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TrkB blockade in the hippocampus after training or retrieval impairs memory: protection from consolidation impairment by histone deacetylase inhibition

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Abstract Relatively little is known about the requirement of signaling initiated by brain-derived neurotrophic factor (BDNF) and its receptor, tropomyosin receptor kinase B (TrkB), in the early phases of memory consolidation, as well as about its possible functional interactions with epigenetic mechanisms. Here we show that blocking TrkB in the dorsal hippocampus after learning or retrieval impairs retention of memory for inhibitory avoidance (IA). More importantly, the impairing effect of TrkB antagonism on consolidation was completely prevented by the histone deacetylase (HDAC) inhibitor sodium butyrate (NaB). Male Wistar rats were given an intrahippocampal infusion of saline (SAL) or NaB before training, followed by an infusion of either vehicle (VEH) or the selective TrkB antagonist ANA-12 immediately after training. In a second experiment, the infusions were administered before and after retrieval. ANA-12 after either training or retrieval produced a significant impairment in a subsequent memory retention test. Pretraining administration of NaB prevented the effect of ANA-12, although NaB given before retrieval did not alter the impairment resulting from TrkB blockade. The results indicate that inhibition of BDNF/TrkB in the hippocampus can hinder consolidation and reconsolidation of IA memory. However, TrkB activity is not required for consolidation in the presence of NaB, suggesting that a dysfunction in BDNF/TrkB signaling can be fully compensated by HDAC inhibition to allow hippocampal memory formation.

Keywords TrkB · Histone deacetylase · Hippocampus · Inhibitory avoidance · Memory consolidation · Reconsolidation

Introduction

Increasing evidence indicates an important role for the tropomyosin receptor kinase B (TrkB, also called receptor tyrosine kinase B), encoded by *NTRK2*, in nervous system development, synaptic plasticity, memory formation, and neuroprotection. TrkB is a member of the neurotrophin receptor kinase family activated by brain-derived neurotrophic factor (BDNF). (Huang and Reichardt 2003; Yoshii and Constantine-Paton 2010). TrkB activation by BDNF stimulates several intracellular signaling cascades involved in synaptic plasticity, including the phospholipase C(PLC)/protein kinase C (PKC), mitogen-activated protein kinase (MAPK), and the phosphatidylinositol 3-kinase (PI3K) pathways (Huang and Reichardt 2003; Minichiello 2009; Yoshii and Constantine-Paton 2010).

Recombinant BDNF stimulates hippocampal long-term potentiation (LTP), whereas pretreatment with an antibody against TrkB impairs LTP maintenance (Kang and Schuman 1995; Korte et al. 1998; Patterson et al. 1996; reviewed by Minichiello 2009). Consolidation of memory for inhibitory avoidance (IA) in rats involves learning-related requirement of BDNF/TrkB activity that accompanies

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protein synthesis in the dorsal hippocampus (Bambah-Mukku et al. 2014), and intrahippocampal administration of an anti-BDNF antibody before training impairs long-term retention (Chen et al. 2012). When given around the time of retention testing, under experimental conditions in which retrieval can trigger extinction or reconsolidation, BDNF might also enhance these processes (Peters et al. 2010; Samartgis et al. 2012; Wang et al. 2012), although it has also been suggested that hippocampal BDNF does not play a role in the reconsolidation of fear memory in rats (Lee et al. 2004).

In different types of cultured brain cells, gene transcription for BDNF is upregulated by inhibitors of histone deacetylases (HDACs) such as sodium butyrate (NaB) (Koppel and Timmusk 2013; Wu et al. 2008). In addition, BDNF can potentiate some effects of HDAC inhibition in vitro (Nör et al. 2011), and treatment with NaB increases protein levels of BDNF in the rat brain (Kim et al. 2009). The action of HDACs is part of the set of epigenetic mechanisms regulating chromatin state and gene expression. HDACs remove acetyl groups from histones, leading to chromatin condensation and repression of gene transcription (Kouzarides 2007), in addition to acting on a number of extranuclear and nonhistone protein substrates (Bolden et al. 2006; Xu et al. 2007). Current evidence increasingly implicates histone acetylation and deacetylation in synaptic plasticity and memory formation (reviewed in Gräff and Tsai 2013; Levenson and Sweatt 2005). Systemic or intracerebral administration of HDAC inhibitors has been used as an approach to produce memory enhancement. NaB and other inhibitors including trichostatin A (TSA), suberoylanilide hydroxamic acid (SAHA), and valproic acid have been shown to enhance LTP and the formation and extinction of memory for fear-motivated tasks (Blank et al. 2014; Bredy and Barad 2008; Lattal et al. 2007; Levenson et al. 2004; Stafford et al. 2012; Vecsey et al. 2007). We have previously shown that infusions of either NaB or TSA into the dorsal hippocampus given immediately or 3 h after training resulted in a long-lasting enhancement of IA memory (Blank et al. 2014), and systemic administration of NaB enhanced memory in aged rats (Blank et al. 2015; Reolon et al. 2011).

The evidence reviewed above suggests that BDNF/TrkB signaling might functionally interact with HDACs to regulate memory formation or its modification by retrieval, and raises the possibility that HDAC inhibition may attenuate memory impairment associated with reduced TrkB activity. To test this hypothesis, we examined the effects of combined pharmacological inhibition of hippocampal TrkB and HDAC on IA memory.

Materials and methods

Animals

Adult male Wistar rats (280–350 g at time of surgery) were obtained from the institutional breeding facility (CREAL, ICBS, UFRGS). Animals were housed three per cage in plastic cages with sawdust bedding, and maintained on a 12-h light/dark cycle at a room temperature of 22 ± 1 °C. The rats were allowed ad libitum access to standardized pellet food and water. All experiments took place between 8 AM and 5 PM. All experimental procedures were performed in accordance with the Brazilian Guideline for the Care and Use of Animals in Research and Teaching (DBCA, published by CONCEA, MCTI) and were approved by the institutional animal care committee under protocol number 130381.

Surgery

Animals were implanted under anesthesia with ketamine (75 mg/kg) and xylasine (25 mg/kg) with bilateral 8.0-mm, 23-gauge guide cannulae aimed 1.0 mm above the CA1 area of the dorsal hippocampus as described in previous studies (Blank et al. 2014; Roesler et al. 2003). Coordinates (anteroposterior, −4.3 mm from bregma; mediolateral, ±3.0 mm from bregma; ventral, −2.0 mm from skull surface) were obtained from the atlas of Paxinos and Watson (2007). Animals were allowed to recover at least 5 days after surgery.

Drugs and infusion procedures

The general procedures for intrahippocampal infusions were described in previous reports (Blank et al. 2014; Jobim et al. 2012). At the time of infusion, a 30-gauge infusion needle was fitted into the guide cannula. The tip of the infusion needle protruded 1.0 mm beyond the guide cannula and was aimed at the CA1 hippocampal area. Drug or vehicle was infused during a 60-s period. The infusion needle was left in place for an additional minute to allow diffusion of the drug away from the needle tip.

NaB (Sigma-Aldrich, St. Louis, USA) was chosen as an HDAC inhibitor. It inhibits preferentially class I HDACs, which are localized predominantly to the cell nucleus, and also act with lower activity on HDAC8 (Bolden et al. 2006). For TrkB inhibition, the novel and highly selective antagonist {[N2–2-2-Oxoazepan-3-yl amino]carbonyl phenyl benzo (b)thiophene-2-carboxamide (ANA-12)]} (Sigma-Aldrich) (Cazorla et al. 2011) was used. In the first experiment, rats received a bilateral 1.0-µl infusion of

saline or NaB (100 mM dissolved in saline) into the dorsal hippocampus 10 min before training, then immediately after training they received vehicle (1 % DMSO in saline) or ANA-12 (0.3, 1, or 3 μg/μl dissolved in vehicle). In the second experiment, rats received a bilateral intrahippocampal 1.0-μl infusion of saline or NaB (100 mM dissolved in saline) and immediately after reactivation they were infused with vehicle (1 % DMSO in saline) or ANA-12 (1.0 μg/μl dissolved in vehicle). The doses of NaB and ANA-12 were chosen on the basis of previous studies (Blank et al. 2014; Spaeth et al. 2012). Drug solutions were freshly prepared before each experiment.

Inhibitory avoidance (IA)

In step-down IA training, animals learn to associate a location in the training apparatus (a grid floor) with an aversive stimulus (footshock). The general procedures for IA training and retention testing were described in previous reports (Blank et al. 2014; Jobim et al. 2012; Pedroso et al. 2013). The IA apparatus was a 50 × 25 × 25-cm acrylic box (Albarsch, Porto Alegre, Brazil) whose floor consisted of parallel caliber stainless steel bars (1 mm diameter) spaced 1 cm apart. A 7-cm wide, 2.5-cm high platform was placed on the floor of the box against the left wall. On training trials, rats were placed on the platform and their latency to step down on the grid with all four paws was measured manually with a digital chronometer. Immediately after stepping down on the grid, rats received a 0.4-mA, 3.0-s footshock and were removed from the apparatus immediately after the footshock. Rats were tested for retention 24 h in the first experiment (examining the effects of drug treatments on consolidation). In the second experiment (verifying the effects of drugs given after retrieval), the first test trial was used as a reactivation session that could induce reconsolidation or extinction, and a second test trial was given 48 h after training. A ceiling of 180 s was imposed on retention test measures. No footshock was presented during retention test trials. Step-down latencies on the retention test trial were used as a measure of IA memory retention.

Histology

Twenty-four to 72 h after behavioral testing, a 1.0-μl infusion of a 4 % methylene blue solution was given into the dorsal hippocampus. Rats were killed by decapitation 15 min later, and their brains were removed and stored in 10 % formalin for at least 72 h. The brains were sectioned and examined for cannulae placement in the hippocampus. The extension of the methylene blue dye was taken as indicative of diffusion of the drugs previously given to each rat, as previously described (Blank et al. 2014; Jobim et al. 2012). Rats with incorrect cannula placements were excluded from the final analysis.

Statistical analyses

Data are shown as mean ± SEM retention test latencies to step-down (s). Since the variable being analyzed (step-down latency) does not follow a normal distribution and we limited the observation to 180 s, comparisons of latencies between groups were made using Kruskal–Wallis analyses of variance followed by Mann–Whitney *U* tests, two-tailed (Blank et al. 2014; Jobim et al. 2012; Pedroso et al. 2013). In all comparisons, $p < 0.05$ was considered to indicate statistical significance.

Results

HDAC inhibition protects from the impairment of IA memory consolidation produced by TrkB antagonism in the dorsal hippocampus

We first verified the effect of intrahippocampal infusions of NaB given before training, ANA-12 given after training, or NaB followed by ANA-12. There was no difference among groups in training latencies ($H = 12.46$, $df = 7$, $p = 0.09$; Table 1). Results for retention test latencies are shown in Fig. 1. Analysis with the Kruskal–Wallis test revealed a significant difference among groups ($H = 40.41$, $df = 7$, $p < 0.001$). Further analysis with Mann–Whitney *U* tests showed that posttraining ANA-12 at any of the three doses used produced a significant impairment of 24-h IA retention (all $p < 0.01$ compared to controls) in rats given saline before training. This result indicates that TrkB activity in the dorsal hippocampus shortly after training is required for IA memory consolidation. Pretraining administration of NaB did not affect retention by itself, but completely prevented the impairing effect of ANA-12. There were no

Table 1 Latencies to step-down during training of rats given intrahippocampal infusions before and immediately after training (treatment groups and retention test latencies are shown in Fig. 1)

Group	*n*	Mean + SEM latency (s)	*p* value
SAL–VEH	8	16.82 ± 3.96	0.09
SAL–ANA-12 0.3 μg/μl	8	9.26 ± 1.60	
SAL–ANA-12 1 μg/μl	8	7.90 ± 1.42	
SAL–ANA-12 3 μg/μl	8	9.27 ± 2.24	
NaB–VEH	11	13.07 ± 2.77	
NaB–ANA-12 0.3 μg/μl	9	10.41 ± 1.86	
NaB–ANA-12 1 μg/μl	9	15.34 ± 2.24	
NaB–ANA-12 3 μg/μl	8	9.64 ± 2.56	

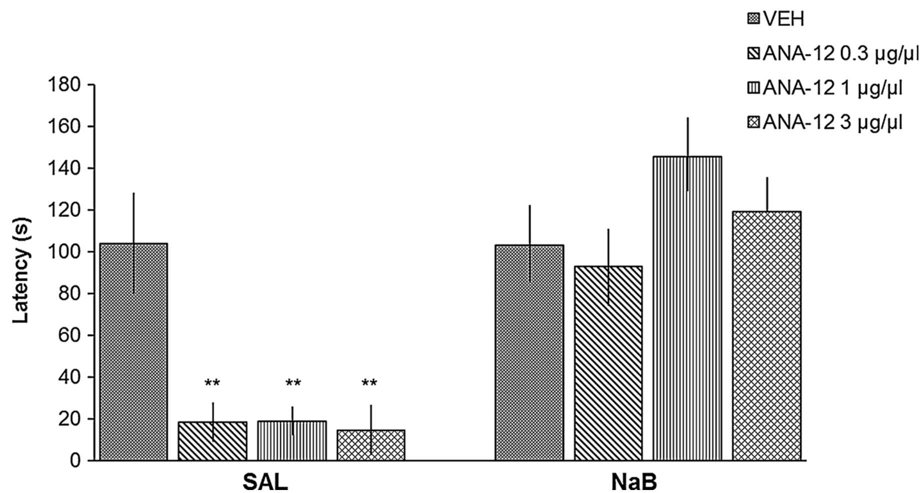

Fig. 1 Administration of an HDAC inhibitor into the hippocampus prevents the impairment of memory consolidation produced by a TrkB antagonist. Rats received a bilateral infusion of saline (SAL) or NaB (100 mM) into the CA1 area of the hippocampus 10 min before IA training, and a bilateral infusion of vehicle (VEH) or ANA-12 (0.3, 1, or 3 μg/μl) into the hippocampus immediately after training (SAL/VEH, $n = 8$; SAL/ANA-12 0.3 μg/μl, $n = 8$; SAL/ANA-12 1 μg/μl, $n = 8$; SAL/ANA-12 3 μg/μl, $n = 8$; NaB/VEH, $n = 11$; NaB/ANA-12 0.3 μg/μl, $n = 9$; NaB/ANA-12 1 μg/μl, $n = 9$; NaB/ANA-12 3 μg/μl, $n = 8$). Retention was tested 24 h later. Data are mean + SEM retention test latencies to step-down (s); $^{**}p < 0.01$ compared to SAL/VEH controls

significant differences between groups treated with NaB combined with any dose of ANA-12 and control rats given saline followed by vehicle. This finding indicates that HDAC inhibition by NaB could fully protect against the memory-impairing effect of TrkB blockade.

HDAC inhibition does not protect from the impairment of IA memory reconsolidation produced by hippocampal TrkB antagonism

In the second experiment, NaB or saline was given before first test trial (which also served as a memory reactivation session), and ANA-12 or vehicle was given immediately after retrieval. Kruskal–Wallis analyses revealed a significant difference among groups in the second test ($H = 17.01$, $df = 3$, $p < 0.001$), but not in the training ($H = 0.76$, $df = 3$, $p = 0.86$; Table 2) or first test trial ($H = 0.92$, $df = 3$, $p = 0.82$). Mann–Whitney U tests showed that, when given immediately after the first test, ANA-12 produced a significant impairment compared to controls in a second retention test ($p < 0.05$). NaB given before test did not affect retrieval or retention in the second test, but rats treated with NaB followed by ANA-12 showed a level of memory impairment at the second test comparable to animals given ANA-12 only ($p < 0.01$) (Fig. 2). These findings indicate, first, that TrkB antagonism in the hippocampus after retrieval might hinder reconsolidation-like processes; and, second, that this effect is not ameliorated by HDAC inhibition before retrieval.

Table 2 Latencies to step-down during training of rats given intrahippocampal infusions before and immediately after the first test (treatment groups and retention test latencies are shown in Fig. 2)

Group	n	Mean + SEM latency (s)	p value
SAL–VEH	9	12.32 ± 1.8	0.86
SAL–ANA-12 1 μg/μl	8	17.06 ± 5.89	
NaB–VEH	9	16.16 ± 5.08	
NaB–ANA-12 1 μg/μl	8	10.84 ± 2.33	

Histology

All animals included in the final analysis (103 rats) had cannula placed in the intended sites. Figure 3 shows schematic drawings of the diffusion of methylene blue, which indicates infusion placements and spread of drug infusions, within the dorsal hippocampus.

Discussion

The role of BDNF/TrkB in the early phases of memory consolidation and reconsolidation remains poorly characterized. Also, previous studies have not fully determined how BDNF signaling can interact with epigenetic mechanisms during memory formation. We show that TrkB activity in the dorsal hippocampus shortly after learning is required for IA memory. In addition, although BDNF has been proposed to be recruited for the consolidation but not reconsolidation of hippocampal fear memory (Lee et al. 2004), we found that blocking TrkB after retrieval can reduce memory in a subsequent test, suggesting its

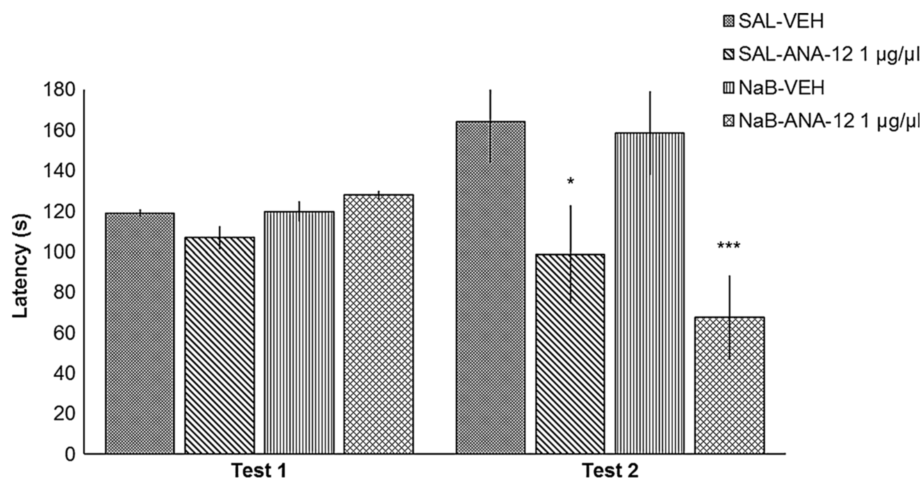

Fig. 2 Blocking TrkB in the hippocampus impairs reconsolidation regardless of HDAC inhibition. Rats were trained and given a retention test trial 1 day later (Test 1). A bilateral infusion of SAL or NaB (100 mM) was given into the hippocampus 10 min before Test 1, and a bilateral intrahippocampal infusion of VEH or ANA-12 (1,0 µg/µl) was given immediately after retrieval (SAL/VEH, $n = 9$; SAL/ANA-12 1 µg/µl, $n = 8$; NaB/VEH, $n = 9$; NaB/ANA-12 1 µg/µl, $n = 8$). Retention was tested again 1 day after the infusion (Test 2). Data are mean + SEM retention test latencies to step-down (s); $*p < 0.05$ compared to SAL-VEH Test 1 latencies; $***p < 0.001$ compared to latencies during Test 2 of NaB/VEH controls

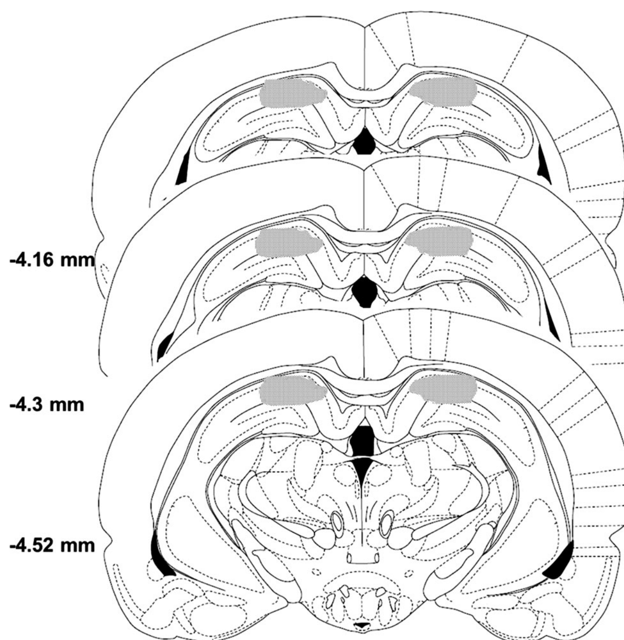

Fig. 3 Infusion placements into the dorsal hippocampus. Schematic diagrams of coronal sections of the rat brain, adapted from the atlas of Paxinos and Watson (2007), depicting the diffusion of methylene blue in the hippocampus for rats included in the final statistical analysis

requirement for reconsolidation. Moreover, the impairment in consolidation produced by TrkB inhibition was prevented by an HDAC inhibitor. Confirming previous findings (Blank et al. 2014), administration of NaB at 100 mM before training did not affect IA retention. Also, although histone acetylation and HDAC inhibitors have been shown to influence reconsolidation (Bredy and Barad 2008; Federman et al. 2012), NaB infused after retrieval changed neither retention tested 24 h later nor the reconsolidation impairment produced by ANA-12.

It is possible that the reduced latency on the second test trial in rats given ANA-12 after retrieval results from accelerated extinction. However, this is unlikely since BDNF has been shown to enhance rather than impair extinction (Chhatwal et al. 2006; Peters et al. 2010), thus facilitated extinction would not be an expected effect of a TrkB antagonist. Previous work from our laboratory has demonstrated that IA memory can undergo reconsolidation dependent on mTOR activity in the hippocampus and amygdala after retrieval (Jobim et al. 2012). Reconsolidation might serve to maintain (Jobim et al. 2012) or strengthen (Fukushima et al. 2014; Pedroso et al. 2013) IA memory.

Perhaps the most important finding of the present study is that BDNF/TrkB activity is not necessary for the early phase of memory formation when HDAC is inhibited. The present study did not investigate the underlying mechanisms for the effects of the combination of TrkB antagonism and HDAC inhibition during consolidation. Therefore, any discussion of possible mechanisms remains speculative at this point. BDNF-induced TrkB stimulation increases gene expression through the activation of multiple protein kinase pathways and transcription factors. It has been recently proposed that learning-related increases in the expression and release of BDNF through a positive autoregulatory feedback loop is crucially involved in the gene expression-dependent phase of IA memory consolidation (Bambah-Mukku et al. 2014).

Blocking BDNF with an antibody prior to IA training abrogates learning-induced induction of hippocampal phospho-cyclic adenosine monophosphate response element-binding protein (pCREB), phospho-Ca^{2+}/calmodulin-dependent protein kinase II (pCamKII), and CCAAT/enhancer binding protein β (C/EBPβ), among other targets related to synaptic plasticity and memory consolidation (Bambah-Mukku et al. 2014; Chen et al. 2012). NaB acts mostly by inhibiting HDAC, thus increasing histone acetylation in cell nucleus to affect chromatin structure allowing its relaxation and promoting the recruitment of transcriptional machinery to gene promoters to activate gene expression. In addition, HDACs have many nonhistone targets including hormone receptors, proteins involved in cytoplasmic signaling, transcription factors, and cytoskeleton proteins (Bolden et al. 2006; Gräff and Tsai 2013; Marks and Dokmanovic 2005; Minucci and Pelicci 2006; Xu et al. 2007). In cultured cells, NaB has been shown to enhance cAMP levels and stimulate the activation of the cAMP/protein kinase A (PKA), PKC, and MAPK signaling pathways (Prasad and Sinha 1976; Rivero and Adunyah 1996, 1998), thus stimulating TrkB downstream signaling and resulting in induction of pCREB and other transcription factors and increased RNA transcription and protein synthesis mediating memory consolidation (Bolden et al. 2006; Xu et al. 2007). Another possible mechanism of interaction involves regulation by HDAC of the expression of BDNF itself (Boulle et al. 2012). For example, HDAC2 has been shown to mediate the repression of the *bdnf exon IV* promoter, decreasing BDNF expression and thus terminating a late phase of the memory consolidation process (Bambah-Mukku et al. 2014), whereas valproic acid, an HDAC inhibitor, potentiates the enhancing effect of extinction training on histone H4 acetylation around the BDNF P1 and P4 gene promoters (Bredy et al. 2007).

In summary, our findings indicate that TrkB signaling is involved in both early consolidation and reconsolidation of hippocampal memory. Most importantly, HDAC inhibition can fully compensate for TrkB blockade during memory formation. From a translational perspective, since BDNF/TrkB signaling can be disrupted in neurodevelopmental and neurodegenerative disorders (Li and Pozzo-Miller 2014; Zuccato and Cattaneo 2009), these findings support the investigation and development of HDAC inhibitors as potential therapeutics to treat cognitive deficits in patients with brain disease.

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Compliance with ethical standards

Conflict of interest None.

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