Neurobiology of Learning and Memory 126 (2015) 1–6

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Rapid Communication

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

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ARTICLE INFO

Article history:
Received 30 March 2015
Revised 6 October 2015
Accepted 10 October 2015
Available online 19 October 2015

Keywords:
NMDA receptor
Protein synthesis
Neural activity
APV
Muscimol

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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http://dx.doi.org/10.1016/j.nlm.2015.10.007
1074-7427/

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

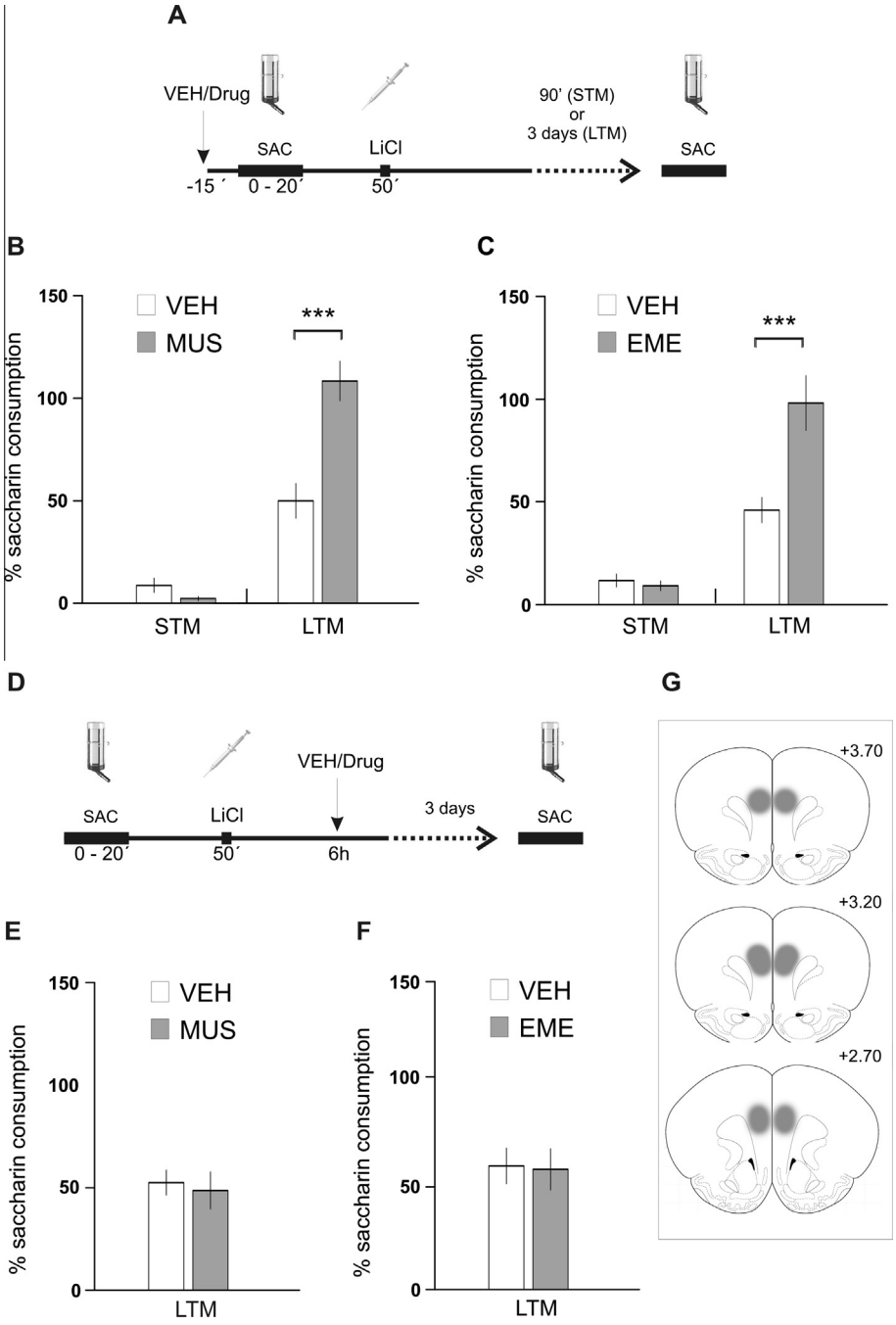

Fig. 1. Neural activity and protein synthesis are required in the dorsal mPFC for CTA memory consolidation. (A and D) Schematic representation of the experimental protocols. CTA STM (90 min) or LTM (3 days) were evaluated after intra-mPFC infusions of vehicle (VEH), (B) muscimol (MUS) or (C) emetine (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. *** $P < 0.001$.

session × 100/consumption in the training session. Placement of the cannulas was histologically verified to exclude subjects with misplaced cannulas from data analysis. Statistical analysis between groups was performed using two-tailed Student's *t* test or ANOVA (Prism 4.01; GraphPad Software). $P < 0.05$ was considered significant. Experimental procedures were performed in accordance with the USA National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Animal Care and Use Committees (CICUAL) of the University of Buenos Aires.

To establish the mPFC requirement in CTA memory consolidation, we performed intra-mPFC infusions of the GABAa receptor agonist muscimol (MUS; 0.1 μg/μl; 1 μl/side) or the protein synthesis inhibitor emetine (EME; 50 μg/μl; 1 μl/side) 15 min before training (Fig. 1A). Both treatments impaired CTA long-term memory (LTM) evaluated 3 days later (Fig. 1B: MUS vs. vehicle (VEH), $t_{(26)} = 4.573$, $P < 0.0001$, $n = 12$, 16; Fig. 1C: EME vs. VEH, $t_{(34)} = 4.038$, $P = 0.0003$, $n = 14$, 22) without affecting CTA short-term memory (STM) evaluated 90 min after training (Fig. 1B: MUS vs. VEH, $t_{(15)} = 1.562$, $P = 0.1390$, $n = 7$, 12; Fig. 1C: EME vs. VEH, $t_{(29)} = 0.6348$, $P = 0.5305$, $n = 14$, 17). The reduction in saccharin consumption during STM retention test is not attributed to hydration or sickness: CS–US: 1.67 + 0.25%; hydration control group: 107.21 + 10.79%; sickness control group: 100.69 + 29.29%; $^{**}P < 0.0006$, Tukey test after ANOVA, $n = 8$. No difference in saccharin consumption during the training session was observed between groups ($P > 0.05$, ANOVA; mean 9.2 ± 0.5 ml). MUS or EME infusion given 6 h after training did not impaired CTA 3-day LTM (Fig. 1E: MUS vs. VEH, $t_{(11)} = 0.3424$, $P = 0.7385$, $n = 7$, 6; Fig. 1F: EME vs. VEH, $t_{(11)} = 0.1254$, $P = 0.9024$, $n = 6$, 7). These results suggest that there is a critical time window where both neural activity and protein synthesis in the dorsal mPFC are needed for CTA consolidation. NMDAr-mediated neurotransmission is known to be crucial for neural plasticity, learning and memory (Cammarota et al., 2000; Morris, 2013; Morris, Anderson, Lynch, & Baudry, 1986). Moreover, pharmacological inactivation of NMDAr in the insular cortex and the amygdala impairs the formation of the aversive taste memory trace (Escobar, Alcocer, & Bermúdez-Rattoni, 2002; Gutiérrez, Hernández-Echeagaray, Ramírez-Amaya, & Bermúdez-Rattoni, 1999; Rosenblum et al., 1997; Yasoshima et al., 2000). We set out to analyze the involvement of dorsal mPFC NMDAr activity (and downstream biochemical pathways) in CTA memory consolidation. We found that intra-mPFC infusions of the NMDAr antagonist D,L-2-amino-5-phosphonovaleric acid (APV; 1 μg/μl; 1 μl/side) 15 min before training impaired CTA LTM evaluated 3 days later (Fig. 2B: APV vs. VEH, $t_{(13)} = 2.643$, $P = 0.0203$, $n = 8$, 7). This treatment apparently did not disrupt CTA acquisition since animals showed intact STM (Fig. 2B: APV vs. VEH, $t_{(5)} = 1.249$, $P = 0.2670$, $n = 6$, 6), indicating that CTA memory expression at very early stages relies on other brain structures, possibly on the insular cortex or the amygdala (Ma et al., 2011). NMDAr signaling is known to activate CaMKII and PKA pathways, which are relevant for memory formation in multiple systems (Abel & Nguyen, 2008; Cammarota et al., 2000; Silva, Stevens, Tonegawa, & Wang, 1992). In order to assess the potential contribution of these signaling pathways in the mPFC, we treated animals with the inhibitor of CaMKII phosphorylating activity KN-93 (25 μg/μl; 1 μl/side) and found that partially impaired CTA LTM when infused 15 min pre-training (Fig. 2C: KN-93 vs. VEH, $t_{(26)} = 2.147$, $P = 0.0413$, $n = 15$, 13); but treatment with the inhibitor of PKA activation RP-cAMP (0.5 μg/μl; 1 μl/side) had no effect on CTA LTM (Fig. 2D: RP-cAMP vs. VEH, $t_{(16)} = 0.2577$, $P = 0.7999$, $n = 8$, 9). These findings suggest that NMDAr signaling might be involved in CTA memory consolidation through a CaMKII-dependent pathway in the dorsal mPFC.

The mPFC is also crucial for recent and remote memory retrieval (Corcoran & Quirk, 2007; Gonzalez et al., 2013). To determine if the dorsal mPFC is required for CTA memory expression we inactivated this cortex with MUS infusions 15 min before a test session carried out either 3 days or 21 days after training. Both recent and remote LTM were disrupted (Fig. 3B: MUS vs. VEH, $t_{(10)} = 3.317$, $P = 0.0034$,

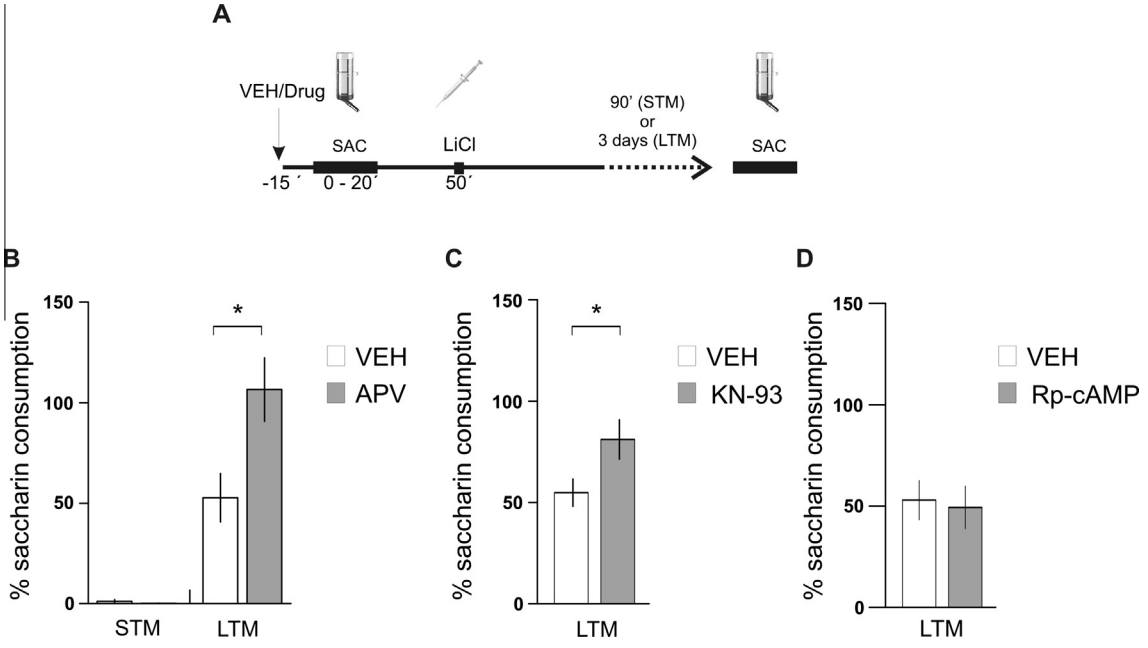

Fig. 2. CTA memory consolidation requires NMDA receptor and CaMKII activity in the dorsal mPFC. (A) Schematic representation of the experimental protocol. (B) CTA STM (90 min) or LTM (3 days) were evaluated after intra-mPFC infusions of vehicle (VEH) or the NMDA receptor antagonist, APV, administrated 15 min before training. LTM was evaluated after intra-mPFC infusions of vehicle (VEH), a selective Ca^{2+}/calmodulin-dependent protein kinase II inhibitor, KN-93 (C) or Rp-cAMP, a competitive inhibitor of the activation of cAMP-dependent protein kinases by cAMP (D), administrated 15 min before training. In all experiments (except APV-treated group tested for LTM in panel B) there were significant differences in saccharin consumption between training and test sessions ($P < 0.001$). Saccharin consumption is expressed as mean percentage ± SEM relative to acquisition session. $^{*}P < 0.05$.

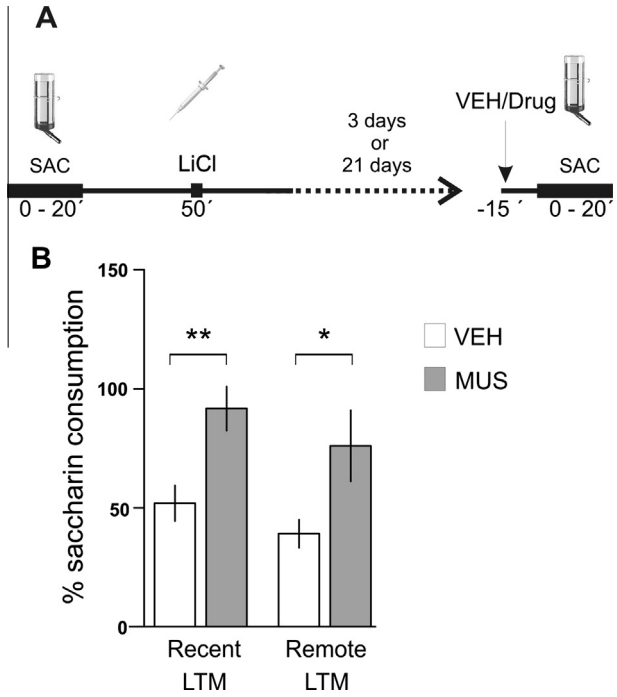

Fig. 3. Activation of the dorsal mPFC is required for the expression of recent and remote CTA LTM. (A) Schematic representation of the experimental protocol. (B) CTA recent LTM (3 days) or remote LTM (21 days) were evaluated after intra-mPFC infusions of vehicle (VEH) or muscimol (MUS) administrated 15 min before the test session. In VEH-treated groups there were significant differences in saccharin consumption between training and test sessions ($P < 0.05$). Saccharin consumption is expressed as mean percentage ± SEM relative to acquisition session. $^{*}P < 0.05$, $^{**}P < 0.01$.

$n = 11, 11$; for recent LTM and $t_{(15)} = 2.407$, $P = 0.0294$, $n = 8, 7$ for remote LTM), indicating that dorsal mPFC neural activity is also essential for CTA memory retrieval.

Our results demonstrate for the first time that the dorsal mPFC is required for CTA memory consolidation. Together with previous findings indicating that CTA training is accompanied by increases in NMDAr and ERK phosphorylation in the mPFC (Marotta et al., 2014) and those showing the role of this brain region in CTA memory retrieval (Reyes-López, Nuñez-Jaramillo, Morán-Guel, & Miranda, 2010), our present findings endorse the idea that dorsal mPFC contributes to the formation and expression of CTA memory. In this study, we used a pharmacological approach that targets multiple components of the machinery involved in memory processing, showing that neural activity, *de novo* protein synthesis, NMDAr neurotransmission and CaMKII activity in this cortex are essential for the normal storage of the taste aversive memory trace. So far, only a small number of studies addressed the role of the mPFC in CTA memory formation, all of them performing lesions in this cortex or pharmacologically targeting the IL prefrontal subdivision. The studies based on irreversible lesions of the region are not consistent. While mPFC neurotoxin administration cause acquisition and retention deficits (Hernádi et al., 2000), ablation of frontal cortex do not impair CTA (Fresquet, Yamamoto, & Sandner, 2003; Mogensen & Divac, 1993). These methodological tools are no longer adequate for addressing the participation of brain structures on memory processing since this kind of intervention has several drawbacks (Izquierdo & Medina, 1998), including a lack of discrimination between memory acquisition, consolidation and/or expression. These facts strongly limit the interpretations and conclusions reached by irreversible lesion studies. Regarding studies with pharmacological approaches, Akirav and coworkers showed that protein synthesis inhibition in the mPFC-IL subdivision is required for extinction but not consolidation of CTA memory (Akirav et al., 2006). This study is in line with previous work demonstrating an involvement of the IL cortex in memory extinction (Maroun, Kavushansky, Holmes, Wellman, & Motanis, 2012; Mickley et al., 2005; Xin et al., 2014; but see Reyes-López et al., 2010). It has been already proposed that the different subregions of mPFC, the IL and the PL, have opposite effects on the modulation of fear memories (Vidal-Gonzalez, Vidal-Gonzalez, Rauch, & Quirk, 2006). While the mPFC-IL is crucial for fear extinction learning (Herry et al., 2010; Pape & Pare, 2010; Peters, Dieppa-Perea, Melendez, & Quirk, 2010), the PL region of the mPFC would be involved in the expression of conditioned fear (Gonzalez et al., 2013; Sierra-Mercado, Padilla-Coreano, & Quirk, 2011). However it is not yet clear in which specific manner the IL and PL regulate CTA task, an aversive experience not driven by fear.

Recently, Uematsu et al. (2014) showed that during CTA learning, PL neuronal activity synchronizes with the amygdala and insular cortex, brain regions essential for CTA acquisition and memory processing. In this context and considering the results presented here, we propose that the dorsal mPFC is part of the brain network recruited during CTA storage. In a more general view, this work supports recent evidence pointing to the dorsal mPFC as an important component of a neural circuit involved in aversion (Bravo-Rivera et al., 2014; Euston et al., 2012; Gonzalez et al., 2014; Lammel et al., 2012; Lee, Vogt, Rubenstein, & Sohal, 2014). This network includes the dopaminergic neurons from the VTA (Pignatelli & Bonci, 2015) and their inputs from the lateral habenula (Lammel et al., 2012), and several targets of the dorsal mPFC such as the amygdala, the insular cortex or the nucleus accumbens (Vertes, 2004, 2006). Therefore, it is tempting to suggest that mPFC may participate in CTA by signaling the aversive component and the saliency of the experience.

The findings presented here contribute to elucidate the basic mechanisms underlying CTA memory consolidation in the dorsal mPFC. Previous works focusing on the insular cortex demonstrated a major role for glutamatergic neurotransmission on CTA memory formation, since blockade of NMDAr around the time of acquisition inhibited taste aversion memory consolidation (Gutiérrez et al., 1999). In the present study, we demonstrate that CTA memory consolidation involves NMDAr-dependent mechanisms in the dorsal mPFC which are, at least in part, likely mediated by CaMKII activity. Given that high doses of KN-93 could also inhibit other CaMK isoforms (Gao et al., 2013), we cannot rule out the possible involvement of CaMKI or CaMKIV in CTA memory formation. However, we can exclude the possibility that the PKA signaling pathway in PFC is involved in CTA memory formation since the dose of 0.5 μg of Rp-cAMPS was previously shown to impair different memory tasks (Barros et al., 2000; Kobori, Moore, & Dash, 2015; Souza et al., 2002; Vianna et al., 2000).

In agreement with previous works that show that the mPFC is involved in recall of recent contextual fear and inhibitory avoidance memories (Einarsson & Nader, 2012; Gonzalez et al., 2013; Holloway & McIntyre, 2011) our results show that the dorsal mPFC is also required for CTA memory expression, regardless of the age of the memory trace.

This study identifies the dorsal mPFC as a new player in the circuitry that leads to the normal storage of the aversive taste memory trace. The diverse (and many times, opposite) roles of the different divisions of the mPFC on memory processing reminds us of the intricacies of top-down interactions modulating complex behaviors. Further studies dissecting the cellular and molecular mechanisms involved will be required to better understand the influence of mPFC activity in aversive memory processing.

Acknowledgments

This study was supported by grants from Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT, Argentina) to J.H.M. and H.V.

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