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Intrahippocampal anisomycin infusions disrupt previously consolidated spatial memory only when memory is updated

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Abstract

Reconsolidation has proven to be a common phenomenon relevant to memory processing. However, the functional significance of this process is still a matter of debate. Previous work has shown that reconsolidation is indeed a process by which updated information is integrated, through the synthesis of proteins, to a memory trace. To further analyze the role that updated information plays in retrieved spatial memory susceptibility to disruption, we injected anisomycin bilaterally in the dorsal hippocampus of Wistar rats. Implanted animals were trained for 5 days on the Morris water maze (MWM) task and injected with anisomycin before the third or fifth training session. When memory was assessed a week later, only animals injected on the third training session showed disruption of long-term memory. Furthermore, when animals were trained for either 3 (middle-trained) or 5 (well-trained) days and a week later anisomycin was infused before a reminder session, only middle-trained rats infused with anisomycin showed reduced performance when tested for long-term memory. Finally, animals trained for 5 days and injected with anisomycin 7 days later on an extinction session showed impaired long-term extinction when tested. These results suggest that for spatial memory tasks acquisition of updated information is a necessary feature to undergo this process. We propose that reconsolidation is not an accurate term because it implies that consolidation happens again. This conception does not fit with the evidence; hence, we suggest that updating consolidation is a more descriptive term to refer to this process.

Keywords: Memory update; Reconsolidation; Spatial memory; Morris water maze; Anisomycin; Hippocampus

1. Introduction

Protein synthesis is a key step in the formation of long-term memories. A number of experimental studies have shown that inhibition of protein synthesis around the time of training causes long-term memory impairment in a large number of species and in different memory tasks (Davis & Squire, 1984; McGaugh, 1966; McGaugh, 2000). Until recently, it was widely accepted that long-term memories require of protein synthesis exclusively during a time window after acquisition (Kandel, 2001; McGaugh, 2000). However, Nader, Schafe, and LeDoux (2000) demonstrated that after retrieval, long-term memories need protein synthesis again to be retained in long-term storage. This finding has been replicated by many others (Dudai, 2004). Consequently, memory retrieval has grasped more attention and is currently seen as a dynamic phase in memory processing (Dudai, 2004; Sara, 2000; Suzuki et al., 2004). Therefore, to describe the relevant features that account for long-term memory dependence on protein synthesis after retrieval is now of general interest in the field.

Most of the reports that have dealt with retrieved memory dependence on protein synthesis have used tasks in which a conditioned stimulus (CS) is paired with an unconditioned stimulus (US). A conditioned response is obtained and used as a measure of memory. Commonly, on the

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retrieval trial, the CS is presented without the US and extinction may be initiated. On extinction, the CS is associated to the absence of the US. The CS–noUS association requires protein synthesis if it is to remain long-lasting. Therefore, a competition between the CS–US and the CS–noUS memories takes place during memory retrieval. In this regard, it has been observed that if the retrieval trial induces extinction, then protein synthesis inhibition disrupts the long-term extinction memory. Conversely, if the retrieval trial does not initiate extinction, then protein synthesis inhibition impairs the long-term CS–US memory (Eisenberg, Kobilo, Berman, & Dudai, 2003; Pedreira & Maldonado, 2003). In addition, it has been reported that stronger and older memories need longer retrieval trials to be disrupted by the blockade of protein synthesis compared to weaker and younger memories as long as the retrieval trial does not lead to extinction (Suzuki et al., 2004). Hence, it seems that the strength and duration of the reminder are pivotal traits directly related to memory susceptibility to disruption after retrieval.

Recently, we have found that in a taste-recognition memory task, retrieved long-term memory is dependent on protein synthesis only when updated information is acquired. So as long as task performance can be improved, protein synthesis inhibition disrupts retrieved memory. Consistently, when task performance has reached an asymptotic level, protein synthesis inhibition does not impair memory after retrieval. These results suggest that retrieved memory can be modified as part of a protein synthesis-dependent process aimed at the integration of updated experience to long-term memory (Rodriguez-Ortiz, De la Cruz, Gutierrez, & Bermudez-Rattoni, 2005).

To support the above, it is important to test whether integration of updated information is an indispensable feature to observe disruption of retrieved memory by protein synthesis inhibition in any given task. Despite recent evidence that points to this direction (Lukowiak, Fras, Smyth, Wong, & Hittel, 2007; Morris et al., 2006; Rossato et al., 2007), acquisition of updated information is not currently seen as a necessary trait for the reconsolidation process. Therefore, we addressed this issue on the Morris water maze (MWM) task, which is an extensively studied spatial memory paradigm. In this task, animals learn to escape from cool water by finding a hidden platform fixed into a swimming pool. Animals guide by extra-maze spatial cues located around the room to learn the platform position (Morris, Garrud, Rawlins, & O'Keefe, 1982). Evidence indicates that the hippocampus is an essential region for spatial memory processing (Eichenbaum, 2000; Squire, Stark, & Clark, 2004). Furthermore, protein synthesis in the hippocampus is required for long-term spatial memory (Guzowski & McGaugh, 1997; Naghdi, Majlessi, & Bozorgmehr, 2003; Rossato, Bevilaqua, Medina, Izquierdo, & Cammarota, 2006). Moreover, it has been reported that after retrieval, MWM memory requires protein synthesis in this region to remain in long-term storage (Rossato et al., 2006). Therefore, in the present study we assessed the role that incorporation of updated information to memory plays in retrieved long-term spatial memory dependence on protein synthesis, by infusing bilaterally anisomycin in the dorsal hippocampus of rats. Parts of the results described herein were previously presented in abstract form (Rodriguez-Ortiz, Benavidez, Ballesteros, Garcia, & Bermudez-Rattoni, 2005).

2. Materials and methods

2.1. Subjects

Male Wistar rats from Instituto de Fisiología Celular breeding colony weighing between 280 and 320 g at the beginning of the experiment were housed individually in plastic cages and kept on a 12/12 light/dark cycle. All manipulations were performed during the dark cycle. Food and water were freely available throughout experiments.

2.2. Surgery and microinjection

Animals under ketamine–xylazine (76–8 mg/kg) anesthesia were bilaterally implanted with stainless-steel guide cannulae in the dorsal hippocampus. Coordinates from bregma were: posterior 3.6 mm, lateral +/− 3.0 mm and ventral 2.3 mm. These coordinates were selected to inhibit protein synthesis in the CA3–CA1 region (Fig. 1). The behavioral procedures were performed after at least 5 days post-surgery. For bilateral microinjections, an injector (30 ga) was inserted into each guide cannula

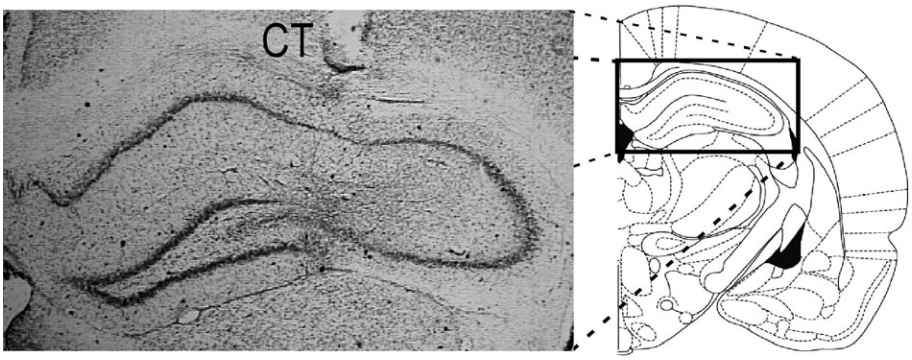

Fig. 1. Photomicrography of a coronal section of an anisomycin-injected rat showing cannula track (CT) location in the dorsal hippocampus. Similar results were observed for the rest of the implanted animals. On the left is a coronal diagram of the dorsal hippocampus (Reprinted with permission from Paxinos & Watson, 1998).