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Review Paper

Neuropharmacology of memory consolidation and reconsolidation: Insights on central cholinergic mechanisms

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ABSTRACT

Central cholinergic system is critically involved in all known memory processes. Endogenous acetylcholine release by cholinergic neurons is necessary for modulation of acquisition, encoding, consolidation, reconsolidation, extinction, retrieval and expression. Experiments from our laboratory are mainly focused on elucidating the mechanisms by which acetylcholine modulates memory processes. Blockade of hippocampal alpha-7-nicotinic receptors (α7-nAChRs) with the antagonist methyllycaconitine impairs memory reconsolidation. However, the administration of a α7-nAChR agonist (choline) produce a paradoxical modulation, causing memory enhancement in mice trained with a weak footshock, but memory impairment in animals trained with a strong footshock. All these effects are long-lasting, and depend on the age of the memory trace. This review summarizes and discusses some of our recent findings, particularly regarding the involvement of α7-nAChRs on memory reconsolidation.

Contents

1. Introduction

Memory is the ability to recall past experiences defining our identity (Dudai, 2004). When a new learning occurs, depending on several conditions and factors, the acquired information could be stored for later retrieval (McGaugh, 1966, 2000). A successful retrieval and the behavioral expression of a memory suggest that the information was stored (Cahill et al., 2001); however, the opposite is not always true and several caveats remain, as we shall comment later (Blake et al., 2012; Caffaro et al., 2012). Initially, new memories are vulnerable and sensitive to disruption but progressively strengthened over time (McGaugh, 1966, 2000). The process by which memory is initially stored is termed memory consolidation (McGaugh, 2000). Once memory is stored it could be retrieved and then, by decision making processes, could take control of the behavior (memory expression) (Blake et al., 2012). As there is no way for measuring learning or memory directly, we are only able to infer it from behavior, and so an operational definition of memory is determined by a change in the behavior as a consequence of a learning experience (Cahill et al., 2001).

Traditionally it had been accepted that once memory consolidation is completed memory becomes permanent (Squire and Davis, 1981). However, several studies have also shown that when a well-stabilized memory is reactivated (recalled) it again becomes

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sensitive to most of the treatments that could have affected memory consolidation when given after training. This new period of sensitivity was named memory reconsolidation (Lewis, 1979, p. 197; Przybyslawski et al., 1999). This process shares many features with memory consolidation, although they are not identical (Alberini et al., 2006; Lee et al., 2004; Taubenfeld et al., 2001; Tronson and Taylor, 2007), serving as a mechanism to reformulate memories in order to respond to similar environmental retrieval situations. The modifications occurring after memory retrieval gives memory an outstanding malleability; still "all that glitters is not gold" since memory changes through reactivation could render memory unreliable (see false memories) (Laney and Loftus, 2005; Loftus and Davis, 2006).

The particular emphasis of the review concerns some studies carried out in our laboratory regarding the neuropharmacology of memory consolidation and reconsolidation. We will consider particularly the involvement of central cholinergic mechanisms in an inhibitory avoidance (IA) task.

2. Memory consolidation, reconsolidation, and extinction. Methodological considerations

During a training session, a conditioned stimulus (CS) and an unconditioned stimulus (US) are presented sequentially, so the individual learns that the CS is followed by the US. Many tasks require the subject to be repeatedly exposed to CS–US pairings for establishing the association. The one-trial step-through IA task has the advantage of being learned in a brief single session, and has been a standard method for studying memory consolidation in rodents (rats and mice) (Gold, 1986). This is an operant conditioning procedure in which the animal associates entering into a dark compartment (CS) with receiving a footshock (US). During the retention test, the animal displays a conditioned response: it avoids the punishment (the footshock) by inhibiting its natural behavioral response (inhibiting entering the dark compartment). The latency of entrance into the dark compartment is taken as an indication of memory: the longer the latency, the stronger this memory to control the behavior. Pharmacological and non-pharmacological interventions at different time-points before or after the training session are commonly used in the study of memory consolidation (McGaugh, 2000). Post-training treatment serves as a useful tool to study memory consolidation without influencing acquisition, and reveals the time-dependent participation of neural system and cellular processes involved in lasting memories (McGaugh, 2000).

The study of memory consolidation seems to be of illusory easiness, but is actually extremely complex and many points are still elusive. This complexity is even greater when studying memory reconsolidation, plenty of drawbacks and obstacles. To evidence reconsolidation, memory must be previously destabilized during a reactivation session, which is performed presenting the CS not followed by the US (Misanin et al., 1968; Nader et al., 2000). Since no repetition of CS–US pairing was presented during the memory reactivation session, the subject is now exposed to a different information which should lead to store a new memory in which the CS is not followed by the US (that is, entering the dark compartment is not followed by the footshock). In the IA task, it would be observed as an animal entering the dark compartment increasingly faster (shortening the latency to step-through). This progressive reduction of the conditioned response due to repeated presentation of the CS in the absence of the US is known as memory extinction (Myers and Davis, 2002). Memory extinction can be modulated by interventional treatments: if this process is enhanced, the reduction of the conditioned response is faster, but if impaired, the animal is expected to behave not reducing the conditioned response.

In a typical reconsolidation study, manipulations (by the use of pharmacological and non-pharmacological interventions) are performed immediately after the reactivation session, and memory is again evaluated in subsequent tests (Baratti et al., 2009; Blake et al., 2013; Tronson and Taylor, 2007). If reconsolidation is impaired, the conditioned response is absent (or decreased), but if reconsolidation is improved, the conditioned response should increase.

Learning to fear threats in the environment is highly adaptive; it allows the experimental subjects to anticipate and organize their behavior in response to different situations (Bolles, 1970; Fanselow and Lester, 1988). However this form of learning may also lead to pathological memories, such as panic disorder and post-traumatic stress disorders in humans (Bouton et al., 2001). These pathological memories could be altered either reducing its expression by extinction procedures, such as exposure therapy (Bouton, 1988), or by interfering immediately after its retrieval, affecting memory reconsolidation processes (Misanin et al., 1968; Nader et al., 2000). Unfortunately, the behavioral results obtained using extinction procedures are transient (Myers and Davis, 2002). On the other hand, many authors have found that post-retrieval manipulations yield a non-recoverable loss of performance, suggesting that destabilized memory traces vanished (Boccia et al., 2006, 2004; Nader et al., 2000). However, others have found that performance impairments after these manipulations are transient, suggesting that temporary retrieval failures, rather than disruption of the memory trace underlie the effects on post-retrieval manipulations of memory (Lattal and Abel, 2004; Power et al., 2006).

There are also several boundary conditions regarding memory reconsolidation: strength of the US used during training (Boccia et al., 2004; Suzuki et al., 2004), the age of the memory (Boccia et al., 2006; Milekic and Alberini, 2002), the structure of the reminder: duration of the CS (Pedreira and Maldonado, 2003), mismatch between what is expected and what actually happens (Pedreira et al., 2004).

3. The neverending discussion: impaired reconsolidation or enhanced extinction?

Thus, when a subject is exposed to a reactivation session, this reactivation triggers at least one of two memory processes: reconsolidation and/or extinction. For example, if a treatment is administered immediately after the reactivation session, and in the next test the animal shows impaired memory, the result might be interpreted either as due to impairment of memory reconsolidation or to enhanced memory extinction. Extinction and reconsolidation are mostly treated as mutually exclusive, employing manipulations aimed to affect one or the other; however, almost every result might still be interpreted as a consequence of any of both processes being modulated. The discussion regarding what process is affected as a consequence of an interventional treatment might be endless, and to determine whether the change in the performance could be attributable to specific effects of the manipulation on memory reconsolidation or on memory extinction, a careful behavioral and interventional protocol must be designed, and different controls must be carried out.

To consider that a treatment is affecting memory reconsolidation, the intervention should be ineffective in the absence of the reactivation session and a time-dependent window of susceptibility should be observed, as well as the specificity for previously trained stimuli or context (Tronson and Taylor, 2007).

Regarding the IA task, the strength of the footshock employed during training is considered determinant for studying whether the manipulation affects memory reconsolidation or memory

extinction (Boccia et al., 2004, 2005, 2006; Duran-Arevalo et al., 1990). As an animal trained with a weak footshock frequently enter the dark compartment in about 120 s during the reactivation session, this training condition allows memory to be either enhanced or impaired, and favors the development of extinction processes. On the other hand, animals trained with a strong footshock do not enter into the dark compartment during the reactivation session, thus impairing – or at least limiting – the development of extinction phenomena (Blake et al., 2012; Boccia et al., 2003, 2004, 2005, 2006, 2010); so, the use of a strong footshock favors the observation of impairing effects of interventions. Control over-reinforced mice (those trained with a strong footshock) can really extinguish their avoidance memory, but need several successive extinction trials, and show spontaneous recovery (Baratti et al., 2008). Furthermore, once extinction is fully developed, the avoidance behavior can be reinstated by using a saving protocol (Bouton, 2004; Rescorla, 2004). The fact that animals do not enter the dark compartment in the reactivation session, but enter after several sessions, suggests that extinction processes can develop despite mice stay away of the dark chamber. It could be also indicating that the conditioned stimulus is more complex than just entering the dark chamber, and different information provided by the environment could be actually influencing animal performance.

Despite the apparent simplicity of the previous description, extinction and reconsolidation are very complex processes consisting of interacting molecular substrates, cellular mechanisms and neuronal circuits. At the molecular level, the activation profile of CREB is different following short or longer memory reactivation sessions (probably triggering reconsolidation and extinction respectively). In a contextual fear conditioning, CREB-mediated gene expression is induced in the hippocampus after a short reactivation session, but not after a longer one, suggesting that during prolonged re-exposures to CS this induction is not produced (Mamiya et al., 2009). The opposite profile can be observed in the prefrontal cortex, where longer reactivation sessions increase CREB activation 30 min after the end of the re-exposure, but this effect is not observed after a short reactivation period (Mamiya et al., 2009). A differential profile of CREB activation was also described in the amygdala. These results could be indicating that when reconsolidation is triggered, CREB is selectively activated in the hippocampus, but when extinction is occurring, CREB activation is produced in the prefrontal cortex. Interestingly, the activation profile of CREB in the hippocampus is very similar to activation of NF-κB. This transcription factor is activated after brief re-exposures, but not after longer ones. It was proposed that a molecular switch between reconsolidation and extinction processes is the protein calcineurin, which would trigger memory extinction through upstream negative regulation of NF-κB in the hippocampus (de la Fuente et al., 2011).

4. The other issue: is there a storage failure?

At this point we might ask whether a treatment after a reactivation session inducing memory impairment could be attributed either to a failure in storage or any other process involved (memory retrieval or memory expression). In order to tackle this question, four behavioral protocols can be used to evidence memory recovery: (1) spontaneous recovery, (2) saving, (3) renewal, (4) reinstatement (Myers and Davis, 2002). Accordingly, lack of reversal of amnesia could support storage deficit interpretations, similar to the type of deficit assumed to occur after consolidation blockade. In contrast, reversibility of amnesia favors retrieval or expression deficit interpretations (Dudai and Eisenberg, 2004). In our interpretation, "memory expression deficit" is different from "memory retrieval deficit" (Blake et al., 2013). Memory retrieval is the access, selection, reactivation or reconstruction of an internal representation (Dudai, 2002), but memory expression means this internal representation effectively taking control of behavior (Izquierdo and Medina, 1993).

5. Memory consolidation and reconsolidation: the cholinergic system

It is well known that endogenous Ach release is necessary for long-term memory (LTM) consolidation (Power et al., 2003). In this sense, post-training inhibition of Ach synthesis by hemicholinium-3 (HC-3), a specific inhibitor of high-affinity choline uptake (HACU) (Gardiner, 1961), leads to memory impairment in a one-trial step-through IA task in mice (Boccia et al., 2004). It is worth pointing out that the effects of HC-3 on HACU were transient, but the memory impairment was long-lasting: the HACU in the hippocampus of the HC-3-treated mice, that was reduced 50% 60 min after HC-3 infusion, was recovered at the time of the retention test (performed 2 or 7 days after training), despite the animals showed impaired memory. This apparent dissociation between neurochemistry and behavior suggests that the effects of HC-3 are probably not directly exerted on memory retrieval, and indicates that HACU inhibition took place at early stages of memory consolidation (Boccia et al., 2004). These results are in concordance with experimental and clinical evidence suggesting that brain Ach plays an essential role in mnemonic phenomena (Decker and McGaugh, 1991; Power et al., 2003).

Similarly, HC-3 also impairs memory reconsolidation. The icv administration of HC-3 immediately after memory reactivation produced a deleterious effect on retention which was not observed if memory reactivation was omitted. These results suggest that the impaired retention could not be attributed to a non-specific effect of the pharmacological treatment (Boccia et al., 2004). HC-3 was effective only when the time-interval between training and the first test (memory reactivation) was among 2 and 7 days and was no longer seen afterwards (14–30 days). The older the memory, the less effective the disruption of Ach synthesis on memory reconsolidation of an IA task in mice (Boccia et al., 2006). No spontaneous recovery of the HC-3 impaired memory was observed (Boccia et al., 2004).

Since HC-3 blocks choline uptake, the rate-limiting step in acetylcholine (Ach) synthesis, we further investigated which Ach receptor was involved in the memory disrupting effect of HC-3. Acetylcholine stimulates both muscarinic and nicotinic cholinergic receptors. Nicotinic receptors (nAchR) are ligand-gated ion channels whose activation always cause a rapid increase in cellular permeability to Na^+ and Ca^{2+}, and consequently depolarization and excitation (Albuquerque et al., 2009). By contrast, muscarinic receptors (mAchR) are G protein-coupled receptors, the responses to their activation are slower, and they may be either excitatory or inhibitory (Eglen, 2005; Langmead et al., 2008). Both types of receptors are known to participate in encoding and retrieval, but their participation on post-retrieval memory processes has begun to be elucidated (Boccia et al., 2010; Buckingham et al., 2009; Power et al., 2003).

The nAchRs are composed of five homologous subunits organized around a central pore and are further divided in two groups: muscle type and neuronal type. Neuronal nAchRs are widely expressed in peripheral ganglia, the adrenal medulla, numerous areas of the brain and non-neuronal cells (Albuquerque et al., 2009). Nicotinic receptors have homo or heteropentameric structure and have been implicated in several physiological functions, among them learning and memory (Levin et al., 2006), and in

several disorders (neuromuscular and neurodegenerative) (Taly et al., 2009).

To date, for the neuronal nicotinic receptor, 12 genes have been identified: nine α (α2–α10) and three β (β2–β4). The different neuronal nAChR subunits combine in various permutations to form functional receptors. Of the many possible subtypes of nAChRs that have previously been described, the α7 and the α4β2 receptors are the two main subtypes widely expressed in the brain, particularly in the hippocampus (Albuquerque et al., 2009), and have been implicated in several nervous system disorders such as Alzheimer's disease (AD), schizophrenia, depression, attention deficit hyperactivity disorder and tobacco addiction (Taly et al., 2009).

The hippocampus has a key role in the consolidation of many forms of memory, including IA and maze tasks (Izquierdo et al., 2002). Intra-hippocampal administration of nicotine enhances working memory (Felix and Levin, 1997; Levin et al., 2006); while nAChR antagonists, such as dihydro-β-erythroidine (DHE) (Felix and Levin, 1997; Levin et al., 2002) and mecamylamine (Ohno et al., 1993) impair it. Nicotinic receptor in the CA1 region of the hippocampus has been involved in short- and long-term memory consolidation, and in retrieval processes of an IA response in rats, giving support to the hypothesis of a modulatory role of nAchRs in different types of memories and, also, in different phases of memory (consolidation and retrieval of LTM) (Martí Barros et al., 2004).

Several markers of cholinergic activity are reduced in AD (both pre- and post-synaptic) (Quirion, 1993). In particular, cholinergic nicotinic receptors were found to be reduced in 30–40%, mainly due to reduction of the α4β2 subtype, with relative preservation of the α7-nicotinic receptors (Court et al., 2001; Perry et al., 1995). For this reason, α7-nAChRs appear as a promising pharmacological target for treatment.

In this sense, if a α7-nAchR agonist (choline, Ch) is given in the mouse hippocampus immediately after training, memory of the IA task is improved. This effect was time-dependent and seemed to be specific. On the other hand, a α7-nAchR antagonist (methyllycaconitine, MLA) produces memory impairment. These results suggest that α7-nAchR receptors are involved in memory consolidation of an IA task in mice (Krawczyk, 2012).

If the α7-nAChR antagonist MLA is given immediately after memory reactivation, memory reconsolidation is impaired in mice trained either with a mild or a high footshock (Boccia et al., 2010). Lack of spontaneous recovery suggests that MLA effects were long lasting (Rescorla, 2004). Besides, when the α7-nAChR agonist Ch is given immediately after the reactivation session, its effects depend on the strength of the unconditioned stimulus used during the training trial. If mice were trained using a weak footshock, memory was improved by the administration of Ch, but if mice were trained with the strong footshock, the avoidance memory was impaired (Boccia et al., 2010). These apparently contradictory effects of Ch, when administered immediately after reactivation, on retention performance depending on the training conditions are very similar to those reported by Gold and van Buskirk (1976), despite the methodological differences. In that case, they administered a dose of epinephrine after the training session instead of the reactivation one, observing enhanced retention performance after a low-footshock training or amnesia if administered after high-footshock training. Our results are very similar, but in our case Ch was administered immediately after retrieval. Hence post-retrieval treatments could have important roles in modulating memory processes occurring after retrieval that appear to be very similar, though not identical, to that occurring after learning.

Additionally, we recently found that intrahippocampal injection of the non selective muscarinic agonist, oxotremorine, immediately after memory reactivation, either impaired or enhanced memory reconsolidation depending on the training conditions. These effects were prevented by the intrahippocampal co-administration of scopolamine (SCP), a non selective muscarinic antagonist suggesting a potential involvement of muscarinic receptor signaling on memory reconsolidation (unpublished data). It was reported that scopolamine did not impair memory of a contextual fear conditioning in rats when given after retrieval (Bucherelli et al., 2006). However, our results support recent findings, which indicated that memory reconsolidation of morphine-conditioned place preference is disrupted by scopolamine (Zhai et al., 2008).

Altogether, these results suggest that either impairment or enhancement of retention induced by post-retrieval administration of either, Ch or MLA, could not be attributed to non-specific influences on performance (Milekic and Alberini, 2002; Nader et al., 2000; Tronson et al., 2006).

Despite Ch participates as a precursor of acetylcholine synthesis, and may modify cholinergic activity in different ways, the effects of post-reactivation administration of Ch on memory are likely due to its binding to the α7-nAChRs, since its effect is completely blocked by the co-administration of the specific α7-nAChRs antagonist MLA (Boccia et al., 2010).

The modulatory effects of Ch on post-retrieval memory processes also depend on the age of the reactivated memory (Baratti et al., 2008; Boccia et al., 2006; Milekic and Alberini, 2002). Young reactivated memories are more sensitive to modulation than older memories (Alberini, 2005), in accordance with Ribot's law (Ribot, 1906). This fact was clearly demonstrated for protein synthesis inhibitors such as anisomycin or cycloheximide (Alberini, 2005; Milekic and Alberini, 2002). Age-dependence was also demonstrated for the acetylcholine synthesis inhibitor hemicholinium-3 (Boccia et al., 2006). Similarly, recent memories were very sensitive to the effects of Ch, but older ones were more resistant. Recent published data from our laboratory showed evidence that recent memories (2–7 days old) are labile but remote ones (14–21 days old) become progressively insensitive to Ch administration (Blake et al., 2012).

Several observations suggest that the hippocampus contributes to consolidation of memories over long periods (McGaugh and Izquierdo, 2000). Hence, information processing depends on hippocampal function, but the temporal dependence is different among species. Hippocampal lesions in mice cause retrograde amnesia for events occurring a few hours prior to the damage (McGaugh and Izquierdo, 2000). On the contrary, hippocampal lesions in human beings produce retrograde amnesia of several years (Corkin, 2002; Squire and Wixted, 2011). This difference shows that hippocampal processing of information is more prolonged in humans than in mice. For many events, the elapsed time in mice life is very shorter than the same in humans (Flurkey et al., 2007). Therefore, the period of 7 days within which a memory is very susceptible to enhancement by post-reactivation administration of Ch in mice may represent several years in humans.

However, other factors apart from the age of the memory, might contribute to memory destabilization. In this sense, anisomycin given to mice before a 3 min CS re-exposure using a contextual fear conditioning, impaired reconsolidation of 1- and 3-week-old memories but not 8-week-old ones. However, increasing the duration of the re-exposure period to 10 min made 8-week-old memories susceptible to disruption by the protein synthesis inhibitor (Suzuki et al., 2004). These findings support the notion of a temporal gradient in the activation of reconsolidation processes; however these older memories are still susceptible to reconsolidation with adjustments to the reactivation parameters. Thus, it is easier to destabilize younger memories than older; however these older memories could be destabilized with greater re-exposure periods.

Post-training administration of atropine, a central muscarinic antagonist, completely prevented the facilitatory effects of the central β2 adrenoreceptor agonist, clenbuterol (Introini-Collison and Baratti, 1992). These findings suggest a possible interaction between central adrenergic and cholinergic mechanisms on mem-

ory consolidation of an IA response in mice. β-adrenergic signaling in the lateral amygdala was also implicated in memory consolidation (Introini-Collison et al., 1991) and reconsolidation (Debiec and Ledoux, 2004). A well consolidated auditory fear memory following single memory retrieval was susceptible to modulation through interference or enhancement with propranolol or isoproterenol respectively (Debiec and Ledoux, 2004, p. 2011; Dębiec et al., 2011).

Recently we reported evidence of recovery from scopolamine-induced memory impairment produced by post-retrieval memory enhancement by Ch. This recovery depended on memory reactivation, and only occurred if the treatment was administered within a temporal window. Besides, to provide compelling evidence that Ch acts specifically on the mechanisms mediating memory reconsolidation, as opposed to producing nonspecific effects, it is necessary to show that the change does not occur shortly after retrieval, but is observed later (Boccia et al., 2007; Nader et al., 2000). Along this line, Ch effects were observed only in the test performed 24 h and not 1 h after its administration (immediately after memory reactivation) (Blake et al., 2012).

All these facts suggest that the effects of Ch were exerted on memory reconsolidation.

Reconsolidation memory process is mostly revealed by its absence. Typically, when amnesia for a memory that is one or more days old is induced in a manner that is dependent upon reactivation of that memory through retrieval, reconsolidation is said to have been impaired (Dudai, 2004; Nader et al., 2000). However, as mentioned, experimental treatments targeting memory reconsolidation can also result in subsequent improvements (Blaiss and Janak, 2006; Tronson et al., 2006). Moreover, the ability to improve a memory through post-retrieval processing suggests a potentially adaptive function for the reconsolidation process. Rather than simply being a process that restabilizes a memory following its retrieval, it represents a special state, providing an opportunity for renewed memory plasticity and modulation (Dudai, 2004, 2007). Memory reconsolidation could also be enhanced by naturalistic phenomena such as water deprivation (Frenkel et al., 2005; Sierra et al., 2013) and the administration of glucose (Rodriguez et al., 1999). Therefore, the capability to modify (e.g. strengthen) a previously acquired memory in a potentially adaptive manner is not limited to exogenous pharmacological treatment but is likely to be relevant to naturalistic situations of memory updating.

We can speculate that post-retrieval treatments have important roles in modulating memory processes occurring after retrieval and seem to be very similar, though not identical, to that occurring after learning.

Therefore, memory reconsolidation processes allow not only memory updating but might also serve to change the strength with which memory is able to guide behavior (memory expression) in later tests, among other functions.

6. Concluding remarks

We provided evidence of the importance and critical participation of central cholinergic mechanisms on memory consolidation and with particular emphasis on reconsolidation in mice. Translational applications of these results are far beyond the scope of this review. However, the use of reconsolidation-disrupting drugs is applicable in the treatment of the maladaptive memories that subserve drug addiction and post-traumatic stress disorders. Moreover, recent work from our lab support the hypothesis that modulation of memory reconsolidation may be a useful strategy for recovery from pharmacological- and non-pharmacological-induced amnesias, opening new avenues regarding the significance and the physiological function of memory reconsolidation.

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References

Alberini, C.M., 2005. Mechanisms of memory stabilization: are consolidation and reconsolidation similar or distinct processes? Trends Neurosci. 28, 51–56. http://dx.doi.org/10.1016/j.tins.2004.11.001.

Alberini, C.M., Milekic, M.H., Tronel, S., 2006. Mechanisms of memory stabilization and de-stabilization. Cell. Mol. Life Sci. 63, 999–1008. http://dx.doi.org/10.1007/s00018-006-6025-7.

Albuquerque, E.X., Pereira, E.F.R., Alkondon, M., Rogers, S.W., 2009. Mammalian nicotinic acetylcholine receptors: from structure to function. Physiol. Rev. 89, 73–120. http://dx.doi.org/10.1152/physrev.00015.2008.

Baratti, C.M., Boccia, M.M., Blake, M.G., Acosta, G.B., 2008. Reactivated memory of an inhibitory avoidance response in mice is sensitive to a nitric oxide synthase inhibitor. Neurobiol. Learn. Memory 89, 426–440. http://dx.doi.org/10.1016/j.nlm.2007.11.001.

Baratti, C.M., Boccia, M.M., Blake, M.G., 2009. Pharmacological effects and behavioral interventions on memory consolidation and reconsolidation. Braz. J. Med. Biol. Res. 42, 148–154.

Blaiss, C.A., Janak, P.H., 2006. Post-training and post-reactivation administration of amphetamine enhances morphine conditioned place preference. Behav. Brain Res. 171, 329–337. http://dx.doi.org/10.1016/j.bbr.2006.04.018.

Blake, M.G., Boccia, M.M., Krawczyk, M.C., Delorenzi, A., Baratti, C.M., 2012. Choline reverses scopolamine-induced memory impairment by improving memory reconsolidation. Neurobiol. Learn. Memory 98, 112–121. http://dx.doi.org/10.1016/j.nlm.2012.07.001.

Blake, M.G., Boccia, M.M., Krawczyk, M.C., Baratti, C.M., 2013. Hippocampal α7-nicotinic cholinergic receptors modulate memory reconsolidation: a potential strategy for recovery from amnesia. Neurobiol. Learn. Memory 106, 193–203. http://dx.doi.org/10.1016/j.nlm.2013.09.001.

Boccia, M.M., Blake, M.G., Acosta, G.B., Baratti, C.M., 2003. Atropine, an anticholinergic drug, impairs memory retrieval of a high consolidated avoidance response in mice. Neurosci. Lett. 345, 97–100.

Boccia, M.M., Acosta, G.B., Blake, M.G., Baratti, C.M., 2004. Memory consolidation and reconsolidation of an inhibitory avoidance response in mice. Effects of i.c.v. injections of hemicholinium-3. Neuroscience 124, 735–741.

Boccia, M.M., Blake, M.G., Acosta, G.B., Baratti, C.M., 2005. Memory consolidation and reconsolidation of an inhibitory avoidance task in mice. Effects of a new different learning task. Neuroscience 135, 19–29.

Boccia, M.M., Blake, M.G., Acosta, G.B., Baratti, C.M., 2006. Post-retrieval effects of icv infusions of hemicholinium in mice are dependent on the age of the original memory. Learn. Memory 13, 376–381.

Boccia, M., Freudenthal, R., Blake, M., de la Fuente, V., Acosta, G., Baratti, C., Romano, A., 2007. Activation of hippocampal nuclear factor-kappa B by retrieval is required for memory reconsolidation. J. Neurosci. 27, 13436–13445. http://dx.doi.org/10.1523/JNEUROSCI.4430-07.2007.

Boccia, M.M., Blake, M.G., Krawczyk, M.C., Baratti, C.M., 2010. Hippocampal α7 nicotinic receptors modulate memory reconsolidation of an inhibitory avoidance task in mice. Neuroscience 171, 531–543. http://dx.doi.org/10.1016/j.neuroscience.2010.08.027.

Bolles, R.C., 1970. Species-specific defense reactions and avoidance learning. Psychol. Rev. 77, 32–48. http://dx.doi.org/10.1037/h0028589.

Bouton, M.E., 1988. Context and ambiguity in the extinction of emotional learning: implications for exposure therapy. Behav. Res. Ther. 26, 137–149.

Bouton, M.E., 2004. Context and behavioral processes in extinction. Learn. Memory 11, 485–494. http://dx.doi.org/10.1101/lm.78804.

Bouton, M.E., Mineka, S., Barlow, D.H., 2001. A modern learning theory perspective on the etiology of panic disorder. Psychol. Rev. 108, 4–32.

Bucherelli, C., Baldi, E., Mariottini, C., Passani, M.B., Blandina, P., 2006. Aversive memory reactivation engages in the amygdala only some neurotransmitters involved in consolidation. Learn. Memory 13, 426–430. http://dx.doi.org/10.1101/lm.326906.

Buckingham, S.D., Jones, A.K., Brown, L.A., Sattelle, D.B., 2009. Nicotinic acetylcholine receptor signalling: roles in Alzheimer's disease and amyloid neuroprotection. Pharmacol. Rev. 61, 39–61. http://dx.doi.org/10.1124/pr.108.000562.

Caffaro, P.A., Suárez, L.D., Blake, M.G., Delorenzi, A., 2012. Dissociation between memory reactivation and its behavioral expression: scopolamine interferes with memory expression without disrupting long-term storage. Neurobiol. Learn. Memory 98, 235–245. http://dx.doi.org/10.1016/j.nlm.2012.08.003.

Cahill, L., McGaugh, J.L., Weinberger, N.M., 2001. The neurobiology of learning and memory: some reminders to remember. Trends Neurosci. 24, 578–581.

Corkin, S., 2002. What's new with the amnesic patient H.M.? Nat. Rev. Neurosci. 3, 153–160. http://dx.doi.org/10.1038/nrn726.

Court, J., Martin-Ruiz, C., Piggott, M., Spurden, D., Griffiths, M., Perry, E., 2001. Nicotinic receptor abnormalities in Alzheimer's disease. Biol. Psychiatry 49, 175–184.

de la Fuente, V., Freudenthal, R., Romano, A., 2011. Reconsolidation or extinction: transcription factor switch in the determination of memory course after

retrieval. J. Neurosci. 31, 5562–5573. http://dx.doi.org/10.1523/JNEUROSCI.6066-10.2011.
Debiec, J., Ledoux, J.E., 2004. Disruption of reconsolidation but not consolidation of auditory fear conditioning by noradrenergic blockade in the amygdala. Neuroscience 129, 267–272. http://dx.doi.org/10.1016/j.neuroscience.2004.08.018.
Dębiec, J., Bush, D.E.A., LeDoux, J.E., 2011. Noradrenergic enhancement of reconsolidation in the amygdala impairs extinction of conditioned fear in rats–a possible mechanism for the persistence of traumatic memories in PTSD. Depress Anxiety 28, 186–193. http://dx.doi.org/10.1002/da.20803.
Decker, M.W., McGaugh, J.L., 1991. The role of interactions between the cholinergic system and other neuromodulatory systems in learning and memory. SYNAPSE 7, 151–168.
Dudai, Y., 2002. Molecular bases of long-term memories: a question of persistence. Curr. Opin. Neurobiol. 12, 211–216.
Dudai, Y., 2004. The neurobiology of consolidations, or, how stable is the engram? Annu. Rev. Psychol. 55, 51–86.
Dudai, Y., 2007. Post-activation state: a critical rite of passage of memories. In: Bontempi, B., Silva, A.J., Christen, Y. (Eds.), Memories: Molecules and Circuits, Research and Perspectives in Neurosciences. Springer, Berlin, Heidelberg, pp. 69–82.
Dudai, Y., Eisenberg, M., 2004. Rites of passage of the engram: reconsolidation and the lingering consolidation hypothesis. Neuron 44, 93–100.
Duran-Arevalo, M., Cruz-Morales, S.E., Prado-Alcala, R.A., 1990. Is acetylcholine involved in memory consolidation of over-reinforced learning? Brain Res. Bull. 24, 725–727.
Eglen, R.M., 2005. Muscarinic receptor subtype pharmacology and physiology. Prog. Med. Chem. 43, 105–136. http://dx.doi.org/10.1016/S0079-6468(05)43004-0.
Fanselow, M.S., Lester, L.S., 1988. A functional behavioristic approach to aversively motivated behavior: predatory imminence as a determinant of the topography of defensive behavior. In: Bolles, R.C., Beecher, M.D. (Eds.), Evolution and Learning. Lawrence Erlbaum Associates Inc., Hillsdale, NJ, England, pp. 185–212.
Felix, R., Levin, E.D., 1997. Nicotinic antagonist administration into the ventral hippocampus and spatial working memory in rats. Neuroscience 81, 1009–1017.
Flurkey, K.M., Currer, J., Harrison, D.E., 2007. Chapter 20 – mouse models in aging research. In: Fox, J.G., Davisson, M.T., Quimby, F.W., Barthold, S.W., Newcomer, C.E., Smith, A.L. (Eds.), The Mouse in Biomedical Research (Second Edition). Academic Press, Burlington, pp. 637–672.
Frenkel, L., Maldonado, H., Delorenzi, A., 2005. Memory strengthening by a real-life episode during reconsolidation: an outcome of water deprivation via brain angiotensin II. Eur. J. Neurosci. 22, 1757–1766. http://dx.doi.org/10.1111/j.1460-9568.2005.04373.x.
Gardiner, J.E., 1961. The inhibition of acetylcholine synthesis in brain by a hemicholinium. Biochem. J. 81, 297–303.
Gold, P.E., 1986. The use of avoidance training in studies of modulation of memory storage. Behav. Neural Biol. 46, 87–98.
Gold, P.E., van Buskirk, R., 1976. Effects of posttrial hormone injections on memory processes. Horm Behav. 7, 509–517.
Introini-Collison, I.B., Baratti, C.M., 1992. Memory-modulatory effects of centrally acting noradrenergic drugs possible involvement of brain cholinergic mechanisms. Behav. Neural Biol. 57, 248–255.
Introini-Collison, I.B., Miyazaki, B., McGaugh, J.L., 1991. Involvement of the amygdala in the memory-enhancing effects of clenbuterol. Psychopharmacol. (Berl.) 104, 541–544.
Izquierdo, I., Medina, J.H., 1993. Role of the amygdala, hippocampus and entorhinal cortex in memory consolidation and expression. Braz. J. Med. Biol. Res. 26, 573–589.
Izquierdo, L.A., Barros, D.M., Vianna, M.R.M., Coitinho, A., deDavid e Silva, T., Choi, H., Moletta, B., Medina, J.H., Izquierdo, I., 2002. Molecular pharmacological dissection of short- and long-term memory. Cell. Mol. Neurobiol. 22, 269–287.
Krawczyk, M.C., 2012. Participación del Sistema Colinérgico en los Procesos de Consolidación, Reconsolidación y/o Extinción de la Memoria. Tesis de Licenciatura. Facultad de Ciencias Exactas y Naturales. Universidad de Buenos Aires.
Laney, C., Loftus, E.F., 2005. Traumatic memories are not necessarily accurate memories. Can. J. Psychiatry 50, 823–828.
Langmead, C.J., Watson, J., Reavill, C., 2008. Muscarinic acetylcholine receptors as CNS drug targets. Pharmacol. Ther. 117, 232–243. http://dx.doi.org/10.1016/j.pharmthera.2007.09.009.
Lattal, K.M., Abel, T., 2004. Behavioral impairments caused by injections of the protein synthesis inhibitor anisomycin after contextual retrieval reverse with time. Proc. Natl. Acad. Sci. USA 101, 4667–4672. http://dx.doi.org/10.1073/pnas.0306546101.
Lee, J.L.C., Everitt, B.J., Thomas, K.L., 2004. Independent cellular processes for hippocampal memory consolidation and reconsolidation. Science 304, 839–843. http://dx.doi.org/10.1126/science.1095760.
Levin, E., Bradley, A., Addy, N., Sigurani, N., 2002. Hippocampal α7 and α4β2 nicotinic receptors and working memory. Neuroscience 109, 757–765.
Levin, E.D., McClernon, F.J., Rezvani, A.H., 2006. Nicotinic effects on cognitive function: behavioral characterization, pharmacological specification, and anatomic localization. Psychopharmacol. (Berl.) 184, 523–539. http://dx.doi.org/10.1007/s00213-005-0164-7.
Lewis, D.J., 1979. Psychobiology of active and inactive memory. Psychol. Bull. 86, 1054–1083.
Loftus, E.F., Davis, D., 2006. Recovered memories. Annu. Rev. Clin. Psychol. 2, 469–498. http://dx.doi.org/10.1146/annurev.clinpsy.2.022305.095315.
Mamiya, N., Fukushima, H., Suzuki, A., Matsuyama, Z., Homma, S., Frankland, P.W., Kida, S., 2009. Brain region-specific gene expression activation required for reconsolidation and extinction of contextual fear memory. J. Neurosci. 29, 402–413. http://dx.doi.org/10.1523/JNEUROSCI.4639-08.2009.
Martí Barros, D., Ramirez, M.R., Dos Reis, E.A., Izquierdo, I., 2004. Participation of hippocampal nicotinic receptors in acquisition, consolidation and retrieval of memory for one trial inhibitory avoidance in rats. Neuroscience 126, 651–656. http://dx.doi.org/10.1016/j.neuroscience.2004.03.010.
McGaugh, J.L., 1966. Time-dependent processes in memory storage. Science 153, 1351–1358.
McGaugh, J.L., 2000. Memory – a century of consolidation. Science 287, 248–251. http://dx.doi.org/10.1126/science.287.5451.248.
McGaugh, J.L., Izquierdo, I., 2000. The contribution of pharmacology to research on the mechanisms of memory formation. Trends Pharmacol. Sci. 21, 208–210.
Milekic, M.H., Alberini, C.M., 2002. Temporally graded requirement for protein synthesis following memory reactivation. Neuron 36, 521–525.
Misanin, J.R., Miller, R.R., Lewis, D.J., 1968. Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace. Science 160, 554–555.
Myers, K.M., Davis, M., 2002. Behavioral and neural analysis of extinction. Neuron 36, 567–584.
Nader, K., Schafe, G.E., Le Doux, J.E., 2000. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature 406, 722–726. http://dx.doi.org/10.1038/35021052.
Ohno, M., Yamamoto, T., Watanabe, S., 1993. Blockade of hippocampal nicotinic receptors impairs working memory but not reference memory in rats. Pharmacol. Biochem. Behav. 45, 89–93.
Pedreira, M.E., Maldonado, H., 2003. Protein synthesis subserves reconsolidation or extinction depending on reminder duration. Neuron 38, 863–869.
Pedreira, M.E., Pérez-Cuesta, L.M., Maldonado, H., 2004. Mismatch between what is expected and what actually occurs triggers memory reconsolidation or extinction. Learn. Memory 11, 579–585. http://dx.doi.org/10.1101/lm.76904.
Perry, E.K., Morris, C.M., Court, J.A., Cheng, A., Fairbairn, A.F., McKeith, I.G., Irving, D., Brown, A., Perry, R.H., 1995. Alteration in nicotine binding sites in Parkinson's disease, Lewy body dementia and Alzheimer's disease: possible index of early neuropathology. Neuroscience 64, 385–395.
Power, A.E., Vazdarjanova, A., McGaugh, J.L., 2003. Muscarinic cholinergic influences in memory consolidation. Neurobiol. Learn. Memory 80, 178–193.
Power, A.E., Berlau, D.J., McGaugh, J.L., Steward, O., 2006. Anisomycin infused into the hippocampus fails to block "reconsolidation" but impairs extinction: the role of re-exposure duration. Learn. Memory 13, 27–34. http://dx.doi.org/10.1101/lm.91206.
Przybyslawski, J., Roullet, P., Sara, S.J., 1999. Attenuation of emotional and nonemotional memories after their reactivation: role of beta adrenergic receptors. J. Neurosci. 19, 6623–6628.
Quirion, R., 1993. Cholinergic markers in Alzheimer disease and the autoregulation of acetylcholine release. J. Psychiatry Neurosci. 18, 226–234.
Rescorla, R.A., 2004. Spontaneous recovery. Learn. Memory 11, 501–509. http://dx.doi.org/10.1101/lm.77504.
Ribot, T., 1906. Les maladies de la mémoire (18e édition)/par Th. Ribot, F. Alcan (Paris).
Rodriguez, W.A., Horne, C.A., Padilla, J.L., 1999. Effects of glucose and fructose on recently reactivated and recently acquired memories. Prog. Neuropsychopharmacol. Biol. Psychiatry 23, 1285–1317.
Sierra, R.O., Cassini, L.F., Santana, F., Crestani, A.P., Duran, J.M., Haubrich, J., de Oliveira Alvares, L., Quillfeldt, J.A., 2013. Reconsolidation may incorporate state-dependency into previously consolidated memories. Learn. Memory 20, 379–387. http://dx.doi.org/10.1101/lm.030023.112.
Squire, L.R., Davis, H.P., 1981. The pharmacology of memory: a neurobiological perspective. Annu. Rev. Pharmacol. Toxicol. 21, 323–356.
Squire, L.R., Wixted, J.T., 2011. The cognitive neuroscience of human memory since H.M. Annu. Rev. Neurosci. 34, 259–288. http://dx.doi.org/10.1146/annurev-neuro-061010-113720.
Suzuki, A., Josselyn, S.A., Frankland, P.W., Masushige, S., Silva, A.J., Kida, S., 2004. Memory reconsolidation and extinction have distinct temporal and biochemical signatures. J. Neurosci. 24, 4787–4795. http://dx.doi.org/10.1523/JNEUROSCI.5491-03.2004.
Taly, A., Corringer, P.-J., Guedin, D., Lestage, P., Changeux, J.-P., 2009. Nicotinic receptors: allosteric transitions and therapeutic targets in the nervous system. Nat. Rev. Drug Discov. 8, 733–750. http://dx.doi.org/10.1038/nrd2927.
Taubenfeld, S.M., Milekic, M.H., Monti, B., Alberini, C.M., 2001. The consolidation of new but not reactivated memory requires hippocampal C/EBPbeta. Nat. Neurosci. 4, 813–818. http://dx.doi.org/10.1038/90520.
Tronson, N.C., Taylor, J.R., 2007. Molecular mechanisms of memory reconsolidation. Nat. Rev. Neurosci. 8, 262–275. http://dx.doi.org/10.1038/nrn2090.
Tronson, N.C., Wiseman, S.L., Olausson, P., Taylor, J.R., 2006. Bidirectional behavioral plasticity of memory reconsolidation depends on amygdalar protein kinase A. Nat. Neurosci. 9, 167–169. http://dx.doi.org/10.1038/nn1628.
Zhai, H., Wu, P., Chen, S., Li, F., Liu, Y., Lu, L., 2008. Effects of scopolamine and ketamine on reconsolidation of morphine conditioned place preference in rats. Behav. Pharmacol. 19, 211–216. http://dx.doi.org/10.1097/FBP.0b013e3282fe88a0.