Blockade of Lactate Transport in the Insular Cortex Impairs Reconsolidation, but not Retrieval, of Morphine-associated Memory and Prevents Subsequent Reinstatement

Haichen Niu[1], Qiang Zhang[1], Lili Guo[1], Min Hu[2]*

[1]*Department of Genetics, Xuzhou Medical College, Xuzhou city, PR China*
[2]*Department of Ophthalmology, The Second People's Hospital of Yunnan Province, Kunming City, PR China*

Abstract

Drug-associated memories are critical for addictive behaviors, as these memories can trigger drug seeking and relapse by contextual cues. The transfer of lactate from astrocytes to neurons plays an important role in reward memory. Recently, studies have indicated that the insular cortex has a vital role in addictive procedure, which can be induced by contextual cues using both rat and human memory models. However, the neural locus in which the role of astrocyte–neuron lactate transport in long-term conditioning is required for reward memories is unclear. In investigating the involvement of insular astrocyte–neuron lactate transport in the processing of reward memory, using the conditioned place preference (CPP), we show that the local blockage of astrocyte–neuron lactate transport via the infusion of an inhibitor of glycogen phosphorylase (DAB) into the insular cortex impairs CPP expression of reconsolidation, but not extinction. Co-administering L-lactate and DAB confirmed that lactate could restore DAB-induced memory deficit. The expression of c-fos in the insula cortex, the product of an immediate early gene, is also inhibited following memory reactivation. We found that the administration of DAB in the insula prior to reactivating the memory could inhibit the reconsolidation of reward memory, which could be reversed by the co-administration of DAB and L-lactate, and decrease the number of c-fos-positive cells. However, these treatments have no contribution to the extinction procedure, thereby indicating that the inhibitory contribution is reactivation dependent. Our results demonstrate that insular astrocyte–neuron lactate transport has a role in the processing of drug memory and that the blockage of insular astrocyte–neuron lactate transport could inhibit the reconsolidation of reward memory. This offers a novel therapeutic target to reduce the long-lasting conditioned responses to drug abuse.

Keywords: Reward memory; Drug reward; Reconsolidation; Conditioned place preference; Insular cortex; Astrocyte–neuron lactate transport

Introduction

Drug addiction is a type of brain disease that is characterized by behavioral features and is thought to be a form of distorted memory [1]. During the usage of the addicted substance, both reward effects and environmental cues are entered into reward memory after consolidation, thereby resulting in the context-cue stimulus being able to induce the drug craving behavior [2]. The consolidated memories are stable and difficult to disturb [1]. However, other studies have indicated that the retrieval of memory traces could induce an additional labile phase after reactivation/retrieval [3,4]. This phase was termed as the reconsolidation of memory, which has been thought of as an important component of long-term memory processing [5]. In 2000, Nader et al. challenged consolidation during the Pavlovian association of a tone (CS) with a shock (US), thereby showing that a CS-alone reminder that is presented long after the consolidation phase was completely re-engaged during the temporary susceptibility phase of memory access [6]. In memory formation, protein synthesis is needed, thereby suggesting that disturbances in protein synthesis may prevent memory formation [7]. Previous studies have considered that the stabilization of a new memory occurs through consolidation, which requires gene expression. Importantly, memories can again become transiently labile and sensitive to protein synthesis inhibitors if memories are reactivated after consolidation [8,9]. Many studies have indicated that disturbing the reconsolidation of different memories, including reward memory and fear-conditioned memory, could destroy consolidated memories [10-12]. Therefore, disturbing the reconsolidation of reward memory to inhibit drug-craving behavior has become a novel target for curing the addiction.

***Corresponding author:** Min Hu, Department of Ophthalmology, The Second People's Hospital of Yunnan Province, Kunming City, PR China, Tel: 086-15996914018; E-mail: fudanhumin@sina.com

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compartment. Furthermore, there was a signi cant interaction between morphine conditioning and DAB treatments ($F_{2, 44}=11.32$, $p < 0.001$; Figure 1B). Subsequent *post hoc* tests (LSD) showed that insular infusions of 30 DAB blocked the reconsolidation of CPP ($p < 0.05$) in

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