Life Sciences 148 (2016) 279–285

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Environmental enrichment reverses cognitive impairments provoked by Western diet in rats: Role of corticosteroid receptors

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ARTICLE INFO

Article history:
Received 14 September 2015
Received in revised form 4 February 2016
Accepted 4 February 2016
Available online 23 February 2016

Keywords:
Western diet
Enriched environment
Cognitive function
Water maze
Glucocorticoid receptor
Mineralocorticoid receptor

ABSTRACT

Aims: Previous studies demonstrated that the Western diet (WD), which is rich in saturated fat (HFD) and refined sugar (HSU), is related to the impairments of hippocampus-dependent learning and memory and forebrain synaptic plasticity in rodents. The environmental enrichment (EE) has been shown to enhance learning and memory in the HFD-induced cognitive deficits, but the exact mechanism is still not clearly understood. Therefore, the present study aimed to clarify the effects of the EE on spatial memory in WD-fed rats, and to analyze the potential role of corticosteroid receptors in the EE conditioning.

Main methods: Male Wistar albino rats were housed in either an enriched or standard environment and fed with the HFD (35% of energy as fat), HSU (100% of carbohydrate as sucrose) or standard rat chow for 4 weeks. We used the Morris' water maze test (MWM) to assess the learning and memory performance, and measured plasma levels of corticosterone (CORT) and adrenocorticotropic hormone (ACTH), as well as glucocorticoid (GR) and mineralocorticoid receptor (MR) levels in the hippocampus. Key findings: The results showed that HFD-fed rats displayed poorer learning and memory performance evaluated with MWM than controls. The EE reversed the cognitive deficits caused by the HFD. In addition, the EE resulted in an increase of GR and MR levels without affecting plasma CORT and ACTH concentrations.

Significance: Based on these findings, it could be suggested that the EE plays an important role in amelioration of the HFD-induced cognitive impairments, but this intervention is independent of the hypothalamic–pituitary–adrenal axis and hippocampal corticosteroid receptor levels.

1. Introduction

Obesity, which is predominantly induced by a diet rich in high-fat and/or refined sugar (commonly known as Western diet), has become a pandemic disease in Western countries, and causes serious health problems such as cardio metabolic disorders, diabetes mellitus, and Alzheimer's disease. Indeed, aging populations possess higher prevalence of glucose intolerance and non-insulin-dependent diabetes mellitus; however, high-calorie diets exaggerate the risk for these pathological disturbances. It is established that high-fat diet notably contributes to the development of dementia and Alzheimer's disease in humans [11]. Additionally, preclinical researches showed that the high-fat diet provokes not only weight gain and metabolic syndrome, but also the deterioration of hippocampal learning and memory functions. Rodents fed with a diet that is rich in fat widely display cognitive impairments in learning and memory tasks, including Morris' water maze [28], radial arm water maze [2], object recognition [10], and eight arm radial maze tests [39]. The exact mechanism of adverse effects of the high-fat diet still remains obscured, but there are some plausible explanations. Previous findings suggest that neural insulin resistance generated by high-calorie intake is important in the pathophysiology of high-fat diet-induced cognitive impairments [28, 29]. In addition, the decrement of hippocampal brain-derived neurotrophic factor (BDNF), synapsin I, and cyclic AMP-response element-binding protein (CREB) levels generated by high-fat and refined sugar containing diets plays a role in the cognitive deficits [21]. Recently, Soares et al. [36] demonstrated that the Western diet disturbs hippocampus-dependent short- and long-term spatial memory through decreasing hippocampal glucocorticoid receptor levels in rodents. Despite growing knowledge, therapeutic approaches targeting high-fat diet-induced cognitive decline did not reach a desired point yet.

The environmental enrichment (EE) is defined as “a complex combination of social and inanimate stimulation” [31]. In comparison to

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http://dx.doi.org/10.1016/j.lfs.2016.02.011

standard housing conditions, the EE provides animals with adequate space for physical exercises, and for the enhancement of sensory, cognitive and motor stimulation. All items used to create an EE such as running wheel, toys, and tunnels are relocated at regular intervals to obtain a recurring impulse, because the increase of complexity and novelty results in a higher stimulation which enhances learning and memory processes [27]. It is well-documented that the EE counteracts cognitive deficits induced by prenatal chronic stress [42], chronic cerebral hypoperfusion [46], traumatic brain injury [15], postnatal *anti*-glutamatergic exposure [23], and stroke [44] in rats. Nevertheless, there are few reports demonstrating the beneficial effects of the EE against Western diet-induced cognitive decline [20, 41]. Furthermore, underlying events that drive cognitive impairments are poorly recognized, even though the beneficial effects of the EE on learning and memory have been evidenced. Glucocorticoid receptors are abundant in the hippocampus, a brain region which involves mainly in the regulation of spatial orientation and learning and the activation of hippocampal glucocorticoid receptors improves memory consolidation in learning tasks [19, 36, 45]. High-calorie diet or environmental enrichment influences corticosteroid receptor levels and this is associated with the learning and memory performance. The rats fed with a high-calorie diet display lower hippocampal corticosteroid receptor levels, which is linked with spatial learning and memory deficits [36], and chronic cerebral hypoperfusion-related learning and memory impairments are relieved in rats housed in an enriched environment, compared to that in standard cages, by the way of the increase of corticosteroid receptors [45].

The present study is designed to investigate cognitive effects of environmental enrichment by using Morris' water maze test on high-calorie diet-induced spatial learning and memory impairments, and to explore the role of hypothalamic–pituitary–adrenal axis and corticosteroid receptors in cognitive impairments in adult rats.

2. Materials and methods

2.1. Experimental groups and diets

Forty-eight male Wistar strain rats, weighing 350 ± 30 g and aged 10–12 weeks, were obtained from Necmettin Erbakan University Experimental Medicine Research and Application Center (Konya, Turkey). The rats were housed in a climate controlled room (22 ± 2 °C temperature and 50 ± 5% humidity) on a 12/12 h light/dark cycle (lights on between 07:00 and 19:00), with ad libitum food and fresh water. The animals were randomly divided into environmentally enriched (EE; $n = 24$) and standard condition (SC; $n = 24$) groups, and fed with either standard rat chow, high-fat diet (HFD) or high-sucrose diet (HSU) (for each $n = 8$) for a period of 4 weeks. In the high-fat diet, 35% of the total energy was provided by suet, whereas 100% of carbohydrate-derived energy was provided from sucrose in the high-sucrose diet. The chows were purchased from a local supplier (Nukleon Ltd., Ankara, Turkey) in a proportionally adjusted ready-to-use form. The experimental procedures are illustrated in Fig. 1. All procedures were performed in accordance to the guidelines of the National Institutes of Health Guide for the Care and Use of Laboratory Animals (publication no.: 86-23, revised 1996) and were approved by the Institutional Animal Care and Use Committee of Necmettin Erbakan University (Konya, Turkey).

2.2. Housing conditions

The animals in EE group were housed in specially designed cages (90 × 75 × 45 cm) containing a variety of stimulating objects such as toys, platforms, running wheels, tunnels, balls, and stairs, which were made from wood, plastic or metal (Fig. 2). Enhanced social stimulation was acquired by group-housing (8 rats in each cage). The objects were relocated twice a week to maintain novelty in the environment. The SC group was housed in Eurostandard Type IV polycarbonate rat cage (60 × 38 × 20 cm) as 4 animals per cage without any stimulating object. The rats were stayed in these experimental conditions for 4 weeks. Ad libitum food (either standard or specialized, according to the belonging group) and fresh water were available for both groups throughout the experiment.

2.3. Cognitive performance

The Morris' water maze test (MWM) was employed as described previously [25] to assess spatial learning and memory performances of rats. The test was performed in a circular pool (150 cm diameter and 60 cm height) filled with warm water (25 ± 1 °C) to a depth of 45 cm and virtually divided into 4 equal-sized quadrants as southwest, southeast, northwest, and northeast. A square-shaped escape platform (10 × 10 cm) was submerged 2 cm below the water surface in the northeast quadrant of the pool. All animals were subjected to 4 consecutive training sessions, consisting of 4 trials per session with an inter-trial break for 5 min. In each trial, the rats were released into one another quadrant of the pool as facing to the wall. The animals were allowed to locate the hidden platform for 90 s. The animals that have failed to find the platform in 90 s were gently grasped and placed onto the platform to let them inspect visual clues around the pool for 30 s. The escape latency (time to reach the platform), swimming speed (cm/s), and swimming path length (cm) were measured in training trials. On the day after completion of the training, the platform was removed and animals were left to swim freely to search the platform area (probe trial). The time spent in the target quadrant (sec), swimming speed, swimming path length, and the count of crossings over the platform area were evaluated. The trials were video-recorded and estimations were done by using a computer software (EthoVision XT v.9.0, Noldus Information Tech., Wageningen, The Netherlands). Both training and probe trials were established between the hours of 09:00 and 12:00.

2.4. HPA axis function

At the end of the cognition test, the rats were anesthetized with a single intraperitoneal injection of the ketamine and xylazine combination (respectively, 60 and 10 mg/kg). The blood samples were obtained by cardiac puncture and transferred into EDTA-containing tubes. The plasma was separated by cold-centrifugation (+4 °C) at 3000 rpm for

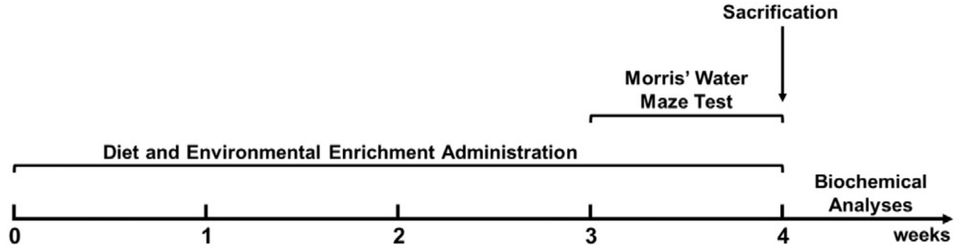

Fig. 1. The scheme illustrates the experimental procedures.