Behavioural Brain Research 292 (2015) 233–240

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Research report

TNF-alpha inhibition prevents cognitive decline and maintains hippocampal BDNF levels in the unpredictable chronic mild stress rat model of depression

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HIGHLIGHTS

- Unpredictable chronic mild stress (UCMS) impairs learning and memory in MWM and PAT.
- UCMS decreases expression of BDNF in CA1 and CA3 fields of hippocampus.
- Chronic administration of Infliximab prevents stress-induced memory impairment.
- Chronic administration of Infliximab prevents stress-induced reduction in hippocampal BDNF.

ARTICLE INFO

Article history:
Received 10 April 2015
Received in revised form 18 May 2015
Accepted 20 May 2015
Available online 23 June 2015

Keywords:
TNF-alpha
Chronic stress
Cognitive function
BDNF
Hippocampus

ABSTRACT

Previous findings have shown that patients with depression express higher levels of proinflammatory cytokines such as TNF-α and IL-6. We have recently found that Infliximab (a TNF-α inhibitor) decreased anhedonia and despair-like behavior in the rat unpredictable chronic mild stress (UCMS) model of depression suggesting that inflammation might play an important role in depression. An increasing number of studies suggest that inflammation is also associated with cognitive impairments. The current study aimed to investigate the effect of UCMS on the cognitive performance of rats and their hippocampal BDNF levels and the effect of chronic Infliximab (5 mg/kg/weekly, i.p.) treatment on these measures. Rats were subjected to different types of stressors daily for a period of 56 days to induce depression-like state. The UCMS resulted in impairments in spatial and emotional memory acquisition and retention with no effect on the level of locomotor activity. These behavioral effects of UCMS were accompanied by reduction in the level of BDNF in the CA1 and CA3 regions of the hippocampus. Chronic Infliximab treatment prevented the UCMS-induced cognitive impairments as well as the reduction in the levels of hippocampal brain-derived neurotrophic factor (BDNF). These results suggest that Infliximab improves the spatial and emotional memory impairments induced by chronic stress in rats likely through its effects on hippocampal function by modulating inflammation.

1. Introduction

An increasing number of studies suggest that the overproduction of proinflammatory cytokines by the activation of immune-inflammatory process is related to the pathophysiology of depression [1]. Convergent lines of evidence have consistently supported this claim. For instance, in the clinic many depressed patients were found to have increased levels of proinflammatory cytokines such as TNF-α and IL-6 [2]. Furthermore, antidepressant

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http://dx.doi.org/10.1016/j.bbr.2015.05.062
0166-4328/

compounds have been found to have anti-inflammatory effects in both depressed patients [3] as well as animal models of depression [4,5] and anti-inflammatory drugs, which block the production or activity of proinflammatory cytokines have been reported to exert antidepressant effects in clinical studies [6]. The relation between inflammation and depression suggested by these findings has been recently supported by a study that reported the anti-depressant efficacy of Infliximab in the UCMS rat model of depression [7].

Chronic mild stress does not only lead to depression-like behaviors suggesting alteration in affective processes but also impaired cognitive performance as assessed in several learning and memory paradigms such as Morris water maze and object recognition test [8–10]. Among the multiple neurochemical changes that occur in response to stressors, excessive inflammation processes is thought to play a major role in resultant cognitive impairments [11]. Several studies have indeed reported that exposure to stressors increased the release of TNF-α in the plasma [9] and that there is a relationship between inflammatory cytokines and various types of learning and memory [11].

The current study aimed to investigate the effect of anti-inflammatory Infliximab on UCMS-induced memory acquisition and retention impairments in the rat using passive avoidance and Morris water maze tests. This study also aimed to relate the behavioral effects with neurobiological processes by investigating the effect of UCMS and Infliximab on the levels of brain-derived neurotrophic factor (BDNF) in the CA1 and CA3 fields of hippocampus.

2. Materials and methods

2.1. Animals and standard procedures

Adult male albino Wistar rats (Kocaeli University, Experimental Medical Research and Application Center, Kocaeli, Turkey) weighing 300–400 g were kept in an animal colony at a density of approximately 5–6 per cage for 2 weeks prior to experimentation. All experiments were conducted between 9:00 a.m. and 12:00 p.m. under standard laboratory conditions (22 ± 2 °C room temperature; 12-h light/dark cycle with lights on at 7:00 A.M.). Tap water and food pellets were provided ad libitum. All rats used in this study were naive to the experimental tests, and different groups of rats were used in each experiment. The experiments were conducted in accordance with the Regulation of Animal Research Ethics in Turkey. The ethical approval was granted by the Kocaeli University Animal Research Ethics Committee (Project number 2012/8, Kocaeli, Turkey).

Animals were divided into three groups ($n = 12$ per group): Control, UCMS and UCMS + Infliximab. The Control and UCMS groups received physiological saline (intraperitoneally) and UCMS + Infliximab group received Infliximab (intraperitoneally, 5 mg/kg) weekly during 8 weeks of chronic mild stress treatment. The selected Infliximab dose was chosen based on previously reported studies. [7,12,13]. Behavioral tests started three days after the final injection and they were conducted on consecutive days in the following order: locomotor activity test, passive avoidance test, and Morris water maze test.

2.2. Drugs

Infliximab (Schering-Plough) was dissolved in physiologic saline. Drugs were prepared immediately prior to use and administered intraperitoneally (i.p.) to the rats in a volume of 0.1 ml per 100 g body weight.

2.3. Unpredictable chronic mild stress procedure

Unpredictable chronic mild stress (UCMS) has been widely used as an experimental animal model of depression-like disorders, and it is regarded to have resemblances to the unavoidable stressors of everyday life in humans [14]. UCMS was applied as previously described by Yazir et al. [15]. Briefly, both UCMS groups were subjected to different types of stressors: restraint for 4 h, cage tilting for 24 h, wet bedding for 24 h, swimming in 4 °C cold water for 5 min, swimming in 45 °C hot water for 5 min, pairing with another stressed animal for 48 h, level shaking for 10 min, nip tail for 1 min, and inversion of the light/dark cycle for 24 h. These nine stressors were randomly applied over 56 days, and each stressor was applied 4–5 times during this time period. Rats received one of these stressors per week day and the same stressor was not applied for two days in order to minimize the predictability of the occurrence of each stimulation. The stress procedure did not involve any food or water deprivation. The rats in the control group were not exposed to any of the stressors and had free access to food and water.

2.4. Locomotor activity test

Locomotor activity was assessed using a fully-automated animal activity monitoring system (Commat Ltd., Ankara, Turkey) composed of a Plexiglas chamber, a computer, and open field activity software. The Plexiglas chamber (42 cm × 42 cm × 30 cm) was equipped with 15 pairs of infrared photobeams and detectors were mounted horizontally every 2.5 cm (bottom) and vertically every 4.5 cm (upper). Interruptions of photocell beams were detected and recorded by the software. The total locomotor activity was measured as the sum of stereotypic, ambulatory, and vertical activities. The activity was monitored continuously for 10 min following acclimation to the test room for a period of an hour.

2.5. Passive avoidance test

A one-trial, light-dark passive avoidance apparatus (Ugo Basile model 7551, Italy) was used for evaluating emotional memory based on contextual fear conditioning paradigm [16]. In this task, the animal learns to avoid the compartment associated with an aversive stimulus. The latency to cross between compartments was used as an index of learning. The apparatus had two compartments (dimensions of each compartment were 22 × 21 × 22 cm). The illuminated white box was connected to the dark box. The dark box was equipped with an electrifiable grid floor that was used to deliver an inescapable electrical shock via a shock generator. A flat-box partition including an automatically operated sliding door at the floor level separated the two boxes.

A training trial was conducted as described by Monleón et al. [17]. On the first day of training (preacquisition trial), rats were placed individually into the light compartment and they were allowed to explore the boxes. The animal could move freely into the dark compartment after the door between the two boxes was opened (after 30 s). Fifteen minutes after the preacquisition trial, an acquisition (training) trial was performed. Rats were again placed in the light compartment of the passive avoidance apparatus. After 30 s of familiarization with the apparatus, the door between the compartments was opened. When the animal entered the dark compartment completely, the sliding door between the chambers was closed, followed by the delivery of an electric foot-shock (0.5 mA) for 3 s through the grid floor. The time taken to enter the dark compartment was noted as the training latency. The animals were then removed from the dark box and put back in their home cages. If the animal did not cross over to the dark compartment within 300 s, it was excluded from the experiment. In order to