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Treadmill exercise alleviated prenatal buprenorphine exposure-induced depression in rats

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ABSTRACT

Mounting evidence suggests that physical exercise shows health benefits in a range of diseases, including psychiatric disorders. Perinatal opioid exposure produces neurobehavioral abnormality, which includes depression symptoms, in patients and their offspring following chronic use of buprenorphine, a mixed agonist/antagonist with a high affinity to opioid receptors, for pain control. Previously, we demonstrated that prenatal buprenorphine exposure in pregnant Sprague-Dawley rats starting from gestation day 7 and lasting for 14 days caused the development of depression-like phenotypes in pups at postnatal day 21. Using the same prenatal buprenorphine exposure model, we further demonstrated that a 4-week course of moderate treadmill exercise conducted on pups starting from postnatal day 22 improved depression-like neurobehaviors. Prenatal buprenorphine exposure-induced neurobehavioral changes were accompanied by reductions of neuronal survival, neural stem cell-associated genes, plasma level of brain-derived neurotrophic factor (BDNF) and serotonin, phosphorylated tropomyosin-related kinase receptor type B (TrkB), phosphorylated extracellular signal-regulated kinase (ERK), PKA activity, phosphorylated cAMP response element-binding protein (CREB), and CREB DNA binding activity, as well as elevation of repressor element-1 silencing transcription factor (REST), oxidative stress, and inflammatory responses. Those changes in parameters of plasma and brain were improved by treadmill exercise. In conclusion, the findings of the current study suggest that a non-pharmacological option, i.e., moderate treadmill exercise, alleviated the development of depression-like neurobehaviors by resolving the oxidative and inflammatory burden as well as by enhancing neurochemical and neuroendocrine signaling.

Abbreviations: ANOVA, one-way analysis of variance; BDNF, brain-derived neurotrophic factor; CREB, cAMP response element-binding protein; ELISA, enzyme-linked immunosorbent assay; EMSA, electrophoretic mobility shift assay; ERK, extracellular signal-regulated kinase; FITC, fluorescein isothiocyanate; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; IL-1β, interleukin-1β; JNK, c-Jun N-terminal kinase; MAP-2, microtubule-associated protein 2; MDA, malondialdehyde; PKA, protein kinase A; REST, repressor element-1 silencing transcription factor; RT-PCR, reverse transcriptase polymerase chain reaction; SNAP-25, synaptosomal-associated protein 25; TBARS, thiobarbituric acid reactive substances; TrkB, tropomyosin-related kinase receptor type B.

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1. Introduction

Depression is a chronic mood disorder with a heterogeneous etiology. Social isolation, chronic stress, diseases, drug abuse, obesity, and menopause are risk factors in patients suffering from depression (Barichello et al., 2010; Hauser et al., 2011; Hong et al., 2015; Lee et al., 2015; Liu et al., 2012; Lu et al., 2014; Park et al., 2017; Roh et al., 2016). Genetic predisposition and dysregulation of neurotransmitter and neurohormonal pathways have been implicated in the pathogenesis of depression. Moreover, increasing evidence also highlights the pathogenic roles of inflammation, oxidative stress, and impaired neurogenesis in the development and progression of depression (Chung et al., 2013; Hariri and Holmes, 2006; Kim and Leem, 2014; Liu et al., 2013; Otsuka et al., 2016; Wang et al., 2016; Xu et al., 2006). Since the risk factors and pathogenic mechanisms of depression are multifactorial, a better understanding of its molecular and biochemical basis may be of practical value in the prevention and treatment of depression.

Clinically, tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors are therapeutic drugs that are routinely prescribed to patients with depression. However, adverse effects are the major concern with respect to their clinical application (Zhou et al., 2017). Nowadays, the use of physical exercise is increasingly becoming a non-pharmacological strategy for health promotion and as a therapeutic treatment, including psychotherapy. The beneficial effects of voluntary exercise have been reported in patients with depression and in rodent models of depression caused by glucocorticoid exposure, social isolation, chronic mild stress, stroke, obesity, and ovariectomy (Hong et al., 2015; Lee et al., 2015; Liu et al., 2012; Lu et al., 2014; Park et al., 2017; Roh et al., 2016). Experimental studies have further revealed that exercise has a role in neurogenesis, angiogenesis, apoptosis, inflammation, as well as oxidative stress, and exercise-induced expression of neurotrophins and neurochemicals was associated with substantially improved depressive symptoms (Boehme et al., 2011; Ferrira et al., 2011; Hong et al., 2015; Kiuchi et al., 2012; Lee et al., 2015; Liu et al., 2013; Lu et al., 2014; Moon et al., 2012; Shin et al., 2013; Speisman et al., 2013; Wang et al., 2016; Zhang et al., 2013).

Opioid-dependent patients often develop psychiatric disorders and depression is one such common complication with a poor prognosis (Rounsaville et al., 1982). Buprenorphine, a partial agonist of the μ-opioid receptor and an antagonist of the κ- and δ-opioid receptors, is prescribed as a maintenance therapy for opioid addicts (Alto and O'Connor, 2011). Although buprenorphine has been suggested to have an antidepressant-like effect, a wide range of clinical observations and rodent studies have demonstrated the reverse, i.e., the use of the drug was found to be closely associated with worse neurobehaviors, including depression-like phenotypes (Almatroudi et al., 2015; Blandthorn et al., 2011; Browne et al., 2015; Coyle et al., 2012; Jansson et al., 2011; Lund et al., 2013; Richards et al., 2017; Stein et al., 2015). These findings raise concerns about the potential adverse effects related to neurobehavioral development following buprenorphine treatment, particularly in pregnant mothers.

Our previous studies showed that prenatal buprenorphine exposure in pregnant rats caused a depression-like effect in weanlings (Hung et al., 2013; Wu et al., 2014). We also found treadmill exercise improved botulinum toxin-degenerated skeletal muscles (Tsai et al., 2012). The beneficial effects of treadmill exercise have been demonstrated in several types of disease models of depression (Hong et al., 2015; Kim and Leem, 2014; Lee et al., 2015; Otsuka et al., 2016; Roh et al., 2016; Wang et al., 2016), whereas, its effect on maternal depression has not been characterized. To extend the scope of relevant studies, we therefore undertook the present investigation to examine the effects of treadmill exercise on prenatal buprenorphine exposure-produced depression-like changes in rat weanlings and to identify the causative mediators involved.

2. Materials and methods

2.1. Animals and buprenorphine treatment

The protocols of animal experiments in this study were reviewed and approved by the Animal Experimental Committee of Taichung Veterans General Hospital. The pregnant Sprague-Dawley rats (200–250 g) (40 rats in total) were housed in a regular animal facility with a 12-hour light-dark cycle and free access to food and water *ad libitum*. On day 7 of gestation, these pregnant rats (20 rats per group) started to receive daily (9:00 a.m.) single intraperitoneal injection of buprenorphine (0 and 1 mg/kg in normal saline, Unichem Bhavan, Mumbai, India) for 14 days according to our previously reported protocols (Hung et al., 2013; Wu et al., 2014). After birth, the litters were kept separate and subjected to treadmill exercise starting from postnatal day 22. After the completion of treadmill exercise, subsequent analyses were done by randomly selecting 1 pup from each litter for each assay. Since our previous studies reported that prenatal buprenorphine exposure caused depression-like neurobehavioral change independent of gender (Hung et al., 2013; Wu et al., 2014), in this study the main focus of investigation was the female pups. Schematic diagram of study design is shown in Fig. 1.

2.2. Treadmill exercise

Normal saline- and buprenorphine-treated rats were divided into control and treadmill exercise subgroups (10 rats per subgroup). Pups were subjected to treadmill exercise for 5 days per week for 4 weeks in a treadmill apparatus (Model T306, Diagnostic & Research Instruments Co., Taoyuan, Taiwan). The speeds and durations of treadmill exercise were 2 m/min for the first 5 min, 3 m/min for the next 5 min, and then 4 m/min for the last 20 min with 0% grade. The pups of the control subgroup were kept on the treadmill without running for 30 min according to previously reported protocols with some modifications (Lee et al., 2015; Tsai et al., 2012).

2.3. Behavioral evaluations

The behavioral evaluation of the forced swimming test, tail suspension test, and locomotor activity were carried out in accordance with previously reported methods by a technician blinded to the treatments (Hung et al., 2013; Wu et al., 2014). For the measurement of the forced swimming test, animals were forced to swim for 5 min and the immobility time was recorded in seconds. In the tail suspension test, animals were individually suspended by the tail for 6 min and the immobility time was recorded in seconds. The spontaneous locomotion, including travel distance and moving time, was measured for a period of 30 min using an open field test.

2.4. Measurement of lipid peroxidation

At the end of the study, animals were euthanized and the tissues of the prefrontal cortex were collected. A thiobarbituric acid reactive substances (TBARS) assay kit (ZeptoMetrix, Buffalo, NY, USA) was used to measure the lipid peroxidation products, malondialdehyde (MDA) equivalents, according to the manufacturer's instructions.