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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.

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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