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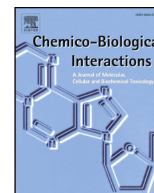

Dietary hydrogenated vegetable fat exacerbates the activation of kynurenine pathway caused by peripheral lipopolysaccharide immune challenge in aged mice

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ABSTRACT

Sickness behavior is a normal immune response of body to fight infection, accompanied by endocrine and behavioral alterations. Lipopolysaccharide (LPS) causes sickness behavior in rodents through the increase of proinflammatory cytokines, generating peripheral inflammation and thus overactivation of kynurenine pathway (KP). In the present study we investigated the effects of dietary hydrogenated vegetable fat (HVF) in sickness behavior induced by LPS in aged mice. Male C57BJ/6 aged mice received a supplementation with HVF for six months. After HVF supplementation mice were treated with LPS (0.15 mg/kg; i. p. injection). Twenty-four hours post LPS injection mice were submitted to behavioral tests and then, the hippocampus, striatum and prefrontal cortex were removed for neurochemical determinations. Our results showed that dietary HVF did not exacerbate the behavioral alterations induced by LPS. Although HVF did not modulate the proinflammatory cytokines analyzed, it caused a potentiation in the increase of brain tumor necrosis factor-alpha levels induced by LPS. Moreover, dietary HVF aggravated LPS-induced KP activation in the brain of mice, mainly by further increase of neurotoxic metabolite quinolinic acid and further decrease of kynurenic acid/kynurenine ratio, a marker of neuroprotective branch of KP. Overall, our study demonstrated that dietary HVF did not worsen the sickness behavioral induced by LPS administration. However, HVF aggravated the activation of KP and exacerbated the shift of KP metabolism towards the neurotoxic branch.

1. Introduction

Sickness behavior has been well described both experimentally and observationally, in a variety of animal species [1]. The sickness behavior, which is a normal immune response of body to fight infection, is manifested by reduced mobility, fatigue, cognitive impairment and inability to derive pleasure from otherwise enjoyable situations [2]. This endocrine and behavioral alterations is triggered by proinflammatory cytokines.

The lipopolysaccharide (LPS) is a component of the outer cell wall of gram-negative bacteria, and its administration has been used as a predictive model for sickness behavior in rodents [2]. LPS stimulates the immune system and induces a release of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, and interlukin-6 (IL-6) [3]. By this mechanism it generates an acute peripheral inflammation, which activates an immune response. The interaction between the immune system and central nervous system (CNS) is important for regulating the immunological, physiological, and behavioral responses to immune stimulation [4]. Likewise, an inflammatory response that is generated peripherally can affect the brain because cytokines can reach the CNS via neural and humoral pathways [5].

It has been demonstrated that proinflammatory cytokines in the CNS were able to activate the kynurenine pathway (KP). The kynurenine is a catabolite of the amino acid tryptophan, which is generated by catalytic action of the rate-limiting enzyme of KP indoleamine-2,3-dioxygenase (IDO) [6]. In the brain, IDO activation plays a key role in the development of depressive-like behavior [7]. Thus, KP metabolism

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has been related to neuroinflammation and diseases of the CNS.

The hydrogenated vegetable fat (HVF) is obtained basically from vegetable oils, by the hydrogenation process which generates trans isomers. The consumption of HVF has been steadily increasing since the 20th century and now accounts for 1.7–8% of the world dietary fat intake [8]. In fact, processed foods have been widely consumed in Western countries in recent decades [9]. Due to great increase of HVF consumption in the last decades, the number of studies began to increase as a result of the effect of this type of fat on human health and neurological diseases. It is well documented that dietary HVF can be quickly incorporated into membrane phospholipids, thus decreasing membrane fluidity and altering the biochemical properties as well the functionality of their proteins [10]. By altering membrane properties and functionality, HVF may contribute to CNS dysfunctions. Experimental evidence has reported that HVF is proinflammatory [11]. HVF can induce the increase of inflammatory eicosanoids and cytokines, which adversely influence mental health [12].

In this context, the objective of the present study is to investigate whether the consumption of HVF could exacerbates sickness behavior induced by peripheral administration of LPS in mice. Moreover, neurochemical parameters related to inflammatory status and KP activation were evaluated in the hippocampus, striatum and prefrontal cortex.

2. Materials and methods

2.1. Animals

Experiments were performed using male C57BJ/6 mice (30–40 g, 2 years old). The aged mice were used because age is the most predominant risk factor for the development of neurodegenerative diseases [13]. Our model induces a large neuroinflammation, which is involved in the etiology of several neurodegenerative diseases that affect the elderly population. Animals were maintained at 22–25 °C with free access to water and food, under a 12:12 h light/dark cycle, with lights on at 7:00 a.m. All manipulations were carried out during light phase on the day. All efforts were made to minimize animal suffering and to reduce the number of animals used. The procedures of this study were conducted according to the guidelines of the Committee on Care and Use of Experimental Animals Resources and with the approval of Ethical Committee for Animal Use (CEUA protocol # 010/2016) of Federal University of Pampa, Brazil.

2.2. Mouse treatments

Food was placed in dry-diet feeder jars to avoid significant food loss that often accompanies overhead pellet feeding, and the jars were weighed daily to determine the amount of food consumed. General animal health was also monitored during the test periods. Diet consisted of defined mouse diet AIN-93 M (Puro Trato, RS). This diet was isocaloric, isonitrogenous, 60.1% carbohydrate, 18.2% protein, 10.2% fat, and approximately 90% dry matter. The animals were divided into 4 groups: Control group (Corn oil + PBS), LPS group (LPS + Corn Oil), HVF group (HVF + PBS) and LPS/HVF group (LPS + HVF). The animals were supplemented by gavage (3 g/kg; p. o.) [14] with corn oil (control) or hydrogenated vegetable fat (HVF-rich in trans fatty acids) for 180 days [14]. The period of 180 days of HVF supplementation was determined by the previous study by Trevisol et al. [14]. Thus, the animals consumed hydrogenated vegetable fat almost 1/4 of their life, reproducing the chronic consumption of fat by elderly people. Aged animals in the HVF group were treated with the diet for 180 days prior LPS injection. LPS treatment involved an intraperitoneal injection of freshly made solutions of 0.15 mg/kg LPS (L-020M4062, serotype 0127:B8; Sigma, St. Louis, MO) prepared with sterile endotoxin free isotonic PBS or PBS (equivolume). This dose of LPS was chosen to induce sickness behaviors and cytokine activation at the time point of measurement, while still providing room for the potential of elevated responses. This range of LPS doses was selected based upon previous studies demonstrating that 0.33 mg/kg LPS produced prolonged sickness behavior in aged, compared to young mice and 0.02 mg/kg being the lowest dose capable of inducing statistically significant changes in sickness behaviors when compared to saline treated mice [15].

2.3. Body weight and locomotor activity

Sickness behavior was assessed by changes in body weight and locomotor activity (LMA) at 24 h after LPS injection. Decreased LMA in a novel environment is a sensitive measure of sickness behavior [16]. For this test, mice were individually placed into a clean, novel cage (30 L X 19 W × 12 H cm) devoid of bedding or litter, and LMA was video-recorded for a 5-min period. Videos were analyzed by dividing the cage into four virtual quadrants and counting the number of quadrant entrances over the 5- min period; counting was done by a trained observer who was blind to experimental treatments. Changes in locomotor activity and depression-like behavior were assessed 24 h after drug administration. We selected behavioral endpoints that we had already demonstrated to be very sensitive to systemic inflammation-induced sickness [17].

2.4. Corticosterone levels

Blood was collected on ice and separated in a refrigerated centrifuge at 4 °C (4000 g for 10 min). Serum was stored at −20 °C until assays were performed. Serum corticosterone levels were measured using a commercial kit based on enzyme immune assay (ELISA). The corticosterone levels were expressed as ng/l.

2.5. Sucrose preference test

Separate groups of mice were evaluated in sucrose preference test. At 24 h after treatment, anhedonia was measured by preference for a sucrose solution over water, using a two-bottle free choice method [18]. Each animal was presented simultaneously to two bottles, one containing 1% sucrose solution (w/v), and the other containing tap water. Blunted sucrose intake, in this test, is proposed to reflect impaired sensitivity to reward and model anhedonia, a core symptom of major depression [19]. Tap water and 1% sucrose solution were placed in premeasured bottles in the cages, and fluid intake was monitored for 24 h. Before the start of the protocol the mice were exposed only to a 1% sucrose solution for 24 h aiming the adaptation to sucrose solution. Mice were private food and water for about 20 h before each sucrose preference test. Sucrose preference was evaluated via the sucrose uptake rate, namely, the ratio of volume of sucrose consumption to the volume of sucrose consumption plus tap water consumption (sucrose preference = sucrose consumption/(sucrose consumption + water consumption) × 100%).

2.6. Tail suspension test

Mice were suspended 50 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail. The immobility time was recorded for 6 min. The immobility behavior was defined according to the method described previously [20].

2.7. Tissue preparation for neurochemical determinations

After behavioral tests, mice were euthanized with barbiturate overdose (pentobarbital sodium 150 mg/kg; i. p. route) and transcardiacally perfused with 10 ml ice-cold saline via the aorta. The brain dissection was performed according to the method of Spijker [21], a method to dissect multiple brain regions from a single brain based on existing atlases [22]. Prefrontal cortex, striatum and hippocampus were bilaterally removed and rapidly homogenized in 50 mM Tris–Cl, pH 7.4.

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