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Valsartan reverses depressive/anxiety-like behavior and induces hippocampal neurogenesis and expression of BDNF protein in unpredictable chronic mild stress mice

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ABSTRACT

Valsartan is a synthetic non-peptide angiotensin II type 1 receptor antagonist that dilates blood vessels and reduces blood pressure by blocking the action of angiotensin, and is safe and well tolerated in hypertensive patients. Population-based studies have suggested a positive role of sartans in reducing the risk of depression. This study aimed at investigating the effects of valsartan on unpredictable chronic mild stress (UCMS) mice by means of open-field test (OFT), novel-suppressed feeding test (NSF), tail suspension test (TST), forced swimming test (FST) and sucrose preference test (SPT). The effects of valsartan on antidepression/antianxiety, hippocampal neurogenesis and BDNF expression were evaluated in these behavior tests. Chronic administration of valsartan (5–40 mg/kg/d, p.o.) increased the time spent in the center of the field in OFT and the latency to eat in NSF, reduced the immobility time in both TST and FST, and increased the sucrose preference in SPT. A similar effect was observed in the positive control group of which the mice were treated with imipramine (30 mg/kg/d, i.p.) and tested by OFT, NSF, TST, FST and SPT. In this study, an impairment in hippocampal neurogenesis which parallelled with a reduced BDNF level in the hippocampus was observed in the mice that were treated with UCMS for 6 weeks. But the proliferation of progenitor cells and generation of new hippocampal neurons were restored after these mice were treated with valsartan (40 mg/kg/d, p.o.) for 4 weeks. These findings demonstrate that valsartan is an effective antidepressant/antianxiety reagent and can promote the hippocampal neurogenesis and expression of BDNF.

1. Introduction

Depression and anxiety are the most common mental health problems which affect a person's thoughts, behavior, feeling and physical wellbeing. Drugs that are used for treatment of major depressive disorder include selective serotonin-reuptake inhibitors (SSRIs), tricyclic antidepressants, monoamine oxidase inhibitors, and norepinephrine reuptake inhibitors. Although these antidepressant agents can produce a rapid increase of serotonin (5-HT) and/or noradrenaline (NA) at synaptic levels, it usually takes at least 3 to 4 weeks to obtain an appreciable clinical effect (Santarelli et al., 2003; Wong and Licinio, 2001). This delay suggests that slow neurochemical and structural changes have taken place in neurotransmitter systems within the monoaminergic projections of the target limbic areas.

The hippocampus is one major component of the limbic system that is implicated in the pathophysiology and treatment of mood disorders (Warner-Schmidt and Duman, 2006). An emerging hypothesis linking the modulation of hippocampal neurogenesis with the onset and subsequent treatment of depression and anxiety may provide an alternative explanation for successful behavioral changes that are induced by chronic antidepressant administration (Surget et al., 2011). Indeed, recent post mortem and brain imaging studies have revealed atrophy or loss of neurons in the prefrontal cortex and hippocampus of the patients who suffered with depression or anxiety (Shah et al., 1998). Stressful experiences, both physical and psychosocial, have been reported to decrease the proliferation of hippocampal subgranular zone (SGZ) progenitor cells and suppress the formation of hippocampal granule neurons among a number of mammalian species, and chronic antidepressant drugs administration can counteract this effect (Czeh et al., 2001). This counteraction is related with an increase in the expression of a neurotrophic factor, brain-derived neurotrophic factor (BDNF), and its primary receptor, tropomyosin-receptor-kinase B (TrkB) (Castren, 2004). These events seem to be necessary for mediating the therapeutic effects of antidepressants and regulating the survival and fate of the

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progenitor cells in the adult brain (Donovan et al., 2008). And the behavioral responses to antidepressants appear to be blocked if the induced neurogenesis is disrupted (Perera et al., 2011).

Clinically, mood disorders such as depression and anxiety have been linked to either increased or decreased activity of the brain renin–angiotensin system (Liu et al., 2012). Selective AT1 receptor antagonists have been increasingly used in treatment of hypertension and its complications (Gottdiener, 1999; Mueck et al., 1999). It should be noted that any adverse effects of these drugs on mood would be of great importance for all patients especially those that need to perform skilled activities as their routine work. However, very little is known regarding the effect of AT1 receptor antagonists on depression while they exert a clinical effect on hypertension and its complications. It was previously demonstrated that administration of valsartan, a prototype non-peptide AT1 receptor antagonist, prevents Aβ-related spatial memory reference deficits in the AD mouse model (Wang et al., 2007). And valsartan treatment increases the retention of a passive avoidance behavior and improves object recognition (Karwowska-Polecka et al., 1997).However, Karwowska's group also found that the selective ligand of AT1 angiotensin receptors losartan (1 μg given intracerebroventricularly) could abolish angiotensin II facilitation of recall of the passive avoidance, object recognition and the increase in apomorphine stereotypy in rats of both peptide treated group and control group. It is important to extend these findings and further investigate whether valsartan can reverse the neurogenic and behavioral effects in a rodent model of depression and anxiety. To address this, we studied the effects of valsartan on hippocampal neurogenesis and BDNF expression by using unpredictable chronic mild stress (UCMS) mice. Our findings demonstrate that administration of valsartan to UCMS animals significantly prevents the anxiety/depressive-like behavior and increases the hippocampal neurogenesis. These observations are corresponded with an increase in hippocampal BDNF protein level following valsartan treatment but not in response to the administration of imipramine. This suggests that valsartan has an effective antidepressive/antianxiety effect via promoting hippocampal neurogenesis and expression of BDNF in hippocampus.

2. Materials and methods

2.1. Animals

Male C57BL/6J mice (6–7 weeks old) were obtained from Nanjing Medical University (Jiangsu, China). The mice were housed in a temperature-controlled and humidity-controlled room with a 12-h light/dark cycle with free access to food and water. The experiments were conducted in accordance with the Experimental Animal Care and Use Committee of Nanjing Medical University and complied with the Guide for the Care and Use of Laboratory Animals (NIH publication, 8th edition, 2011).

2.2. Drugs

Valsartan and imipramine hydrochloride were bought from Sigma-Aldrich and dissolved in water containing 0.5% methylcellulose solution respectively. Valsartan (5–40 mg/kg/d) was administered by oral (p.o.) route in a volume of 10 ml/kg body weight using the gavage technique, and the corresponding control group was administered with water containing 0.5% methylcellulose by oral gavage. Imipramine (30 mg/kg/d) was administered by intraperitoneal (i.p.) route in a constant volume of 10 ml/kg body weight.

Five-bromo-2′-deoxyuridine (BrdU, Sigma-Aldrich, St. Louis, MO), a thymidine analog that is incorporated into the DNA of dividing cells during the S phase, was used to label the newborn cells. BrdU (50 mg/kg) was dissolved in 0.9% saline to a concentration of 10 mg/ml and was given by intraperitoneal injection (i.p.) every 8 h for 3 times on the first day of the third week of the chronic mild stress (CMS) treatment.

2.3. Assessment of blood pressure

Potential alteration in blood pressure in response to chronic treatment with valsartan was assessed with a commercial blood pressure analysis system designed specifically for small rodents (Hatteras Instruments). The mice were trained for at least 2 consecutive days to adapt to the apparatus before the study was initiated. To record the blood pressure, the mice were placed on a heated pad (35 °C) and measured with a programmable tail-cuff sphygmomanometer in steady state. The average of 10 readings from each mouse was recorded (Wang et al., 2007).

2.4. UCMS and behavioral testing

UCMS used in this study was designed as described previously (Nollet et al., 2011). In brief, the mice were subjected daily to various CMS procedures according to an unpredictable schedule for 6 weeks. The CMS protocol consists of the sequential application of a variety of mild stressors including restraint, forced swimming, water and/or food deprivation, and pairing with another stressed animal in wet sawdust, housing in wet sawdust, reversal of the light/dark cycle, and housing in constant illumination or darkness each for a period ranging from 10 min to 24 h in a schedule that lasts for 6 weeks. UCMS-induced modifications in mice were assessed using physical state (PS), body weight, immobility time in the tail suspension test (TST) and forced swimming test (FST), open field test (OFT), novelty-suppressed feeding (NSF) test and sucrose preference test (SPT). Pharmacological treatment started 2 weeks after the beginning of the UCMS protocol. Behavioral tests were performed in week 6, at least 24 h after the last treatment.

2.4.1. OFT

For OFT, the mice were individually placed in a cuboid Plexiglass box ($30 \times 30 \times 40$ cm^3) with the gray floor divided into 16 equal squares. The percent of the time that the mice spent in the center four squares (15×15 cm^2), the number of rearings and the total field crossings in all areas were calculated during a period of 5 min. After each trial, the plate was cleaned with 75% EtOH.

2.4.2. NSF

The NSF testing apparatus consisted of a plastic box ($50 \times 50 \times 20$ cm^3), the floor of which was covered with wooden bedding. NSF test procedure induces a conflict between the drive to eat and the fear of venturing into the center of brightly lit arena. NSF test was performed during a 5 minute period, as described previously (Surget et al., 2008). All of the food was removed from the home cage 24 h before the behavioral testing. At the time of testing, each mouse was placed in a corner of the box where a single pellet of food (regular chow) was placed on a white paper platform positioned in the box center. The latency to eat was recorded.

2.4.3. FST

The FST was carried out in a cylindrical container (11 cm in diameter; 25 cm high) filled with water to the height of 15 cm. The temperature of the water was maintained at 25 ± 1 °C. After swimming, animals were kept warm before they were returned to their home cage. Immobility times were recorded during the 5 minute swimming test using a digital video camera.

2.4.4. TST

The TST apparatus was a wood box ($25 \times 25 \times 30$ cm^3), and the front side of the box was open. Mice were suspended from the top of the box with their tail adhesive to a hook by adhesive tape. The trails were recorded for a period of 6 min by a digital video. The total duration of immobility during test was calculated as behavioral despair.

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