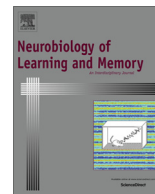




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BDNF controls object recognition memory reconsolidation

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ABSTRACT

Reconsolidation restabilizes memory after reactivation. Previously, we reported that the hippocampus is engaged in object recognition memory reconsolidation to allow incorporation of new information into the original engram. Here we show that BDNF is sufficient for this process, and that blockade of BDNF function in dorsal CA₁ impairs updating of the reactivated recognition memory trace.

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1. Introduction

Cognitive representation of the environment requires object recognition memory (ORM). ORM reactivation induces hippocampus-dependent reconsolidation only when it occurs concomitantly with the acquisition of information about a novel object (Rossato et al., 2007). This suggests that novelty may modulate ORM persistence. Therefore, understanding the involvement of the hippocampus in ORM reconsolidation is necessary to develop new therapies to prevent the pervasive recollection of distressing declarative memories and treat its consequences. Brain-Derived Neurotrophic Factor (BDNF) is a member of the neurotrophin family of growth factors essential for synapse formation and maintenance (Cowansage, LeDoux, & Monfils, 2010; Panja & Bramham, 2014). In the rat hippocampus, BDNF mediates spatial and recognition memory formation (Francis et al., 2012; Furini et al., 2010; Harvey et al., 2008; Petzold, Psotta, Brigadski, Endres, & Lessmann, 2015; Silhol, Arancibia, Maurice, & Tapia-Arancibia, 2007) and is sufficient for reconsolidation of fear extinction (Radiske et al., 2015). Thus, we wondered whether this neurotrophin also maintains the recognition memory trace upon reactivation.

2. Materials and methods

2.1. Subjects and surgery

We used 3-month-old naïve male Wistar rats weighting 300–350 g at the start of the experiments. We kept the animals in groups of five with free access to food and water at 23 °C under a 12:12 h light/dark cycle (lights on at 06:00 AM). We implanted the animals with 22-gauge guides aimed to the CA₁ region of the dorsal hippocampus (stereotaxic coordinates: anteroposterior, –4.2 mm; laterolateral, ± 3.0 mm; dorsoventral, –3.0 mm) under ketamine/xylazine anesthesia. Immediately after surgery, the animals received a single dose of meloxicam (0.2 mg/kg; subcutaneous) as analgesic. All experiments were in accordance to the national animal care legislation and guidelines (Brazilian Law 11794/2008) and approved by the UFRN Animal Welfare Committee.

2.2. Behavioral procedures and data analysis

One week after surgery, we handled the animals and allowed them to habituate to the training arena (a 60 cm $\times$ 60 cm $\times$ 60 cm open field) for 20 min/day during 4 days. Twenty-four hours after the last habituation session, we trained the animals in a novel object recognition memory task (NOR), as previously described (Balderas, Rodríguez-Ortiz, & Bermudez-Rattoni, 2013, 2015; Dix & Aggleton, 1999; Ennaceur & Delacour, 1988; Ennaceur, Neave, & Aggleton, 1997; Myskiw et al., 2008; Rossato et al., 2007). NOR

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is based on the rodents' natural preference to explore novel objects and involves a 5-min long exposure session to two novel stimuli objects (Objects A and B) made of metal, glass or glazed ceramic in the training arena (Training Session). Twenty-four hours after training, we re-exposed the animals for 5 min to one of the objects presented during training (Object A) alongside with a novel object (Object C) to reactivate the recognition memory trace (Reactivation Session). One or seven days later, we exposed the animals to either the familiar Object A and novel Object D (Group AD), to the familiar Object B and a novel Object D (Group BD), or to the familiar Object C and a novel Object D (Group CD) for five minutes to evaluate long-term memory (LTM) retention (Test Session). We defined exploration as sniffing or touching the stimuli objects with the muzzle and/or forepaws. A discrimination index ($DI = (\text{Time exploring novel object} - \text{Time exploring familiar object}) / \text{Total object exploration time}$) was used as a measure of discrimination between familiar and novel objects (Aggleton, Albasser, Aggleton, Poirier, & Pearce, 2010; Aubele, Kaufman, Montalman, & Kritzer, 2008; Langston & Wood, 2010; Cohen et al., 2008; Till et al., 2015). DI varies between -1 and $+1$. Positive DI scores indicate the rats' preference for novel objects. A DI score of zero indicates chance performance (i.e. no discrimination). Data were analyzed using one-sample t test with theoretical mean = 0 to determine object preference. Groups were compared by one-way or two-way ANOVA followed by Bonferroni's multiple comparisons, as appropriate.

2.3. Drugs and infusion procedure

Anisomycin (ANI; 100 $\mu\text{g}/\text{side}$), α -amanitin (AMA; 45 ng/side) and muscimol (MUS; 0.1 $\mu\text{g}/\text{side}$) were from Sigma-Aldrich and were dissolved (0.1% DMSO in sterile saline; pH 7.2) and stored protected from light at -20°C until use. Function-blocking anti-BDNF antibody (BDNF_{ab}; 0.5 $\mu\text{g}/\text{side}$; Bekinschtein et al., 2007) and control sheep IgG were from Merck Millipore and were dissolved in sterile saline and stored at -20°C until use. Drug doses were chosen based on previous studies (Da Silva et al., 2008; Rossato et al., 2007; Cholvin et al., 2016). At the time of drug delivery, infusion cannulas were fitted into the guides and injections (1 $\mu\text{l}/\text{side}$) carried out over 60 s with a microinjection pump. The cannulas were left in place for 60 additional seconds to minimize backflow. Placement of the cannulas was verified postmortem: 2–4 h after the last behavioral test, 1 μl of 4% methylene-blue was infused as described above and the extension of the dye 30 min thereafter taken as indication of the diffusion of the drug previously injected. Only data from animals with correct cannula placement (96% of the total) were considered for statistical analysis.

2.4. Immunoblotting

Animals were killed by decapitation at different times after ORM reactivation (5, 30, 120 or 360 min) and the CA₁ region of the dorsal hippocampus rapidly dissected out and homogenized in ice-chilled homogenization buffer (20 mM Tris-HCl, pH 7.4, containing 0.32 M sucrose, 1 mM EDTA, 1 mM EGTA, 1 mM PMSF, 10 $\mu\text{g}/\text{ml}$ aprotinin, 15 $\mu\text{g}/\text{ml}$ leupeptin, 10 $\mu\text{g}/\text{ml}$ bacitracin, 10 $\mu\text{g}/\text{ml}$ pepstatin, 50 mM NaF, and 1 mM sodium orthovanadate). Protein concentration was determined using the BCA protein assay kit (Pierce). SDS/PAGE was performed under reducing conditions and proteins were electro-transferred onto PVDF membranes (Immobilon-P, Merck Millipore). Blots were blocked for 2 h in TTBS (100 mM Tris-HCl, 0.9% NaCl, 0.1% Tween 20, pH 7.5) and then incubated with anti-BDNF (1:5000 dilution; Santa Cruz Biotechnology), anti-pro-BDNF (1:5000 dilution; Sigma-Aldrich) or anti- β -tubulin (1:20,000; Abcam) antibodies overnight at 4°C . The blots

were then washed and incubated with HRP-coupled anti-IgG antibody. Immunoreactivity was detected using the West-Pico enhanced chemiluminescence kit (GE Healthcare). Blots were quantified using an Amersham Imager 600 RGB system (GE Healthcare). Data were analyzed using repeated-measures ANOVA followed by Dunnett's multiple comparisons.

3. Results

To analyze the involvement of hippocampal BDNF in ORM reconsolidation, we trained rats in the NOR task using two different stimuli objects (Object A and Object B). Twenty-four hours later, we re-exposed the animals to a familiar object (Object A) alongside a novel object (Object C) for 5 min to reactivate the ORM trace. Immediately after that, the animals received bilateral intra-CA₁ infusions of vehicle (VEH; control sheep IgG) or function-blocking anti-BDNF antibody (BDNF_{ab}; 0.5 $\mu\text{g}/\text{side}$). One day later, the animals were randomly assigned to one out of three experimental groups and allowed to explore either the familiar Object A and a novel Object D (Group AD), the familiar Object B and a novel Object D (Group BD), or the familiar Object C and a novel Object D (Group CD), to evaluate long-term memory (LTM) retention. Animals that received VEH after ORM reactivation discriminated between novel and familiar objects during the test (Fig 1A). This indicates that they remembered Objects A and B, which were both present during the training session, and also that they acquired memory for Object C during the reactivation session. Animals that received BDNF_{ab} after ORM reactivation did not discriminate familiar Objects A and C from novel Object D, indicating that blockade of BDNF function impaired retention of the memory for Object A, which was firstly presented during training, and hindered memory formation for Object C, presented during reactivation (Fig 1A: $t_{(18)} = 5.020$, $p < 0.0001$ vs VEH; $t_{(15)} = 2.710$, $p = 0.0161$ vs VEH in unpaired Student's t test, respectively). BDNF_{ab} did not affect memory for Object B, which was present during training but not during reactivation (Fig 1A). The time elapsed between reactivation and test sessions had no effect on the amnesia caused by BDNF_{ab} (Fig 1B: $t_{(15)} = 2.952$, $p = 0.0099$ vs VEH for Group AD; $t_{(14)} = 3.467$, $p = 0.0038$ vs VEH for Group CD in unpaired Student's t test). BDNF_{ab} did not affect retention when given 6 h after ORM reactivation (Fig 1C). Likewise, BDNF_{ab} had no effect on retention when administered immediately after ORM reactivation with two familiar objects (Fig 1D), when injected after a 5-min long exploration session of the training box arena in the absence of stimuli objects (Fig 1E), or when given 24 h after training in the absence of memory reactivation (Fig 1F). When administered in dorsal CA₁ 15 min before memory reactivation, the GABA_A receptor agonist muscimol (MUS; 0.1 $\mu\text{g}/\text{side}$) impaired ORM expression (Fig 1G, Objects AC: $t_{(32)} = 6.132$, $p < 0.0001$ vs VEH in unpaired Student's t test) and impeded the amnesia caused by post-reactivation BDNF_{ab} (Fig 1G, Objects AD: $F_{(1, 29)} = 4.241$, $p = 0.0485$ pre-reactivation treatment effect and $F_{(1, 29)} = 6.764$, $p = 0.0145$ post-reactivation treatment effect; VEH-BDNF_{ab}: $t_{(29)} = 2.922$, $p < 0.05$ vs VEH-VEH and $t_{(29)} = 3.357$, $p < 0.05$ vs MUS-VEH; MUS-BDNF_{ab}: $t_{(29)} = 0.3760$, ns vs VEH-VEH and $t_{(29)} = 0.6545$, ns vs MUS-VEH in Bonferroni's multiple-comparison test after two-way ANOVA). Confirming and extending previous results (Rossato et al., 2007), we found that intra-CA₁ administration of the protein synthesis blocker anisomycin (ANI; 100 $\mu\text{g}/\text{side}$) or of the RNA polymerase II inhibitor α -amanitin (AMA; 45 ng/side) immediately after ORM reactivation in the presence of a novel object, impaired LTM retention for Objects A and C (Fig 2A: $F_{(2, 26)} = 4.594$, $p = 0.0196$ treatment effect for objects AD and $F_{(2, 24)} = 4.268$, $p = 0.0259$ treatment effect for objects CD; Objects AD: $t_{(26)} = 2.604$, $p < 0.05$ for ANI vs VEH; $t_{(26)} = 2.623$, $p < 0.05$

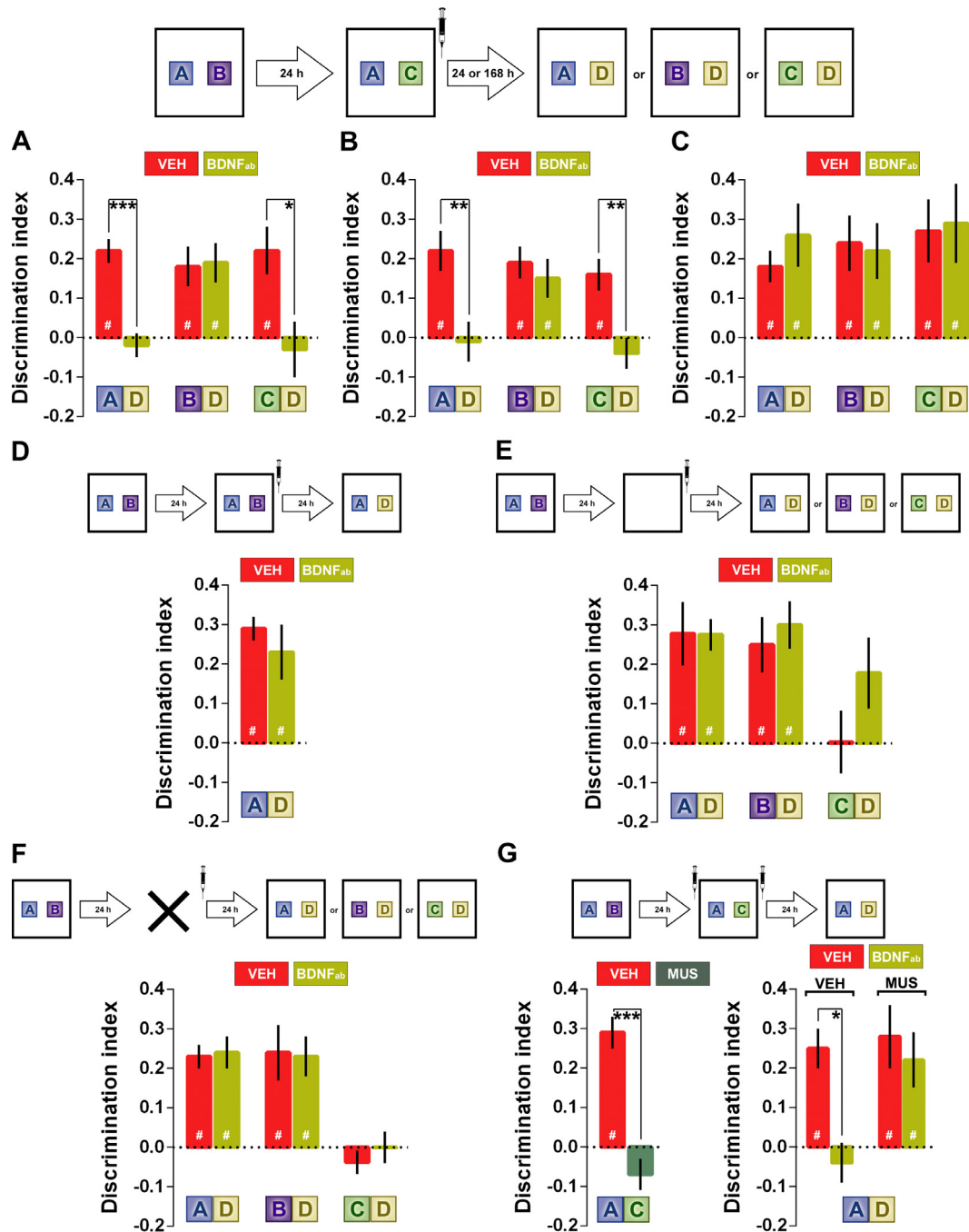


Fig. 1. ORM reconsolidation requires BDNF. (A) Rats were trained in NOR using two different stimuli objects (A and B) and 24 h post-training submitted to a 5-min long ORM reactivation session in the presence of a familiar (A) and a novel object (C). Immediately after memory reactivation, animals received bilateral intra-CA₁ infusions (1 μ l/side) of vehicle (VEH; control sheep IgG in sterile saline) or function-blocking anti-BDNF antibody (BDNF_{ab}; 0.5 μ g/side). One day later, animals were exposed to a familiar (A, B or C) and a novel object (D) for five extra minutes to evaluate LTM retention. (B) Animals were treated as in A, except that LTM was evaluated 168 h after ORM reactivation. (C) Animals were treated as in A, except that they received intra-CA₁ infusions of VEH or BDNF_{ab} 6 h after ORM reactivation. (D) Rats were treated as in A, except that ORM was reactivated in the presence of two familiar objects (A and B). (E) Rats were treated as in A, except that 24 h after training they were left to freely explore the training arena in the absence of stimuli objects. (F) Rats were trained in NOR using two different objects stimuli (A and B). One day after training, the animals received intra-CA₁ infusions of VEH or BDNF_{ab} and were evaluated for retention 24 h later. (G) Animals were treated as in A, except that 15 min before ORM reactivation they received intra-CA₁ infusions of saline or muscimol (MUS; 0.1 μ g/side) and immediately after the reactivation session were given either VEH or BDNF_{ab} in dorsal CA₁. Data (mean $\pm$ SEM) are presented as discrimination index. The dashed lines represent chance level. * p < 0.05 in one-sample Student's t -test with theoretical mean = 0. *** p < 0.001, ** p < 0.01 and * p < 0.05 in unpaired t -test or Bonferroni's multiple-comparison test after two-way ANOVA; n = 7–11 per group.

for AMA vs VEH; Objects CD: $t_{(24)} = 2.491$, $p < 0.05$ for ANI vs VEH; $t_{(24)} = 2.492$, $p < 0.05$ for AMA vs VEH in Bonferroni's multiple-comparison test after one-way ANOVA). ANI and AMA did not affect memory for Object B (Fig 2A: $F_{(2, 24)} = 1.625$, $p = 0.2179$ in Bonferroni's multiple-comparison test after one-way ANOVA) and had no effect on ORM retention when administered after explo-

ration of two familiar objects (Fig 2B: $F_{(2, 31)} = 1.234$, $p = 0.3050$ in Bonferroni's multiple-comparison test after one-way ANOVA). Co-infusion of recombinant BDNF (0.25 μ g/side) right after ORM reactivation reversed the amnesia caused by ANI and AMA (Fig 2C: $F_{(2, 30)} = 0.8159$, $p = 0.4518$ in Bonferroni's multiple-comparison test after one-way ANOVA). Immunoblot analysis of total homoge-

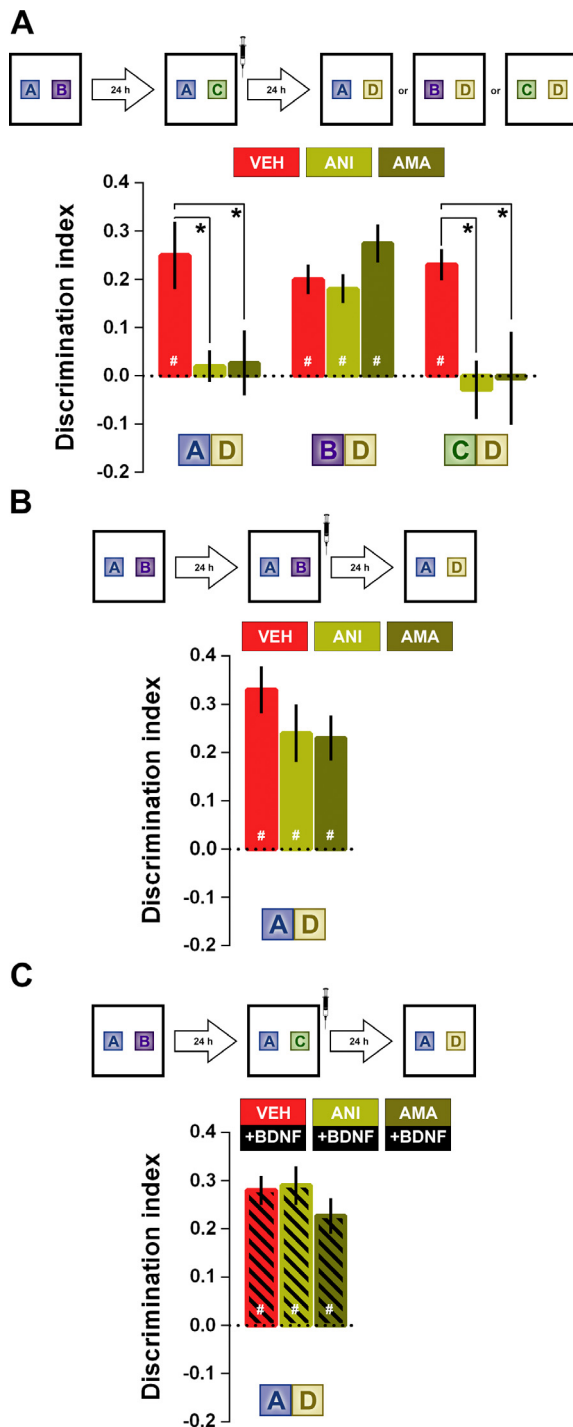


Fig. 2. BDNF reverses the amnesia induced by protein synthesis or gene expression inhibition. (A) Rats were trained in NOR using two different stimuli objects (A and B). Twenty-four hours post-training the animals were submitted to a 5-min long ORM reactivation session in the presence of a familiar (A) and a novel object (C). Immediately after memory reactivation, the animals received bilateral intra-CA₁ infusions (1 μ l/side) of vehicle (VEH), anisomycin (ANI; 100 μ g/side) or α -amanitin (AMA; 45 ng/side). One day later, the animals were exposed to a familiar (A, B or C) and a novel object (D) for five minutes to evaluate LTM. (B) Rats were treated as in A, except that ORM was reactivated in the presence of two familiar objects (A and B). (C) Rats were treated as in A, except that VEH, ANI and AMA were co-infused with BDNF (0.25 μ g/ μ l). Data (mean $\pm$ SEM) are presented as discrimination index. The dashed lines represent chance level. # $p < 0.05$ in one-sample Student's t -test with theoretical mean = 0. * $p < 0.05$ in unpaired t -test or Bonferroni's multiple-comparison test after one-way ANOVA; $n = 7$ –13 per group.

nates prepared from the CA₁ region of the dorsal hippocampus showed that ORM reactivation increased BDNF expression (Fig 3A: $F_{(4, 20)} = 4.390$, $p = 0.0104$). This increase was accompanied by a reduction in pro-BDNF protein levels (Fig 3B: $F_{(4, 20)} = 4.035$, $p = 0.0147$), suggesting that ORM reactivation induces BDNF maturation in the hippocampus.

4. Discussion

Previously, we demonstrated that ORM requires gene expression and *de novo* protein synthesis in the hippocampus for reestablishment after retrieval (Rossato et al., 2007). Here, we confirmed that reactivation in the presence of a novel object destabilizes ORM to initiate reconsolidation in the hippocampus, and demonstrated that BDNF is sufficient for this process, controlling the integration of new information into the recognition trace. We also presented evidence showing that ORM retrieval increases BDNF levels in dorsal CA₁ and that activation of BDNF signaling after ORM reactivation reverses the amnesia caused by inhibitors of mRNA and protein synthesis. Exogenous BDNF impedes the amnesic effect of protein and gene expression blockers on several other preparations, including conditioned taste aversion and spatial memory consolidation as well as fear memory extinction (Martínez-Moreno, Rodríguez-Durán, & Escobar, 2011; Ozawa, Yamada, & Ichitani, 2014; Radiske et al., 2015), maybe through a process that involves PKM ζ processing (Mei, Nagappan, Ke, Sacktor, & Lu, 2011). In fact, pathways downstream BDNF receptor activation regulate PKM ζ synthesis and activity (Kelly, Crary, & Sacktor, 2007). Moreover, this neurotrophin can sustain PKM ζ enzymatic activity to maintain the late-phase of long-term potentiation in the hippocampus, even when protein synthesis has been blocked, possibly by inhibiting PKM ζ turnover (Mei et al., 2011). In addition, BDNF increases the expression of a variety of synaptic and translational machinery elements suggesting that it enhances translational capacity at synapses (Liao et al., 2007). Indeed, BDNF regulates mTOR-dependent translation (Takei et al., 2004) and controls the local synthesis of plasticity related proteins such as CaMKII, Arc, Homer 2 and GluR1 (Schratt, Nigh, Chen, Hu, & Greenberg, 2004; Slipczuk et al., 2009; Yin, Edelman, & Vanderklisch, 2002), which are functionally linked to memory reconsolidation (Chia & Otto, 2013; Rich et al., 2016). Some reports, dealing mainly with fear-motivated learning tasks, indicate that BDNF participates in memory consolidation but not reconsolidation (Lee, Everitt, & Thomas, 2004; Lee & Hynds, 2013; Schulz-Klaus, Lessmann, & Endres, 2013). However, this differential involvement of BDNF in memory processing does not seem to be a common property of all kind of memories. For example, exogenous BDNF enhances reconsolidation of avoidance memory in chickens (Samartgis, Schachte, Hazi, & Crowe, 2012), and conditioned taste aversion memory reconsolidation requires BDNF synthesis and signaling in the rat insular cortex (Wang et al., 2012). Duclot and co-workers demonstrated that contextual fear reconsolidation increases BDNF expression in the rat medial prefrontal cortex (Duclot, Perez-Taboada, Wright, & Kabbaj, 2016), and this neurotrophin is essential for reconsolidation of extinction memory, too (Radiske et al., 2015). Moreover, BDNF gene polymorphism has deep effects on fear memory reconsolidation in humans (Asthana et al., 2016). We also found that blocking ORM expression with muscimol prevents the amnesia caused by BDNF_{ab}, confirming that retrieval is necessary for ORM reconsolidation in the hippocampus. On the contrary, previous reports showed that blockers of reconsolidation are effective despite memory expression inhibi-

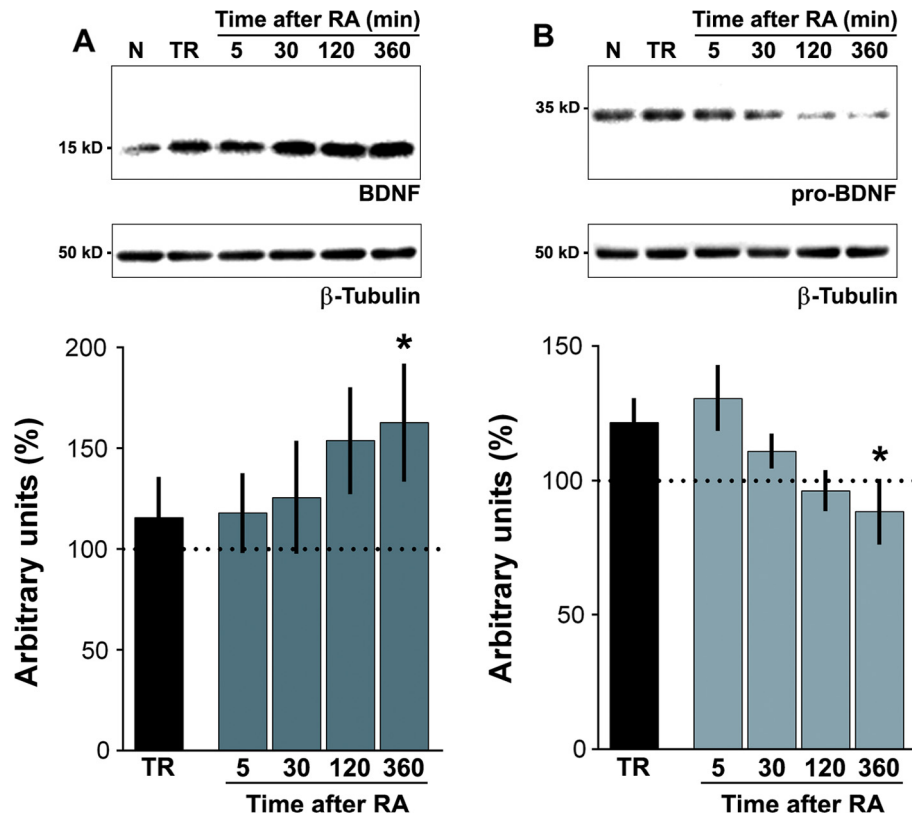


Fig. 3. ORM reactivation increases BDNF levels in dorsal CA₁. Rats were trained in NOR using two different stimuli (A and B). Twenty-four hours post-training the animals were submitted to a 5-min long ORM reactivation session in the presence of a familiar (A) and a novel object (C). At different times thereafter (5–360 min), animals were killed by decapitation, the CA₁ region of the dorsal hippocampus dissected out and homogenized to determine proBDNF (A), BDNF (B) and β-tubulin (A, B) levels by immunoblotting. N: naïve animals. TR: animals trained in ORM. RA: reactivation session. Data are presented as mean ± SEM. **p* < 0.05 in Dunnett's multiple-comparisons test after repeated-measures ANOVA; *n* = 6 per group.

tion (Balderas, Rodríguez-Ortiz, & Bermúdez-Rattoni, 2013; García-Delatorre, Pérez-Sánchez, Guzmán-Ramos, & Bermúdez-Rattoni, 2014; Milton et al., 2013; Rodríguez-Ortiz, Balderas, García-DeLaTorre, & Bermúdez-Rattoni, 2012; Yasoshima, Yamamoto, & Kobayashi, 2005), suggesting that retrieval is not required for memory destabilization. However, memory expression impairment does not necessarily imply reactivation or retrieval failure, and alternative interpretations must be considered. Given the hierarchical participation and interaction of several brain structures during memory retrieval (Henson & Gagnepain, 2010), it is possible that memory reactivation occurs even when the behavioral output is impaired by inactivation of a single brain region (Rossato et al., 2015). Altogether, our data confirm the involvement of the hippocampus in ORM processing and reveal the participation of BDNF in declarative memory reconsolidation. Studying the molecular basis of ORM is fundamental not only to understand explicit memory processing but also to further develop therapeutic strategies aimed to modify declarative knowledge through reconsolidation. Our data indicate that targeting BDNF signaling could be a promissory approach to modulate the persistence of this type of memories after retrieval.

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