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Carnosine alleviates Motivational Deficit under Chronic Stressful-like Conditions in Mice (#370)

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Introduction

The World Health Organization has reported over 450 million people have an episode of mental disorder induced by chronic stress, and the number of patients is increasing now. It is important that the mental disorder have to be prevented to onset while its initial symptom is presented. The motivational deficit is one of initial symptoms of mental disorder including depression, anxiety and schizophrenia. Therefore, we focused on the motivational deficit induced by chronic stress. Recently, cytokine hypothesis in mental disorder has been proposed, since there are a lot of evidences about the relationships between chronic stress and brain inflammation. Thus, lipopolysaccharide (LPS) model has been paid attention to study the mechanism for chronic stress. LPS injection induces the inflammatory response as well as chronic stress in animal body including the brain, resulting in the release of inflammatory cytokines and chemokines. In this way, physiological response in LPS injected conditions well mimics that in chronic stressful conditions. In fact, depression-like behavior was caused by high concentration of LPS (800 μg/10 mL/kg), while few papers reported about the initial symptoms of mental disorder, which is including motivational deficit, induced by lower LPS dosages. Our preliminary studies revealed that the motivational deficit is induced in LPS model. Carnosine (β-alanyl histidine) which is principally distributed in mammalian skeletal muscle and brain is known to exert the anti-inflammatory and anti-oxidant effects. Therefore, we investigated that daily supplementation of carnosine affects the motivated behavior in LPS model in mice.

Methods

Male seven-week old ICR mice were orally administered the distilled water (10 ml/kg) or carnosine solution (0.8 mmol/ 10 ml/kg) for 8 days. On Day 7, each mouse was freely explored in the experimental arena (width: 60 cm × length: 60 cm × height: 40 cm) for 5 minutes, followed by the intraperitoneal injection of PBS (10 ml/kg) or LPS solution (400 μg/ 10 ml/kg). After 24 hours from an injection, every mice were re-explored the same experimental arena in which two novel objects were placed for 5 minutes. In this experiment, the total duration of object exploration was observed as an index for motivated behavior in mice. The exploratory behavior to novel objects was defined as touching with their two hands. Immediately after each behavioral observation, the mouse was sacrificed under anesthesia, and the hippocampus was dissected from the brain on iced dish, homogenized, and the water-soluble component was extracted. The remaining sample was freeze-dried, derivatized samples were subjected to GC-MS. GC-MS results were analyzed by MS-DIAL version 2.82 (http://prime.psc.riken.jp/) and Metaboanalyst 4.0 (https://www.metaboanalyst.ca/). The statistical analysis was performed using ANOVA accompanied by Tukey-Kramer test or t test.

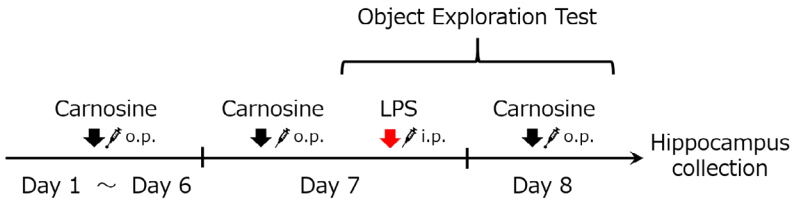
Results

The total duration of object exploration was significantly decreased by LPS administration, indicating the decline of motivation. However, daily carnosine treatment slightly attenuated the decline of motivation induced by LPS administration. Therefore, carnosine supplementation may be useful for alleviating the motivational deficit. In the present study, metabolome analysis proposed the alteration of metabolic pathways in the hippocampus under the loss of motivation induced by LPS treatment. LPS treatment predominantly influenced the glucogenesis and glycolysis. These metabolic dysfunctions may lead the loss of motivation. In addition, the present study revealed that carnosine supplementation partially improved metabolic dysfunction induced by LPS treatment. Daily supplementation of carnosine cancelled the significant increase of phosphoethanolamine level in LPS treated mice. Previous studies reported that phosphoethanolamine is released from nerve extracellular in the brain under ischemic state and increased by chronic stress such as social defeat stress. The brain in LPS treated mice might have damaged by chronic stress-like conditions, and consequently phosphoethanolmine level might have increased in the hippocampus. There is a possibility that the prevention of increase in phosphoethanolamine links to therapy of LPS-induced brain dysfunction. Alleviation of motivational deficit induced by carnosine supplementation may be mediated by the reinstatement of the abnormal phosphoethanolamine level in the hippocampus of LPS injected mice.

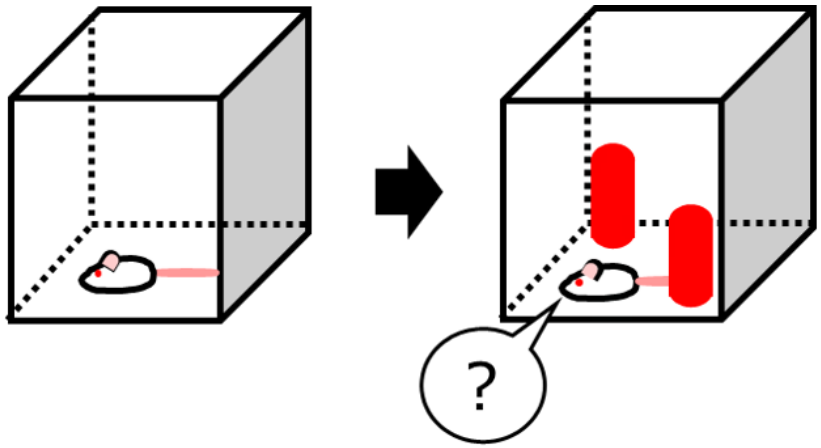
Conclusion

Dietary carnosine slightly attenuated the depressed motivation under chronic stressful-like conditions induced by LPS treatment in mice. LPS treatment affected various metabolic dysfunctions in the hippocampus. However, carnosine supplementation reinstated the elevated phosphoethanolamine level induced by LPS treatment. Resultant this improvement might have alleviated the motivational deficit in LPS injected mice.

Notes



Experiment procedure.



The motivated behavior was evaluated by Object Exploration Test .

Notes