal consumption ad libitum) for two weeks. They then underwent the radial arm maze training, which adhered to standard procedures.

2.3. Radial arm training

The radial arm consisted of one central arena (30 cm in diameter) from which eight radial arms were extended (60 cm × 10 cm). The rats were exposed to one habituation period of 10 min in the maze. On the following day, a second habituation period was conducted, and the rats were exposed to the fruit cereal (Fruit Loops), which was used as the reward. One day after the rats consumed the reward in the maze, the training began. All eight arms were baited for the test. Each rat was placed in the central area of the maze for a 30 s period, during which time access to the arms was blocked by a white cylinder. At the end of the 30 s period, the cylinder was moved and the trial was begun. The experimenter recorded the visited arms until 10 min had elapsed or until the rat had consumed all of the rewards placed in the containers at the ends of the arms. The rat was later removed from the maze and returned to its home cage for 20 min, after which it was again placed in the maze for a second trial. The rats were trained over seven consecutive days. The total errors – omission errors (the rat entered the arm did not proceed to the end of the arm or did not consume the cereal) and re-entry errors (entries previously visited arms) – were compared. The number of re-entry errors and the time to complete the task (mean of the two trials per day) were also compared. Inter-group comparisons were made using an ANOVA for repeated measures (days of training as the

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