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Invited Review

Molecular signatures and mechanisms of long-lasting memory consolidation and storage

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ABSTRACT

A body of evidence emerged in the last decade regarding late posttraining memory processing. Most of this new information comes from aversively motivated learning tasks that mainly depend on hippocampus, amygdala and insular cortex, and points to the involvement of long-lasting changes in gene expression and protein synthesis in late stages of memory consolidation and storage. Here, we describe recent advances in this field and discuss how recurrent rounds of macromolecular synthesis and its regulation might impact long-term memory storage.

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1. Introduction

Long-term memory (LTM) is conventionally defined as that lasting more than several hours and there is a vast amount of information regarding the participation of many biochemical pathways and brain circuits in LTM formation. In 1900, Muller and Pilzecker (1900) proposed that formation of permanent memory takes time and that during this time, memory remains vulnerable to disruption. The process of developing stable memory is referred to as "consolidation" (McGaugh, 1966, 2000). A dominant idea that emerged two decades ago is that memory consolidation comprises two stages or phases: the initial stage, called cellular or synaptic consolidation, is fast, lasting from several hours to a couple of days. This process is thought to take place at synapses of the neuronal circuits encoding the experience-dependent internal representation such as the hippocampus and related non-cortical structures (Dudai, 2002). Cellular consolidation involves the activation of transcription factors to modulate gene expression, as well as synthesis, posttranslational modification and reorganization of proteins at synapses and soma, which finally ends in synaptic remodeling that makes the memory trace stable and precise (Alberini, 2009; Lamprecht & LeDoux, 2004; Morris, 2006; Ruediger et al., 2011). In other words, cellular consolidation has been defined as the transition of memory from protein synthesis and gene expression-dependence to independence in specific brain regions involved in acquisition of a particular learning experience (Medina, Bekinschtein, Cammarota, & Izquierdo, 2008).

The second phase is slower, and entails the participation of neocortical regions and their interactions with medial temporal lobe structures reorganizing the recently learned material (Squire, 1992) by gradually binding together the multiple cortical regions that store memory for a whole event. This phase is called systems-level consolidation and lasts several days to weeks or months in most learning tasks studied so far (Frankland & Bontempi, 2005). Systems consolidation is usually referred to as the process by which memory becomes independent of the hippocampus.

The standard model of memory consolidation posits that the hippocampus is primarily involved in consolidating and recalling recent episodic-like memories while some cortical regions, including prelimbic, orbitofrontal, and anterior cingulate areas, are mostly implicated in remote memory processing (Frankland, Bontempi, Talton, Kaczmarek, & Silva, 2004; Lesburgueres et al., 2011; Maviel, Durkin, Menzaghi, & Bontempi, 2004; Shan, Chan, & Storm, 2008). However, strong alternative hypotheses emerged in the last few years stating that some cortical regions outside the temporal lobe have indeed a role in the very first moments of memory formation and participate in recalling both recent and remote memories (Einarsson & Nader, 2012; Katche et al., 2013; Leon, Bruno, Allard, Nader, & Cuello, 2010; Tse et al., 2011).

Although much is known about LTM consolidation, what puts the "long" in LTM is its persistence over time. Most of the acquired

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information is bound to disappear or may leave an undetectable trace. In addition, and although it is not the subject matter of this review, it is essential to point here that recent findings strongly suggest that behavioral and neurohumoral conditions at the moment of memory retrieval could play a key role in modifying already consolidated memories or, conversely, helping to strength the reactivated memory trace or keep it stable for longer periods of time through a protein synthesis-dependent reconsolidation process. Moreover, quite recently it has been shown that, as happens during memory consolidation (see below), administration of protein synthesis inhibitors late after reactivation hampers the persistence of fear memory (Nakayama et al., 2013). Therefore, the matter of memory persistence is central in understanding the neurobiology of learning and memory.

The main goal of this review article is to describe what has been published about long-lasting molecular changes in memory processing, and specifically this article deals with those molecular mechanisms involved in long-lasting LTM. Therefore, we will focus on cellular consolidation mechanisms in hippocampus and related brain regions (including some cortical areas) involved in late posttraining consolidation periods that lead to persistent memories. Several of long-lasting molecular changes shown below are good examples of molecular changes that seem to last well beyond times suggested for the formation of memory. Unraveling the functional role of these molecular signatures is, in most cases, in progress and permits us to envision new ways of thinking memory consolidation.

2. Long-lasting changes in glutamate receptors, protein kinases, protein synthesis, and gene expression as molecular signatures of long-lasting LTM

2.1. Glutamate receptors and protein kinases

The first study that demonstrated a long-lasting process in the hippocampus required for LTM consolidation is that of Riedel et al. (1999). They demonstrated that ongoing activity in the hippocampus is required for spatial memory consolidation during several days after training rats in a water maze. Consistent with this there are some reports demonstrating that different types of glutamate receptors undergo long-lasting changes and/or are needed at very late posttraining time points in the hippocampus for memory formation (Cammarota, Bernabeu, Izquierdo, & Medina, 1996; Riedel & Micheau, 1999). We and others (Cammarota et al., 1995; Whitlock, Heynen, Shuler, & Bear, 2006) found that AMPA receptors are up-regulated in close association with memory consolidation. More importantly, we also found that these changes last at least 2 days in CA3 region and dentate gyrus. It is feasible that these long-lasting changes may facilitate the reactivation of the hippocampal circuit that may entail extra-hippocampal structures in which the memory trace is eventually stored. Metabotropic glutamate receptors (mGluRs) also undergo long-lasting modifications after training. By using specific antibodies Riedel, Casabona, Platt, Macphail, and Nicoletti (2000) showed an early and transient increase in the expression of mGluR 5 in the CA3 region of the hippocampus. This was paralleled by an increase in mGluR 5 in CA1 and dentate gyrus 10 days posttraining, suggesting that these long-lasting changes in the expression of hippocampal AMPA and mGluRs could participate in the maintenance phase of memory consolidation.

In addition, NMDA receptor (NMDAr) reactivation in CA1 is required during the first days after spatial learning or after contextual fear conditioning (CFC) (Shimizu, Tang, Rampon, & Tsien, 2000). Cui et al. (2004) demonstrated that inducible and reversible knockout mice in which NMDAr are temporarily switch off during the storage state showed impairments in memory persistence.

Using a similar technology, Wang et al. (2003) demonstrated that reactivation of alpha-CaMKII activity in the forebrain during the first, but not the second or third week after training mice in CFC is crucial for remote memory consolidation. In addition, CaMKII heterozygeous knockout mice showed neocortical alterations in plasticity and normal retention fear memory when tested 1 day posttraining but impaired fear memory 10–50 days after training (Frankland, O'Brien, Ohno, Kirkwood, & Silva, 2001). Together, these findings suggest that persistent activity of NMDAr and alpha-CaMKII for the first several days after training is important for establishing remote memories and that NMDAr also have a role in maintaining long-lasting LTM.

ERKs are protein kinases involved in memory consolidation (Atkins, Selcher, Petraitis, Trzaskos, & Sweatt, 1998). Some reports showed two waves of ERKs activation after training. The first one is rapid and transient; the second is delayed and persistent, lasting for at least 24 h in the CA3 region (Trifilieff, Calandreau, Herry, Mons, & Micheau, 2007; Trifilieff et al., 2006). These modifications coincide with changes in CREB activation (see later). It has been also shown that ERK2 expression increases 24 h in the dorsal hippocampus after IA training and that ERK1/2 participates late after training to sustain memory storage of two different hippocampus-dependent learning tasks (Bekinschtein et al., 2008; Eckel-Mahan et al., 2008). Interestingly, a circadian oscillation of the phosphorylation state of ERK1/2 in the hippocampus has been implicated in memory persistence (Eckel-Mahan, 2012). Recently, it has been shown that inducible and targeted deletion of ERK5 resulted in attenuation of adult neurogenesis in the dentate gyrus and specific impairment in remote IA memory (Pan, Chan, Kuo, Storm, & Xia, 2012).

Another example of signaling molecules involved in memory persistence is represented by neuronal adenylyl ciclases. Knocking-down adenylyl ciclase 1 (AC1) and 8 (AC8) in mice down-regulates the expression of several genes in the hippocampus. Interestingly, most of these genes are up-regulated in wild-type mice 48 h after behavioral training (Wieczorek, Maas, Muglia, Vogt, & Muglia, 2010). These data are consistent with previous reports showing that $Ca2^{+}$-stimulated adenylyl cyclase activity is required for hippocampus-dependent memory maintenance (Wong et al., 1999), and suggest that AC1 and AC8 regulate long-lasting transcriptional changes important for memory persistence. To further substantiate this assumption, using an inducible and forebrain-specific forms of Ca^{2+}-stimulated AC, Shan et al. (2008) found that AC1 is essential for remote memory retention, and that when AC8 is turned on during training and switched off 48 h later, CF memory retention is impaired 1 month posttraining (Wieczorek et al., 2010).

Several years ago it was shown that hippocampal PKA activity is required for memory consolidation in at least two time intervals: one around training and the other several hours later (Bernabeu et al., 1997). A persistent activation of PKA lasting around 20 h was also observed after synaptic facilitation in Aplysia (Sutton, Masters, Bagnall, & Carew, 2001).

During the last decade the autonomously active isoform of PKC, PKMζ, went from being an almost unknown coadjuvant to an essential player in the processes mediating LTP maintenance and memory storage (Sacktor, 2008, 2011). Thus, findings showing that blocking PKMζ activity by pharmacological or dominant negative inhibitors disrupts well-consolidated LTM even in the absence of memory reactivation suggest that LTM is apparently maintained by the persistent activity of this kinase in different neural circuits. PKMζ appears to keep memory storage by regulating GluR2-dependent AMPA receptor trafficking (Migues et al., 2010). Indeed, it has been reported that PKMζ persistently enhances synaptic strength

by increasing the number of functioning AMPAr and overexpressing PKMζ indeed enhance LTM retention in insects (Drier et al., 2002) as well as in mammals (Shema et al., 2011). In fact, it has been reported that BDNF augments PKMζ expression (Adasme et al., 2011) and BDNF-LTP persistence is mediated by PKMζ (Mei, Nagappan, Ke, Sacktor, & Lu, 2011). However, two recent studies failed to find any memory impairment in PKMζ deficient mice, casting doubts on the role of this kinase in memory processing (Lee et al., 2013; Volk, Bachman, Johnson, Yu, & Huganir, 2013). Moreover, these works questioned the specificity of action of ZIP, a peptide widely-used to block PKMζ:

Volk et al. (2013) found that ZIP disrupted LTP not only in normal mice, but also in PKMζ-deficient mice, and Lee et al. (2013) described that ZIP erased spatial memory storage in both normal and PKMζ-deficient mice.

2.2. Protein synthesis and gene expression

2.2.1. Protein synthesis

LTM formation is thought to involve changes in gene expression and protein synthesis that induce functional and structural modifications in selected but distributed neuronal populations (Davis & Squire, 1984; Hernandez & Abel, 2008; Kandel, 2001; McGaugh, 2000). For instance, to sustain changes in spine number in hippocampal neurons upon learning it is necessary *de novo* protein synthesis (Hubener & Bonhoeffer, 2010). More importantly, after training in CFC and in the spatial version of the water maze (WM), two well-known hippocampus-dependent learning tasks, there is a substantial increase in the number of excitatory synapses made by mossy fibers terminals onto inhibitory interneurons of the CA3 region (McGonigal, Tabatadze, & Routtenberg, 2012; Ruediger et al., 2011). These plastic structural modifications are evident at different times posttraning depending of the training protocol. Although it occurs 1–4 h after training in CFC, it happens between 6 and 8 days posttraining in the WM (Tabatadze et al., 2012). On the other hand, it has been recently demonstrated that, in mice, fear conditioning results in dendritic spine elimination in hippocampus and prelimbic cortex (Lai, Franke, & Gan, 2012; Sanders, Cowansage, Baumgartel, & Mayford, 2012). In the context of the present overview it is worth noting that a late and sustained CPEB-dependent protein synthesis-dependent phase is essential to stabilize the synaptic growth needed for long-term facilitation in *Aplysia* (Miniaci et al., 2008).

From these and other studies showing that a late wave of protein synthesis is required for persistence of LTM (see later), it is clear that cellular consolidation requires not only an early posttraining wave of gene expression and protein synthesis (Abel et al., 1997; Bourtchouladze et al., 1998; Grecksch & Matthies, 1980; Igaz, Vianna, Medina, & Izquierdo, 2002; Quevedo et al., 1999) but also one or more late posttraining events of macromolecular synthesis. Consistent with this assumption is the finding of long-lasting changes in the expression levels of several proteins 24 h after IA training (Igaz, Bekinschtein, Izquierdo, & Medina, 2004). These results led us to wonder whether there were more waves of protein synthesis involved in consolidation of this task. To answer this question we did some experiments by injecting the protein synthesis inhibitor anisomycin (ANI), which has been broadly used to block memory formation in a wide variety of behavioral paradigms (Berman & Dudai, 2001; Luft, Buitrago, Ringer, Dichgans, & Schulz, 2004; Montarolo et al., 1986; Santini, Ge, Ren, Pena de Ortiz, & Quirk, 2004; Schafe & LeDoux, 2000; Tiunova, Anokhin, & Rose, 1998), at different posttraining time points between 0 and 24 h after IA acquisition. We found that *de novo* protein synthesis in the CA1 region of the dorsal hippocampus 12 h posttraining was crucial for memory persistence, but not for memory formation; i.e. ANI blocked memory retention at 7, but not at 2 days after training when given 12 h posttraining. When given 9, 18, or 24 h after training, this general inhibitor of protein synthesis was without effect at any time interval tested (Bekinschtein et al., 2007, 2010). These findings are consistent with current views in the field suggesting that memory for one-trial tasks would be consolidated (cellular consolidation) between 10^1 and 10^2 h after training (Sutherland & Lehmann, 2011) (Fig. 1). Consolidation of IA memory trace expressed 7 days after training could be independent from consolidation of the one expressed at 24 or 48 h. If this were the case, ANI injection 12 h after acquisition would be blocking consolidation of a memory that is expressed at 7 days but not at 24 h, and so, there should be a treatment able to prevent consolidation of the memory expressed at 24 h after training, while leaving intact that governing behavior 7 days later. We found that pre-training intra-hippocampus infusion of ANI, which causes amnesia when LTM is tested 24 h after training, also affects memory when rats are tested 7 days later, suggesting that the consolidation process that takes place during the first few hours posttraining is indeed needed for expression of late IA LTM.

Since blocking hippocampus protein synthesis 12 h posttraining affects memory expression 7 days later, there should be changes in protein expression beyond the first few hours after acquisition. Indeed we, and others, demonstrated that a late posttraining increase in the expression of BDNF is important for the persistence of LTM storage in rats (Bekinschtein et al., 2007; Ma et al., 2011; Ou, Yeh, & Gean, 2010; Rossato, Bevilaqua, Izquierdo, Medina, & Cammarota, 2009). Depending on the learning task and the brain structure the increase BDNF occurs between 6 and 12 h after training (see Table 1). In addition, BDNF is capable of reverting the deficit in conditioning taste aversion LTM caused by protein synthesis inhibition at 5–7 h after training (Martinez-Moreno, Rodriguez-Duran, & Escobar, 2011) or at 12 h after IA learning (Bekinschtein et al., 2007). We also found that BDNF is not only required but sufficient for long-lasting storage of IA memory (Bekinschtein et al., 2008). These BDNF-dependent late consolidation periods are under the control of dopaminergic inputs from the VTA (Rossato et al., 2009), and modulated by noradrenergic and cholinergic influences (Katche et al., 2010; Parfitt, Campos, Barbosa, Koth, & Barros, 2012). It is noteworthy that BDNF-sensitive dopaminergic control of the induction and maintenance of LTP in CA1 is localized to apical dendrites (Navakkode, Sajikumar, Korte, & Soong, 2012), which are the main receptive field of the direct glutamatergic inputs from the temporoammonic pathway. Selective lesion of this pathway impairs remote but not recent hippocampus-dependent spatial memory (Remondes & Schuman, 2004).

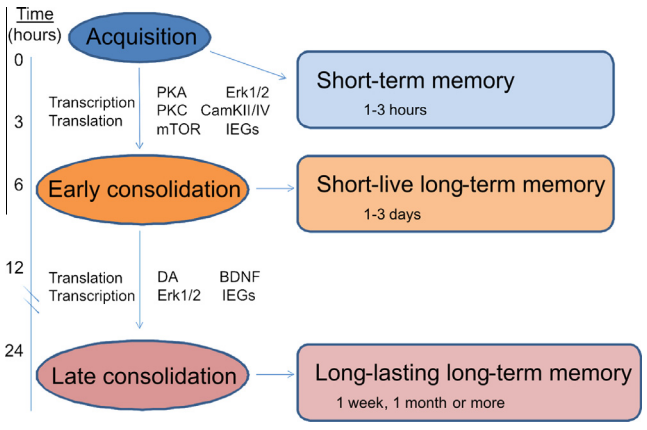

Fig. 1. Timeline of memory processing of a one-trial learning task, depicting different phases of processing and some of the molecular signatures involved.

Table 1
Learning induces delayed biochemical changes in the hippocampus, amygdala and related cortical regions.

Protein	Levels	Structure	Time	Task	References
AMPAr	↑	Hipp	2–48 h	IA	Cammarota et al. (1996, 1995)
Arc	↑	Hipp and PCx	8 and 24 h	OF	Ramirez-Amaya et al. (2005)
BDNF	↑	Hipp	12 h	IA	Bekinschtein et al. (2007)
BDNF	↑	Amyg	12 h	CFC	Ou et al. (2010)
BDNF	↑	Amyg and ICx	8–12 h	CTA	Ma et al. (2011)
C/EBPb	↑	Hipp	9–28 h	IA	Taubenfeld, Milekic, Monti, and Alberini (2001)
C/EBPb	↑	Hipp and ICx	18 h	CTA	Yefet et al. (2006)
CamKIIα	↑	Hipp	18–24 h	IA	Igaz et al. (2004)
CaN	↓	Amyg	3 d	CTA	Baumgartel et al. (2008)
C-Fos	↑	Hipp	18–24 h	IA	Bekinschtein et al. (2007)
ERK-2	↑	Hipp	18–24 h	IA	Igaz et al. (2004)
Homer 1a	↑	Hipp	24 h	IA	Igaz et al. (2004)
IGF-II	↑	Hipp	20 h	IA	Chen et al. (2011)
mGluR5	↑	Hipp	Up to 10 days	CFC	Riedel et al. (2000)
MMP-9	↑	Hipp	6–48 h	IA	Nagy et al. (2007)
NCAM	↑	Hipp	12 h	CFC	Sandi et al. (2003)
pCREB	↑	Hipp	9–20 h	IA	Taubenfeld et al. (2001)
pCREB	↑	Hipp	9 h	CFC	Trifilieff et al. (2006)
pCREB	↑	Amyg, Hipp and PCx	3–6 h	CFC	Stanciu, Radulovic, and Spiess (2001)
pERK	↑	Hipp	9–12 h	CFC	Trifilieff et al. (2006)
pERK 1/2	↑	Amyg	9 h	UFC	Trifilieff et al. (2007)
Syntaxin 1a	↑	Hipp	18–24 h	IA	Igaz et al. (2004)
pTrkB	↑	Hipp	12 h	IA	Slipczuk et al. (2013)
pTrkB	↑	Amyg and ICx	8–12 h	CTA	Ma et al. (2011)
Zif-268	↑	Hipp	18–24 h	IA	Bekinschtein et al. (2007)
Zif-268	↑	Amyg	3 d	CTA	Baumgartel et al. (2008)

The table summarizes findings regarding changes in gene expression, protein synthesis, and activation of intracellular signaling cascades several hours after learning. IA: inhibitory avoidance; CTA: conditioned taste aversion; CFC: contextual fear conditioning; UFC: Unpaired fear conditioning; OF: open field. C/EBPb: CAAT/enhancer-binding protein beta; pCREB: phosphor-cAMP response element binding protein; pERK: phospho-extracellular regulated kinase; pTrkB: phospho-TrkB; AMPAr: AMPA receptor; mGluR5: metabotropic glutamate receptor 5; CaMKIIα: calcium/calmodulin-dependent protein kinase II; BDNF: brain-derived neurotrophic factor; IGF-II: insulin-like growth factor 2; MMP-9: metalloproteinase 9; NCAM: neural cell adhesion molecule; Arc: activity-regulated cytoskeleton-associated protein; CaN: Calcineurin; Hipp: Hippocampus; PCx: Prefrontal cortex; ICx: Insular Cortex; Amyg: Amygdala.

In the last decade, several groups have shown that memories are accompanied by late modifications in the levels and/or activity of CREB (Taubenfeld, Wiig, et al., 2001; Trifilieff et al., 2006), Zif-268 (Baumgartel et al., 2008), ERK2 (Bekinschtein et al., 2008; Eckel-Mahan et al., 2008; Igaz et al., 2004; Trifilieff et al., 2006), calcineurin (Baumgartel et al., 2008), Homer 1a (Igaz et al., 2004) and several synaptic proteins (Table 1).

2.2.2. Gene expression

The first genes regulated by activity and/or experience identified in neurons, were responsive to mitogens or growth factors. Most of them were transcription factors (Morgan & Curran, 1986) such as *Zif-268, c-fos* and *c-jun* which are important for activating a wave of delayed early genes. Lately, the list of genes regulated by experience has grown to incorporate more than 500 genes (Leslie & Nedivi, 2011) including, among others, *bdnf, homer 1a, arc* and *tPA*. A classical view in modern biology is that a rapid and transient expression of IEGs is tightly coupled to cellular activity. In the brain, IEGs expression plays an important role in regulating synaptic plasticity and some IEGs, including *c-Fos*, have been associated with the first transient transcriptional steps involved in memory formation (Kandel, 2001; Lamprecht & Dudai, 1996; McGaugh, 2000). In this context, and unexpectedly, the late wave of BDNF expression observed 12 h after IA training (Bekinschtein et al., 2007), through the activation of ERK1/2, results in an increased expression of different IEGs, including c-Fos, Zif-268, and Arc at 18–24 h after training. Interestingly, short-lived IA LTM is not associated with delayed expression of c-Fos and zif-268 in the hippocampus. Only those memories that are persistent exhibit a late wave of IEGs expression, which is necessary for maintenance of IA LTM storage (Katche, Goldin, Gonzalez, Bekinschtein, & Medina, 2012; Katche et al., 2010) (Fig. 1). Moreover, inhibition of transcription in the dorsal hippocampus 24 h after training hinders persistence, but not formation of LTM. These findings indicate that a tardy phase of transcription is essential for maintenance of a hippocampus-dependent memory trace and support the hypothesis that recurrent rounds of consolidation-like events take place late after learning in the dorsal hippocampus in order to maintain memories. In this context, it is interesting to note that a downstream gene of c-fos, matrix metalloproteinase 9 (MMP-9), is activated late after IA training (Nagy, Bozdagi, & Huntley, 2007). In fact, the activity of this extracellular protease is already increased in the hippocampus between 3 and 6 h after IA training and peaks 24–48 h thereafter and preventing this increase by infusing MMP-9 inhibitors impairs memory consolidation. Additionally, two other genes have been involved in remote memory formation*: integrin β2* and *steryl-O-acyl transferase* (Soat1) (Matynia et al., 2008). Using a contextual fear conditioning in mice the authors found that integrin β2 and Soat1 mutants exhibit normal 1-day memory but impaired 7-day memory, suggesting that these two genes are required well beyond the initial consolidation phases of memory processing.

These data indicate that there is a complex dynamic regulation of transcription and translation involved in memory storage. In this respect, using a IA learning task, Alberinís group reported several years ago a delayed and persistent increase in two transcription factors, CREB and c-EBPbeta (Taubenfeld et al., 2001) repeatedly shown to be involved in memory formation (Alberini, 2009; Silva, Kogan, Frankland, & Kida, 1998). A delayed increase in p-CREB has been also found in other labs (Gold, 2008; CK and JHM; unpublished observations) Interestingly, antisense-mediated knockdown of C/EBPbeta in the hippocampus blocks late consolidation of IA memory 5 h and 24 h, but not 1 h or 46 h after training (Taubenfeld et al., 2001).

Several attempts have been made in the last decade to determine learning-specific changes in gene expression late after acquisition. We screened for candidate long-lasting LTM-modulated genes in the hippocampus at 3 h and 24 h after IA training. Training

regulated 33 genes out of 1176. Regarding the time course of the changes 26 genes were modulated at 3 h posttraining and only 7 at 24 h after training (Igaz et al., 2004). IA learning was associated at 3 h posttraining with an increased expression of several genes coding protein kinases and phosphatases (alpha-CaMKII, ERK 2, AKT, tyrosine phosphatase), synaptic proteins (syntaxin1A, metabotropic glutamate receptor 7), several cell metabolism proteins and transcriptional and translational regulators. It is interesting to note here, that a crucial factor that controls translation and also memory formation (Costa-Mattioli et al., 2007), eIF2-alpha, was down-regulated by training, and that IGF2 which has been recently shown to play a role in memory consolidation (Chen et al., 2011) appears to be up-regulated 3 and 6 h after IA training (D'Agata and Cavallaro, 2003; Igaz et al., 2004). Only 6 genes were up-regulated 24 h posttraining, including 3 important membrane receptors: dopamine D1 receptor, neuregulin and TrkB. Using microarrays to analyze more than 12,000 genes in the CA1 and DG regions of mice, Levenson et al. (2004) found that after CFC there is an initial burst of gene expression (1 h), followed by a period of gene repression (2–4 h). The next 2 h (4–6 h posttraining) are marked by a second wave of gene expression. These finding are in line with several works demonstrating that there is a second wave of protein synthesis and gene expression in several learning tasks (see for reference Slipczuk et al., 2009). They also found that regulatory elements for several transcription factors (c-rel, c-EBP, AP-1) are over-represented among those genes up-regulated during CF memory consolidation. More than 90 genes are up-regulated and 140 are down-regulated in the mice amygdala 48 h after CFC training. About 70 genes are up-regulated and only 13 down-regulated in the hippocampus at the same posttraining time point (Wieczorek et al., 2010). Cluster analysis reveals a balance between up- and down-regulated genes in amygdala but a consistent up-regulation of gene expression over time within the hippocampus. The functional categories of the top clusters in the hippocampus include transcription, communication, metabolic and signaling processes.

DNA methylation is a self-perpetuating biochemical reaction that represses gene expression (Holliday & Pugh, 1975). However, it has been shown that DNA methylation status is dynamically regulated in the adult brain, particularly in the hippocampus, and participates in memory formation (Miller & Sweatt, 2007). Consistent with a role of DNA methylation in long-lasting memory processing is the finding that hypermethylation of calcineurin and reelin genes in the anterior cingulate cortex (ACC) occurs 1 and 7 days after CFC training in rats (Miller et al., 2010). This lasting change in cortical DNA methylation reflects associative learning, because blocking CFC with an NMDAr antagonist prevents calcineurin and reelin gene hypermethylation. Moreover, hypermethylation of calcineurin gene persists over 30 days after training and, consistent with the role of DNA methylation as a transcriptional repressor, calcineurin mRNA and protein were specifically reduced following retrieval 30 days posttraining. Importantly, pharmacological blockade of DNA methytransferases in ACC 30 days after training disrupts remote fear memory, indicating that methylation of specific genes in the prefrontal cortex helps to maintain memories. In addition, these findings reveal a molecular change that lasts long enough to sustain the persistence of LTM, which is in agreement with the long-standing idea that a self-perpetuating mechanism is needed to explain the "long" in long-term memory (Lisman, 1985; Roberson & Sweatt, 2001).

Quite recently, and in line with findings on the role of hippocampal BDNF in maintenance of long-lasting LTM, it has been demonstrated that transcription of specific BDNF exons in the hippocampus changed during long periods after contextual fear conditioning and that hypomethylation of BDNF exon III was detected at 30 min and maintained up for 24 h after training (Mizuno, Dempster, Mill, & Giese, 2012). Another recent example of epigenetic control of long-lasting molecular changes involved in the persistence of memory storage is the finding that 5-HT-induced memory-related long-term synaptic facilitation in Aplysia is associated with a delayed (12–24 h after 5-HT pulse) increase in DNA methylation of CREB2 under the control of piRNAs (Rajasethupathy et al., 2012). This transcription factor represses long-term facilitation. Therefore, a long-lasting and late down-regulation of CREB2 expression leads to enhanced long-term facilitation and may contribute to the establishment of stable long-lasting changes in neurons for maintaining storage of information. Although a body of evidence has recently emerged on the role of histone acetylation on memory formation (see Peixoto & Abel, 2013), little is known about this epigenetic mechanism in long-lasting memory storage.

2.2.2.1. Sleep and late changes in memory formation. Numerous studies have demonstrated the beneficial role of sleep in memory consolidation (Diekelmann & Born, 2010). It has been described that spatial–temporal neuronal firings observed during waking experience reappear in the hippocampus during ensuing slow-wave and rapid-eye movement (REM) sleep (Nadasdy, Hirase, Czurko, Csicsvari, & Buzsaki, 1999; Wilson & McNaughton, 1994). Immediately after a spatial experience, there is a replay in the hippocampus in an inverse sequential order (Foster & Wilson, 2006); conversely, replays during sleep take place in the same sequence in which they were experimented during acquisition (Lee & Wilson, 2002). This replay could activate calcium-dependent cascades known to be involved in learning and memory (Chauvette, Seigner, & Timofeev 2012; Luo, Phan, Yang, Garelick, & Storm 2013; Vecsey, Billie, Jaganath, et al., 2009), coupling the electrical activity to gene expression in neurons.

In addition, some studies have revealed late changes in plasticity related genes during sleep (Ribeiro et al., 2002, 2007; Ulloor & Datta, 2005). These changes induced by a previous novel experience or by LTP induction occur in the hippocampus and cortical regions during REM sleep (Ribeiro et al., 2002, 2007). Ribeiro et al. (2002) have described three rounds of induction of zif268 beginning 30 min after LTP stimulation and during the sequential REM sleep following LTP, with different pattern expression in the brain. It seems strong in the hippocampus at first and weak in the cortex, but following REM episodes gene expression gets stronger in the cortex and weaker in the hippocampus (Ribeiro et al., 2002). Ulloor & Datta (2005) found that REM sleep induces an experience-dependent upregulation of the IEG Arc, and also of pCREB and BDNF 6 h after two-way active avoidance task.

These studies showed some process that could be referred to as "off-line" memory consolidation, and this memory processing is not affected by the interference of waking state. Since there are several rounds of SW and REM sleep, it could be possible that each one contribute to the establishment of a given memory trace over time. However, it must be pointed out that there is no evidence so far on the functional relationship between sleep-induced replays and gene expression changes on memory storage.

3. Concluding remarks

The findings reviewed in this article suggest that long-lasting memory processing is associated with a plethora of late posttraining changes in several brain regions. The studies on a critical phase involved in persistence of LTM storage that we commented here open a potential avenue of research on the mechanisms of late memory consolidation. For instance, is this process the end of the cellular consolidation phase? Is this phase a necessary link between cellular and system consolidation? Is the cortex involved in this process? Regardless of the involvement of the hippocampus

in storage or retrieval of many memories, the late protein synthesis- and BDNF-dependent phase is surely not the end of the story. In other words, it is feasible to suppose that this critical window happening about 12 h after acquisition is only the first of a series of recurrent rounds of protein synthesis in the hippocampus and extra-hippocampal areas necessary to persistently store new information. The study of some of the potential signatures outlined here may help understand the maintenance of LTM storage. In addition, several questions about the significance of different temporal domains of LTM formation and persistence deserve further clarification. For instance, are the different temporal windows of gene expression and protein synthesis connected in some way? Are they occurring in the same or in different sets of neurons? Are the late phases of gene expression dependent on the activity of distributed groups of neurons inside and outside the hippocampus? Or they are "cell autonomous" and independent of the network activity? All of these are, in our opinion, open questions. Very little is known regarding these issues. Some experiments performed in *Drosophila* provided preliminary evidence for understanding whether behavioral memory is the sum of temporally and mechanistically different cellular memory traces activating distinct sets of neurons (Akalal, Yu, & Davis, 2010).

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