Brain, Behavior, and Immunity 61 (2017) 297–305

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

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

Full-length Article

Leptin receptor knockout-induced depression-like behaviors and attenuated antidepressant effects of exercise are associated with STAT3/SOCS3 signaling

Weina Liu, Jiatong Liu, Jie Xia, Xiangli Xue, Hongmei Wang, Zhengtang Qi *, Liu Ji *

Key Laboratory of Adolescent Health Assessment and Exercise Intervention of Ministry of Education, East China Normal University, Shanghai 200241, China
School of Physical Education & Health Care, East China Normal University, Shanghai 200241, China

ARTICLE INFO

Article history:
Received 24 November 2016
Received in revised form 24 December 2016
Accepted 5 January 2017
Available online 7 January 2017

Keywords:
Leptin receptor
Depression
Exercise
IKKβ/NFκB signaling
STAT3/SOCS3 signaling

ABSTRACT

Relatively little has been known about pathophysiological mechanisms contributing to the development of neuropsychiatric symptoms in the context of metabolic syndrome. Impaired leptin signaling activation in db/db mice has been proposed as a potential link between behavioral and metabolic disorders. Our previous studies have shown that exercise has the beneficial effects on a depression-like and insulin-resistant state in mice. The present study aimed to determine whether and how leptin receptor knockout (db/db) induces depression-like behaviors, and to identify the antidepressant effects of swimming exercise in db/db mice. Our results support the validity of db/db mice as an animal model to study depression with metabolic abnormalities, but fail to confirm the improvement of exercise on depression. LepRb knockout-induced depression-like behaviors are associated with STAT3/SOCS3 signaling but independent of IKKβ/NFκB signaling. Our findings suggest the potential importance of LepRb as an exercise-regulated target for depression, also representing a new target underlying treatment-resistant depression.

1. Introduction

Relatively little has been known about pathophysiological mechanisms contributing to the development of neuropsychiatric symptoms in the context of metabolic syndrome. Impaired leptin signaling activation in db/db mice has been proposed as a potential link between behavioral and metabolic disorders. The db/db mice, a mouse model of metabolic syndrome, display type II diabetes mellitus, obesity, hyperglycemia, hyperinsulinemia and insulin-resistance as a consequence of inactivating mutation for the gene encoding the long isoform of the leptin receptor LepRb (Chen et al., 1996). Consistent with the link between psychiatric and metabolic disorders, it has been shown that db/db mice exhibit behavioral abnormalities, including impairments in memory function and long-term potentiation (Li et al., 2002), as well as psychosis-like behaviors (Sharma et al., 2010). Depression is considered the major co-occurring psychological disorder with diabetes (Lin et al., 2004). The risk of depression in diabetic patients is approximately double compared to those without diabetes (Anderson et al., 2001). Recently, significant genetic overlap between depression and diabetes has been found in Swedish and Danish twin registries (Kan et al., 2016). Therefore, the first aim of the present study is to identify whether LepRb knockout (db/db) mice display depression-like behaviors, thus being employed as a useful model to study depression with metabolic abnormalities.

Converging evidence suggests that inflammation may be involved in the comorbidity of neuropsychiatric symptoms and metabolic syndrome. The db/db mice have been reported anxiety-like behaviors related to hippocampal inflammation (Dinel et al., 2011). Although db/db mice display blunted depression-like behaviors after lipopolysaccharide treatment, increased expression of inflammatory cytokines in hippocampus is shown to be associated with decreased hippocampal expression of brain-derived neurotrophic factor (Dinel et al., 2014), which is

Abbreviations: FST, forced swim test; GSK-3β, glycogen synthase kinase-3β; HDL, high density lipoprotein; IKKβ, inhibitor of κB kinase β; IL, interleukin; LepRb, leptin receptor; NFκB, nuclear factor kappaB; OFT, open field test; PTP1B, protein tyrosine phosphatase 1B; SPT, sucrose preference test; SOCS3, suppressor of cytokine signaling 3; STAT3, signal transducer and activator of transcription pathway 3; TG, triglyceride; TNF-α, tumor necrosis factor-α; TST, tail suspension test.

* Corresponding authors at: Key Laboratory of Adolescent Health Assessment and Exercise Intervention of Ministry of Education, School of Physical Education & Health Care, East China Normal University, 500 Dongchuan Road, Shanghai 200241, China.

E-mail addresses: qzht79@163.com (Z. Qi), lji@tyxx.ecnu.edu.cn (L. Ji).

http://dx.doi.org/10.1016/j.bbi.2017.01.001
0889-1591/

widely considered as an indicator of depression (Molendijk et al., 2014). In db/db mice, Panellus serotinus (Mukitake) can alleviate hepatic injury through the IKKβ(inhibitor of κB kinase β)/NFκB (nuclear factor kappaB) signaling pathway (Nagao et al., 2010). Similarly, the herbal extract can attenuate endoplasmic recticulum stress in db/db mice, via inhibiting IKKβ/NFκB pathway stimulated by tumor necrosis factor-α (TNF-α) Yeo et al., 2011. In hyperphagia-related obesity, hypothalamic IKKβ/NFκB signaling can be activated by inflammatory cytokines (Ropelle et al., 2010).

It has been recently reported that a possible mechanism for central leptin resistance may be a state of chronic inflammation in hypothalamus, in which signal transducer and activator of transcription pathway 3 (STAT3) is involved Lian et al., 2016. Phosphorylated STAT3 can reduce the activity of glycogen synthase kinase-3β (GSK-3β), thus to control hippocampal neurogenesis in stressed rats with leptin treatment (Garza et al., 2012). Suppressor of cytokine signaling 3 (SOCS3), a key inhibitor of STAT3-activated leptin signaling (Paz-Filho et al., 2015), is a classical indicator of cytokine signaling pathway (Lebel et al., 2000). The db/db mice have been reported increasing levels of SOCS3 and cytokines such as interleukin (IL) and TNF-α Dinel et al., 2011. The other intracellular factor that negatively regulates STAT3 signaling is protein tyrosine phosphatase 1B (PTP1B). In db/db mice, magnolia officinalis extract plays the role of anti-diabetic drug via targeted on PTP1B (Sun et al., 2015), which can be activated by TNF-α (Nieto-Vazquez et al., 2007). It is well known that inflammation is involved in both obesity and depression. Inflammation associated with obesity disrupts leptin hypothalamic action through IKKβ/NFκB regulation of SOCS3 (Zhang et al., 2008). Thus, we put forward the hypothesis that IKKβ/NFκB pathway combining with STAT3/SOCS3 pathway mediates leptin signaling in db/db mice, which may be a potential therapeutic target for neuropsychiatric and metabolic disorders.

Exercise is able to promote recovery of depressive patients and diabetic patients, but the mechanisms underlying its beneficial effects still remain unknown. Inflammatory cytokines are considered as predictors of antidepressant effects of exercise in depression (Rethorst et al., 2013). Our earlier study has demonstrated that swimming exercise inhibits inflammation activation, thereby ameliorates depression induced by chronic stress (Liu et al., 2013). We recently have confirmed that swimming exercise can improve both metabolic and inflammatory response in depression rats (Liu et al., 2015), and treadmill training can ameliorate the depression-like and insulin-resistant state induced by the co-treatment of high-fat diet and corticosterone in mice (Liu et al., 2014). Other studies show that swimming exercise suppresses hypothalamic IKKβ/NFκB activation induced by overnutrition, depending on the proinflammatory cytokine IL-6 (Ropelle et al., 2010). In addition, exercise improves metabolic signatures in db/db mice (Xiang et al., 2015), and decreases SOCS3 expression (Sarvas et al., 2015) and PTP1B activity (Ropelle et al., 2006). Therefore, the second aim of the current study is to investigate whether IKKβ/NFκB pathway combining with STAT3/SOCS3 pathway regulates the antidepressant effects of swimming exercise in db/db mice.

2. Materials and methods

2.1. Animals and groups

Male db/db (BKS.Cg-Dock7^{m} +/+ Lepr^{db}/JNju, n = 16) and non-diabetic lean control (C57BLKS/JNju, n = 16) mice between 3 and 4 weeks of age (18–40 g), purchased from Model Animal Research Center of Nanjing University (China), were housed with a 12-h light:dark cycle under controlled temperature (22 ± 2 °C) and humidity (50 ± 10%), and were given standard diet and water ad libitum. All mice were divided into four groups: wild type (WT), WT + Swim, LepRb knockout (KO), KO + Swim; n = 6–8 per group. All procedures were in accordance with the guidelines for the use of laboratory animals published by the People's Republic of China Ministry of Health (No. 55 order, January 25, 1998) and were approved by the Experimental Animal Care and Use Committee at East China Normal University (ECNU 2006-05).

2.2. Exercise protocol

As an innate ability of rodents, swimming exercise presents advantages over treadmill running; moreover, swimming requires an unelaborate device relative to treadmill running and spontaneous wheel exercise (Seo et al., 2014). Moreover, studies using this model revealed similarities in the adaptations to the exercise in relation to those observed in humans (Voltarelli et al., 2002; CA and Mello MA, 2001). Thus, swimming is the most used in exercise physiology studies and induces various changes in the functions of the brain (Ra et al., 2002). Mice were trained in a moderate swimming program with no weight loading in free style, the antidepressant effects of which have been validated by our previous studies (Liu et al., 2013, 2015, 2012) and other reports (Liu et al., 2010; Jiang et al., 2014). Daily swimming exercise was performed in a large glass water tank (100 cm(L) × 60 cm(W) × 80 cm(H)) at 32 ± 1 °C, a thermostat being used to maintain water temperature and an aquarium thermometer being stuck on the glass to present real-time temperature. The water depth was 60 cm so that the mice could not support themselves by touching the bottom with their feet; additionally, liquid soap was added to reduce surface tension and to abolish floating behavior (Mazzardo-Martins et al., 2010). The swimming was continuously supervised. The animals were swum as a group of six to eight mice, because it has been demonstrated that the intensity of swimming exercise was significantly raised by interaction among the animals (Iemitsu et al., 2004). The swimming program included two phases: adaptation and training. During the first week for adaptation, the training was graded beginning with 15 min on the first day until 60 min on the last day. The adaptation was aimed at reducing the water-induced stress without promoting physiological alterations in relation to the physical training (Contarteze, 2008). Then, the training period began with intensity of 60 min/day, 5 d/week, for a total of 4 weeks. Generally, swimming 1 h a day for 5 days a week is considered as moderate exercise, while swimming more than that is classified as strenuous exercise (Seo et al., 2014). Damghani et al. have suggested that only 14 days of swimming exercise (45 min/day, five days per week) is sufficient to reduce depression in rats (Damghani et al., 2016). Exercise was performed at the same time every day (between 9:00 and 11:00a.m.). After swimming, mice were toweled dry and kept warm by electric heater.

2.3. Behavioral testing

Except sucrose preference, a videocomputerized tracking system (DigBehav, Jiliang Co. Ltd., Shanghai, China) was used to record the behaviors of the animals. All testing equipment was thoroughly cleaned between each session.

2.3.1. Sucrose preference test (SPT)

The procedure was performed as described previously (Willner et al., 1987). Briefly, 72 h before the test mice were trained to adapt 1% sucrose solution (w/v): two bottles of 1% sucrose solution were placed in each cage, and 24 h later 1% sucrose in one bottle was replaced with tap water for 24 h. After adaptation, mice were deprived of water and food for 24 h, followed by the sucrose preference test, in which mice housed in individual cages had free access to two bottles containing 200 ml of sucrose solution (1%