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ScienceDirect
Neurobiology of Learning and Memory 89 (2008) 574–581
Neurobiology of Learning and Memory
www.elsevier.com/locate/ynlme

Intracranial self-stimulation improves memory consolidation in rats with little training

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Received 5 September 2007; revised 19 November 2007; accepted 27 November 2007
Available online 22 January 2008

Abstract

Post-training intracranial electrical self-stimulation can improve learning and memory consolidation in rats. However, the molecular mechanisms involved are not known yet. Since previous paradigms of this kind of facilitation are relatively unsuitable to try a molecular approach, here we develop a single and short model of learning and memory facilitation by post-training self-stimulation that could make easier the research of its neural and molecular basis. Thus, three consecutive experiments were carried out to ascertain whether post-training self-stimulation is able to facilitate memory when learning consists of only a brief (5 trials) two-way active avoidance conditioning session. The results of Experiment 1 showed that it is actually possible, and that 48 h after the acquisition session is a very good time to observe the memory improvement. As a way to probe the retroactive effect of self-stimulation, in Experiment 2 we observed that the same self-stimulation treatment given to the subjects not post-training but 48 h before a single two-way active avoidance session does not improve the acquisition of conditioning. In Experiment 3, we showed that the SS facilitative effect observed 48 h after the acquisition session in Experiment 1 was still maintained one week later. We concluded that post-training intracranial self-stimulation can consistently improve memory consolidation even when little acquisition training is given to the animals in a single training session.

Keywords: Deep brain stimulation; Avoidance learning; Memory; Learning facilitation; Avoidance conditioning

1. Introduction

Intracranial self-stimulation (SS) was discovered in 1953 at McGill University, when James Olds and his graduate student Peter Milner reported that rats with electrodes implanted in the brain's septal region would press continuously a lever to receive electrical stimulation. Since then, many experiments have been done in different laboratories to explore the nature of such a phenomenon and its functional implications. Many of them tried to know if SS could serve to improve cognitive processes. As a result, different experiments have shown facilitation of learning and memory by post-training intracranial self-stimulation in a wide variety of paradigms and types of conditioning in rats (Coulombe & White, 1980, 1982; Destrade & Jaffard, 1978; Huston & Mueller, 1978; Huston, Mueller, & Mondadori, 1977; Segura-Torres, Portell-Cortés, & Morgado-Bernal, 1991; Soriano-Mas, Redolar-Ripoll, Aldavert-Vera, Morgado-Bernal, & Segura-Torres, 2005). We have highlighted it in subjects with a low capacity for learning (Aldavert-Vera, Segura-Torres, Costa-Miserachs, & Morgado-Bernal, 1996) and in animals with cognitive deficit caused by aging (Aldavert-Vera et al., 1997) or brain lesions (Redolar-Ripoll et al., 2003). We have also postulated that the main effect of post-training SS is an acceleration of memory consolidation (Aldavert-Vera et al., 1996). Our previous research mainly consisted of designs of several

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doi:10.1016/j.nlm.2007.11.005

two-way active avoidance sessions, each with a minimum of 10 trials and a maximum of 50 trials, immediately followed by SS treatment. Although these kind of designs have been very useful to know the capacity of SS to improve learning and memory in normal and aging or brain-damaged rats, the difficulty to decide the critical moments along the experimental course to analyze what is happening inside the brain of the subjects makes those designs unsuitable or not very useful to investigate the molecular basis of learning and memory facilitation by SS. For example, in a distributed design with post-training SS producing a progressive facilitation along the different sessions it is not easy to know when it is the best time to study molecular changes in its brains. Testing different times can make longer the experimental designs and procedures as well as more difficult to understand the findings. Otherwise, a long single training session could make difficult to observe the molecular effect of SS if they are masked by the ones of prolonged training. It seems therefore that a simple, shorter and consistent paradigm of memory facilitation by post-training SS could make the investigation of the molecular mechanisms involved in it easier. This is why this study investigates the effect of post-training SS treatment upon a single and brief learning experience of two-way active avoidance.

2. Experiment 1

This experiment was done to ascertain (1) whether the kind of post-training SS treatment which was able to improve memory in our previous experiments with several two-way active avoidance sessions (Redolar-Ripoll, Aldavert-Vera, Soriano-Mas, Segura–Torres, & Morgado-Bernal, 2002; Segura-Torres, Capdevila-Ortís, Martí-Nicolovius, & Morgado-Bernal, 1988) is also able to facilitate memory when applied immediately after a single and brief conditioning session, and (2) when is a good time to observe that facilitative effect.

2.1. Methods

2.1.1. Subjects

Seventy-two naive male Wistar rats, obtained from our laboratory breeding stock were used, with a mean age of 94.40 days ($SD = 3.40$) at the beginning of the experiment, and mean weight of 482,69 g ($SD = 47.41$) at the time of surgery. All rats were singly housed (size cage: $25 \times 25 \times 14$ cm), always kept under conditions of controlled temperature (20–24 °C) and humidity (40–70%), and subjected to an artificial light/darkness cycle of 12/12 h (lights on at 08:00 h). Food and water were available ad libitum. The rats were tested during the first half of the light cycle. The experiments were carried out in compliance with the European Community Council Directive for care and use of laboratory animals (CEE 86/609) and the Generalitat de Catalunya (DOGC 2073 10/7/1995, DARP protocol number 2381).

2.1.2. Stereotaxic surgery

Under general anesthesia (150 mg/kg Ketolar® *Ketamine chlorhydrate* and 0.08 mg/kg Rompun® *Xylazin*), all rats were implanted with a monopolar stainless steel electrode (150 μm in diameter) aimed at the lateral hypothalamus (LH), into the fibers of the medial forebrain bundle, with the incisor bar set at -2.7 mm below the interaural line and according to coordinates from the stereotaxic atlas of Paxinos & Watson (1998)), $AP = -1.8$ mm from bregma, $L = 2.0$ mm (right hemisphere) and $P = -8.5$ mm with the cranium surface as dorsal reference. SS electrodes were anchored to the skull with jeweler's screws and dental cement. Before surgery, the rats were given once-daily handling sessions on three consecutive days.

2.1.3. Procedure

Once the rats had recovered from surgery (7 days), they were taught to self-stimulate by pressing a lever in a conventional Skinner box ($25 \times 20 \times 20$-cm). Electrical brain stimulation consisted of 0.3 s trains of 50 Hz sinusoidal waves at intensities ranging from 10 to 400 μA. The SS behavior was shaped for each subject to establish the range of current intensities that would cope with responding to on a continuous reinforcement schedule. After the shaped phase, the subjects were randomly distributed in two groups, Control and SS, according to the independent variable "SS-treatment". Each of these two groups was then randomly distributed in three subgroups, Rt24, Rt48 and Rt72, according to the independent variable "Retention-time". As a result, the final six experimental groups were SS-Rt24, SS-Rt48, SS-Rt72, Control-Rt24, Control-Rt48 and Control-Rt72.

On two consecutive days, all the SS animals were trained to self-stimulate and an optimum current intensity (OI, the one giving rise to the maximum response rate) of SS was established for each subject (as described in Segura-Torres, P. 1991). Four days later, all the rats were trained in a single 5-trial session of a two-way active avoidance task (acquisition session). Active avoidance conditioning was conducted in a $50 \times 24 \times 23$-cm two-way automated shuttle-box (Letica LI-916), enclosed in a sound-attenuating box ventilated by an extractor fan. The conditioned stimulus (CS) was a 60 dB and 1 kHz tone of 3 s duration. The unconditioned stimulus (US) was a 0.5 mA electrical scrambled footshock, presented for a maximum of 30 s. Just before the acquisition session, each rat was allowed 10 min of free ambulation in the shuttle box to become familiarized with the learning environment. The trials followed a variable interval schedule of 1 min ±10 s. Besides the number of avoidance responses (considered as the level of performance of the task), intertrial crossings and crossings during the 10 min of free ambulation before training (considered as an index of locomotor activity) were also scored. Immediately after this training session, all SS rats were placed in the self-stimulation box and received a SS treatment consisting of 2000 trains at the 100% of their respective OI. Rats in Control groups did not receive SS