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Brain Research

Research Report

Different effects of low frequency stimulation to infralimbic prefrontal cortex on extinction of aversive memories ☆

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ARTICLE INFO

Article history:
Accepted 13 October 2012
Available online 23 October 2012

Keywords:
Extinction
Synaptic plasticity
mPFC
Rat
Infralimbic

ABSTRACT

Experimental extinction is a behavioral technique in which animals learn to extinguish previously learned fear responses. The infralimbic cortex (IL) of the medial prefrontal cortex has an important role in extinction of aversive memories. We have recently shown that electrical stimulation of the IL in a form of high-frequency stimulation (HFS), which induces potentiation in the IL, was associated with enhanced ability to extinguish aversive memory in two aversive paradigms, the fear conditioning and the conditioned taste aversion paradigms. These results suggest that the induction of potentiation in the IL is associated with better ability to extinguish. In the present study we examined the opposite hypothesis that inducing depression in the IL by the application of low-frequency stimulation (LFS) will result in impairments in extinction. Our results show that the application of LFS to the IL retards extinction of fear conditioning only, suggesting that the application of LFS to the IL results in impairments in extinction of conditioned fear. In the conditioned taste aversion paradigm (CTA), LFS to the IL was associated with delayed enhancement of extinction of CTA that was apparent 48 h following stimulation. These results suggest that localized electrical stimulation to the IL may be an effective method for manipulating learned fear and affecting the ability to extinguish aversive associations.

1. Introduction

Experimental extinction is defined as the decline in the frequency or intensity of a conditioned response following the withdrawal of reinforcement and hence extinction is a behavioral technique leading to suppression of the acquired fear association.

The infralimbic region of the medial prefrontal cortex (IL-mPFC) plays an important role in extinction of aversive associations as measured using Pavlovian conditioned fear and taste aversion paradigms (Akirav et al., 2006b; Milad and Quirk, 2002; Quirk and Mueller, 2007; Santini et al., 2001).

To better understand the mechanisms by which the mPFC encodes extinction we have recently addressed the question of whether fear and its subsequent extinction are reflected by changes in plasticity in the mPFC. Monitoring changes in the evoked field potentials (EFPs) in the mPFC, induced by stimulation of the basolateral amygdala (BLA), showed that extinction of fear is associated with potentiation of these EFPs (Vouimba and Maroun, 2011). In contrast, reinstatement

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http://dx.doi.org/10.1016/j.brainres.2012.10.026

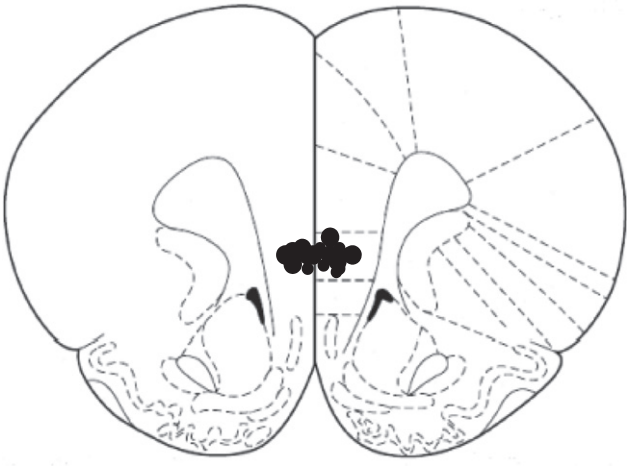

Fig. 1 – Schematic drawing of representative electrodes tip positions in the medial prefrontal cortex. Adapted with permission from Elsevier© Paxinos and Watson, 1988.

of fear which was associated with the return of freezing resulted in depression of the EFPs in the mPFC. These bi-directional changes confirm the dynamic and plastic nature of the mPFC.

Additionally, these results suggest that manipulating these patterns of plasticity in the mPFC should affect extinction. Indeed electrical stimulation of the IL-mPFC during extinction training has been found to reduce the expression of conditioned fear and enhance extinction in rats (Milad et al., 2004; Vidal-Gonzalez et al., 2006). Further, we have recently shown that High-Frequency Stimulation (HFS) to the IL which induces potentiation, immediately after the memory retrieval of either auditory fear conditioning or conditioned taste aversion (CTA) results in facilitation in the ability to extinguish aversive associations (Maroun et al., 2012). These results confirmed previously reported data in which it was shown that mice that had HFS applied to the mediodorsal thalamus, which projects to the mPFC, had better extinction compared to the control animals. This better extinction was reflected by decrease in fear responses 24 h following HFS. In contrast to the effects of HFS to the dorsal thalamus, the application of low-frequency stimulation which is associated with depression in the evoked field potentials in the mPFC, had the opposite effect and was associated with the return of fear (Herry and Garcia, 2002). In this aforementioned study of Herry and Garcia (2002), LFS was applied before the extinction session and hence targeting two processes at least, the acquisition of extinction and the consolidation of extinction. Further, LFS was applied before each extinction session and thus limiting the ability to conclude whether single application of LFS would exert similar effects on extinction. Finally, LFS was applied to mediodorsal thalamus which projects to the mPFC and not directly to the mPFC. Thus, the aims of our present study were (1) to evaluate the effects of single application of LFS to the IL of mPFC on extinction and (2) to specifically target the consolidation phase of extinction and hence LFS was applied immediately after the first non-reinforced test in which animals were exposed to the conditioned stimulus without the aversive stimulus and (3) to determine whether the effects of LFS on extinction were specific to fear, or also affected another form of IL-mediated extinction, conditioned taste aversion (CTA), a task that is biologically meaningful for rodents, but is not fear-related (Akirav et al., 2006a; Mickley et al., 2004).

2. Results

2.1. *IL-LFS immediately after fear retrieval of the conditioned fear impairs fear extinction*

Prior to stimulation, the sham and LFS groups did not differ in freezing during the fear memory retrieval test (Ret) [Control ($n=10$): $80.5\pm3.6\%$; LFS ($n=11$)$=79.1\pm3.4\%$; t (19)$=0.04$; $P>0.05$].

Three-factor ANOVA (Group × Day × trial) with repeated measures for day (2 testing days: Ext1, Ext2) and trial (4 trials: T1…T8–10) following LFS showed significant effects of stimulation group [$F_{(1,19)}=5.4$; $P<0.05$], extinction day [$F_{(1,19)}=46.7$; $P<0.01$], trial ($F_{(3,19)}=74.1$, $P<0.01$), but no significant interactions ($P>0.05$). Freezing in the LFS stimulated group was significantly higher than those of the non-stimulated rats and both groups showed significant reductions in freezing across extinction days and extinction trials (Fig. 2B). Hence the application of LFS to the IL after the retrieval of fear was associated with impairments in extinction of fear which persisted over two days.

2.2. *IL-LFS prior to fear conditioning does not alter fear retrieval or fear extinction*

Next we examined the effects of LFS before conditioning on the ability to acquire the association and on subsequent fear extinction. During conditioning, freezing levels were compared between the two groups (Sham $n=5$; LFS $n=6$) on the 1st CS (before the first US) as compared to the 3rd CS (post the 2nd US). ANOVA with repeated measures show no significant effect of group [$F_{(1,19)}=0.03$; ns] but a significant effect of CS [$F_{(1,19)}=683$; $P<0.01$], demonstrating no difference in fear acquisition and confirming the success of the conditioning.