Behavioral/Cognitive

HDAC Inhibition Facilitates the Switch between Memory Systems in Young But Not Aged Mice

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Chromatin modifications, especially histone acetylation, are critically involved in gene regulation required for long-term memory processes. Increasing histone acetylation via administration of histone deacetylase inhibitors before or after a learning experience enhances memory consolidation for hippocampus-dependent tasks and rescues age-related memory impairments. Whether acutely and locally enhancing histone acetylation during early consolidation processes can operate as a switch between multiple memory systems is less clear. This study examined the short- and long-term behavioral consequences of acute intra-CA1 administration of the histone deacetylase inhibitor Trichostatin A (TSA) on cue versus place learning strategy selection after a cue-guided water maze task and competition testing performed 1 or 24 h later in mice. Here, we show that intra-CA1 TSA infusion administrated immediately post-training biased young mice away from striatum-dependent cue strategy toward hippocampus-dependent place strategy under training condition that normally promotes cue strategy in vehicle controls. However, concomitant infusions of TSA with either PKA inhibitor, Rp-cAMPS, into CA1 or cAMP analog, 8Br-cAMP, into dorsal striatum failed to bias young mice to place strategy use. Behavioral and immunohistochemical analyses further indicated that post-training TSA infusion in aged mice rescued aging-associated deregulation of H4 acetylation in the CA1 but failed to reverse phosphorylated CREB deficits and to produce strategy bias on the 24 h probe test. These findings suggest that post-training intra-CA1 TSA infusion promotes dynamic shift from striatum toward the hippocampal system in young but not aged animals, and support the possibility of a role for CREB in the TSA-mediated switch between these two memory systems.

Introduction

Chromatin remodeling via acetylation at multiple lysine residues on the *N*-terminal tail of specific histone proteins plays a crucial role in regulating hippocampus-dependent synaptic function and long-term memory formation (Sweatt, 2009; Stilling and Fischer, 2011; Peixoto and Abel, 2013). Age-dependent declines in histone acetylation and resulting disruption of plasticity-related target genes are key mechanisms contributing substantially to the deterioration of hippocampal synaptic function and deficits in many forms of hippocampus-dependent memory in rodents (Peleg et al., 2010; Zeng et al., 2011; Castellano et al., 2012). For example, several reports provided evidence that decreased acetylation of histone H4 in the hippocampus is implicated with associative memory declines in aged mice (Peleg et al., 2010) and in mouse models for Alzheimer's disease (Francis et al., 2009). Increasing histone acetylation via treatments with nonselective histone deacetylase (HDAC) inhibitors, such as sodium butyrate or Trichostatin A (TSA), enhances synaptic plasticity and memory formation in young rodents (Haggarty and Tsai, 2011) and prevents or rescues memory deficits associated with aging as well as cognitive disorders in animal models of neurological diseases (Fischer et al., 2010; Stilling and Fischer, 2011). While beneficial effects of pre-training treatments with HDAC inhibitors (HDACi) on learning and memory are well established, few studies have examined how post-training administration of HDACi, by specifically acting on the consolidation phase, modulates memory (Vecsey et al., 2007; Federman et al., 2009; Stefanko et al., 2009; Roozendaal et al., 2010; Hawk et al., 2011; Reolon et al., 2011). Post-training HDACi infusion into the hippocampus or the insular cortex strengthens long-term memory for object location and object recognition, respectively (Roozendaal et al., 2010; Hawk et al., 2011). One mechanism by which HDAC inhibition may enhance memory at the time of early consolidation processes is by increasing the strength of functional connectivity between the hippocampus and interconnected structures (Stafford et al., 2012). Whether locally enhancing histone acetylation during early consolidation processes controls the formation of multiple forms of memory remains presently unknown.

To identify the role of hippocampal histone acetylation in modulation of strategies selection and memory formation, we trained mice in a water maze task that can be solved with equal efficiency using either a striatum-based cue/response strategy or a hippocampus-based place strategy. The strategy used in retention depends on the training regimen experienced during acquisition

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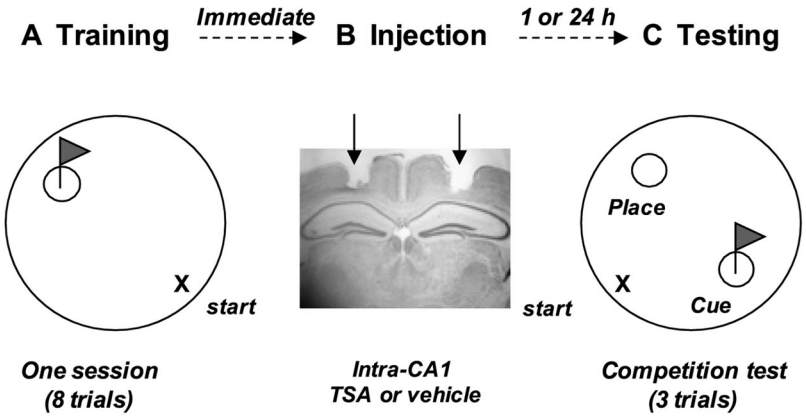

Figure 1. Schematic representation of the experimental procedure. ***A***, In the eight-trial training session, both young and aged mice learned to search for a submerged cue-marked platform. ***B***, Immediately post-training, mice received bilateral infusion of TSA or vehicle into the CA1. Illustration of cannulae placements in the dorsal CA1 region (arrows). ***C***, During the probe test performed 1 or 24 h later, mice had to choose between a submerged platform located in the same position as during the training session (place strategy) and the cue-marked platform located in the opposite quadrant of the pool (cue strategy). For detailed explanations, see Material and Methods.

and correlates with the temporal dynamic of CREB phosphorylation in the dorsal hippocampal CA1 during memory consolidation (Martel et al., 2007; Blanchard et al., 2008). We chose a training condition in which the use of the cued strategy prevails over spatial strategy to examine the modulatory influence of post-training intra-CA1 TSA infusion on consolidation processes mediated by the dorsal hippocampus and dorsal striatum in young adult and aged mice. We also investigated the effects of post-training intra-CA1 TSA infusion on cognitive strategy-specific changes in histone H4 acetylation and CREB phosphorylation. Finally, we examined whether the behavioral effects of TSA observed in young mice can be disrupted by pharmacological manipulation of CREB function in the hippocampus and dorsal striatum.

Materials and Methods

Animals

A total of 120 male C57BL/6 mice, aged 4 ($n = 80$) and 18–20 ($n = 40$) months, from Charles River Laboratories were individually housed in a temperature-controlled colony room (22 ± 1°C) with a 12 h light-dark cycle (lights on at 7:00 A.M.) and *ad libitum* access to food and water. Mice were handled daily for 5 d before training. Young and aged mice that were infused with either TSA or vehicle into the CA1 immediately after water maze training and received a competition test either 1 or 24 h later (Fig. 1; for detailed methods, see Behavioral procedure, below). All mice subjected to the 1 h probe test were killed immediately after testing for immunohistochemical localizations of histone H4 acetylation and CREB phosphorylation. Changes in H4 acetylation were also performed in mice killed immediately after the 24 h probe test. The results were compared with resting values from young and aged mice infused with TSA or vehicle (Veh) and killed 1 h later directly from their home cage (Young-Veh, naive: $n = 6$; Aged-Veh, naive: $n = 6$; Young-TSA, naive: $n = 5$; Aged-TSA, naive: $n = 4$). In additional experiments, cohorts of young mice received post-training intra-CA1 TSA administration with concomitant infusion of the competitive antagonist of cAMP-induced activation of PKA cAMPs-Rp, triethylammonium salt (Rp-cAMPS) into the CA1 or cAMP analog 8-bromoadenosine-3′,5′-cyclic monophosphate (8Br-cAMP) into the dorsal striatum and were subjected to the 24 h probe test. All experimental procedures were conducted in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC).

Surgery

Mice were anesthetized with a mixture of ketamine (100 mg/kg body weight, i.p.) and xylasine (6 mg/kg body weight, i.p.) (Bayer) and placed in a stereotaxic apparatus (Kopf Instruments). Stainless-steel guide cannulae (26 gauge, 8 mm length) were implanted bilaterally 1 mm above the dorsal hippocampus (anteroposterior, −2 mm; mediolateral, ±1.4 mm; dorsoventral, 0.9 mm; relative to dura and bregma; Fig. 1*B*), according to the atlas of Franklin and Paxinos (1997). Guide cannulae were fixed to the skull with dental cement and three jewel screws. Mice from the 8Br-cAMP experiment were implanted with two sets of bilateral cannulae, one pair into the dorsal hippocampus as described previously and the second pair 1 mm above the dorsal striatum (anteroposterior, 0.9 mm; mediolateral, ±2 mm; dorsoventral, 1.5 mm; relative to dura and bregma) according to the atlas of Franklin and Paxinos (1997). Mice were allowed to recover for 10 d before further experiments.

Behavioral procedure

Apparatus. The experiments were conducted in a round tank, 150 cm diameter and 55 cm in height, filled with water made opaque with white nontoxic paint. The water temperature was maintained at 21 ± 1°C. Two hidden platforms (PF, 13 cm diameter) made of transparent Plexiglas were submerged 1 cm below water surface. A 10 cm height cue (a cylinder structure with black and white striped pattern) was placed on the submerged platform to indicate its location. Several distal visual cues were placed on the walls of the water maze room.

Procedure. Mice were submitted to one training session of eight trials followed 1 or 24 h later by a series of three test trials. Acquisition consisted of a spatial and nonspatial reference memory task during which one PF remained in a fixed position and was marked by a cue. In each trial, mice were released facing the wall at a constant start position (middle of the southeast quadrant) and allowed to swim until they found and climbed onto the cued PF (northwest quadrant) or 90 s had elapsed. If a mouse failed to find the PF within 90 s, it was gently guided to the cued-platform by hand, where it was left for 20 s. After each training trial, mice were dried, returned to their home cage, and placed in a warm box equipped with dark lamps. Mice were trained in squads of five or six animals with an intertrial interval of 10–12 min and fully counterbalanced with respect of age and treatment. Escape latency (in seconds) from the releasing point to the PF was analyzed to assess learning during acquisition session.

Mice were submitted 1 or 24 h after the last training trial to three test trials (intertrial interval 5 min) in which two PF were submerged to assess the search strategy used. One PF remained in the spatial location of the training PF (northwest quadrant). The second PF, located in the opposite quadrant (southeast), was marked by the cue. The start position was equidistant from both platforms (southwest). If the animals swam to the original PF (currently hidden), a place response was noted; if the animal swam to the new and cued PF, a cue response was noted. Performance was calculated for each mouse as mean percentage of a particular response over the three test trials.

Quantification and analysis of behavioral data. A video camera mounted above the pool was used to record swim trials. Data were analyzed using an automated tracking system (Videotrack). The acquisition performances were analyzed for each trial, defined as the mean latency (in seconds) to escape from the releasing point to the submerged platform. Data were analyzed by repeated-measures ANOVAs, with Age as between-subject factor and Trial as within-subject factors, using StatView 5.01 (SAS Institute). For the competition tests, escape latency and swim distance were analyzed using one- or two-way ANOVAs with Age and Treatment as between-subject factors. Individual strategy selection was categorized as cue-guided or place response according to the choice made by the animal. χ^2 analyses with Yates corrections (a conservative adjustment to allow for cells with frequencies of <5) were computed to determine whether any training groups exhibited a significant tendency

to display one type of strategy selection over the three probe trials. Within-group comparison between the percentages of each strategy selection used paired *t* tests to determine which response type was preferred. For all comparisons, a probability of $p < 0.05$ was considered significant.

Local drug infusion

The HDACi TSA (2.5 μg/μl; Tocris Bioscience) was dissolved in 20% dimethyl sulfoxide (DMSO) and diluted in artificial CSF (aCSF). Bilateral injections of 0.5 μl of TSA (4 nmol per side) or its vehicle were infused into the dorsal hippocampal CA1 immediately after training. Bilateral infusion took ~5 min and the cannulae were left in place for an additional 1 min before removal to allow diffusion of the drug away from the cannulae tips. The Rp-cAMPS (Tocris Bioscience), a membrane-permeable PKA inhibitor, was dissolved in 20% DMSO and diluted in aCSF (35.6 μg/μl; 40 nmol dissolved in 0.5 μl per side). The concentration was based on both published evidence in rats (Taylor et al., 1999; Ramos et al., 2003) and our recent study in C57BL/6 mice (Baudonnat et al., 2011). Bilateral Rp-cAMPS infusion occurred in combination with TSA infusion into the dorsal hippocampus. The cAMP analog 8Br-cAMP (Sigma-Aldrich) was dissolved in aCSF (Vehicle). The 8Br-cAMP concentration (2.5 μg/μl; 3 nmol dissolved in 0.5 μl per side) was based on previous studies (Bernabeu et al., 1997). Mice received infusion of 8Br-cAMP or vehicle into the dorsal striatum immediately after training, with concomitant infusion of TSA or vehicle into the dorsal hippocampus.

Histological controls

All surgical implantations were controlled after experiments using thionin blue coloration. Animals were anesthetized with Avertin (10 ml/kg, i.p.) and perfused transcardially with 4% paraformaldehyde in 0.1 M phosphate buffer (PB). Brains were stored overnight in the same solution and then in paraformaldehyde containing 30% sucrose for 72 h before being cut in 60 μm sections with a freezing microtome (Leica SM2400). After being collected onto gelatin-coated slides, brain sections were stained with thionin and coverslipped.

Immunohistochemistry and quantification

Animals were deeply anesthetized with Avertin (10 ml/kg, i.p.) and perfused transcardially with ice-cold 4% paraformaldehyde in 0.1 M PB. Brains were removed and stored overnight in the same fixation solution, sectioned (50 μm) on a vibratome (Leica) and kept in a solution containing 30% ethylene glycol, 30% glycerol, 0.1 M PB at −20°C until processed for immunohistochemistry, as previously described (Porte et al., 2011). Free-floating sections were incubated with rabbit primary polyclonal antibodies anti-acetyl(Lys5,8,12,16)H4 (1:4000) and anti-phospho(ser133)-CREB (1:4000) (Millipore). The specificity of anti-acetyl(Lys5,8,12,16)H4 antibody has been previously established in rat hippocampus (Levenson et al., 2004; Tsankova et al., 2004). Then sections were incubated with a biotinylated goat anti-rabbit IgG secondary antibody (1:2000; Jackson ImmunoResearch). This was followed by incubation with an avidin-biotinylated horseradish peroxidase complex (Vectastain Elite kit, Vector Laboratories). The peroxidase reaction was visualized in a Tris solution containing diaminobenzidine tetrahydrochloride and hydrogen peroxide. Sections were mounted on gelatin-coated slides, dehydrated, and coverslipped. All images were acquired using an imaging analysis system (Biocom Visiolab 2000, V4.50). For each animal, positive nuclei were quantified in the dorsal hippocampal CA1 region and dorsal part of the striatum according to Franklin and Paxinos (1997). At least three consecutive serial sections were examined bilaterally, and the number of positive nuclei/mm^2 was averaged to produce Group mean + SEM and compared with that of home cage (naive) mice. Data were statistically analyzed using software Statview 5.01 (SAS Institute) using one- or two-way ANOVAs with Age and Treatment as between-group factors followed by *post hoc* tests (Fisher's PLSD) when appropriate. The data were considered to be statistically significant when $p < 0.05$.

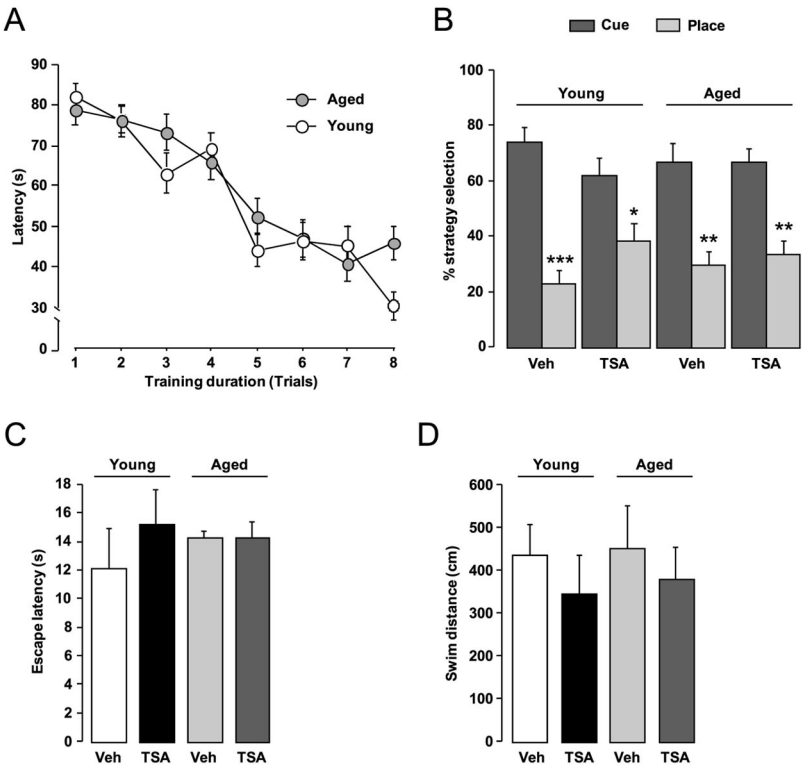

Figure 2. Post-training intra-CA1 infusion of TSA does not affect strategy selection or memory performance during the short-term retention test. ***A***, Learning curves of Young (open circles, $n = 29$) and Aged (gray circles, $n = 30$) mice during the training session. Data are expressed as mean latencies ± SEM (in seconds) to find the platform over the eight consecutive trials. ***B***, Mean percentage (+SEM) of (cue, place) strategy selection for young and aged mice infused with TSA (Young-TSA: $n = 6$; Aged-TSA: $n = 6$) or vehicle (Young-Veh: $n = 8$; Aged-Veh: $n = 8$) and subjected to the 1 h probe test. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; cue versus place strategy selection. ***C***, ***D***, Memory performances expressed as mean latencies + SEM (in seconds) (***C***) and mean distance + SEM (in centimeters) (***D***) to reach one of the platforms during the 1 h probe test. Young and aged mice exhibited a preference for the cue-guided platform, regardless of treatment.

Results

Post-training TSA infusion into the CA1 potentiates long-term consolidation of spatial memory in young but not aged mice

During the acquisition phase, both young and aged mice learned to locate the cue-guided PF as attested by a progressive decrease in escape latencies over the eight training trials (Fig. 2*A*). Two-way repeated-measures ANOVA confirmed no significant effect of Age ($F_{(1,57)} < 1$; $p = 0.4$), a significant effect of Trials ($F_{(7,399)} = 33.73$; $p < 0.0001$) and no significant Age × Trial interaction ($F_{(7,399)} = 1.57$; $p = 0.1$). On the 1 h competition test, analysis of the percentage of (cue, place) response strategy for each age group indicated no difference on strategy preference between TSA- and vehicle-infused animals (χ^2 comparisons: $ps > 0.1$). As shown in Figure 2*B*, both age groups showed a significant bias toward the cue-guided PF, regardless of whether or not they previously received TSA infusion (paired comparisons: $p < 0.001$ for Young-Veh; $p < 0.01$ for Aged-Veh or TSA; $p < 0.05$ for Young-TSA). In addition to strategies, there was no statistically signifi-

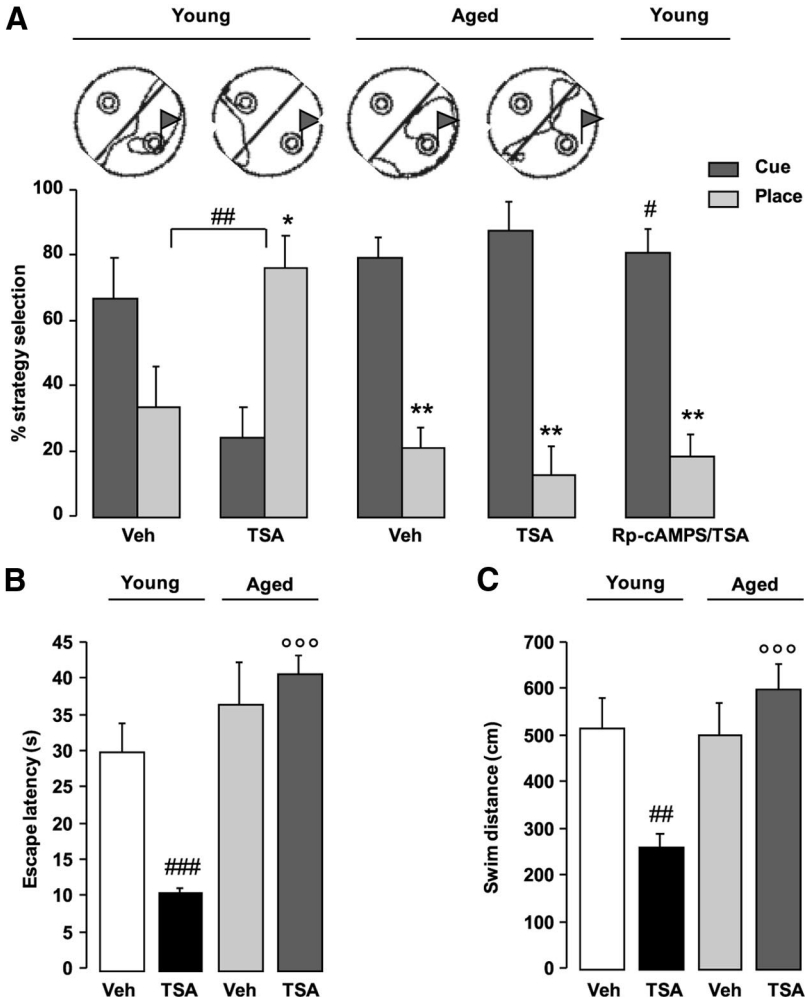

Figure 3. Post-training intra-CA1 infusion of TSA facilitates the shift to the use of place strategy and enhances long-term memory performance in young but not aged mice. ***A***, Top, Swim paths from a representative "place learner" of the TSA-infused young group (Young-TSA: $n = 7$) and representative "cue learners" of the vehicle-infused young group (Young-Veh: $n = 8$) and vehicle- or TSA-infused aged groups (Aged-Veh: $n = 8$; Aged-TSA: $n = 8$). Bottom, Mean percentage (+SEM) of (cue, place) strategy selection during the 24 h probe test in Young-Vehicle and Young-TSA (left), Aged-Vehicle and Aged-TSA (middle), and Rp-cAMPS/TSA young mice (right; $n = 9$) receiving post-training coinfusion of TSA and the PKA inhibitor Rp-cAMPS into CA1. Disruption of hippocampal CREB function completely blocked the TSA-induced bias toward the use of place strategy. ***B***, ***C***, Memory performances expressed as mean latencies + SEM (in seconds) (***B***) and mean distance + SEM (in centimeters) (***C***) to reach one of the platform during the 24 h probe test. Young mice infused with TSA showed greater preference for the place platform compared with other groups. $^{*}p < 0.05$, $^{**}p < 0.01$: cue versus place strategy; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$: main effect of Treatment; $^{\circ\circ\circ}p < 0.001$: main effect of Age.

cant difference between TSA- and vehicle-infused groups for performance parameters such as swim latency and distance to reach the PF (Fig. 2*C*,*D*; $ps > 0.05$). These results indicated that post-training TSA infusion into the CA1 did not affect short-term memory for cue learning in young and aged mice.

When examining the effects of immediate post-training infusion of TSA on learning strategy selection during the 24 h competition test, our data indicated that mice behaved differently according to their age (Fig. 3*A*). Analysis of the percentage of (cue, place) strategy selection for young animals indicated that the difference in the distribution of place/cue learners between TSA- and vehicle-infused groups was of borderline significance ($\chi^2 = 3.36$; $p = 0.06$). In contrast, there was no difference on strategy preference between TSA- and vehicle-infused aged groups ($\chi^2 < 1$; $p = 0.5$). As shown in Figure 3*A*, left, most of young adults previously given intra-CA1 TSA infusion showed a clear bias toward the use of the place strategy (two-tailed paired *t* test, $t_{(6)} = 2{,}75$; $p = 0.033$), whereas vehicle controls did not display significant preference but kept a bias toward the use of the cue strategy (two-tailed paired *t* test, $t_{(7)} = -1.33$; $p = 0.2$). Figure 3*A*, right, shows that aged mice displayed a clear bias toward the cue-guided strategy, regardless of whether they received TSA infusion or not (TSA, paired *t* test, $t_{(7)} = 4.27$; $p = 0.003$; Vehicle, paired *t* test, $t_{(7)} = 4.78$; $p = 0.002$; TSA vs Vehicle, $p = 0.45$). Two-way ANOVAs for additional performance parameters confirmed a significant effect of Age (latency: $F_{(1,27)} = 21.78$; $p < 0.0001$; distance: $F_{(1,27)} = 7.69$; $p < 0.01$) and a significant Age × Treatment interaction (both $F_{(1,27)} > 9$; both $p < 0.01$). *Post hoc* comparisons indicated that young mice receiving TSA had shorter latencies ($p < 0.001$; Fig. 3*B*) and swam more direct routes ($p < 0.01$; Fig. 3*C*) than did vehicle-infused young controls. *Post hoc* comparisons further revealed that aged mice receiving TSA displayed longer escape latencies and swim distance to reach the PF than TSA-infused young adults (both $p < 0.001$), whereas the vehicle-infused groups did not differ from each other (both $p > 0.3$). Together, these results indicated that immediate post-training TSA infusion into the CA1 facilitates long-term memory for place learning in young mice but is inefficient in aged animals.

Blockade of cAMP-PKA pathway in dorsal CA1 interferes with the TSA-induced bias toward the use of a hippocampus-based place strategy in young mice

Previous studies have indicated that intact CREB function is required for beneficial effects of HDAC inhibition on hippocampus-dependent learning and memory (Chwang et al., 2007; Vecsey et al., 2007; Haettig et al., 2011). We therefore thought to examine the consequence of post-training blockade of cAMP-PKA-CREB pathway into the CA1 on the "place" bias effect induced by TSA infusion in young mice. To this end, young mice received concomitant intra-CA1 infusion of TSA and the cAMP inhibitor Rp-cAMPS immediately post-training and then were submitted to the 24 h competition test. Importantly, Rp-cAMPS/TSA animals kept a clear bias toward the use of the cue-guided strategy (two-tailed paired *t* test, $t_{(8)} = -3.9$; $p = 0.004$) and significantly differed from the TSA-infused young group ($\chi^2 = 6.13$; $p = 0.013$) (Fig. 3*A*, right), supporting the hypothesis that the effects of post-training TSA infusion on hippocampus-dependent memory consolidation are dependent on hippocampal cAMP-PKA-CREB cascade.

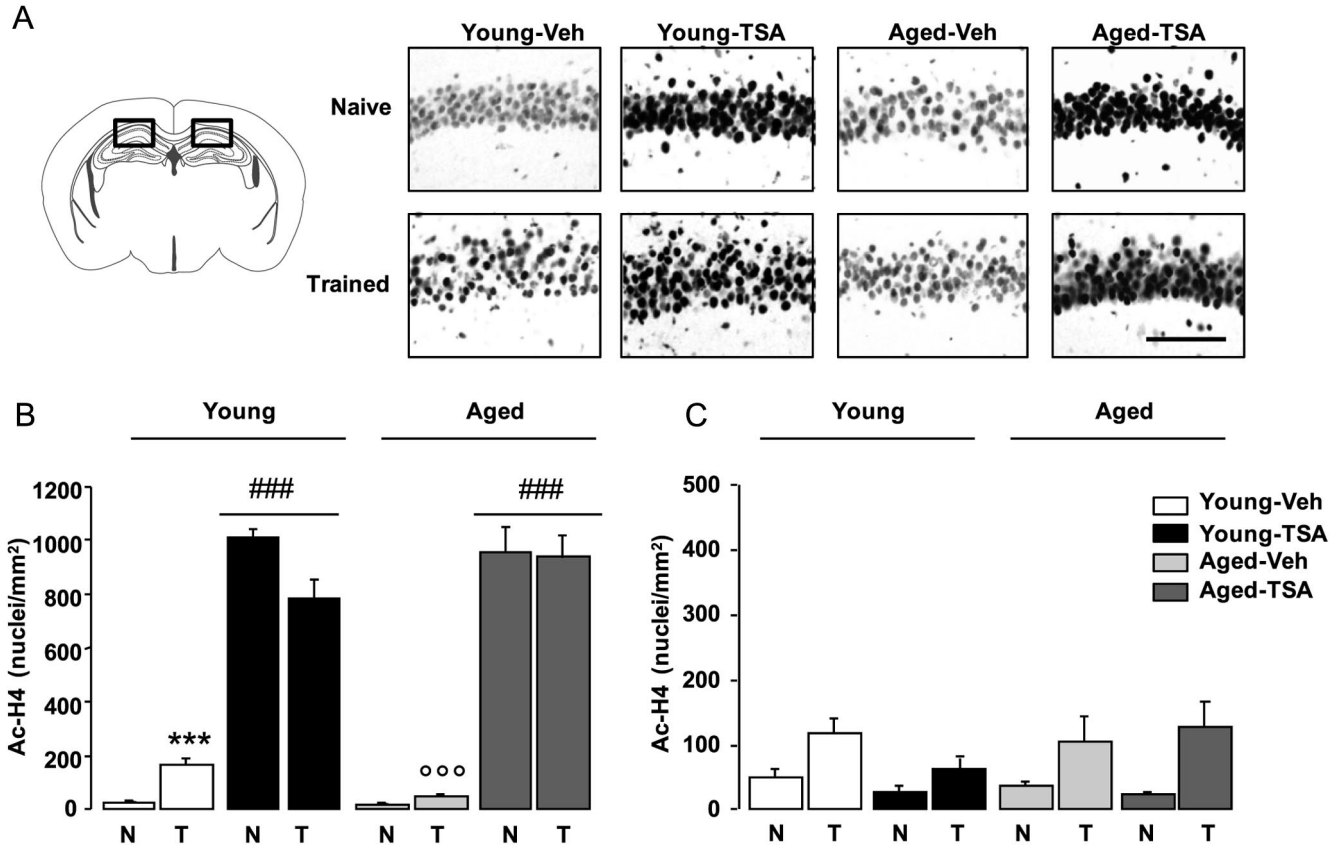

Figure 4. Age-dependent effects of TSA infusion on histone H4 acetylation in the dorsal hippocampus and the dorsal striatum. Animals were killed immediately after the 1 h retention test. Levels of Ac-H4 in the dorsal CA1 and the striatum from vehicle-infused young mice [Young-Veh, naive (N): $n = 6$; trained (T): $n = 8$], TSA-infused young mice (Young-TSA, naive: $n = 5$; trained: $n = 6$), vehicle-infused aged mice (Aged-Veh, naive: $n = 6$; trained: $n = 8$), and TSA-infused aged mice (Aged-TSA, naive: $n = 4$; trained: $n = 6$). ***A***, Representative Ac-H4 immunostainings in the dorsal CA1 for the different naive (top) and trained (bottom) groups. Scale bar, 40 μm. ***B***, Levels of Ac-H4 in the dorsal CA1 were significantly reduced in the Aged-Veh-Trained mice relative to matched Young-Veh-Trained animals. All mice infused with TSA showed significantly greater H4 acetylation levels in the dorsal CA1 than corresponding vehicle controls, regardless of age or training condition. ***C***, Neither aging nor TSA infusion significantly altered H4 acetylation in the dorsal striatum. Data are expressed as mean (+SEM) number of positive Ac-H4 nuclei/mm^2. ***$p < 0.001$: main effect of Training; $^{###}p < 0.001$: main effect of Treatment; $^{°°°}p < 0.001$: main effect of Age.

Effects of post-training intra-CA1 infusion of TSA on histone H4 acetylation and CREB phosphorylation

We next examined the changes in acetylated H4 (Ac-H4) in the dorsal hippocampal CA1 and dorsal striatum in groups of mice killed immediately after the 1 h competition test (Fig. 4). First, naive control mice infused with TSA displayed greater hippocampal Ac-H4 levels than age-matched vehicle controls, regardless of age (Fig. 4*A*, top; quantitated data, Fig. 4*B*). A two-way ANOVA performed on these data confirmed a significant effect of Treatment ($F_{(1,17)} = 628$; $p < 0.0001$) but no effect of Age ($F_{(1,17)} = 0.37$; $p = 0.5$) or Age × Treatment interaction ($F_{(1,17)} = 0.32$; $p = 0.6$). Second, Young-Vehicle but not Aged-Vehicle mice displayed a marked increase in the number and intensity of CA1 Ac-H4-positive neurons in response to training (Fig. 4*A*, bottom, *B*). Two-way ANOVA yielded significant effects of Age ($F_{(1,24)} = 29.71$; $p < 0.0001$) and Training ($F_{(1,24)} = 56.63$; $p < 0.0001$) as well as a significant Age × Training interaction ($F_{(1,24)} = 28.30$; $p < 0.0001$). Further analyses confirmed a significant difference between the trained Young-Vehicle and Aged-Vehicle groups ($p < 0.0001$). Importantly, we observed no Age- and Training-dependent changes in Ac-H4 in mice infused with TSA (both $F < 3$; both $p > 0.1$). Indeed, both trained Young-TSA and Aged-TSA groups displayed significantly greater levels of Ac-H4 in CA1 than did matched vehicle groups (Young, $F_{(1,12)} = 106$; $p < 0.0001$; Aged, $F_{(1,12)} = 175$; $p < 0.0001$), reaching similar levels to those observed in naive Young-TSA and Aged-TSA controls (both $p > 0.05$; Fig. 4*A*). Importantly, and as previously observed (Levenson et al., 2004), TSA infusion failed to enhance CA1 Ac-H4 levels in animals killed immediately after the 24 h probe test, underlining the transient effect of TSA on histone acetylation (data not shown). In the dorsal striatum, we found no statistically significant changes in Ac-H4 levels as a function of training status, Age, or Treatment (Fig. 4*C*).

Prompted by evidence linking CREB activation/phosphorylation to enhancement of hippocampus-dependent memory processes by TSA treatment (Vecsey et al., 2007), we next examined learning-related changes in phosphorylated CREB (P-CREB) in mice killed immediately after the 1 h competition test. In agreement with our previous study indicating that the intensity and number of CA1 P-CREB-immunopositive neurons were dramatically reduced by aging (Porte et al., 2008a), training produced an overall increase in CA1 P-CREB levels in young but not aged mice, independent of treatment condition (Figs. 5*A*, 6*A*). Namely, TSA infusion had no effect on CA1 P-CREB levels in naive control animals (Treatment, $F_{(1,17)} = 1.7$; $p = 0.21$; Treatment × Age, $F_{(1,17)} < 1$; $p = 0.93$). Whereas training increased P-CREB levels in CA1 from Young-Vehicle ($F_{(1,12)} = 22$; $p <$

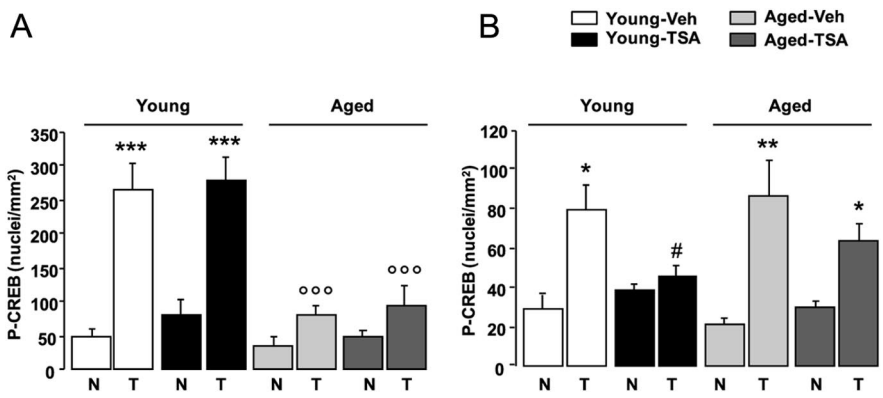

Figure 5. Effects of TSA infusion on CREB phosphorylation in the dorsal hippocampus and the dorsal striatum. Animals were killed immediately after the 1 h retention test. Levels of P-CREB in the dorsal CA1 and the striatum from vehicle-infused young mice [Young-Veh, naive (N): $n = 6$; trained (T): $n = 8$], TSA-infused young mice (Young-TSA, naive: $n = 5$; trained: $n = 6$), vehicle-infused aged mice (Aged-Veh, naive: $n = 6$; trained: $n = 8$), and TSA-infused aged mice (Aged-TSA, naive: $n = 4$; trained: $n = 6$). ***A***, Training-related changes of P-CREB in CA1 were significantly reduced by aging and were not rescued by TSA infusion. ***B***, In the dorsal striatum, training significantly increased P-CREB levels in all groups except the Young-TSA group. Data are expressed as mean (+SEM) number of positive P-CREB nuclei/mm^2. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$: main effect of Training; $^{\#}p < 0.05$: main effect of Treatment; $^{\circ\circ\circ}p < 0.001$: main effect of Age.

0.001) and Young-TSA ($F_{(1,9)} = 26$; $p < 0.001$) mice, no training-related changes were observed in Aged-Vehicle or Aged-TSA animals (both $p > 0.1$; Fig. 6*A*, bottom). Further analyses confirmed that, regardless of whether or not they received TSA infusion, trained young mice displayed significantly greater CA1 P-CREB levels than did aged mice (Vehicle and TSA: both $p < 0.001$; Fig. 6*A*). The patterns of P-CREB in the dorsal striatum are shown in Figures 5*B* and 6*B*. No statistically significant changes were found as a function of Treatment or Age in naive control groups (Fig. 6*B*, top). Training resulted in significantly greater P-CREB levels in the striatum of young and aged mice and significantly differed from naive controls (Young, $F_{(1,21)} = 6.9$; $p = 0.01$; Aged, $F_{(1,20)} = 13.45$; $p = 0.001$). However, compared with age-matched naive controls, the levels of P-CREB in dorsal striatum were significantly increased in Young-Vehicle, Aged-Vehicle, and Aged-TSA groups (all ps < 0.05) but not Young-TSA group ($p = 0.4$) (Fig. 6*B*, bottom).

Enhanced CREB phosphorylation in the striatum reverses the TSA-mediated switch from striatum-based to hippocampus-based memory systems

Because our immunohistochemical data indicated that, compared with age-matched naive controls, all training groups displayed high levels of striatal P-CREB except the Young-TSA group, we next examined whether the effects of intra-CA1 TSA infusion on search strategy preference are relevant to striatal CREB function. To this end, three groups of young mice (8Br-cAMP/TSA, Vehicle/TSA, and Vehicle/Vehicle) received post-training infusions of either the cAMP analog 8Br-cAMP or vehicle into the dorsal striatum with concomitant infusion of TSA or vehicle into the CA1 (Fig. 7). Cannulae placements are schematized in Figure 7*A*. Analyses of the percentage of strategy selection for each group during the 24 h competition test indicated significant difference in the distribution of place/cue learners between the three groups ($\chi^2 = 10.25$; $p = 0.0059$). As shown in Figure 7*B*, animals of the Vehicle/Vehicle and 8Br-cAMP/TSA groups showed a significant bias toward the cue-guided PF (two-tailed paired t test, $t_{(9)} = -3.5$; $p = 0.007$ and $t_{(9)} = -7.8$; $p < 0.0001$, respectively) whereas Vehicle/TSA animals were evenly divided between the use of place and cue strategies (two-tailed paired t test, $t_{(10)} = 0.14$; $p = 0.8$). Importantly, although Vehicle/TSA mice had more modest changes in strategy bias than Young-TSA mice in the first experiment (Fig. 3*A*), significant differences in percentage of strategy selection were found between the Vehicle/TSA and the 8Br-cAMP/TSA ($p = 0.006$) and the Vehicle/Vehicle ($p = 0.031$) groups.

Discussion

When either of two competing (i.e., place and cue/response) strategies can lead to successful resolution of a task, mice predominantly adopt the striatum-dependent cue-guided strategy after a short training regimen, whereas the preference for using a hippocampus-dependent place strategy comes to dominate on the condition that training or preexposure to the spatial environment is sufficient (Nicolle et al., 2003; Martel et al., 2006; , 2007; Sung et al., 2008; Tunur et al., 2010). This is the first study to demonstrate that post-training infusion of TSA in CA1 of young mice facilitates the shift from the use of a striatum-dependent cue/response strategy toward the use of hippocampus-dependent place strategy under training conditions that promote cue-based strategy in vehicle-infused controls. However, this biasing effect of post-training infusion of TSA was observed only in young mice and when probe test was assessed 24 h after learning, indicating that inducing histone hyperacetylation at the time of early consolidation processes promotes transcription of genes required for long-term memory. We provide evidence that inhibiting hippocampal cAMP-PKA-CREB pathway in young mice receiving concomitant infusion of TSA and PKA inhibitor, Rp-cAMPS, into CA1 disrupts the switch from predominantly cue to place strategy preference. Post-training TSA infusion in aged mice rescues aging-associated deregulation of H4 acetylation in the CA1 but fails to reverse P-CREB deficits or to produce a place strategy bias on the 24 h probe test. We further demonstrate that concomitant infusion of intra-CA1 TSA with the cAMP analog, 8Br-cAMP, into the dorsal striatum prevents TSA-infused young mice from predominantly using place strategy. All these findings highlight that post-training intra-CA1 TSA infusion promotes dynamic shift from striatal toward hippocampal memory system in young but not aged animals, and support the possibility of a critical role for CREB in the TSA-mediated switch between these two memory systems.

Systemic or intracerebral administration of HDACi before training facilitates the formation of hippocampus-dependent memory for spatial learning (Fischer et al., 2007; Dash et al., 2009; Ricobaraza et al., 2009), contextual associative fear conditioning (Levenson et al., 2004; Lattal et al., 2007; Kilgore et al., 2010; Peleg et al., 2010), or novel object recognition (Fontán-Lozano et al., 2008; Giralt et al., 2012). In contrast, only a few works have investigated the modulating effects of post-training HDAC inhibition on memory. Studies have shown that intrahippocampal

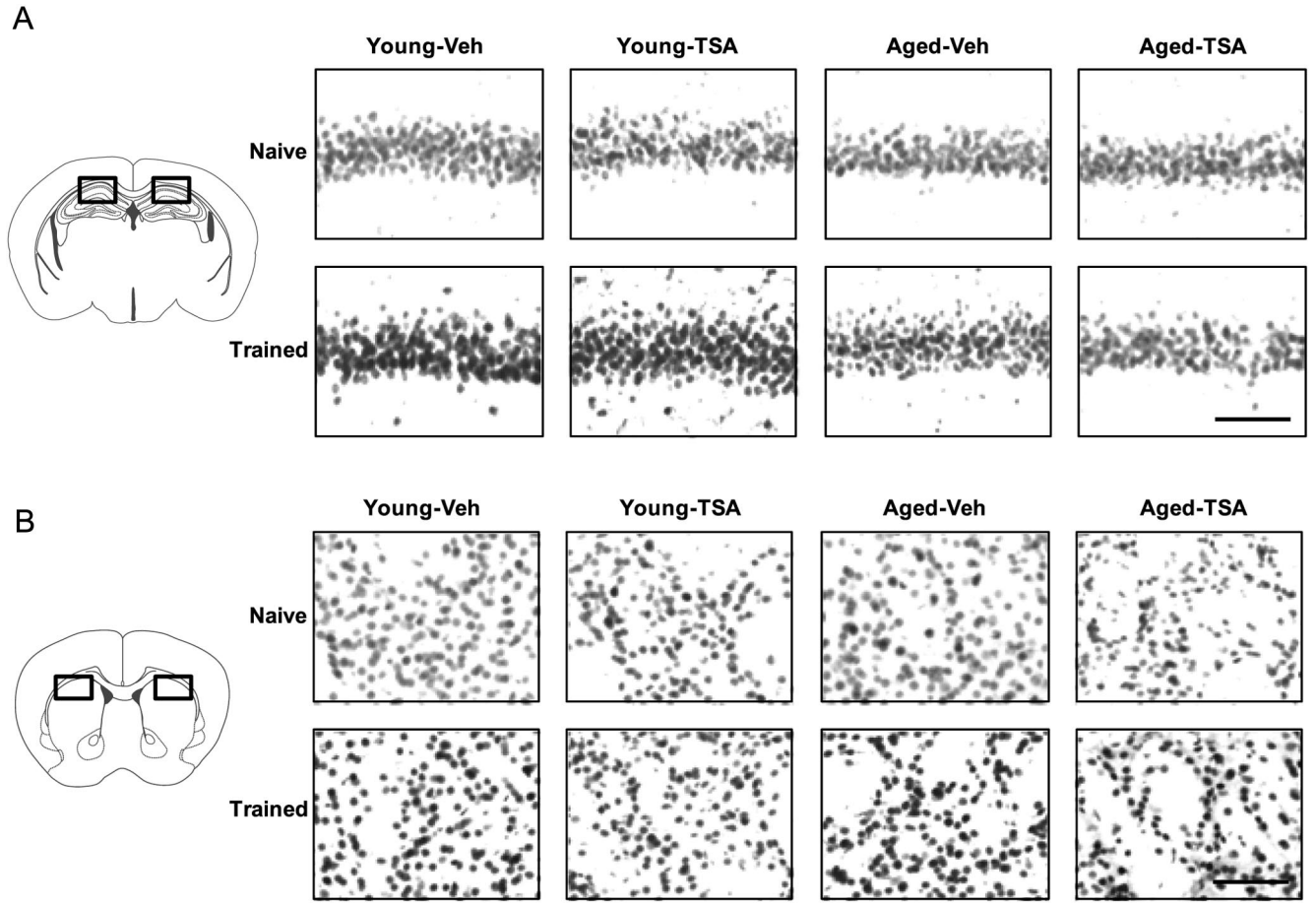

Figure 6. Representative photomicrographs of P-CREB-immunopositive nuclei within the CA1 (***A***) and the dorsal striatum (***B***) from naive (top) and trained (bottom) groups of young and aged animals infused with vehicle or TSA. All trained mice were killed immediately after the 1 h retention test. Scale bar, 50 μm.

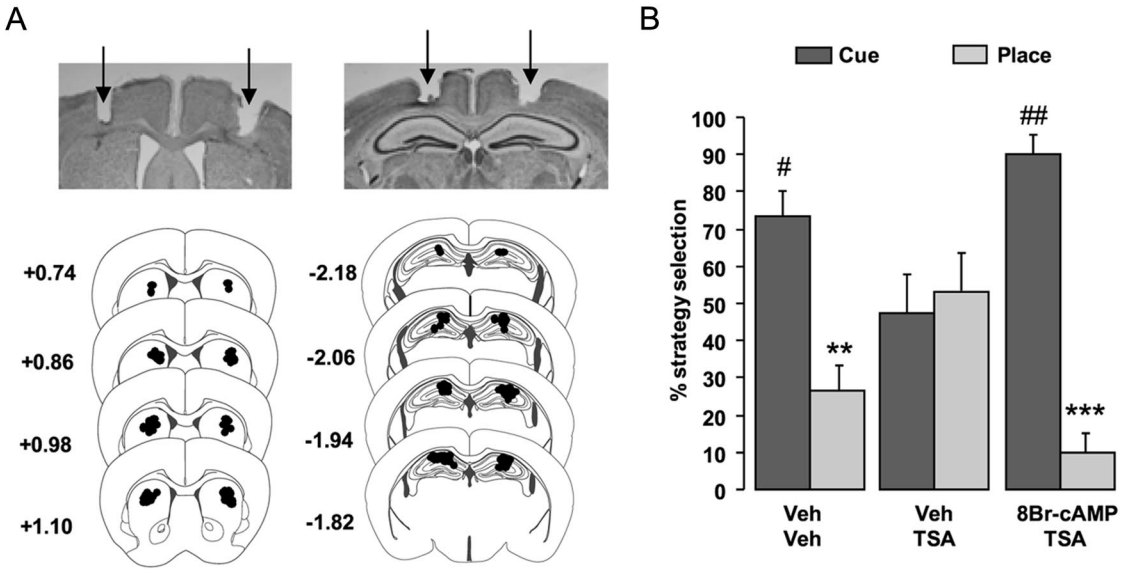

Figure 7. Striatal CREB phosphorylation is critical for the switch from predominantly striatum-based cue to hippocampus-based place strategy. Young mice received post-training intrahippocampal injection of either vehicle or TSA concomitant with intrastriatal administration of vehicle (Veh/Veh: $n = 10$; Veh/TSA: $n = 11$) or cAMP analog, 8Br-cAMP (8Br-cAMP/TSA: $n = 10$) to increase CREB phosphorylation in the striatum. ***A***, Top, Representative views of injection sites in the dorsal striatum (left) and the hippocampus (right) showing tracks of guide cannulae (arrows). Bottom, Histological controls of all stereotaxically implanted mice. Black dots show locations of the tip of injection cannulae. ***B***, Mean percentage (+SEM) of (cue, place) strategy selection during the 24 h probe test. In contrast to Veh/TSA animals, no switch from the use of cue to place strategy preference was observed in 8Br-cAMP/TSA and Veh/Veh groups of mice. $^{**}p < 0.01$, $^{***}p < 0.001$: cue versus place response; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$: main effect of Treatment.

infusion of HDACi immediately after learning enhances long-term memory processes without affecting short-term memory by specifically influencing the consolidation phase (Vecsey et al., 2007). Further, intrahippocampal HDAC inhibition during early memory consolidation can generate a form of long-term memory that persists beyond the point at which normal memory fails (Roozendaal et al., 2010; Hawk et al., 2011). Consistent with these findings, our behavioral results in young mice indicate that inducing histone hyperacetylation in the dorsal hippocampus immediately after learning is sufficient to modulate long-term, but not short-term, memory formation and to control the establishment of different kinds of memory by interacting brain systems during consolidation. Specifically, vehicle-infused young mice subjected to eight-trial acquisition predominantly expressed a cue-guided response independently of the time interval (1 or 24 h) interposed between the acquisition and test sessions. In contrast, TSA-infused young mice predominantly used the cue strategy on the 1 h probe test but switched to the place strategy on the 24 h probe test. These observations suggest that inducing histone hyperacetylation into the CA1 immediately after training does not interfere with short-term memory but facilitates long-term consolidation of spatial information after a training regimen that normally promotes memory consolidation for simple associations between specific behaviors and selective cues. These results further highlight a critical role for histone acetylation into the hippocampus in regulating cellular connectivity between interacting memory systems during consolidation processes. Specifically, post-training intra-CA1 TSA infusion in young mice facilitated switching from striatum- to hippocampus-dependent memory strategy on the 24 h retention test. Consistent with previous observation of a dynamic hippocampus-striatum interplay during the consolidation period (Martel et al., 2007), these findings suggest that increasing hippocampal histone acetylation immediately after training blocks striatum-based cued memory and promotes the formation of hippocampus-dependent spatial memory.

In the hippocampus, remodeling of chromatin via regulation of histone acetylation constitutes a key mechanism to controlling subsets of genes implicated in associative memory formation (Levenson et al., 2004; Chwang et al., 2006; Fischer et al., 2007; Peleg et al., 2010; Sharma, 2010). Accordingly, histone H4 acetylation-dependent transcriptional events in the dorsal hippocampus occur selectively during the consolidation phase (30–60 min after training) of long-term contextual fear memory in mice (Peleg et al., 2010) and spatial memory in rats (Bousiges et al., 2010). Our finding that young mice displayed increased H4 acetylation during the early phase of consolidation (at 1 but not 24 h after learning) is in line with a permissive role for acetylated histones in upregulating subsets of activity-associated genes implicated in plasticity and memory (Levenson et al., 2004). Furthermore, while immediate post-training TSA infusion produced strategy shift on the 24 h retention test, TSA-induced H4 hyperacetylation occurred 1 h, but not 24 h, after training, arguing in favor of a causal role for histone acetylation in the rapid molecular mechanisms engaging transcription-dependent pathways necessary for memory consolidation (Federman et al., 2009; Stefanko et al., 2009; Reolon et al., 2011). This is also consonant with recent observations that increasing hippocampal histone acetylation at the time of early consolidation processes promotes transcription of genes required for long-term memory formation by influencing the strength of functional connectivity between the hippocampus and interconnected structures (Stafford et al., 2012).

Studies in both aged mice (Peleg et al., 2010) and rats (Zeng et al., 2011) have found that reduced histone H4 acetylation in the hippocampus correlates with impaired spatial or contextual memory and that treatments with HDACi before training rescue these deficits. Immediate post-training systemic HDACi administration also efficiently reversed aging-related object recognition memory declines in rats (Reolon et al., 2011). An unexpected result from our study is that, in sharp contrast to previous findings, post-training intra-CA1 TSA infusion rescued the age-associated decrease in H4 acetylation but was not sufficient to bias an aged animal toward the use of place strategy on the 24 h probe test. In addition, post-training TSA infusion was unable to reverse reduced P-CREB levels in aged CA1 neurons, suggesting that post-training TSA infusion, by restoring/enhancing H4 acetylation while keeping P-CREB at low levels in the CA1, might not be sufficient to bias the aged brain toward the use of a hippocampus-based place strategy. These observations are in contrast to recent findings wherein restoration of histone H4 lysine 12 acetylation in aged mice receiving intrahippocampal infusion of the HDACi suberoylanilide hydroxamic acid reinstates the expression of learning-induced genes and leads to the recovery of associative learning behavior (Peleg et al., 2010). We found that a shift toward a place strategy can be prevented by coadministration of TSA with the PKA inhibitor, Rp-cAMPS, into the CA1, which is consistent with studies reporting that HDACi modulates hippocampus-dependent memory in a CREB-dependent manner (Chwang et al., 2007; Vecsey et al., 2007; Chen et al., 2010; Haettig et al., 2011). These findings and recent evidence that modification-specific, bidirectional chromatin regulation is dependent on recent experience, age, and hippocampal subfields (Castellano et al., 2012) caution that use of HDACi may have hazardous consequences when treating cognitive disorders, especially those associated with CREB deficits.

Consistent with previous reports indicating that specific forms of memory depend on region-specific patterns of P-CREB (Pittenger et al., 2002; Colombo et al., 2003; Martel et al., 2007; Lee et al., 2008; Porte et al., 2008b, 2011; Sung et al., 2008), predominant cue search strategy in Aged-Vehicle and Aged-TSA animals was associated with high P-CREB levels in the striatum but not the hippocampus. In contrast, the use of place strategy in Young-TSA mice correlated with high P-CREB in the hippocampus but not striatum, suggesting that P-CREB provides a signature in the hippocampus of TSA-infused young mice that coincides with their bias in selecting place strategy. To gain further insight into the role of CREB in modulating cognitive strategies, young mice received coinfusion of TSA into CA1 and cAMP analog, 8Br-cAMP, into the dorsal striatum. Importantly, young mice infused with 8Br-cAMP/TSA remained to use cue strategy, indicating that striatal PKA/CREB hyperactivity blocked the TSA-induced shift toward the use of a place strategy. These findings suggest that post-training intra-CA1 histone hyperacetylation promotes dynamic shift from predominantly cue to more place learning; this, however, requires accurate regulation of CREB function within the hippocampus and striatum.

Our current findings indicate that enhancing histone acetylation into the dorsal CA1 at the time of early consolidation process is a positive factor facilitating the switch from predominantly striatum-based cue to hippocampus-based place strategy in young mice. These findings and recent reports converge to suggest that both histone H4 and CREB are critical components of the mechanism by which HDACi enhances hippocampus-

dependent memories. Although molecular details on how H4 and CREB interact to regulate memory formation remain to be elucidated, these results may have important therapeutic implications in view of the efforts to design new drugs to target cognitive disorders resulting from normal and pathological aging.

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