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EFFECT OF BRAIN-DERIVED NEUROTROPHIC FACTOR ON BEHAVIOR AND KEY MEMBERS OF THE BRAIN SEROTONIN SYSTEM IN GENETICALLY PREDISPOSED TO BEHAVIORAL DISORDERS MOUSE STRAINS

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Abstract—The effect of brain-derived neurotrophic factor (BDNF) on depressive-like behavior and serotonin (5-HT) system in the brain of antidepressant sensitive cataleptics (ASC)/Icg mouse strain, characterized by depressive-like behavior, in comparison with the parental nondepressive CBA/Lac mouse strain was examined. Significant decrease of catalepsy and tail suspension test (TST) immobility was shown 17 days after acute central BDNF administration (300 ng i.c.v.) in ASC mice. In CBA mouse strain, BDNF moderately decreased catalepsy without any effect on TST immobility time. Significant difference between ASC and CBA mice in the effect of BDNF on 5-HT system was revealed. It was shown that central administration of BDNF led to increase of 5-HT_{1A} receptor gene expression but not 5-HT_{1A} functional activity in ASC mice. Increased tryptophan hydroxylase-2 (Tph-2) and 5-HT_{2A} receptor genes expression accompanied by 5-HT_{2A} receptor sensitization was shown in BDNF-treated ASC but not in CBA mouse strain, suggesting BDNF-induced increase of the brain 5-HT system functional activity and activation of neurogenesis in ''depressive'' ASC mice. There were no changes found in the 5-HT transporter mRNA level in BDNF-treated ASC and CBA mice. In conclusion, central administration of BDNF produced prolonged ameliorative effect on depressive-like behavior accompanied by increase of the Tph-2, 5-HT_{1A} and 5-HT_{2A} genes expression and 5-HT_{2A} receptor functional activity in animal model of hereditary behavior disorders.

Keywords: brain-derived neurotrophic factor, brain 5-HT system, 5-HT_{1A}, 5-HT_{2A} receptor functional activity, 5-HT_{1A}, 5-HT_{2A} receptor, 5-HT transporter, tryptophan hydroxylase-2 genes expression, depressive-like behavior, catalepsy.

INTRODUCTION

Neurotrophic factors were originally identified for their roles in growth and development of the nervous system (Barde, 1990), but now are also considered to play an important role in the pathogenesis of many diseases of the nervous system including depression and, hence, are promising for the therapeutic application (Pittenger and Duman, 2008; Schmidt et al., 2008). Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family widely distributed in the brain with the highest level in the hippocampus (Yan et al., 1997). BDNF has attracted particular attention due to its possible antidepressant properties. It was shown that BDNF serum level is sensitive marker of antidepressant treatment efficiency in patients with depressive disorders (Brunoni et al., 2008; Hellweg et al., 2008; Lee and Kim, 2008; Sen et al., 2008). Chronic antidepressant treatment and electroconvulsive shock exerting antidepressive effects produced increase of BDNF expression in hippocampus and cerebral cortex in animal models of depressive-like states (Nibuya et al., 1995; Itoh et al., 2004; Rogoz and Legutko, 2005). BDNF administration into the hippocampus produced antidepressant effect in the standard behavioral models of depression – the learned helplessness and forced swim paradigms in rats (Shirayama et al., 2002).

Dysfunction of the brain serotonin (5-HT) system is known to be another risk factor of depression. There are a lot of data on implication of brain 5-HT in the mechanism of antidepressant drug action. Selective serotonin transporter (5-HTT) inhibitors (selective serotonin reuptake inhibitors, SSRI's) fluoxetine and citalopram are known to be clinically effective antidepressants (Lader et al., 1986; Kyle et al., 1998; March et al., 2004; Olfson et al., 2006). There are a lot of data demonstrating an increase in the brain BDNF level after chronic treatment with SSRI's (Nibuya et al., 1995; Castren, 2004; Balu et al., 2008). The reduction of 5-HT_{2A} receptor density in the frontal cortex with corresponding changes in the 5-HT_{2A} gene expression was found in the BDNF knockout mice (Klein et al., 2010). Chronic BDNF exposure resulted in a specific decrease in 5-HT_{2A} receptor protein level without any alteration in 5-HT_{1A} receptor protein level in hippocampal neuronal and slice cultures (Trajkovska et al., 2009). Central BDNF administration increased 5-HT and its metabolite 5-HIAA levels in the adult rats' brain structures (Siuciak et al., 1996).

In all these experiments the effect of BDNF on the 5-HT system of ''nondepressive'' animals was studied.

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Abbreviations: ASC, antidepressant sensitive cataleptics; BDNF, brain-derived neurotrophic factor; DOI, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; 5-HT, serotonin; 5-HTT, selective serotonin transporter; 8-OH-DPAT, 8-hydroxy-2-(di-n-propylamino)tetralin; rPol II, RNA-polymerase II; SSRI's, selective serotonin reuptake inhibitors; Tph-2, tryptophan hydroxylase-2; TST, tail suspension test.

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However, these BDNF effects may differ from its therapeutic effect in animals with behavioral and brain dysfunctions. At the same time, the interaction of the brain 5-HT and BDNF systems in depression is not clear.

Catalepsy or pronounced motor inhibition accompanied with a failure to correct an externally imposed awkward posture attracts particular attention due to its association with grave neurological and mental disorders (Sanberg et al., 1988; Singerman and Raheja, 1994; Weder et al., 2008; Daniels, 2009) and as negative consequence of chronic antipsychotic treatment (Caroff et al., 2000; Lee, 2007; Paparrigopoulos et al., 2009).

Hereditary catalepsy in antidepressant sensitive cataleptics (ASC) mice, created from CBA mice (Kondaurova et al., 2006; Kulikov et al., 2008), was significantly attenuated with chronic, but not acute imipramine (Tikhonova et al., 2006) or fluoxetine (Tikhonova et al., 2010a) treatment. At the same time, both acute and chronic administration of fluoxetine failed to reduce hereditary catalepsy in parental CBA mice (Tikhonova et al., 2010a). It was also shown that ASC strain differs from animals of the parental CBA strain by increased time of depressive-like immobility in the forced swim and in the tail suspension tests (TST, Bazovkina et al., 2005), deficit in the locomotion (Bazovkina et al., 2005), immunity (Alperina et al., 2007) and sexual motivation (Tikhonova et al., 2010b). ASC mouse strain has been proposed as a new animal model to study mechanisms of depression and antidepressants action (Popova et al., 2008).

The aim of the present study was to compare the effect of central acute administration of BDNF on: (1) depressive-like behavior; (2) functional activity of 5-HT_{1A} and 5-HT_{2A} receptors and expression of the 5-HT_{1A} and 5-HT_{2A} genes; (3) expression of the genes encoding 5-HTT and key enzyme of the brain 5-HT synthesis Tph-2 in the brain of mice genetically predisposed to psychopathology (ASC as a model of depressive-like behavior and cataleptic ''nondepressive'' mouse strain CBA).

EXPERIMENTAL PROCEDURES

Animals

The experiments were carried out on adult male mice of CBA/Lac and ASC/Icg strains. ASC strain was created in the Laboratory of Behavioral Neurogenomics, Institute of Cytology and Genetics as the result of prolonged breeding of hybrids between catalepsy-prone CBA/Lac and catalepsy-resistant AKR/J strains for high predisposition to catalepsy (Kondaurova et al., 2006; Kulikov and Popova, 2008). The ASC mice used in this study were 30th generation of breeding and highly inbred. All mice were about 8 weeks old, weighted about 25 ± 2 g and were housed under standard laboratory conditions in a natural light–dark cycle (12 h light and 12 h dark) with free access to water and food. Three days before experiment the mice were isolated into individual cages to remove the group effect. All experimental procedures were in compliance with Guidelines for the Use of Animals in Neuroscience Research, 1992. All efforts were made to minimize the number of animals used and their sufferings.

Drugs

Human recombinant BDNF (Sigma, USA) was diluted in sterile water and injected in a dose of 300 ng into left lateral ventricle of mouse (AP: −0.5 mm, L: −1.6 mm, DV: 2 mm; Slotnick and Leonard, 1975). Before central drug administration the animals were anesthetized during 20–30 s with diethyl ether. Sterile water was injected as a control (sham group). The volume of introcerebroventricularly administered solutions was 5 μl. 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT, Research Biochemicals Inc., USA) and 5-HT_{2A} receptor agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI, Sigma, USA) were dissolved in saline and administered intraperitoneally in a doses of 1 mg/kg to study functional activity of corresponding receptor.

Behavioral testing was started 17 days after BDNF injection.

Pinch-induced catalepsy

Catalepsy test was performed according to the early described procedure (Kulikov et al., 1993). Animals were firmly pinched between two fingers for 5 s at the scruff of a neck, placed on parallel bars, with the forepaws at 5 cm above the hind legs and then were released gently. The catalepsy duration was recorded in seconds from the instant when an animal was released to the instant when the animal shifted its front paws from the initial position on the upper bar or made gross body or head movements. The trial ended either when a mouse started to move or after 120 s of immobility. Every animal was submitted to 10 successive trials with 2-min intervals. Mice were kept in the home cages between the trials. The mouse was considered as cataleptic if the time of immobility was above 20 s in no less than 3 of 10 trials. We never observed seizures in BDNF-treated mice.

TST

For TST (Trullas et al., 1989) the animals were fixed and suspended by the tail using adhesive tape on the horizontal crossbar positioned at the 30 cm height. The time of complete immobility was evaluated during 6 min of the test.

Receptor functional activity estimation

The functional activity (sensitivity) of the 5-HT_{1A} and 5-HT_{2A} receptors was estimated 20 days after BDNF administration by means of specific physiological response to the activation of the corresponding receptor.

The 5-HT_{1A} receptor functional activity (sensitivity) was evaluated by intensity of hypothermic response on intraperitoneal administration of 8-OH-DPAT (1 mg/kg) (Overstreet et al., 1996). The body temperature was measured before and 20 min after the drug administration by means of a KJT thermocouple thermometer (Hanna Instruments, Singapore) with a copper-constantan rectal probe for mice (Physitemp Instruments, USA). The hypothermic reaction was expressed as the difference between initial body temperature and body temperature measured at 20 min after drug administration (delta t°C).

The 5-HT_{2A} receptor functional activity (sensitivity) was evaluated by the number of 5-HT_{2A} receptor-mediated head-twitches induced by intraperitoneal administration of DOI (1 mg/kg) (Green and Heal, 1985). The count of head-twitches was started 5 min after the drug administration and lasted for 20 min.

RT-PCR

Two days after the test for 5-HT_{2A} receptor functional activity animals were decapitated, brains were removed on ice and the frontal cortex, hippocampus and midbrain were dissected, frozen in liquid nitrogen and stored at −70 °C. Total RNA was isolated with phenol, guanidine isothiocyanate and chloroform, treated