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Research Report

Exogenous insulin-like growth factor 2 administration enhances memory consolidation and persistence in a time-dependent manner

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ABSTRACT

Memory consolidation is an important process for the formation of long-term memory. We have previously reported that mature brain-derived neurotrophic factor enhances memory consolidation within 9 h after initial learning. Recent studies suggest that insulin-like growth factor 2 (IGF2) significantly enhances memory consolidation and prevents forgetting. Thus, we hypothesized that IGF2 exerts its activity on cognitive performance in a time-dependent manner as observed in our previous study. In the one-trial step-through inhibitory avoidance task, we demonstrate that a bilateral injection of IGF2 into the dorsal hippocampus 6 or 9 h after training significantly enhanced the step-through latencies compared with the vehicle-treated controls in the retention trial, which was conducted 24 h after the acquisition trial. However, 12 h post-training, IGF2 injection did not increase the step-through latencies. Intriguingly, in the retention trial at 21 days after the training, hippocampal IGF2 injection 6, 9 or 12 h after the acquisition trial significantly increased the step-through latencies compared with the vehicle-treated controls. IGF2 administration at 9 h and 12 h after the acquisition trial significantly increased discrimination index and exploration time on the novel-located object in the test trial at 24 h and 21 days, respectively, after the acquisition trial in the novel location recognition task. In addition, IGF2-induced an increase in the step-through latencies in the retention trial 24 h or 21 days, respectively, after the initial learning was completely abolished by co-injected anti-

Abbreviations: Arc, activity-regulated cytoskeleton-associated protein; IGF1R, insulin-like growth factor 1 receptor; IGF2, insulin-like growth factor 2; IGF2R, insulin-like growth factor 2 receptor; LTM, long-term memory; mBDNF, mature brain-derived neurotrophic factor; ANOVA, one-way analysis of variance; PBS, phosphate-buffered saline

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IGF2 receptor antibody. These results suggest that IGF2 enhances memory consolidation within 9 h after initial learning, and increased IGF2 within the 12 h after the acquisition trial, which represents a delayed consolidation phase, is also critical for memory persistence.

1. Introduction

Memory consolidation is a process by which acquired information is transformed from a labile into a more stable state that can be retrieved at a later time (McGaugh, 1966, 2000). Because memory consolidation is required for long-term memory (LTM) formation, numerous efforts have been contributed to elucidate its roles and characteristics. It has previously been reported that the inhibition of *de novo* protein synthesis with anisomysin or cycloheximide in the hippocampus approximately 3–6 h after the initial acquisition impaired memory consolidation, whereas it did not induce impairments 12 h after the acquisition trial (Bekinschtein et al., 2007; Kim et al., 2012). We recently reported that mature brain-derived neurotrophic factor (mBDNF) in the hippocampus enhances memory consolidation within 9 h after initial learning (Kim et al., 2012, 2014; Kwon et al., 2014). Furthermore, several lines of evidence have demonstrated that a late consolidation phase, approximately 12 h after initial learning, is required for the persistence of LTM. In particular, a delayed protein synthesis and BDNF expression in the hippocampus after learning are critical for LTM persistence, but not memory formation (Bekinschtein et al., 2007, 2008). However, it remains unknown which molecule(s) is essential for memory consolidation or persistence and whether BDNF is the only factor required for the memory consolidation or persistence process.

Recently, insulin-like growth factor 2 (IGF2) has received attention as a memory booster (Graff and Tsai, 2011). Alberini and colleagues reported that hippocampal or systemic injection of recombinant IGF2 enhances memory retention and prevents forgetting (Chen et al., 2011; Stern et al., 2014b), and another group has also suggested that the hippocampal IGF2 pathway regulates the extinction of fear memory (Agis-Balboa et al., 2011). Chen et al. (2011)suggested that endogenous hippocampal IGF2 has a role in memory consolidation during a limited time window that lasts less than 4 days. However, it remains unclear whether exogenous IGF2 regulates the memory trace or whether such effects are active until several weeks. Therefore, based on our preliminary mBDNF studies on memory consolidation, we hypothesized that exogenous IGF2 injection into the hippocampus affects memory consolidation or persistence in a time-dependent manner.

To examine our hypothesis, IGF2 was injected at specific time points (6, 9 or 12 h) after the acquisition trial of a step-through inhibitory avoidance task. We also investigated whether the acquired information would be maintained by exogenous IGF2 administration. In addition, we examined whether IGF2 exerts its effect in the aversion-independent task, such as novel location recognition task. Here, we demonstrate that a bilateral IGF2 injection into the dorsal hippocampus enhances memory consolidation and maintains memory traces for at least 3 weeks after the acquisition trial (Fig. 1).

2. Results

2.1. *Hippocampal IGF2 injection 6 or 9 h, but not 12 h, after training enhances memory consolidation*

To determine the effective time window of IGF2 on memory trace, we used a one-trial step-through inhibitory avoidance task, which is a hippocampus-dependent learning task and widely used for the study of memory consolidation (Chen et al., 2011; Gold, 1986; Izquierdo et al., 2006). The mice were injected bilaterally with IGF2 or the same volume of vehicle into the dorsal hippocampus 6, 9 or 12 h after the acquisition trial. The retention trial was conducted 24 h after the acquisition trial. We observed that exogenous IGF2 injection 6 or 9 h after the acquisition trial significantly increased the step-through latency time compared with the vehicle-treated control group [6 h, $t_{(18)}=3.748$, $P<0.05$; 9 h, $t_{(18)}=2.126$, $P<0.05$, Fig. 2]. In contrast, the 12 h post-training IGF2

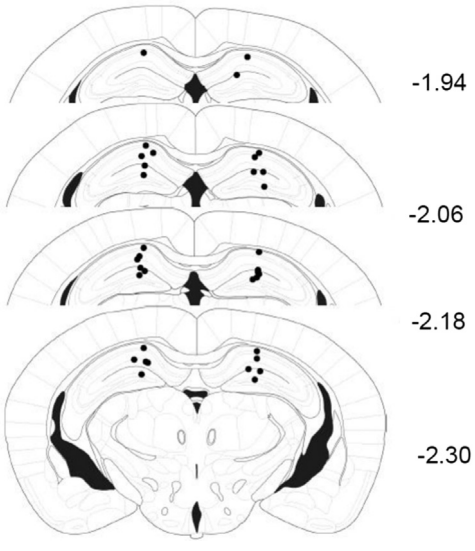

Fig. 1 – Summary of the microinjection site in the hippocampus. The mice with misplaced cannulae were excluded. The drug administration site was confirmed by the infusion of 0.1 μl of 1% Evans Blue into the hippocampus after behavioral testing (coordinates: for hippocampus, AP – 2.00 mm, ML ± 1.5 mm and DV – 1.00 mm).