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Hippocampal noradrenergic activation is necessary for object recognition memory consolidation and can promote BDNF increase and memory persistence

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ABSTRACT

Previously we showed that activation of the Nucleus of the Solitary Tract (NTS)–Nucleus Paragigantocellularis (PGi)–Locus coeruleus (LC) pathway, which theoretically culminates with norepinephrine (NE) release in dorsal hippocampus (CA1 region) and basolateral amygdala (BLA) is necessary for the consolidation of object recognition (OR) memory. Here we show that, while the microinjection of the beta-noradrenergic receptor blocker timolol into CA1 impairs OR memory consolidation, the microinjection of norepinephrine (NE) promotes the persistence of this type of memory. Further, we show that OR consolidation is attended by an increase of norepinephrine (NE) levels and of the expression of brain derived neurotrophic factor (BDNF) in hippocampus, which are impaired by inactivation of the NTS–PGi–LC pathway by the infusion of muscimol into the NTS.

1. Introduction

It is known that emotionally arousal-induced memory consolidation requires noradrenergic activation of the basolateral amygdala (BLA) (Beldjoud, Barsegyan, & Roozendaal, 2015; McGaugh, 2000) as studied in inhibitory avoidance (IA) and other tasks (Beldjoud et al., 2015; McGaugh, 2015). Previous research strongly suggests that the NE release in the BLA during the consolidation of emotional memories depends on arousal induced by activation of the NTS (Nucleus of the Solitary Tract)–PGi (Paragigantocellularis nucleus)–LC (Locus Coeruleus)–BLA pathway: Garcia-Medina and Miranda (2013) found that stimulation of the NTS promotes the release of NE in lateral and basolateral amygdala, and Roozendaal, Williams, and McGaugh (1999) showed that the activation of glucocorticoid receptors in NTS facilitates memory consolidation of inhibitory avoidance learning, among other researches. This pathway (NTS–PGi–LC) was proposed to play a major role in the modulation of the consolidation of aversive behaviors by Cedric Williams, James McGaugh and their associates over 20 years ago (Clayton and Williams, 2000a,b; King & Williams, 2009; Miyashita & Williams, 2004; Williams & McGaugh, 1993) and was suggested to play a similar role in that of OR by two of the present authors two years ago (Mello-Carpes & Izquierdo, 2013).

Previously, our group demonstrated that basolateral and central amygdala noradrenergic activation is not necessary to promote object recognition task (OR) consolidation (Mello-Carpes & Izquierdo, 2013), although others had shown that the noradrenergic activation of basolateral amygdala can modulate the consolidation of this memory (Roozendaal, Castello, Vedana, Barsegyan, & McGaugh, 2008). OR memory is viewed as a relatively non-emotional declarative memory; however, considering that there is a lot of variability across OR procedures among different studies it is not easy to draw a meaningful conclusion about this. However, all OR task protocols do involve the presentation of novelty to the animal, and the detection of and reaction to novelty are major functions of the hippocampus (Acquas, Wilson, & Fibiger, 1996; Menezes et al., 2015; Netto et al., 1985), we hypothesized that this type of memory may also require the participation of this pathway, but using taking as the last stage hippocampal noradrenergic activation, instead of that of the amygdala. In a previous paper (Mello-Carpes & Izquierdo, 2013) we showed that, although the

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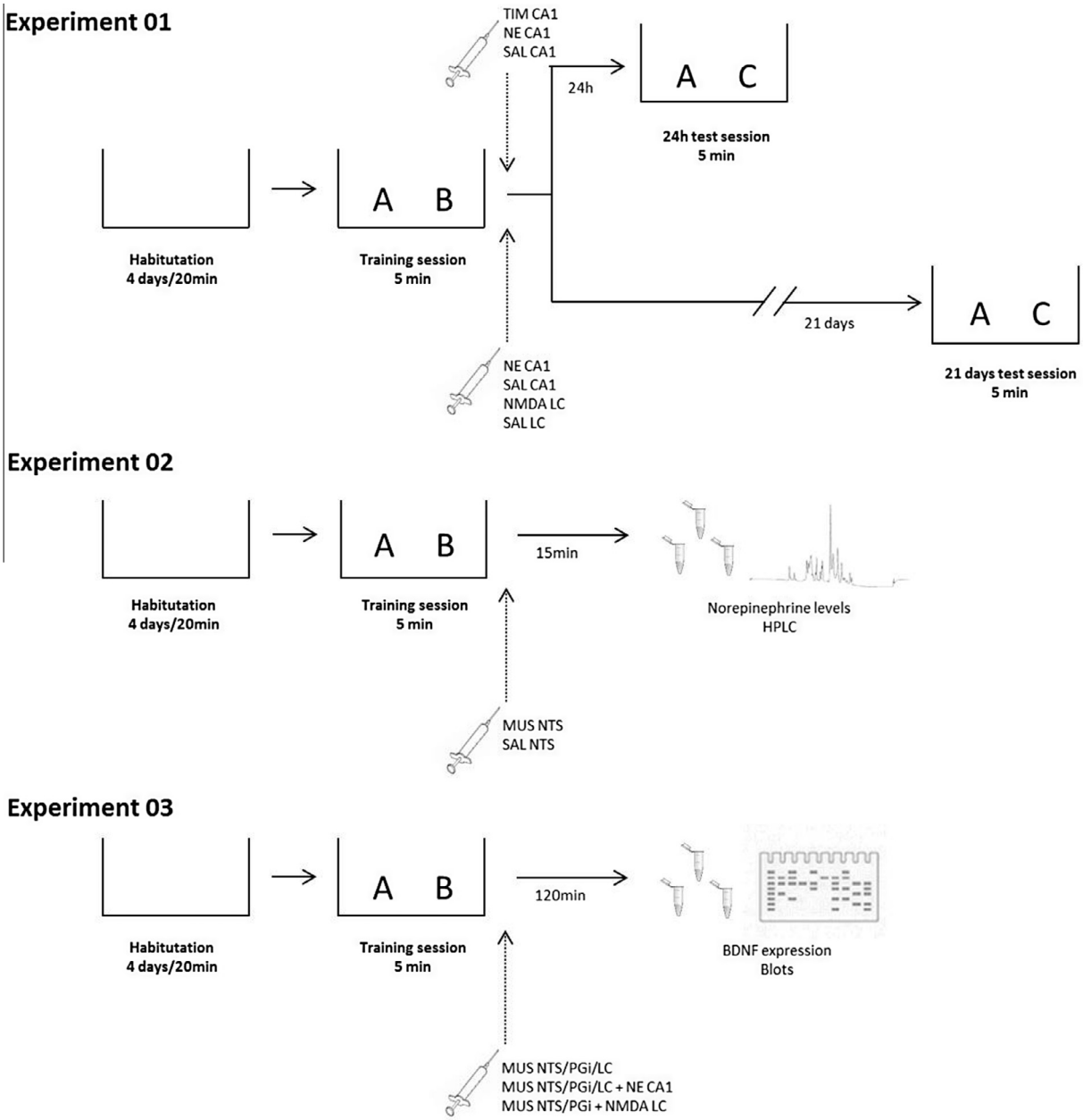

Fig. 1. Experimental design. The experiments were organized in three stages. Experiment 1: The rats were habituated to the object recognition arena without any object for 4 days (20 min/day). In the training session rats were exposed to two different objects (A and B) for 5 min; immediately after that the received bilateral hippocampal infusions (1 μl/side in CA1) of vehicle (VEH; saline), timolol (TIM; 1 μg/μl for CA1) or norepinephrine (NE; 1 μg/μl) and, on the test session, realized 24 h after, animals were exposed to a familiar (A) and a novel object (C) for five minutes to evaluate long-term memory retention. Other group of animals received bilateral LC (Locus Coeruleus) infusions (0.25 μl/side) of vehicle (VEH; saline) or NMDA (NMDA; 0.1 μg/μl) or bilateral hippocampal infusions (1 μl/side in CA1) of vehicle (VEH; saline) or norepinephrine (NE; 1 μg/μl). On the test session, realized 21 days after, all animals were exposed to a familiar (A) and a novel object (C) for five minutes to evaluate long-term memory persistence. Experiment 2: The rats were habituated to object recognition arena without any object for 4 days (20 min/day). On training session rats were exposed to two different objects (A and B) for 5 min and immediately after that received bilateral infusions (0.5 μl/side in NTS) of vehicle (VEH; saline) or muscimol (MUS 0.01 μg/μl); 15 min later the hippocampus were removed and prepared for HPLC determination of norepinephrine levels. Experiment 3: The rats were habituated to object recognition arena without any object for 4 days (20 min/day). On training session rats were exposed to two different objects (A and B) for 5 min and immediately after that received bilateral infusions of different drugs or combinations of drugs and/or vehicle in (MUS in NTS/PGi/LC; or MUS in NTS/PGi/LC + NE CA1; or MUS NTS/PGi + NMDA LC); 120 min later the hippocampus were removed and prepared for immunoblot determination of BDNF protein expression.

connection of the medullary nuclei to the amygdala is not involved in OR consolidation, the connection of NTS–PGi–LC pathway to hippocampus is. Indeed, other evidences from previous works indicates an important role of the hippocampus in the consolidation of this task (Balderas, Rodriguez-Ortiz, & Bermudez-Rattoni, 2015; Clarke, Cammarota, Gruart, Izquierdo, & Delgado-García, 2010; Cohen & Stackman, 2015; Furini et al., 2010; Myskiw et al., 2008).

In addition to our previous data, here we show that, while the hippocampal CA1 injection of β-adrenergic blocker timolol impairs OR memory consolidation, the injection of NE promotes the persistence of this memory. The LC stimulation, which culminates with the increase of NE release in hippocampus, promotes memory persistence too. Also, we demonstrate that OR learning promotes the hippocampal increase of NE levels, which are disrupted by inactivation of NTS–PGi–LC pathway after OR training. These results confirm the hippocampal noradrenergic modulation of OR memory.

Still, considering that recent findings suggest that OR consolidation requires an increase of BDNF expression in CA1 region of