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Rapid Communication

Acute infusion of brain-derived neurotrophic factor in the insular cortex promotes conditioned taste aversion extinction

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) has emerged as one of the most potent molecular mediators not only for synaptic plasticity, but also for the behavioral organism–environment interactions. Our previous studies in the insular cortex (IC), a neocortical region that has been related with acquisition and retention of conditioned taste aversion (CTA), have demonstrated that intracortical microinfusion of BDNF induces a lasting potentiation of synaptic efficacy in the basolateral amygdaloid nucleus (Bla)-IC projection and enhances the retention of CTA memory of adult rats in vivo. The aim of the present study was to analyze whether acute BDNF-infusion in the IC modifies the extinction of CTA. Accordingly, animals were trained in the CTA task and received bilateral IC microinfusions of BDNF before extinction training. Our results showed that taste aversion was significantly reduced in BDNF rats from the first extinction trial. Additionally, we found that the effect of BDNF on taste aversion did not require extinction training. Finally we showed that the BDNF effect does not degrade the original taste aversion memory trace. These results emphasize that BDNF activity underlies memory extinction in neocortical areas and support the idea that BDNF is a key regulator and mediator of long-term synaptic modifications.

1. Introduction

Brain-derived neurotrophic factor (BDNF) has been proposed as a key regulator and mediator of long-term synaptic modifications related to learning and memory (Lu, 2003; Park & Poo, 2013). There is growing interest on the role of BDNF in memory extinction (Andero & Ressler, 2012; Cowansage, LeDoux, & Monfils, 2010; Peters, Dieppa-Perea, Melendez, & Quirk, 2010; Rosas-Vidal, Do-Monte, Sotres-Bayon, & Quirk, 2014; Xin et al., 2014). In this regard, it has been shown that extinction of conditioned fear (Bredy et al., 2007) as well as conditioned place aversion (Wang et al., 2012) increases protein expression and gene transcription of BDNF in prefrontal cortex. In addition, Yu et al. (2009) showed that the variant BDNF-Val66Met polymorphism leads to a specific impairment in extinction of conditioned taste aversion (CTA), a very robust and widely used model for the study of learning and memory processes in which an animal acquires aversion to a novel taste when it is followed by digestive malaise (Bermúdez-Rattoni, 2004; Bermúdez-Rattoni, 2014; Yu et al., 2009). In this line of ideas, it has been reported that BDNF release and synthesis temporally regulate CTA acquisition and consolidation (Ma et al., 2011). Our previous studies in the insular cortex (IC), a region of the temporal cortex in the rat that has been implicated in the acquisition and storage of different aversive-motivated learning tasks like CTA (Bermúdez-Rattoni, 2004; Bermúdez-Rattoni, 2014), have demonstrated that intracortical microinfusion of BDNF induces a long-lasting potentiation of synaptic efficacy in the basolateral nucleus of the amygdala (Bla) to the IC projection of adult rats in vivo (Escobar, Figueroa-Guzmán, & Gómez-Palacio-Schjetnan, 2003). Moreover, intracortical microinfusion of BDNF prior to CTA training enhances the retention of this task (Castillo, Figueroa-Guzman, & Escobar, 2006), in a mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI3K) dependent manner (Castillo & Escobar, 2011). In addition, acute intracortical delivery of BDNF reverses the deficit in CTA memory, caused by inhibition of IC protein synthesis due to anisomycin administration (Moguel-González, Gómez-Palacio-Schjetnan, & Escobar, 2008). Recent studies suggest that BDNF promotes extinction of fear memories (Andero & Ressler, 2012). In this sense, infusion of BDNF 60 min before extinction in infralimbic (IL), but not in prelimbic (Pr) medial prefrontal cortex (mPFC), induces extinction of fear conditioning (Peters et al., 2010; Rosas-Vidal et al., 2014). However, the participation of BDNF in extinction of CTA remains unclear. In the present work we analyzed if the acute intracortical

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infusion of BDNF, in a concentration capable to induce a lasting potentiation of synaptic efficacy in the insular cortex, modifies the extinction of CTA.

2. Methods

2.1. Animals

A total of 95 male Wistar rats weighting 350–380 g were prepared for our experiments. They were housed individually under a 12/12-h light–dark cycle, with food and water ad libitum (except where indicated) and an average room temperature of 22 °C. Methods were carried out using adequate measures to minimize pain or discomfort in accordance with the guidelines of the Norma Oficial Mexicana (NOM-062-ZOO-1999) and the NIH Guide for the Care and Use of Laboratory Animals with the approval of the local animal care committee.

2.2. Cannulae implantation

Animals were implanted bilaterally with 23-gauge stainless steel cannulae under anesthesia (Pentobarbital, 50 ml/kg i.p.) using a previously described procedure (Moguel-González et al., 2008). The tips of the guide cannulae were aimed at 2 mm above the IC (Castillo et al., 2006). Microinjections were delivered through 30-gauge dental needles as microinjectors that extended 2 mm below the previously implanted guide cannulae (reaching the IC area). Dental needle microinjectors were attached by polyethylene tubing to a 10-μl Hamilton syringe driven by a microinfusion pump (Cole Parmer Co., Vernon Hills, IL, USA). After surgery animals were allowed to recover for 7 days. All groups were histologically analyzed in order to verify the injector tip location.

2.3. Conditioned taste aversion

Seven days after surgery, animals were introduced in the CTA training, as previously described (Moguel-González et al., 2008; Rodríguez-Durán, Castillo, Moguel-González, & Escobar, 2011). Briefly, rats were deprived of water for 24 h and then habituated to drink water from a single graduated cylinder twice a day, during 10 min trials for 3 days. On the acquisition day, water was substituted for saccharin solution 0.1% (Sigma, St. Louis, MO, USA), and 10 min later, the animals received 7.5 ml/kg i.p. of a 0.2 M solution of LiCl, which induces digestive malaise. After three more days of baseline consumption, water was substituted newly by a 0.1% saccharin solution to test the aversion. The reduction of saccharin consumption was used as a measure of strength of the aversion. In order to determine the participation of BDNF in the CTA extinction, a total of nine extinction trials were given to all groups.

2.4. Experimental design

To evaluate the effects of IC microinfusion of BDNF on the extinction of CTA, animals were distributed in the following treatment groups: BDNF group ($n = 10$), which received an intracortical infusion of BDNF (2 μg/2 μl, Alomone Labs. Jerusalem; Martínez-Moreno, Rodríguez-Durán, & Escobar, 2011; Moguel-González et al., 2008; Escobar et al., 2003; Castillo et al., 2006); PBS group ($n = 10$) which received an intracortical infusion of phosphate buffer solution (2 μl) as vehicle; CYT-C group ($n = 8$), which received the same treatment as PBS group with PBS containing recombinant cytochrome c from yeast, a protein with similar physical and chemical properties as BDNF (2 μg/2 μl, Sigma, St. Louis, MO; Castillo et al., 2006) and BDNF+K252a group ($n = 9$), which received the same treatment as the BDNF group in combination with K252a, an inhibitor of Trk receptors (2 μg of BDNF/2 μl of K252a, 20 μM, Alomone Labs., Jerusalem; Castillo & Escobar, 2011; Castillo et al., 2006). For all groups, intracortical infusions were given to hand-restrained conscious animals one hour before the first extinction trial and three days after the acquisition session (Peters et al., 2010). An additional control group (CON, $n = 10$) remained intact during the whole procedure.

In order to determine whether the BDNF-induced reduction in taste aversion was independent upon the extinction session, we repeated the previous experiment but omitted the extinction training from the BDNF-infusion day. Animals were distributed in the following treatment groups: BDNF25-3d group ($n = 9$), which received an intracortical infusion of BDNF (2 μg/2 μl, Alomone Labs. Jerusalem) and PBS25-3d group ($n = 8$), which received an intracortical infusion of phosphate buffer solution (2 μl) as vehicle. For both groups, intracortical infusions were given to hand-restrained conscious animals twenty-five hours before the first extinction trial and three days after the acquisition session. Animals were offered to drink water instead of saccharin one hour after the infusions. In order to discard late effects on consolidation of the original memory trace, we delayed the beginning of extinction in two additional groups (BDNF25-10d; $n = 8$ and PBS25-10d: $n = 5$), which in similar conditions as BDNF25-3d and PBS25-3d received intracortical infusions of BDNF or PBS respectively, ten days after the acquisition session.

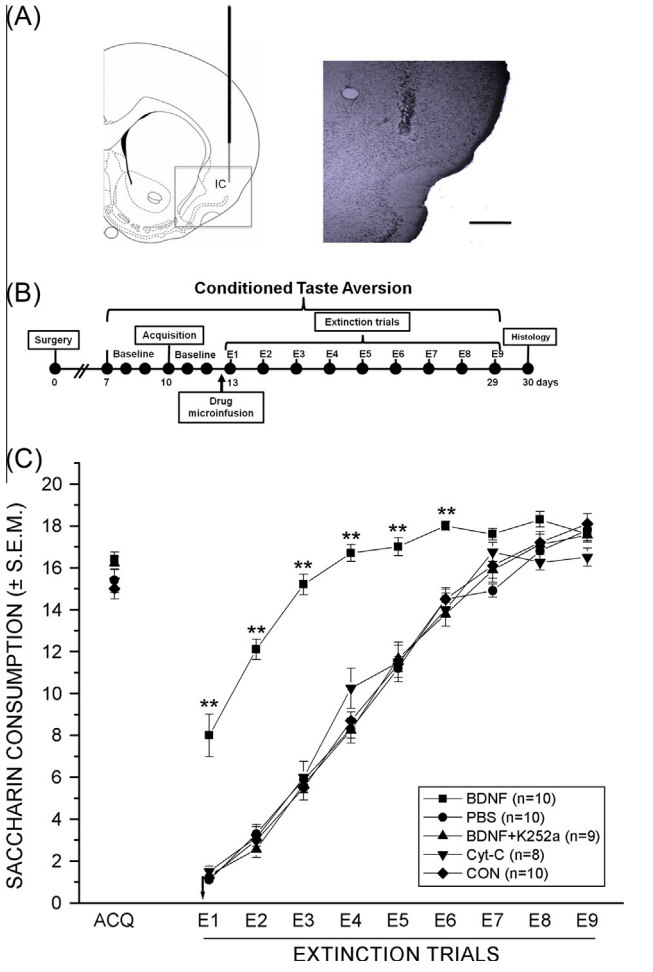

Fig. 1. Insular cortex microinfusion of BDNF promotes CTA extinction. (A) Schematic representation and coronal section showing guide cannulae and microinjector placement in the IC (insular cortex). (B) Diagram of the experimental procedure. (C) Point-plot of the acquisition session (ACQ) and nine extinction trials (E1–E9) given to PBS, BDNF, CyT-C, BDNF+K252a and CON groups. $^{**}p < 0.01$. Arrow indicates the acute intracortical infusion of drugs. Scale bar: 1 mm.