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Extinction of aversive taste memory homeostatically prevents the maintenance of in vivo insular cortex LTP: Calcineurin participation

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ABSTRACT

Accumulating evidence indicates that homeostatic plasticity mechanisms dynamically adjust synaptic strength to promote stability that is crucial for memory storage. Our previous studies have shown that prior training in conditioned taste aversion (CTA) prevents the subsequent induction of long-term potentiation (LTP) in the projection from the basolateral nucleus of the amygdala (Bla) to the insular cortex (IC) in vivo. We have also reported that induction of LTP in the Bla-IC pathway modifies the CTA extinction. Memory extinction involves the formation of a new associative memory that inhibits a previously conditioned association. The aim of the present study was to analyze the effect of CTA extinction on the ability to induce subsequent LTP in the Bla-IC projection in vivo. Thus, 48 h after CTA extinction animals received high frequency stimulation in order to induce IC-LTP. Our results show that extinction training allows the induction but not the maintenance of IC-LTP. In addition, with the purpose of exploring part of the mechanisms involved in this process and since a body of evidence suggests that protein phosphatase calcineurin (CaN) is involved in the extinction of some behavioral tasks, we analyzed the participation of this phosphatase. The present results show that extinction training increases the CaN expression in the IC, as well as that the inhibition of this phosphatase reverts the effects of the CTA-extinction on the IC-LTP. These findings reveal that CTA extinction promotes a homeostatic regulation of subsequent IC synaptic plasticity maintenance through increases in CaN levels.

1. Introduction

Nowadays it is widely considered that learning and memory are supported by cellular mechanisms that generate changes in connectivity within the neural circuits. Specific neuronal activity patterns lead to durable increases or decreases in the strength of synaptic connections, termed long-term potentiation (LTP) and long-term depression (LTD) respectively (Citri & Malenka, 2008; Vitureira & Goda, 2013). Induction of LTP requires postsynaptic depolarization coupled with synaptic stimulation and is usually mediated by release of glutamate and opening of ligand-gated ion channels. Thus, the direction of synaptic change is delicately controlled by the level and pattern of calcium increases and the associated activation of key protein kinases and phosphatases. On the other hand, the maintenance phase of this phenomenon is commonly related to the persisting biochemical signals that last in the cell, like protein synthesis and early activation of transcriptional processes, as well as morphological modifications of synapses (Abraham & Williams, 2003; Nicoll, 2017). Nevertheless, stable but flexible neural activity is critical for proper brain function. In this context, it has been proposed that homeostatic plasticity contributes to the overall regulation of synaptic strength by maintaining it within a dynamic functional range (Müller-Dahlhaus & Ziemann, 2015). Metaplasticity, the process in which the activity history of a given neural network shapes the direction, duration and magnitude of future synaptic changes, is ideally suited to prepare neuronal networks for encoding specific information, thereby ensuring subsequent learning and long-lasting memory storage (Hager et al., 2015; Hulme, Jones, & Abraham, 2013; Li et al., 2017; McHail & Dumas, 2015; Müller-Dahlhaus & Ziemann, 2015; Schmidt, Abraham, Maroun, Stork, & Richter-Levin, 2013).

In this regard, it has been demonstrated that previous acquisition of aversive learning can modify the ability to express subsequent LTP in both the hippocampus (Hirata et al., 2009, Xu et al., 2014) and neocortex (Rivera-Olvera, Rodríguez-Durán, & Escobar, 2016; Rodríguez-Durán, Castillo, Moguel-González, & Escobar, 2011; Rodríguez-Durán & Escobar, 2014). The insular cortex (IC) is a region of the brain that lies in the temporal neocortex and is known for its role in processing aversively motivated learning tasks, like conditioned taste aversion (CTA) (Adaikkan & Rosenblum, 2015; Elkobi, Ehrlich, Belelovsky,

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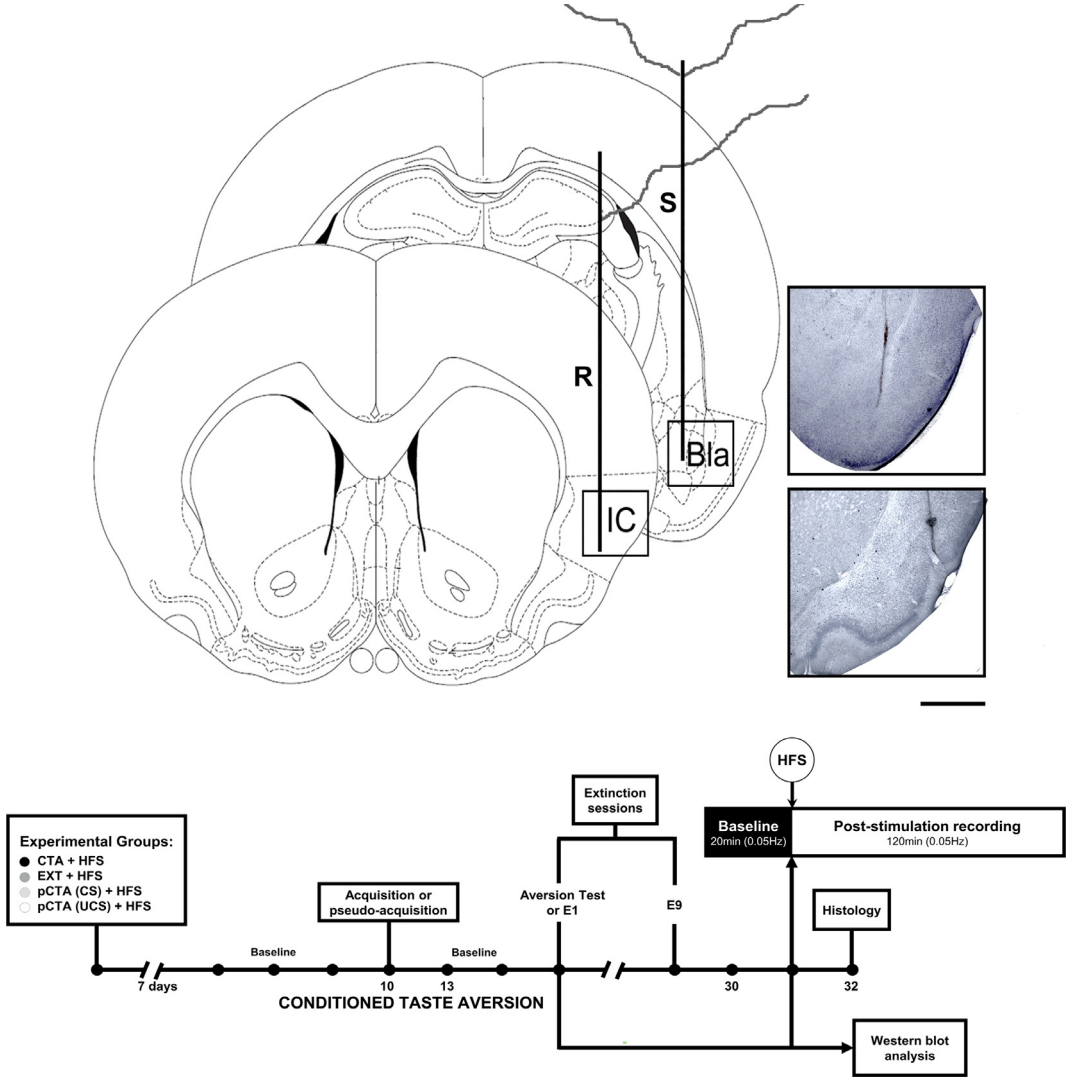

Fig. 1. Schematic representation and representative images of electrode placement showing the stimulated (S) and recorded (R) sites in a coronal plane (upper panel). Diagram of the experimental procedure (lower panel). Bla: basolateral amygdaloid nucleus; IC: insular cortex; HFS: high-frequency stimulation. Scale bar: 1 mm.

Barki-Harrington, & Rosenblum, 2008; Li et al., 2016). CTA is a well-established learning and memory paradigm in which an animal learns to associate a novel taste with nausea, producing a robust and long-lasting memory that can be obtained after a single trial (Bermúdez-Rattoni, 2014; Slouzkey, Rosenblum & Maroun, 2013; Wang et al., 2012; Welzl, D'Adamo, & Lipp, 2001; Yiannakas & Rosenblum, 2017). After the establishment of an association between the two stimuli, the conditioned response will decrease if the taste is presented in the absence of noxious stimulus and this phenomenon is called extinction (Hadamitzky et al., 2016; Maren, 2011; Maroun, Kavushansky, Holmes, Wellman, & Motanis, 2012; Rodríguez-Durán, Martínez-Moreno, & Escobar, 2017).

Currently it is widely accepted that memory extinction involves the formation of a new associative memory that inhibits a previously conditioned association rather than unlearning of acquisition (Bouton, 2004; Maren, 2011; Maroun et al., 2012). In this order of ideas, it has been proposed to depotentiation of excitatory synapses as a cellular mechanism for memory extinction (Dalton, Wang, Floresco, & Phillips, 2008; Hong et al., 2009; Kim et al., 2007; Lin, Lee & Gean, 2003; Lin, Yeh, Leu et al., 2003; Park, & Choi, 2010; Rogan, Leon, Perez, & Kandel, 2005). In this regard, in a recent study carried out by Nabavi and collaborators, it was found that neuronal correlates of fear conditioning in the amygdala, including increases in CS-evoked single-unit firing and synaptic potentiation, are dampened after extinction (Nabavi et al., 2014). On the other hand, it has been demonstrated that fear training induces the phosphorylation of specific protein substrates such as phosphatidylinositol 3-kinase (PI-3K) while extinction is accompanied by an increase in the activation of calcium/calmodulin-dependent protein phosphatase, calcineurin (CaN) (Lin, Yeh, Leu et al., 2003). Likewise, it has been reported that CaN is involved in the induction of LTD in the hippocampal CA1 region (Mulkey, Endo, Shenolikar & Malenka, 1994), as well as that its inhibition blocks the generation of LTP in the rat visual cortex (Funauchi, Haruta, & Tsumoto, 1994).

Our previous studies showed that CTA training modifies the ability to induce subsequent Bla-IC LTP generated either by high frequency stimulation (HFS) (Rodríguez-Durán et al., 2011; Rodríguez-Durán & Escobar, 2014) or by brain-derived neurotrophic factor (BDNF) (Rivera-Olvera et al., 2016). Additionally, we reported that induction of LTP in the Bla-IC projection previous to CTA training increases the retention of this task (Escobar & Bermúdez-Rattoni, 2000), while LTD induction facilitates its extinction (Rodríguez-Durán et al., 2017). However, the modulating effect of the extinction process on the expression of subsequent synaptic plasticity in the neocortex, as well as the mechanisms involved remains unexplored. In the present study, we explored the