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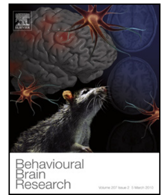

Research report

Luteolin protects against high fat diet-induced cognitive deficits in obesity mice

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HIGHLIGHTS

- Luteolin ameliorated high fat diet-induced cognitive dysfunction.
- Luteolin inhibited obesity-induced oxidative stress in brain.
- Luteolin suppressed obesity-induced neuroinflammation in brain.
- Luteolin reduced obesity-induced neuron insulin resistance in brain.
- Luteolin reduced obesity-induced glucose metabolic disorder in brain.

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ABSTRACT

The epidemic and experimental studies have confirmed that the obesity can lead to neuroinflammation, neurodegenerative diseases and adversely affect cognition. Despite the numerous elucidations on the impact of obesity on cognition decline, the contributors to the impairments in obesity remain unclear. Male C57BL/6J mice were fed either a control or high-fat diet (HFD) for 16 weeks and then randomized into four groups treated with their respective diets for 4 weeks including control diet (CD); control diet + luteolin (CDL); high-fat diet (HFD), high-fat diet + luteolin (HFDL). The dose of luteolin was 10 mg/kg, oral. We showed that adding luteolin in high-fat diet can significantly reduce body weight gain, food intake and plasma cytokines as well as improving glucose metabolism of mice on HFD. Importantly, we showed that luteolin treatment had the effects of alleviating neuroinflammation, oxidative stress and neuronal insulin resistance in the mouse brain, restored blood adipocytokines level to normal. Furthermore, luteolin increased the level of brain-derived neurotrophic factor (BDNF), the action of synapsin I (SYP) and postsynaptic density protein 95 (PSD-95) in the cortex and hippocampus as to that the behavioral performance in Morris water maze (MWM) and step-through task were significantly improved. These results indicate a previously unrecognized potential of luteolin in alleviating obesity-induced cognitive impairment for type-2 diabetes mellitus and Alzheimer disease (AD).

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1. Introduction

Nowadays, obesity has become a worldwide epidemic, overweight status and its medical comorbidities such as heart disease, hypertension, type-2 diabetes mellitus, insulin resistance, stroke and cancer are serious health hazards to humans [1–3]. In particular, the typical diet in most industrialized western societies is rich in saturated fat and refined sugar, and nearly 33% adults in American are obese, obesity has increased 60% within the past 20 years, 66% of American adults are overweight, and one in six children are obese as well as the ratio is increasing [4]. Otherwise, obese individuals show early impairment of cognitive performance which can lead to early onset dementia [3,5].

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There are also gaps in knowledge about the neurophysiological mechanisms underlying the effects of obesity on cognitive function. Many reports indicated that obesity, type-2 diabetes mellitus and insulin resistance are closely interrelated metabolic syndrome [6–8], and can cause metabolism and energetics disruptions, neuronal insulin resistance, and the increase in the levels of oxidative stress and low-grade systematic inflammation in brain [9–11], which are attributed to dysregulated production and release of cytokines and adipokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), resistin, and adiponectin in plasma and macrophage-infiltrated brain tissue [12,13]. Moreover, metabolic alterations and medical comorbidities are associated with abnormal cognition, neuronal changes and the activation of insulin receptor signaling pathways in the brain [7,14,15]. Oxidative stress and inflammation play the important roles in neuronal injury and death in the brain when subjected to many types of insult, including hyperoxia, ischemia, and metabolic disorder brain injury [16–19]. Meanwhile, excessive energy intake impairs the structure and function of the hippocampus, including the synaptic plasticity and neurogenesis which are associated with learning and memory [5]. By contrast, calorie restriction and exercise might be efficient to reverse cognitive impairment and attenuate the neuronal atrophy which is closely related to brain aging and AD [20].

Luteolin, a flavonoid exists in significant amounts of fruits and vegetables, such as celery, carrots, chamomile tea and green pepper. Several pieces of evidence show that luteolin plays effectively role as anti-inflammatory both in vivo and in vitro [21–23]. It also shows potential protective effects on neuron damage [24,25]. In our prior studies, we found luteolin could alleviate the cognition damage in diabetes-associated cognitive decline in rats via the modulation of oxidation stress and neuroinflammation level in brain tissues [26]. While plenty of proofs implicates obesity and metabolic dysfunction are related to brain network dysfunction in cognitive impairment and learning and memory disorder. There is no precise evidence of the connection between obesity and cognitive aging or AD. Meanwhile, no reports are available which are aimed to investigate whether luteolin has a protective effect against cognitive impairment induced by obesity and its medical comorbidities in mice fed on a high-fat diet. The purpose of our present study is designed to attempt to indicate the issue above, and investigate the potential mechanism of protective effects of luteolin on cognitive impairment induced by obesity.

2. Experimental procedures

2.1. Animals treatment and tissue preparation

Eighty male C57BL/6j mice weighted 19–22 g were purchased from the Branch of National Breeder Center of Rodents (Shanghai, China). Before the experiment the animals were housed under a standard light/dark cycle with ad libitum access to food and water for 1 week, with the constant temperature (23 ± 1 °C) and relative humidity (65%). All experiments were performed in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals.

At the end of acclimation of the animals for 1 week on standard mouse chow, the mice were randomized into four groups: control diet (CD); control diet + luteolin (CDL, luteolin 10 mg/kg); high-fat diet (HFD); high-fat diet + luteolin (HFDL, luteolin 10 mg/kg), and assigned to a high-fat diet or a control diet for 20 weeks ($n = 15$ each). CD consisted of the following (in Kcal): protein (19%), carbohydrate (68%), and fat (13%), the HFD consisted of the following (in Kcal): protein (15%), carbohydrate (43%), and fat (42%). 16 weeks later, CD and HFD groups were treated with 0.5% carboxymethylcellulose solution (i.g., once daily) for 4 consecutive weeks. In parallel, CDL and HFDL groups were treated with luteolin (Shanxi Sciphar Biotechnology Co., Ltd. Shanxi, P.R. China, suspended in 0.5% carboxymethylcellulose solution, i.g., once daily), mice body weight and food intake were weekly measured. Following behavioral assessment in Morris water waze (MWM) and step-through task (STT), and insulin sensitivity and glucose tolerance tests mice ($n = 11$ each) were euthanized, followed by the blood sampling without addition of anticoagulants for centrifugation at $3000 \times g$ for 10 min for subsequent determination of clear plasma, and the isolation of brain cortex and hippocampus on ice. The blood samples and brain tissues were rapidly frozen and stored at −80 °C until biochemical determinations. The other mice ($n = 4$ each) were transcardially perfused with 25 mL of normal saline [0.9% (w/v) NaCl]. The whole brain was removed and incubated for 24 h in 100 mM sodium phosphate buffer (pH = 7.4) containing 30% sucrose for Golgi stain test (FROSEN SECTION NEURON GOLGI STAINING KIT, GenMed Scientifics Inc. USA). The process of the study as follows, animals—one week to adapt to environment—assigned to a high-fat diet or a control diet for 20 weeks—Insulin sensitivity and glucose tolerance tests—cognitive testing—Insulin resistance evaluation—Measurement of oxidative stress—Reverse transcriptase-PCR—Western blot—ELISA—Golgi staining test—Statistical analysis.

2.2. Cognitive testing

Subsequent to 19 weeks on a high-fat diet, all behavioral tests were performed at the 20th week.

2.2.1. Morris water maze test

The Morris water maze test was conducted [26,27]. The experimental facilities consisted of a circular water pool (120 cm diameter, 60 cm in height), containing water to a depth of 15.5 cm. The water was controlled at 24 ± 1 °C and was rendered opaque by addition of milk powder. The pool was virtually divided into four quadrants, i.e., NE, SE, SW, and NW, a transparent platform (10 cm in diameter) was hidden 1.5 cm below the surface of water and placed at the midpoint of one quadrant. The mice received four consecutive daily training trials during the following 5 days, with each trial lasted until either the mice had found the platform or for a maximum of 90 s. All mice were allowed to rest on the platform for 20 s. A probe trial was performed [28,29] on the fifth day when the extent of memory consolidation was assessed. In the probe trial, the mice were placed and released opposite the site where the platform had been located. The single-probe trial consisted of a 90 s free swim in the pool without the platform. The time spent in the target quadrant indicates the degree of memory consolidation that has taken place after learning and the percentage of time spent in the former platform was calculated for the probe trial.

2.2.2. Step-through task

Immediately after the MWM test, the step-through passive avoidance response [30] was performed. The step-through task is accepted as a simple and rapid memory test which is widely used throughout the world. The apparatus consisted of an illuminated and a dark compartment, separated by a vertical sliding door. A mouse was initially placed in the illuminated compartment, with its tail toward the dark compartment for 3 min for environmental adaptation. With the door opened, the mice could enter the dark compartment (mice instinctively prefer being in the dark). Following the mice completely entered the dark compartment, it was given an electric shock (36 V, DC). And thereafter the mice returned to its home cage. Training (0 h) was performed for 5 min as mentioned above, and the test was repeated 24 h later. During the training and retention trials, the number of errors and the latency

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