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Review Paper

Epigenetic mechanisms and memory strength: A comparative study

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ABSTRACT

Memory consolidation requires *de novo* mRNA and protein synthesis. Transcriptional activation is controlled by transcription factors, their cofactors and repressors. Cofactors and repressors regulate gene expression by interacting with basal transcription machinery, remodeling chromatin structure and/or chemically modifying histones. Acetylation is the most studied epigenetic mechanism of histones modifications related to gene expression. This process is regulated by histone acetylases (HATs) and histone deacetylases (HDACs). More than 5 years ago, we began a line of research about the role of histone acetylation during memory consolidation. Here we review our work, presenting evidence about the critical role of this epigenetic mechanism during consolidation of context-signal memory in the crab *Neohelice granulata*, as well as during consolidation of novel object recognition memory in the mouse *Mus musculus*. Our evidence demonstrates that histone acetylation is a key mechanism in memory consolidation, functioning as a distinctive molecular feature of strong memories. Furthermore, we found that the strength of a memory can be characterized by its persistence or its resistance to extinction. Besides, we found that the role of this epigenetic mechanism regulating gene expression only in the formation of strongest memories is evolutionarily conserved.

Contents

1. Introduction

Regulation of gene expression is a key process for long-term memory (LTM) storage. During LTM consolidation, the expression of a set of genes leads to proteins synthesis, an important process for the regulation of synaptic function that underlies memory. Macromolecules synthesis induces changes in the morphology of synapses involved and/or genesis of new synapses in the memory trace (Montarolo et al., 1986; Glanzman et al., 1990). Some transcription factors (TFs), such as cyclic AMP responsive element binding protein (CREB) (Kaang et al., 1993; Yin and Tully, 1996), zinc finger inducible factor (ZIF/268) (Tischmeyer and Grimm, 1999; Davis et al., 2003), CCAAT enhancer binding protein (C/EBP) (Alberini et al., 1995; Taubenfeld et al., 2001) and the nuclear factor κappa B (NF-κB) (Romano et al., 2006), have been involved in memory consolidation. Among them, CREB and NF-κB are considered key synapse-nucleus signaling molecules in the induction of gene expression during LTM formation (Alberini, 2009). These two TFs are rapidly activated after learning, regulating the transcription of early and late genes during memory consolidation.

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The magnitude and the extent of the gene expression pattern induced by learning could be regulated by epigenetic mechanisms (Barret and Wood, 2008). The genome of all cells is packaged into a structure called chromatin, comprising deoxyribonucleic acid (DNA) and proteins that are associated to it at different levels, performing the compaction of chromatin structure and generating its different degrees of packing. Epigenetic marks are known as those modifications in chromatin structure which affect transcription of genes. These marks may be post-translational modifications (PTMs) of nucleosomal histones, such as acetylation, phosphorylation, ubiquitination and methylation, as well as changes at the methylation patterns of DNA cytosine residues. Other epigenetic mechanisms include histone variants incorporation to nucleosomes, nucleosome remodeling, and changes in the position of the chromosome in relation to pores in the nuclear envelope (Raisner and Madhani, 2006, Kundu and Peterson, 2009; Draker and Cheung, 2009). All these epigenetic processes occur in an interdependent and coordinated manner, in order to regulate the organization of the various functional genomic microdomains (Mehler, 2008, for a review).

Chromatin-modifying enzymes that carry out acetylation and deacetylation of histones are the histone acetyl transferases (HATs) and deacetylases (HDACs), respectively (Sterner and Berger, 2000). Histone acetylation is generally associated with transcriptional activation, and histone deacetylation with transcriptional repression. The involvement of epigenetic mechanisms such as histones acetylation, phosphorylation and methylation has been described in neuronal plasticity processes in invertebrates and long-term memory consolidation in vertebrates (Guan et al., 2002; Alarcon et al., 2004; Korzus et al., 2004; Levenson et al., 2004; Wood et al., 2005, 2006a; Gupta et al., 2010; Gupta-Agarwal et al., 2012). For example, histone H3 acetylation in the hippocampus has been associated with the formation of conditioned fear memory in rodents (Levenson et al., 2004; Bredy and Barad, 2008; Lubin et al., 2008). The CREB binding protein (CBP) is one of the most studied HAT and it was demonstrated as a chromatin structure regulator during memory consolidation in vertebrate models (Alarcon et al., 2004; Korzus et al., 2004; Oliveira et al., 2007; Vecsey et al., 2007). Some studies showed that genetic disruption of CBP and other HATs activity interferes with memory formation (Alarcon et al., 2004; Korzus et al., 2004; Oliveira et al., 2007; Maurice et al., 2007). Furthermore, it has been demonstrated that inhibition of HDACs activity facilitates memory in rodent models (Yeh et al., 2004; Levenson et al., 2004; Vecsey et al., 2007; Fischer et al., 2007; Stefanko et al., 2009), and it also reverses memory deficits induced by genetic engineering into the *cbp* gene (Alarcon et al., 2004; Korzus et al., 2004; Guan et al., 2009). In contrast, inhibition of HAT activity with drugs has proven challenging, as most inhibitors generated to date cannot be used *in vivo* due to their cell impermeability and/or metabolic instability (Dal Piaz et al., 2010). Some evidence has shown that pharmacological inhibition of p300/CBP impaired memory enhancement by estradiol (Zhao et al., 2012), impaired memory formation (Federman et al., 2013), and enhanced memory extinction (Marek et al., 2011).

The PTMs of histones and chromatin remodeling have been implicated in a wide variety of functions in the nervous system (Bhaumik et al., 2007; Blasco, 2007; Feng et al., 2007; Hsieh and Gage, 2004; Kondo, 2006; McCarthy et al., 2009; Mikkelsen et al., 2007; Ooi and Wood, 2007; Shi et al., 2007; Taniura et al., 2007; Tsankova et al., 2007). The involvement of epigenetic mechanisms in memory formation has been postulated as a continuous supply of gene expression. Their regulation is specifically required for maintaining neuronal long-term changes induced by learning, providing potentially stable marks in the genome (Tsankova et al., 2004; Kumar et al., 2005; Hsieh and Gage, 2005; Barret and Wood, 2008; Levenson and Sweatt, 2006; Colvis et al., 2005; Borrelli et al., 2008). Through these control mechanisms, generation of stable changes in gene expression pattern during memory consolidation could be an important mechanism for its stability (Alberini, 2009). The existence of an *epigenetic code* involved in memory formation has already been proposed, by means of which specific patterns of histones PTMs and DNA methylation contribute to encode the salience of extra and intracellular signals and its contingence (Wood et al., 2006b; Roth and Sweatt, 2009). This *epigenetic code* hypothesis for memory stems from the original idea of a *histone code* proposed by Allis (Jenuwein and Allis, 2001), but it also includes DNA methylation (Roth and Sweatt, 2009; Day and Sweatt, 2011). In this context, *epigenetics* comprises the covalent modifications of chromatin that influence in gene expression, which are induced by neuronal activity and are necessary for cognition. In the last decade, an increasing amount of evidence has begun to shed light on the role of such processes in the encoding, storage and retrieval of acquired information during learning (Peleg et al., 2010; Lesburguères et al., 2011; Gräff et al., 2012). Here we review our work in both invertebrates and vertebrates on the critical role of the histone acetylation in long-term memory.

2. Histone acetylation in context-signal memory: a case in invertebrates

We began our study in the grapsid crab *Neohelice granulata*. In the last 20 years, a considerable research effort has been focused on the study of the context-signal memory (CSM) in this model. In the CSM, repeated presentation of a visual danger stimulus (an opaque screen that moves above the animal) provokes the fading of the initial escape response, which is actively replaced by a freezing response (Lozada et al., 1990) (Fig. 1a). Fifteen or more spaced danger stimulus presentations (trials) induce an association between the iterated stimulus and contextual features (container, room light, etc). A LTM is formed, which lasts at least for a week and entails *de novo* protein and mRNA synthesis (Pedreira et al., 1996), activation of cAMP-dependent protein kinase (PKA) (Locatelli et al., 2002), activation of extracellular signal-regulated kinase (ERK) (Feld et al. 2005), and activation of the NF-kB transcription factor (Freudenthal and Romano, 2000; Merlo et al., 2002). Memory retention of the learning acquired during training is defined as a significantly lower mean response level at testing session of the trained group versus a control group that was not stimulated with the VDS during the training session (Fig. 1b). The memory retention at testing session is similarly evident in animals trained either with the standard (15 trials) or the strong (30 trials) protocols (Freudenthal and Romano, 2000). In contrast, weak protocol of five trials is unable to induce LTM formation (Romano et al., 1996) (Fig. 1b).

Using this invertebrate model, our group has focused the study on histone acetylation during memory consolidation and its relation with memory strength. For this purpose, we trained the animals with two different protocols, standard and strong trainings, using 15 and 30 trials, respectively. We found an increase in the level of histone H3 acetylation in the brain during consolidation only after a strong training protocol (Fig. 2). We also found that the memory induced by a strong training of 30 trials, in contrast to standard training memory, was resistant to extinction (Fig. 3, Federman et al., 2012). Memory extinction is the temporary inhibition of the response acquired during training, and the resistance to extinction is considered as indicative of memory strength (Tully and Quinn 1985; De Oliveira Alvares et al., 2013). Thus, our result showed that the strong training induced in fact a stronger LTM (sLTM).

Furthermore, when we trained the animals with a weak training protocol of 5 trials, pharmacological blockade of the action of

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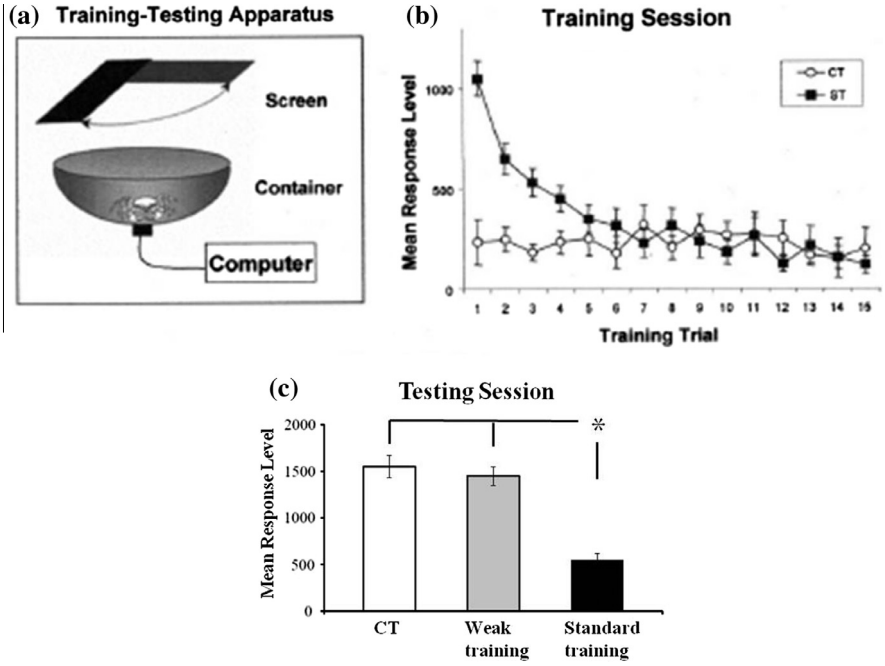

Fig. 1. (a) Spaced training of 15 or more trials induces long-term memory. (a) Left panel illustrates the training–testing apparatus. (b) Mean response level of a spaced training session (15 trials, 3-min inter-trial interval, ST = standard training) and a control group (context-exposed without stimulation; CT). (c) Testing sessions were carried out 24 h after training sessions, and crabs were individually housed during training–testing interval. The panel shows mean response level ± SEM during testing session, from CT and two trained groups: animals training with a weak protocol (5 trials) or animals trained with standard protocol. $^{*}p < 0.05$.

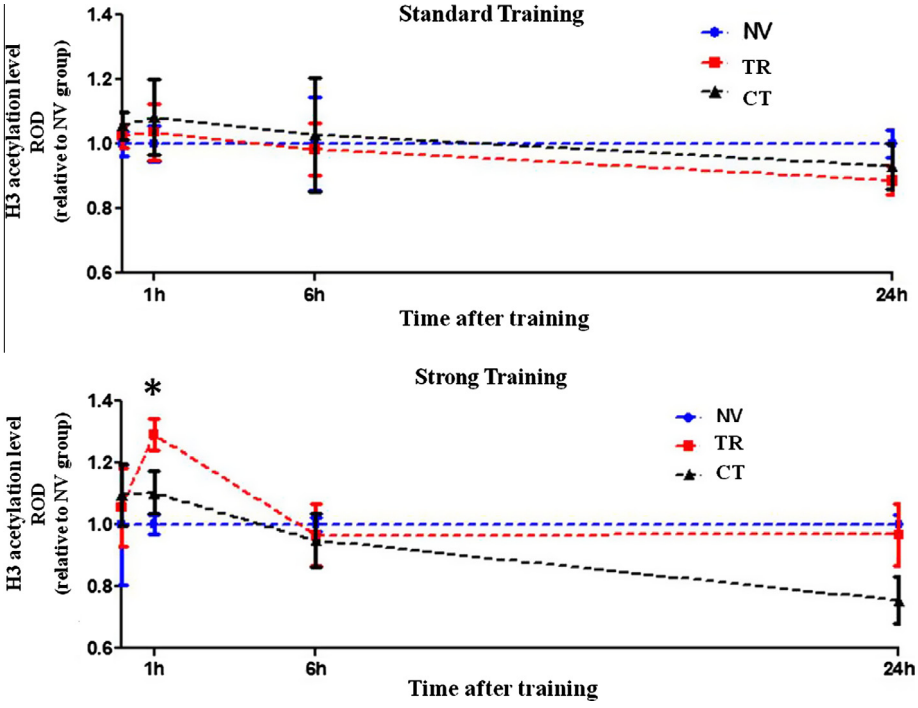

Fig. 2. Levels of histone H3 acetylation in the crab brain during memory consolidation. Upper panel: time course of histone acetylation during memory consolidation after standard training. mean ± SEM of ROD (relative optic density) values of the specific acetyl histone H3 band normalized to NV group mean value. Lower panel: time course of histone acetylation during memory consolidation after strong training. Mean ± SEM of ROD values of the specific acetyl histone H3 band normalized to total H3 antibody ROD values and to NV group mean value. $^{*}p < 0.05$. Data redrawn from Federman et al. (2009).

HDACs by administration of the inhibitors sodium butyrate or Trichostatin A during consolidation induced memory enhancement (Federman et al., 2009) (Fig. 3). Taking account that these two HDACs inhibitors have effect on different members of the HDAC family, there is recent evidence showing that these HDACs inhibitors differentially enhanced the retention of memory for mice inhibitory avoidance when administered to the dorsal hippocampus after training (Blank et al., 2014). However, we found that both of them enhanced the memory retention. This suggests that any of the HDACs affected in both cases could be involved in this

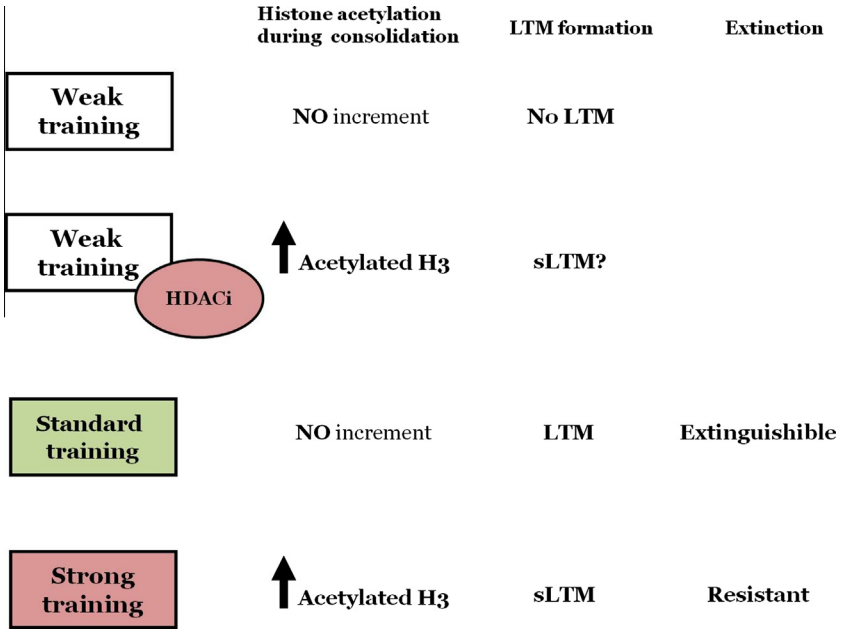

Fig. 3. Outline of histone H3 acetylation involvement in consolidation, in function of training session and the strength of the memory. Summary of main results from the invertebrate model *Neohelice*, adapted from Federman et al. (2012).

mechanism on this invertebrate memory model, and/or the drug specificity on invertebrates is different from vertebrates.

We also studied the role of histone acetylation in memory reconsolidation. This memory phase is triggered in already consolidated memories by the presentation of a reminder that, under certain boundary conditions, induces the reactivation of the memory trace (Tronson and Taylor, 2013). Such a reactivation induces a labilization-reconsolidation process that allows memory disruption, reinforcement or updating (Nader et al., 2000). Therefore, we studied the role of histone acetylation in memory reconsolidation in the CSM model (Federman et al., 2012). Firstly, we found an increase in histone H3 acetylation 1 h after memory reactivation, returning to basal levels after 3 h. Strikingly, this increment was only detected during reconsolidation of a sLTM induced by a strong training, but not for memories induced by weaker trainings as 15 trial training. Furthermore, we showed that a weak memory induced by 5 trials which was enhanced during consolidation by HDAC inhibitors, also recruited histone H3 acetylation in reconsolidation as the sLTM does. In the same line of evidence, in another experiment we found for the first time that the administration of a HAT inhibitor during memory reconsolidation impairs LTM restabilization (Federman et al., 2012).

Thus, we demonstrated that histone acetylation is a reversible and transient mechanism, induced immediately after the acquisition of new information (Federman et al., 2009). In turn, we demonstrated that the induction of histone acetylation correlates with memory strength (Federman et al., 2012). Moreover, although the first evidence for the role of this epigenetic mechanism in neuronal plasticity was obtained in *Aplysia* (Guan et al., 2002), our work in *Neohelice* constituted the first direct evidence of the role of chromatin modifications during the formation of the LTM in invertebrates.

3. Histone acetylation and consolidation of recognition memory

Continuing with our research about the potential role of this epigenetic mechanism on memory strength, we performed studies in a mammalian memory model, using the novel object recognition (NOR) task in mice (Fig 4a). The recognition memory is the ability to judge whether a recently found item, either an object or an episode, had been previously experienced (Squire et al., 2007). Previous studies had evidenced the involvement of epigenetic mechanisms in recognition memory. The activity of the HATs CBP and p300 during recognition memory consolidation was studied in genetically modified mice (Bourtchouladze et al., 2003; Barrett et al. 2011; Oliveira et al., 2011). It was shown that the HAT activity domain of CBP was required for NOR memory consolidation (Korzus et al., 2004; Bourtchouladze et al., 2003; Wood et al., 2005, 2006a) and that knock out of the *cbp* gene prevented the consolidation of recognition memory (Alarcon et al., 2004; Barrett et al. 2011). Furthermore, it has been found that p300 activity is required for memory formation (Oliveira et al., 2007, 2011; Marek et al., 2011; Federman et al., 2013).

We studied the involvement of histone acetylation during memory consolidation, under the hypothesis that this mechanism is a required molecular feature for the formation of enduring memories. To address this question we used three different training protocols: one group of animals received a weak training (3 min of object exploration) which did not induce LTM; another group received a standard training (10 min) that induced a LTM which lasts for 24 h; and the last group received a strong training (15 min) which induced a LTM that lasts for 7 days (Fig. 4b). We found that there was an induction of histone acetylation in the hippocampus only in animals trained with the strong training protocol (Fig. 4c). Then, strong memory consolidation differs at the molecular level from weaker memories by the induction of this epigenetic mechanism. In addition, we showed that it also differs by its persistence (Fig. 4b). These results supported our hypothesis that histone acetylation is a molecular feature of more persistent memories and, taken together with the results found in invertebrates, demonstrated that the role of this mechanism would be evolutionarily conserved.

All in all, our studies from both invertebrate and vertebrate models showed the relationship between the strength of a given memory and a general increment of histone acetylation levels in the nervous system, but not in particular genes. Our next goal was to investigate histone acetylation changes in specific genes involved in memory consolidation, as *Zif268* and *CamKII*.

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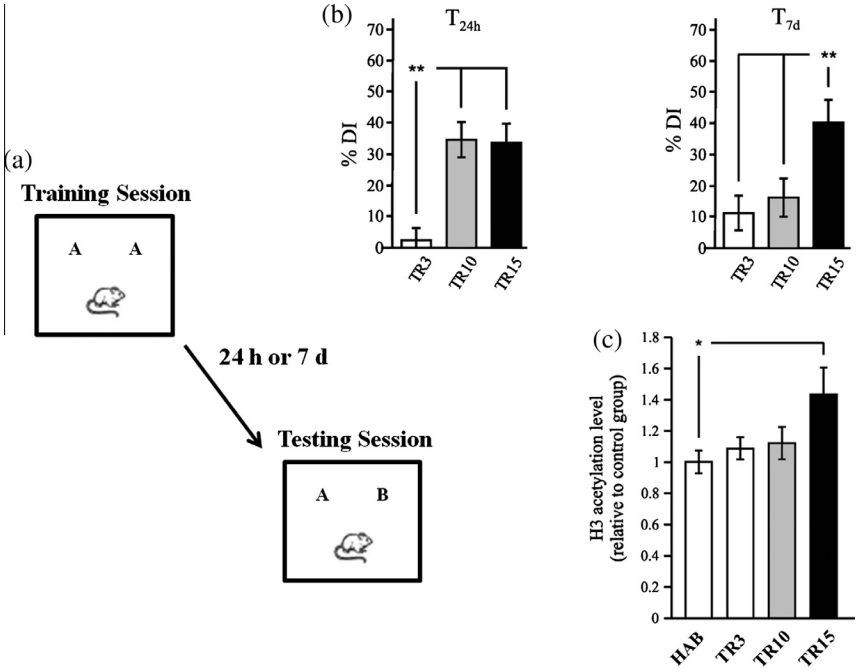

Fig. 4. Strong training induces a persistent recognition memory and general histone acetylation increment during NOR memory consolidation. (a) Diagram outlining the behavioral experimental design. TR3, TR10 and TR15 groups received 3, 10, or 15 min of training session, respectively. (b) Graph representing the mean ± SEM of DI% for each group. The relative time of novel object exploration was calculated as the discrimination index (DI%), as follows: (t novel − t familiar)/(t novel + t familiar) × 100%. The mean DI% value was calculated for the different groups of animals. $^{**}p < 0.01$ in a one-way ANOVA, followed by the Duncan post hoc test. (c) TR3, TR10 and TR15 groups plus a nontrained HAB group. Animals were killed 1 h after training. Graph represents the mean ± SEM of acetyl H3 levels in the hippocampus estimated by Western blot normalized to total H3 levels. $^{*}p < 0.05$, one-way ANOVA, followed by the Duncan post hoc test. Data redrawn from Federman et al. (2013).

4. NF-kB signaling and histone acetylation regulating memory persistence

To explore NF-κB-dependent histone acetylation involved in a specific gene expression we used the three different types of training for NOR task as before. We found that only after strong training, NF-κB inhibition impaired memory persistence and, concomitantly, prevented the induction of general H3 acetylation (Federman et al., 2013). Furthermore, to determine the level of histone acetylation at specific genome locations, we studied promoter regions of particular genes that are associated with neural plasticity and memory. We studied two genes that codify important proteins involved in memory formation: Zif268 and CaMKII delta. *Zif268* (also known as *Egr-1*, *Ngfi-A*, *Krox 24*, *Tis 8*, and *Zenk*) is an immediate-early gene (Davis

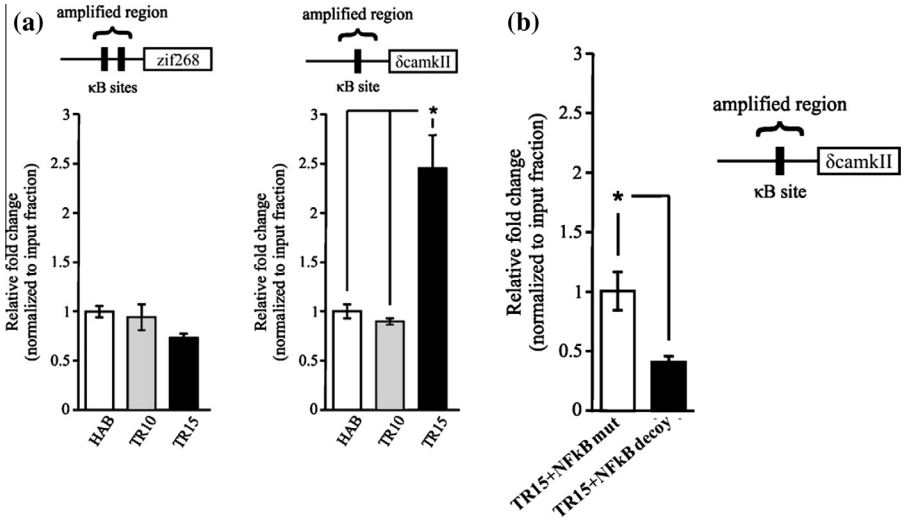

Fig. 5. Acetylation of a promoter region that included an NF-κB consensus sequence is specifically increased after strong training. (a) Left upper diagram: NF-kB-binding sites identified within 1 kbp promoter upstream sequences of the Zif268 gene (GenBank Gene ID: 13653). Left graph: mean ± SEM of the fold change relative to input fraction of histone H3 acetylation at the *Zif268* promoter in the hippocampus, 1 h after training (ChIP assay). Right upper diagram: Bona fide NF-κB-binding site identified within 1 kbp promoter upstream sequences of the *Camk2d* gene (GenBank Gene ID: 108058). Right graph: mean ± SEM of the fold change relative to input fraction of histone H3 acetylation at the *Camk2d* promoter in the hippocampus 1 h after training. $^{*}p < 0.05$, one-way ANOVA, followed by a Duncan post hoc test. (b) Graph represents the mean ± SEM of the fold change relative to input fraction of H3 acetyl levels at the *Camk2d* promoter in the hippocampus 1 h after training and NFkB decoy injection (ChIP assay). NFkB mutant decoy was used as control drug. $^{*}p < 0.05$, Student's t test. Data redrawn from Federman et al. (2013).

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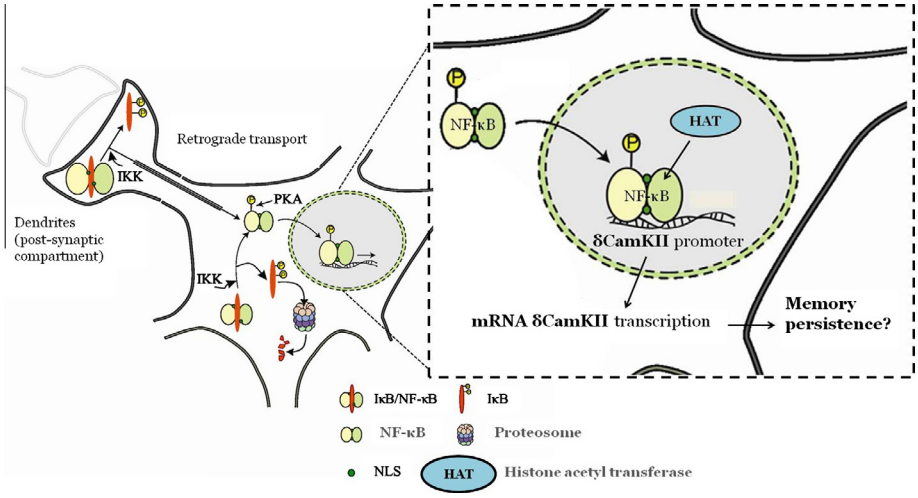

Fig. 6. Neuronal model of the molecular mechanisms showing the activation of NF-κB in synapsis and soma, its nuclear translocation, the NF-kB-dependent histone acetylation and the *Camk2d* gene expression involvement in the regulation of memory persistence.

et al., 2003; Soulé et al., 2008) and calcium/calmodulin kinase II δ (*Camk2d*) is a late gene (Sirri et al., 2010; Lucchesi et al., 2011). In particular, we focused the analysis on promoter regions containing NF-κB-regulatory elements. Accordingly, we found an important increase in histone H3 acetylation at a specific NF-κB-regulated promoter region of the *Camk2d* gene, which was reversed by NF-κB inhibition (Fig. 5). This H3 acetylation increment led to δCaMKII mRNA induction 3 h after strong training, but not after weaker training protocols (Federman et al., 2013). This result showed that δCaMKII expression was only induced during consolidation of persistent forms of NOR memory. This work presented, for the first time, a molecular link between transcription factor activation, an epigenetic mechanism, and late gene expression in the regulation of memory persistence (Fig. 6).

5. Concluding remarks from a comparative study

Our work in the two models of memory showed that histone acetylation mechanism is induced after strong training protocols, 30 VDS presentations in the case of the invertebrate model and 15 min of exposure to the objects in the vertebrate model, by which a strong LTM (sLTM) is formed. Considering that LTM and sLTM are induced by the same type of association between stimuli and both require a consolidation phase that recruits basic molecular mechanisms such as gene transcription and protein synthesis, what might be the molecular differences between these two types of LTM during consolidation which underlie the difference in strength?

As suggested initially by Davis and Squire (Davis and Squire, 1984), it is possible that neurons possess a genetic command to maintain the molecular and morphological changes that occur when memory is consolidated. Since the neurons genomic sequence is not expected to change, it has been postulated that memory can endure, at least in part, by the pattern of gene expression induced during consolidation (Dudai and Morris, 2000; Dudai, 2002; Alberini, 2009). Our evidence argues for this hypothesis and adds another level of molecular regulation for memory persistence (Fig. 6). We postulate that although any type of LTM requires mRNA and protein synthesis, the modulation or regulation of macromolecules synthesis by epigenetic mechanisms is one factor that induces differences on memory retention along time.

In relation to the idea of an *epigenetic code for memory* (Roth and Sweatt, 2009), we suggest that epigenetic mechanisms with different dynamics could be involved in different aspects of memory formation. In the series of experiments reviewed here, we studied only histone acetylation. This epigenetic mechanism highly correlates with the activation of gene expression and the ending of transcription is regularly accompanied by the reverse processes, the deacetylation. Changes in gene expression regulated by rapid and transient epigenetic processes could underlie modifications that occur during LTM consolidation. For instance, histone acetylation could temporarily encode characteristics of the learning episode, such as amount or duration of training. Only after a "training threshold", specific histone acetylation could be induced. The induction of specific genes (e.g. *Camk2d*) due to specific transcription factor activation (e.g. NF-κB) in a tight window after training could be important for signaling activation required for memory persistence. Downstream mechanism consequences of the specific histone acetylation induction could be established. It remains to find direct evidences of epigenetic marks, reversible but potentially stable, that could accompany the duration or persistence of memory itself.

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