



Original Article

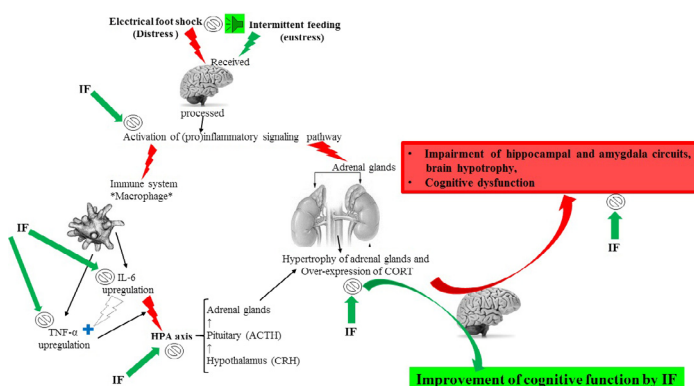
Intermittent fasting could ameliorate cognitive function against distress by regulation of inflammatory response pathway

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HIGHLIGHTS

- IF could significantly modify pathological effects of distress on brain and adrenal glands.
- In distressful condition, IF leads to reduce the plasma level of the stress hormone (CORT).
- IF has an inhibitory effect on neuroinflammation caused by distress.
- IF could strongly improve learning and memory function in distressful condition.

GRAPHICAL ABSTRACT



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ABSTRACT

Undesirable and desirable effects of stressors on the body are assigned to distress and eustress, respectively. Immune system and brain are the most susceptible parts to stressful conditions, whereas long-lasting alterations in putative immune proteins involved in tension such as corticosterone (CORT), interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF- α) can impact learning and memory. Intermittent fasting (IF) is a repeated regular cycle of dietary restriction with well-known beneficial properties on the body. The aim of this study was to identify the eustress effects of IF on cognitive function by assessing the critical inflammatory factors in chronic distress. Forty male mice were divided into four groups (n = 10/group). Distress and control normally received food and water, whereas IF and IF with distress groups were daily deprived of food and water for two hours. In the second week, the electrical foot shock was induced to distress and IF with distress groups. Finally, the cognitive functions of all mice were evaluated by Barnes maze, their blood samples were taken to determine the plasma level of CORT, IL-6 and TNF- α , and the removed brain and adrenal glands were weighed in the third week. A significant gain in plasma level of CORT, IL-6 and TNF- α with a considerable brain hypotrophy and adrenal hypertrophy was found in distress group, whereas IF caused a remarkable reduction of the plasma inflammatory factors, especially in IF with distress mice ($P \leq 0.05$). In conclusion, IF could improve cognitive function and preserve the brain against distress by regulation of inflammatory response pathway.

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Introduction

Stress was nominated as an illness by Hans Selye, however, it was only accepted as a unique concept to find the influence of environmental factors (stressors) on living beings in the 1990s [1]. Generally, chronic stress leads to an adaptation between organism and its environment [2,3], however distress disturbs homeostasis by its adverse effects on the heart [3], digestive system, and brain in the long term [4,5]. Brain messages are changeable and remade by stress to control anxiety, temper, and make right decision [4]. Moreover, stress is an intensive regulator of memory and learning functions [6,7] via the hypothalamic–pituitary–adrenal (HPA) axis [8]. The main part of the brain relevant to learning and memory is the hippocampus (HC) region, which is very sensitive to corticosterone and cytokines [9]. Therefore, brain has a central role in response to all favorable or unfavorable environmental changes for the transmission of the essential signals to all organs via immune system, endocrine, autocrine, and neural mechanisms [5]. Corticosterone is a well-known stress hormone [10]. In fact, it was overexpressed in distress conditions with hypertrophy of adrenal glands and subsequently leads to impairments in hippocampal and amygdala circuits, which play key roles in cognitive function [10].

IL-6 produced by the committed immune cells, is a critical factor in inflammation and subsequently neurodegeneration and brain dysfunction mediated by distress [10]. Besides, IL-6 and TNF- α , other important cytokine in inflammation, is a potent activator of the hypothalamic–pituitary adrenal axis, key element in communication with the neuroendocrine system, and glucocorticoid (e.g. corticosterone) production. Interestingly, this cytokine with its dual conflicting properties, pro- and anti-inflammatory, can alter cognitive function in stressful condition [11,12]. In contrast to distress, the positive responses in the body arise from eustress such as intermittent fasting (IF) [2,9,13]. IF is actually a food deprivation period, which is repeated between a fasting and non-fasting duration with no malnutrition effects [14,15]. The amelioration of neurodegenerative disorders, such as Alzheimer's disease [16,17], regulation of inflammatory responses [13] even in animals with systemic bacterial infection [18], reduction of risk factors for cardiovascular disease [3] and cancer [19] are some positive effects attributed to IF [13,15]. In addition, food deprivation may promote lifespan and brain functions even in the mice with high fat diet fasting [15,20]. There is no reference relevant to IF ability to manage distress. Therefore, with respect to the importance of prevention of learning and memory loss caused by distress, the aim of the current study was to evaluate the eustress effects of IF on cognitive function by assessment of the vigorous inflammatory factors; corticosterone, IL-6 and TNF- α during chronic distress (electrical foot shock).

Experimental

Animals

Forty male BALB/c mice (Pasteur Institute of Iran) with mean weight 25 g were used in this study. They were specifically assigned to four groups (n = 10/group); control, distress and IF as well as IF with distress [16,20]. *Animal experiments were performed based on Ethical Research Committee guidelines of Hormozgan University of Medical Sciences that comply with NIH guidelines (Registration no. 0436).*

Stress induction

Control and distress mice daily received enough food and water for 18 days, while the other groups were under food and water

deprivation for two hours (time: 12–2 pm) daily in the second week. Besides, at this week, while all mice were under sociopsychological stress in the communication box for one hour (time: 9–10 am), electrical foot shock (40 mV, 10 Hz) was induced for 100 s only for distress and IF with distress groups in the box [21].

Evaluation of cognitive function by Barnes maze

Barnes maze is a round platform (diameter, 92 cm) with 20 equal holes (diameter, 7.5 cm) on the circumference and the escape box ((30 × 30 × 20 cm) with some food placed under one of the holes. To determine the cognitive functions in the third week (15th to 18th day), the tool was located 120 cm above the floor. All mice were placed at the center of Barnes maze and examined their learning and memory functions one by one. The elapsed time for finding escape box in the maze was registered by a digital camera connected to a computer system with open control program (as a video-tracking software) [18]. Escape latencies of 15th–18th day were considered as criteria for learning and memory assessment.

Blood and tissue collection

After the last cognitive function assay (18th day), blood samples (Max. 1 mL) were taken from retroorbital sinus of all mice and diluted by 0.5 mL sodium citrate 1%. Finally, the mice were sacrificed and their adrenal glands and brains were removed and weighed.

Determination of TNF- α , IL-6, and corticosterone

TNF- α and IL-6 ELISA KITS were purchased from Diaclone Company (Besancon Cedex, France) and corticosterone ELISA was provided by DRG Company (Marburg, Germany). The plasma levels of these critical factors were measured exactly via the protocols stated by the manufacturer.

Statistical analysis

The data analysis was performed by SPSS version 17.0 (IBM Corporation, USA) with significant $P < 0.05$. The results were presented as mean \pm SD and statistical significance was assessed by ANOVA with Tukey's method (HSD). Based on the calculated P , all alterations of the determined parameters were compared between distress and other three groups.

Results

IF could significantly modify pathological effects of distress on adrenal glands and brain

The adrenal glands and brain of the mice were removed, dried, and weighed at the end of the study. Data analysis of weighing showed that there was a significant weight gain in adrenal glands between distress and the other groups, however IF could suppress hypertrophy of adrenal glands in IF with distress mice (Fig. 1A). Besides, a significant weight loss was found in the brain between distress and the other groups, IF could remarkably moderate the brain hypotrophy in the mice with distress (Fig. 1B).

IF led to reduce the plasma level of the stress hormone (CORT) in distressful condition

Distress significantly increased plasma corticosterone level without any notable alteration in the other groups. However, IF could firmly inhibit this elevation in the mice with distress (Fig. 2).

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