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Research report

Antidepressant-like effects of sodium butyrate in combination with estrogen in rat forced swimming test: Involvement of 5-HT_{1A} receptors

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ABSTRACT

Sodium butyrate (NaB), a histone deacetylase inhibitor, has been implicated in the antidepressant-like effects either injected as a single drug or in combination with selective serotonin reuptake inhibitor (SSRI), such as fluoxetine. Estrogen is also demonstrated to have antidepressant effect especially together with fluoxetine. We investigated whether NaB administered in combination with estradiol benzoate (EB) exerted antidepressant-like effect in forced swimming test (FST) in ovariectomized female rats. Furthermore, we detected the mRNA expressions of serotonin receptors and neuropeptides in hypothalamus, both of which participate in the mood disorder. Ovariectomized female SD rats were treated with vehicle, NaB, EB or NaB combined with EB for 7 days and then subjected to FST. The expressions of serotonin receptors (5-hydroxytryptamine receptor), corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) mRNA in the hypothalamus were detected by real time PCR. We found that co-treated with NaB and EB resulted in a significant decrease in immobility behavior in FST, a measure for depression-like behavioral. 5-HT_{1A} antagonist, WAY 100635, significantly block the antidepressant-like effects induced by NaB plus EB. The mRNA expression of the serotonin-1A [5-hydroxytryptamine 1A (5-HT_{1A})] receptor was increased in the co-treated group in hypothalamus, while there was no difference in the mRNA expression of 5-HT_{2A} or 5-HT_{2C}. The mRNA expression of CRH or AVP was not significantly altered either. In conclusion, NaB may exert antidepressant-like effects in combination with EB in ovariectomized female rats through 5-HT_{1A} receptor, via altering the expression of 5-HT_{1A} in the hypothalamus.

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1. Introduction

Increasing evidence reveal the gender difference in response to antidepressant treatment and the prevalence of depression [5,27,29], which indicates that sex hormones play a pivotal role in the affective disorders and in the response to antidepressant. Estrogen replacement therapy (ERT) is sometimes used as adjunctive therapy in the treatment of depression [14]. Numbers of clinical studies on perimenopausal women who suffered from mood disorders suggested the efficacy of ERT in depressed perimenopausal or postmenopausal women [8,38,40].

Not only can estrogen be used as antidepressant medication alone, but also can be administrated in combination with other traditional antidepressants, such as selective serotonin reuptake inhibitors (SSRI). And ERT is demonstrated to be effective in augmenting the effects of conventional antidepressants, to enhance the antidepressant action and to shorten the time to response, and to counter resistance to such treatment [14]. Increasing evidence in laboratory animals reinforce the antidepressant effects of estrogen combined with SSRI. A sub-active dose of estrogen was reported to facilitate two different kinds of traditional antidepressants, fluoxetine (FLX, an SSRI) or desipramine (DMI, a tricyclic antidepressant), in rat forced swimming test (FST) [10].

Deacetylation of hippocampal histone was reported to block the ability of the tricyclic antidepressant imipramine in mice exposed to chronic psychosocial stress [44]. Recently, sodium butyrate (NaB), a histone deacetylase (HDAC) inhibitor, has been implicated to exert antidepressant-like effects in male mice [41]. To our knowledge, there is no report on the antidepressant-like effect of HDAC inhibitor in female animals.

The FST is an animal model for screening of the effects of antidepressant [20,33,34], in which antidepressants induce a decrease in immobility [4,31]. Detke et al. pointed out that in addition to

Abbreviations: AVP, arginine vasopressin; CRH, corticotrophin-releasing hormone; EB, estradiol benzoate; FST, forced swimming test; HDAC, histone deacetylase; NaB, sodium butyrate; SSRI, selective serotonin reuptake inhibitor.

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immobility, it is also possible to infer which neurotransmitter system participates in the antidepressant-like action of drugs in FST, according to the other two active behavioral scores, swimming and climbing [7,20]. SSRIs such as FLX, paroxetine, or sertraline decrease immobility and increase swimming [7,25], while the selective noradrenergic and dopaminergic reuptake inhibitors, like DMI, maprotiline, and bupropion, decrease immobility accompanied by an increase in climbing behavior [7,15].

As we know, hypothalamic–pituitary–adrenal (HPA) axis and the serotonergic system play very important role in the stress system and mood disorders. The HPA system is the final common pathway in the stress response [1]. Hypothalamic arginine vasopressin (AVP) and corticotrophin-releasing hormone (CRH) are two major regulatory peptides in the HPA system. Previous studies revealed the increased vasopressin-expressing neurons in the paraventricular nucleus (PVN) of the hypothalamus in depression [35]. CRH neurons in PVN were also reported to be hyperactivated in major depression patients [30]. Serotonin receptors have a lot of subtypes, including 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C}, which are believed to be involved in stress system [6] and in the depression [3,18]. 5-HT_{1A} was reported to stimulate CRH and adrenocorticotropic hormone (ACTH) releasing, both of which were important components of the stress system [22,26]. Antagonist of 5-HT_{1A}, WAY 100635, was reported to block the antidepressant-like action of estrogens in the FST [11,12].

Besides, both HPA axis and serotonergic systems are regulated by the estrogens [13,39]. Estrogen is believed to regulate HPA axis activity. Estradiol increased CRH messenger RNA (mRNA) levels in the paraventricular nucleus of OVX female rats [28] and in monkeys [34]. The effect of estrogen on serotonin receptor mRNA expression depends on receptor subtype, brain area, and duration of treatment [2]. It was reported that hypothalamic 5-HT_{1A} receptor mRNA decreased in monkey following chronic estradiol treatment [19]. On the contrary, no change in 5-HT_{1A} receptor mRNA was found in hippocampus, dorsal raphe, prefrontal and cingulate cortex by 2-week estrogen supplementation [17]. In the study of Birzniece et al., 5-HT_{1A} receptor gene expression in the dentate gyrus and the CA2 region of the dorsal hippocampus was found to decrease after 2-week estradiol supplementation [2].

Hence, in this study by measuring the behavioral changes of FST, we aimed to investigate the antidepressant-like effects of NaB alone and NaB in combination with estrogen in ovariectomized female rats. Further, we focused on the alteration of HPA axis and the serotonergic system, which might participate in the behavior test.

2. Materials and methods

2.1. Animals

Adult female Sprague–Dawley rats (250–350 g) were housed in groups of 4/cage with food and water ad libitum, under 12-h light/dark cycle. Animals were allowed to acclimate to new housing for at least 5 days before experimental manipulation. All animal procedures were carried out in accordance with Institutional Animal Care and Use (IACUC) guidelines.

2.2. Surgery and treatments

Experiment 1: 37 rats in all were ovariectomized (OVX) under anesthetization with chloral hydrate (7%, 1.5 ml/250 g body weight). Three to four weeks after the surgery, rats received daily subcutaneous (s.c.) injections of vehicle (sesame oil; $n = 7$), NaB (1.2 g/kg, purchased from Sigma, USA; $n = 6$), EB (2.5 μg/rat, purchased from Sigma, USA; $n = 6$) or NaB (1.2 g/kg) in combination with EB (2.5 μg/rat) ($n = 6$) for 1 week. Three hours after the last injection, pre-test of the forced swimming test paradigm was carried out as described below. The rats not committed to forced swimming test ($n = 6$ for each group, non-FST) were decapitated 29 h after the last injection without the behavioral test, that is 2 h after the 5-min swimming test.

Experiment 2: 21 rats were ovariectomized under anesthetization with chloral hydrate (7%, 1.5 ml/250 g body weight). Three weeks after the surgery, rats were divided into three groups: vehicle (sesame oil, daily for 7 days) + saline injected 30 min before FST ($n = 9$), NaB (1.2 g/kg) in combination with EB (2.5 μg/rat) + saline injected 30 min before FST ($n = 6$) and NaB (1.2 g/kg) in combination with EB (2.5 μg/rat) + 5-HT_{1A} antagonist WAY 100635 injected 30 min before FST ($n = 6$).

2.3. Forced swimming test

The FST was carried out according to the method of Porsolt et al. [32,33] with some modification. The behavioral cylinder was 60 cm high and 25 cm in diameter maintained at 24–25 °C, filled with 30 cm of water, so that rats could not support themselves by touching the bottom with their paws or tail. The FST paradigm includes 2 sections: an initial 15-min pre-test followed by a 5-min test 24 h later. After each session, the rats were removed from the cylinders, dried with towels and placed into heated cages for 15 min, and then returned to their home cages. Test sessions were run between 13:00 and 16:00 h and videotaped for later scoring. Rats were considered to be immobile when they did not make any active movements. Struggling was considered when the rats make active movements with their forepaws in and out of the water along the side of the swim chamber. Swimming was considered when the rats make active swimming or circular movements.

2.4. Tissue collection

Rats were decapitated and the brains were removed 29 h after the last injection, which is 2 h after the 5 min-swimming test. (1) Hypothalamus: hypothalamic parts were dissected according to Forsling and co-workers [46] with the following limits: anterior border of the optic chiasm, anterior border of the mamillary bodies, and lateral hypothalamic sulci. The depth of dissection was approximately 3 mm. (2) Hippocampus: the rat brain was cut into two hemispheres. The hippocampal parts of the right hemispheres were rolled out with the spatula and were cut from the entorhinal cortex. All the dissections were performed on a glass plate full of iced 0.01 M phosphate buffered saline (PBS), placed on top of crushed ice. And all the tissues collected were quickly frozen in liquid nitrogen and preserved at −80 °C.

2.5. RNA isolation and real time PCR

Each frozen hypothalamus or hippocampus was homogenized, and total RNA was isolated using Trizol Reagent (Invitrogen) according to the manufacture's instructions. All the extracted RNA samples were digested by RNase-free DNase (Promega).

RT and PCR procedures were carried out separately. Equal amounts of total RNA (2 μg/each) were mixed with 1 μl oligo(dt) and heated at 72 °C for 5 min. Then 1 μl dNTP (10 mM) and 1 U RNase Inhibitor and 1× MMLV buffer were added and incubated at 37 °C for another 5 min. After chilled on ice, the mix was added with 1 U M-MLV and incubated at 42 °C for 60 min. The reaction was terminated at −20 °C for 10 min and stored at −80 °C.

Q-PCR was performed using SYBR Green PCR Kit (Applied Biosystems, USA) and an ABI Prism 7000 Sequence Detector system in 50 μl volume for 50 cycles. All the primers were shown in Table 1. The relative mRNA expression of target gene was calculated using the $2^{-\Delta\Delta Ct}$ method. All the relative amplification efficiencies of the primers were tested and shown to be similar.

2.6. Statistical analysis

The data are presented as means ± S.E.M. The significant difference between the means was calculated by one-way ANOVA followed by LSD post hoc test. Statistical significance was considered at the $P < 0.05$.

Table 1
Primers

β-Actin	F: 5′-TTGCTGACAGGATGCAGAA-3′ R: 5′-ACCAATCCACACAGAGTACTT-3′
5-HT_{1A}	F: 5′-CCGCACGCTTCCGAATCC-3′ R: 5′-TGTCCGTTCAGGCTCTTCTTG-3′
5-HT_{2A}	F: 5′-AACGGTCCATCCACAGAG-3′ R: 5′-AACAGGAAGAACACGATGC-3′
5-HT_{2C}	F: 5′-TTGGACTGAGGGACGAAAGC-3′ R: 5′-GGATGAAGAATGCCACGAAGG-3′
CRH	F: 5′-CAGAACAA CAGTGCGGGCTCA-3′ R: 5′-AAGGCAGACAGGGCGACAGAG-3′
AVP	F: 5′-CAGATGCTCGGCCCGAAG-3′ R: 5′-TTCCAGAACTGCCCAAGAG-3′

The primers used in real time PCR for mRNA expressions of ratβ-actin, serotonin receptor 1A (5-HT_{1A}), serotonin receptor 2A (5-HT_{2A}), serotonin receptor 2C (5-HT_{2C}), corticotrophin-releasing hormone (CRH), arginine vasopressin (AVP).

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