Neuroscience Letters 618 (2016) 159–166

Contents lists available at ScienceDirect

Neuroscience Letters

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

Research paper

Antidepressant-like effects of sodium butyrate and its possible mechanisms of action in mice exposed to chronic unpredictable mild stress

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HIGHLIGHTS

- NaB has beneficial effects on mice exposed to chronic unpredictable mild stress.
- NaB reverses the depressive behaviors caused by chronic unpredictable mild stress.
- NaB increase 5-HT concentration in the hippocampus.
- NaB increases BDNF expression in the hippocampus.
- NaB up-regulates Occludin and ZO-1 levels, suggesting it restores BBB impairments.

ARTICLE INFO

Article history:
Received 27 October 2015
Received in revised form 24 February 2016
Accepted 2 March 2016
Available online 5 March 2016

Keywords:
Sodium butyrate
Chronic unpredictable mild stress (CUMS)
5-HT
BDNF
Blood–brain barrier (BBB)
Antidepressant

ABSTRACT

Sodium butyrate (NaB) has exhibited neuroprotective activity. This study aimed to explore that NaB exerts beneficial effects on chronic unpredictable mild stress (CUMS)-induced depression-like behaviors and its possible mechanisms. The behavioral tests including sucrose preference test (SPT), open field test (OFT), tail suspension test (TST) and forced swimming test (FST) were to evaluate the antidepressant effects of NaB. Then changes of Nissl's body in the hippocampus, brain serotonin (5-HT) concentration, brain-derived neurotrophic factor (BDNF) and tight junctions (TJs) proteins level were assessed to explore the antidepressant mechanisms. Our results showed that CUMS caused significant depression-like behaviors, neuropathological changes, and decreased brain 5-HT concentration, TJs protein levels and BDNF expression in the hippocampus. However, NaB treatment significantly ameliorated behavioral deficits of the CUMS-induced mice, increased 5-HT concentration, increased BDNF expression, and up-regulated Occludin and zonula occludens-1(ZO-1) protein levels in the hippocampus, which demonstrated that NaB could partially restore CUMS-induced blood–brain barrier (BBB) impairments. Besides, the pathologic changes were alleviated. In conclusion, these results demonstrated that NaB significantly improved depression-like behaviors in CUMS-induced mice and its antidepressant actions might be related with, at least in part, the increasing brain 5-HT concentration and BDNF expression and restoring BBB impairments.

1. Introduction

Depression is a mental disorder, which involves emotion, cognition, and physical symptoms with considerable morbidity and mortality [2]. It was frequently elicited by diverse factors, including psychological, social, environmental, genetic and metabolic factors [55,65]. World Health Organization (WHO) forecasts that depression will be the 2nd highest disease to threaten human's health [37]. Clinical depression is characterized by low mood,

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http://dx.doi.org/10.1016/j.neulet.2016.03.003
0304-3940/

anhedonia, reduced cognition, low or impaired psychomotor activity and sleep disturbance [22]. Currently, the typical antidepressant drugs in clinical treatment are mainly abided by the hypothesis of monoamine deficiency [15], neurotrophin deficiency [49] and hypothalamic–pituitary–adrenal (HPA) axis [42]. Several studies have shown that long-term exposure to chronic unpredictable mild stress (CUMS) may lead to decrease the level of serotonin (5-HT) in the hippocampus associated with memory deficits, and induce anxiety-like behaviors [26]. Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, most of the widely prescribed classes of antidepressants, have been a first-line pharmacological therapy for depression [20,64]. Additionally, several reports suggested that brain-derived neurotrophic factor (BDNF), which is related to synapses and neuronal development and maintenance, is involved in the pathophysiology and treatment of depression [49,59]. Indeed, several studies have indicted that the BDNF availability in brain areas was decreased in depressive patients, while treatment with antidepressants could elevate BDNF levels in the brain [44,62]. Hence, BDNF has been considered as a possible target for antidepressants. Recently, the blood–brain barrier (BBB) has been proposed to play a pivotal role in the pathophysiology of a variety of neurodegenerative disorders [34,56]. BBB breakdown is related to the occurrence of depressive behaviors and cognitive impairment [8]. Consistently, much strong evidence indicated that some neuroprotective agents can attenuate the decrease of hippocampal tight junctions (TJs) proteins such as Occludin and zonula occludens-1(ZO-1) expression [9,71]. Taking into account the facts that depression is associated with 5-HT, neurotrophic factor, and BBB mechanisms, natural, safe and effective antidepressant agents are under urgent need.

Sodium butyrate (NaB), a kind of histone deacetylase (HDAC) inhibitor [25], is known to possess multiple actions against a variety of behavioral deficits and morbid state [61,66]. It can cross the BBB to exert neuroprotective effects in neurodegenerative disorders [11,18,36] and cerebral ischemia/reperfusion injury [61], and also improve spatial learning and memory ability [19]. Previous studies have showed that NaB may possess antidepressant properties potentially, which were exhibited to alleviate cognition deficits[27], enhance neurotrophic expression including BDNF [57] and alter histone deacetylation regionally[17]. In addition, NaB treatment could increase the protein expression level of human (h) 5-HT1B receptors in HEK 293 cells and h5-HT1D receptors in C6 glioma cells approximately 3 fold [38]. Moreover, a previous research suggested that valproic acid, an HDAC inhibitor, is beneficial to modulating BBB dysfunction in cerebral ischemia on a rat model [69]. Although there are several reports showed that NaB may have an antidepressant effect, it is necessary to attempt to fully elucidate the molecular mechanisms of NaB against CUMS-induced depression.

Therefore, the present study was to investigate the antidepressant-like effects of NaB treatment in a mouse model of CUMS-induced depression. The behavioral tests such as sucrose preference test (SPT), open field test (OFT), tail suspension test (TST) and forced swimming test (FST) were evaluated the antidepressant effects of NaB. Meanwhile, we assessed brain 5-HT concentration and analyzed hippocampal TJs protein levels and BDNF expression to interpret the possible molecular mechanisms of its antidepressant effects.

2. Material and methods

2.1. Animal

Male C57BL/B6 mice weighing 20–25 g were obtained from the Wenzhou Medical University Experiment Animal Center. Each individual animal was fed in single standard plastic cage and maintained on a 12 h light/dark cycle at room temperature 23–25 °C and humidity 55% ± 5%. Normative laboratory food and water were freely available except during experimental procedures. Animals were acclimatized to the laboratory conditions for at least one week prior to use. All procedures involving animals were conformed to the guidelines of the Institutional Animal Care Committee of Wenzhou Medical University.

2.2. Drugs and treatment

NaB was purchased from sigma Co. Ltd, and Fluoxetine hydrochloride (positive control drug) was purchased from Eli Lilly and Company. NaB and fluoxetine were dissolved in 0.03% sodium carboxymethyl cellulose (CM C-Na). Mice were randomly divided into four groups (n = 10 per group): control group (Con), CUMS + 0.03% CM C-Na model group (CUMS), CUMS + 200 mg/kg NaB treatment group (NaB), and CUMS + 20 mg/kg fluoxetine treatment group (Flu). Every morning, all drug treatment groups were treated intragastrically at doses of 0.5 mL once daily for consecutive two weeks (the initial treatment was 15th day after exposed to CUMS).

2.3. CUMS procedure

The procedure of CUMS was performed as described previously [70], with a slight modification. All groups except for the Con group were exposed to CUMS. In brief, the CUMS protocol consisted of the sequential application of a variety of mild stressors: 24 h food and water deprivation, tail pinch, tilt cage, cold swimming, physical restraint, reversed light-dark cycle, soiled bedding, foot shot, heat stimulation and suspension. One of these stressors (in random order) was given every day for 4 weeks. The procedural sequence was performed as following (Fig. 1): (1) stress procedure: weeks 1–4; (2) drug treatment: weeks 3–4; (3) sucrose preference test (SPT): week 0, week 1, week 2, week 3, and week 4CUMS exposure; (4) open-field test (OFT): at day 28; (5) tail suspension test (TST): at day 29; and (6) forced swimming test (FST): at day 29.

2.4. Behavioral test

2.4.1. SPT

SPT is a measure of CUMS-induced anhedonia state, a key depressive-like behavior [42]. The test was performed at the week 0, at the end of week 1, week 2, week 3, and week 4CUMS exposure, as described previously [40], with minor modifications. The sucrose preference value was calculated as a percentage of the consumed 1% sucrose solution relative to the total amount of liquid intake.

2.4.2. OFT

OFT is a measure to evaluate the locomotion and exploratory behavior of mice (crossing: horizontal movement scores reflect range of motion; rearing: vertical movement scores reflect exploratory behaviors), as previously described [68].

2.4.3. TST

TST was performed based on the previous method [60] that the mouse was hung 25 cm above the floor by the tip of the tail (1 cm) tied up to the level. The immobility time was counted during a test period of 6 min (prior 1 min to adapt and recorded the last 5 min) using a chronograph. And only when the mouse hung passively and completely motionless, it could be regarded as immobile. Mice that climbed their tails during the trials were excluded from data analysis.