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Rapid Communication

Dorsal medial prefrontal cortex contributes to conditioned taste aversion memory consolidation and retrieval

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ABSTRACT

The medial prefrontal cortex (mPFC) is known for its role in decision making and memory processing, including the participation in the formation of extinction memories. However, little is known regarding its contribution to aversive memory consolidation. Here we demonstrate that neural activity and protein synthesis are required in the dorsal mPFC for memory formation of a conditioned taste aversion (CTA) task and that this region is involved in the retrieval of recent and remote long-term CTA memory. In addition, both NMDA receptor and CaMKII activity in dorsal mPFC are needed for CTA memory consolidation, highlighting the complexity of mPFC functions.

Several studies in humans, non-human primates and rodents describe the participation of the prefrontal cortex (PFC) in diverse cognitive and executive functions, such as decision making, behavioral control, error detection and working memory (Dalley, Cardinal, & Robbins, 2004; Euston, Gruber, & McNaughton, 2012). Besides these well-known functions, recent research efforts began to show that the PFC also plays a role in the consolidation and expression of a broad range of memories (Corcoran & Quirk, 2007; Runyan, Moore, & Dash, 2004; Zhang, Fukushima, & Kida, 2011).

In the conditioned taste aversion (CTA) paradigm, animals associate a novel taste (conditioned stimulus, CS) with a visceral malaise (unconditioned stimulus, US) and show a reduction of the CS consumption as the conditioned response (Garcia, Kimmeldorf, & Koelling, 1995). CTA memory consolidation depends on protein synthesis and NMDA receptor (NMDAr) signaling in the insular cortex (Moguel-González, Gómez-Palacio-Schjetnan, & Escobar, 2008; Rosenblum, Berman, Hazvi, Lamprecht, & Dudai, 1997; Rosenblum, Meiri, & Dudai, 1993) and the amygdala (De la Cruz, Rodriguez-Ortiz, Balderas, & Bermudez-Rattoni, 2008; Lamprecht & Dudai, 1996; Yasoshima, Morimoto, & Yamamoto, 2000). The rodent medial PFC (mPFC) projects to and receives inputs from these two brain structures (Vertes, 2004). In addition, the mPFC is part of the brain circuit that generates aversion (Lammel et al., 2012) and is activated during taste memory formation together with the amygdala and the insular cortex (Uematsu, Kitamura, Iwatsuki, Uneyama, & Tsurugizawa, 2014). It is important to bear in mind that the mPFC is not a uniform brain territory, especially when considering the paucity of studies exploring the role of the dorsal division of the mPFC in CTA memory. A recent study showed that CTA acquisition is associated with ERK and NMDAr NR1 subunit phosphorylation in the prelimbic (PL) region of the PFC, suggesting a role of this cortex in CTA behavior (Marotta et al., 2014). Nevertheless, most of the previous work targeted the infralimbic (IL) region of the mPFC and/or described its role in CTA extinction (Akirav et al., 2006; Mickley, Kenmuir, Yocom, Wellman, & Biada, 2005; Mickley et al., 2007), leaving aside the study of dorsal regions (PL and cingulate cortices) of the mPFC and, importantly, its role in CTA memory. In this context and given that we recently showed that the dorsal mPFC participates in aversive memory processing using an inhibitory avoidance task (Gonzalez et al., 2013), we investigated the involvement of the dorsal mPFC in CTA memory formation and expression.

We utilized 3-month-old male Wistar rats (250–300 g) maintained under a 12-h light/dark cycle (lights on at 7:00 a.m.) at 23 °C with water and food *ad libitum* unless otherwise stated.

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One week before experimental manipulations, animals were anesthetized and bilaterally implanted with 22-G guide cannulas aimed to the dorsal mPFC (Fig. 1G: AP + 3.20/LL ± 0.75/DV − 3.20 mm from bregma, according to Paxinos & Watson, 1997). For the CTA task, animals were deprived of water for 24 h and habituated to drink water from a graduated tube (20 min each day, for 3 days). In training session (CS–US association), water was substituted with saccharin, (CS, 0.1% w/v) and 30 min later the animals were injected intraperitoneally (ip) with LiCl (US, 0.15 M; 7.5 ml/kg). Rats were tested for retention only once: 90 min, 3 days or 21 days after training. We performed two control groups in the 90-min retention experiments to exclude hydration or sickness effect on behavior. In the hydration control group, rats were trained with saccharin and 30 min later received an ip injection of saline. In the sickness control group saccharin was associated with LiCl ip injection and tested with water instead of saccharin. Training and test sessions lasted 20 min. Saccharin consumption percentage was calculated as follows: consumption in the test

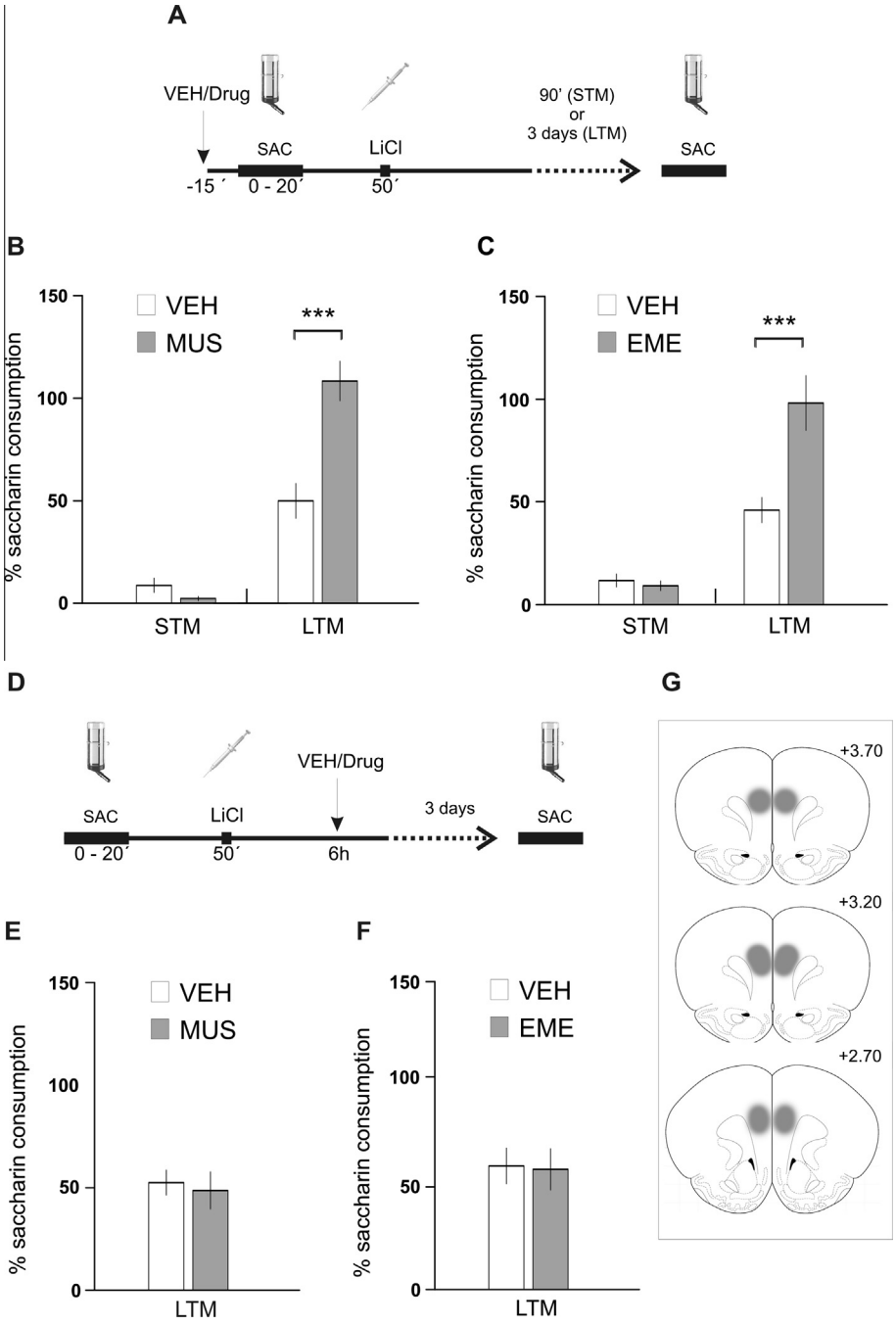

Fig. 1. Neural activity and protein synthesis are required in the dorsal mPFC for CTA memory consolidation. (A and D) Schematic representation of the experimental protocols. CTA STM (90 min) or LTM (3 days) were evaluated after intra-mPFC infusions of vehicle (VEH), (B) muscimol (MUS) or (C) emetine (EME) administrated 15 min before training. In another set of experiments, CTA LTM was also evaluated after intra-mPFC infusions of MUS (E) or EME (F) administrated 6 h after training. In all experiments (except for MUS and EME treatments tested for LTM in panels B and C) there were significant differences in saccharin consumption between training and test sessions ($P < 0.05$). (G) Schematic representation of drug infusion areas, showing rat brain sections at three rostrocaudal planes (+3.70, +3.20 and +2.70 from bregma) taken from the atlas of Paxinos and Watson (1997). In shading, the extension of the area reached by the infusions in mPFC. Saccharin (SAC) consumption is expressed as mean percentage ± SEM relative to acquisition session. *** $P < 0.001$.