

Acute stress effect on hypothalamus BDNF expression, monoamines levels and adrenal catecholamines in mouse lines differed by 5-HT1A receptor function

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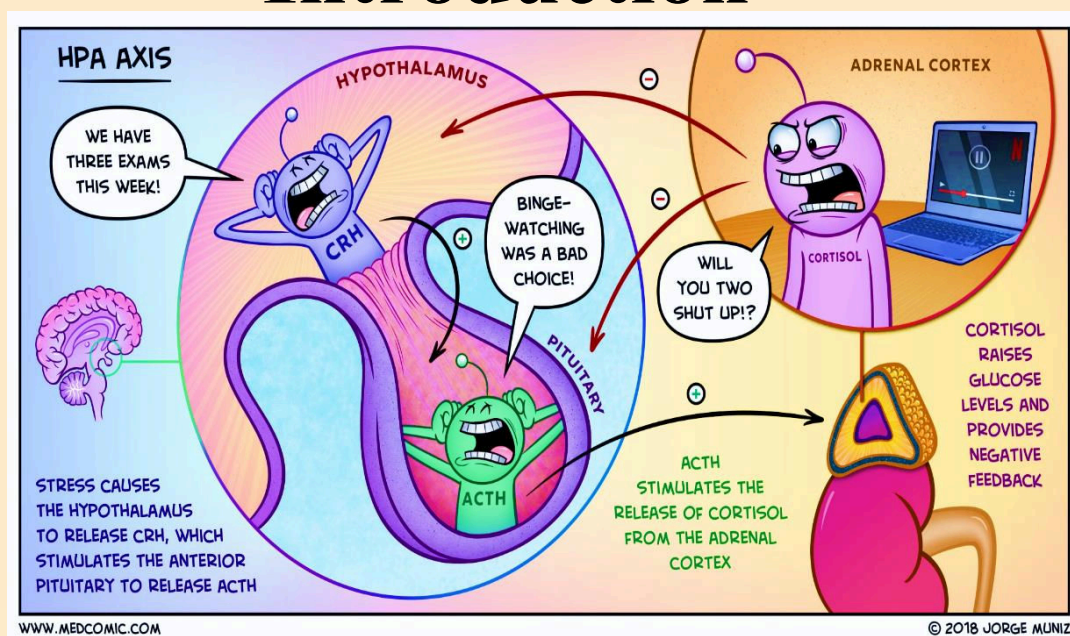
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Introduction



Stress is a normal and adaptive reaction to various threatening stimuli. Stress affects the hypothalamic-pituitary-adrenal (HPA) axis resulting in constant secretion of corticosterone from the adrenal gland (Pacák, Palkovits 2001, Morales-Villagrán 2013) & increase in the expression of the *c-fos* rapid response gene in brain neurons which is used as a marker for neuronal activity in the brain following exposure to stressful stimuli (Seo et al 2013). The brain serotonin (5-HT) system is involved in the regulation of a multiple forms of behavior (Jacobs, Fornal 1995), neuroendocrine regulation (Naumenko and Popova 1975) and the reaction to stress (Graeff 1993, Chaouloff 1993, Chaouloff et al 1999). Brain derived neurotrophic factor (BDNF) and its precursor proBDNF are considered to play an important role in the pathogenesis of many disorders of the nervous system. BDNF is suggested as stress-responsive messenger (Nibuya et al., 1995; Itoh et al., 2004; Rogoz and Legutko, 2005; Brunoni et al., 2008; Hellweg et al., 2008; Lee and Kim 2008; Sen et al., 2008) with high stress sensitivity. It is known to be involved in the regulation of hypothalamic neuropeptides (Tapia-Arancibia et al., 2004).

New recombinant B6.CBA-D13Mit76C and B6.CBA-D13Mit76B mouse lines on the base of C57Bl/6 genetic background, were created. The transfer of the fragment of chromosome 13 containing the 5-HT1A receptor derived from the catalepsy-prone CBA strain led to an increase in postsynaptic and decrease in presynaptic functional responses mediated by 5-HT1A receptors in B6.CBA-D13Mit76C mice (Kulikova et al 2016) Also it was suggested that B6.CBA-D13Mit76C genotype is more susceptible model to study the effects of acute stress. The B6.CBA-D13Mit76C mice showed the increased expression of the *Arc* gene in striatum and reduced expression of *Bdnf* gene in hypothalamus after exposure to stress in comparison to the control group (Kulikova et al 2017).

The aim of the present study was to evaluate the effect of acute stress (40 min) on BDNF, proBDNF protein, levels of monoamines in the hypothalamus and catecholamines in adrenal glands in mice of B6.CBA-D13Mit76B (control) and B6.CBA-D13Mit76C recombinant lines.

Materials and methods

Emotional stress



Real Time PCR

Western blot analysis

HPLC

Breeding of mouse lines

Two recombinant lines B6.CBA-D13Mit76C (B6-M76C) and B6.CBA-D13Mit76B (B6-M76B) were generated by transferring 102.73-110.56 Mbp fragment of chromosome 13 containing the 5-HT1A receptor derived from the catalepsy-prone CBA strain and catalepsy-resistant C57BL/6 strain to the C57BL/6 (B6) genome (Kulikov et al., 2003, Kulikova et al., 2016).

Emotional stress procedure

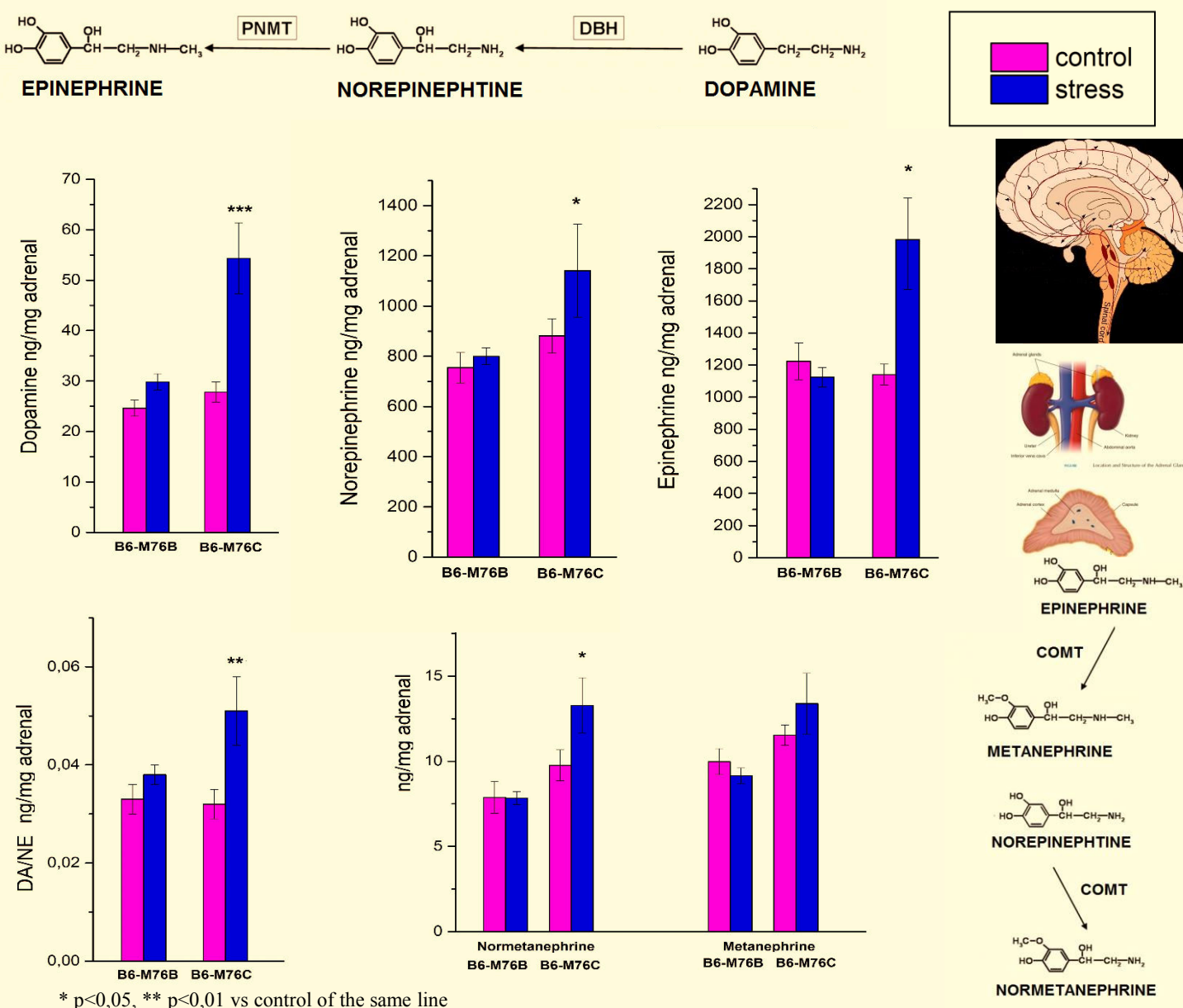
For the induction of emotional stress, mice were restricted for 40 min in small cylindrical metal cage (8.5 cm x 2.5 cm) with 48 ventilating openings of 0.4 cm in diameter. The restriction device allowed mice to stretch their legs but not to move within the tube

Statistical analysis

All values were presented as means \pm SEM and compared with two-way factorial ANOVA with genotype (B6-M76B vs. B6-M76C) and stress (intact vs. restricted) followed by the Fisher's post-hoc analysis. Statistical significance was set at $p < 0.05$

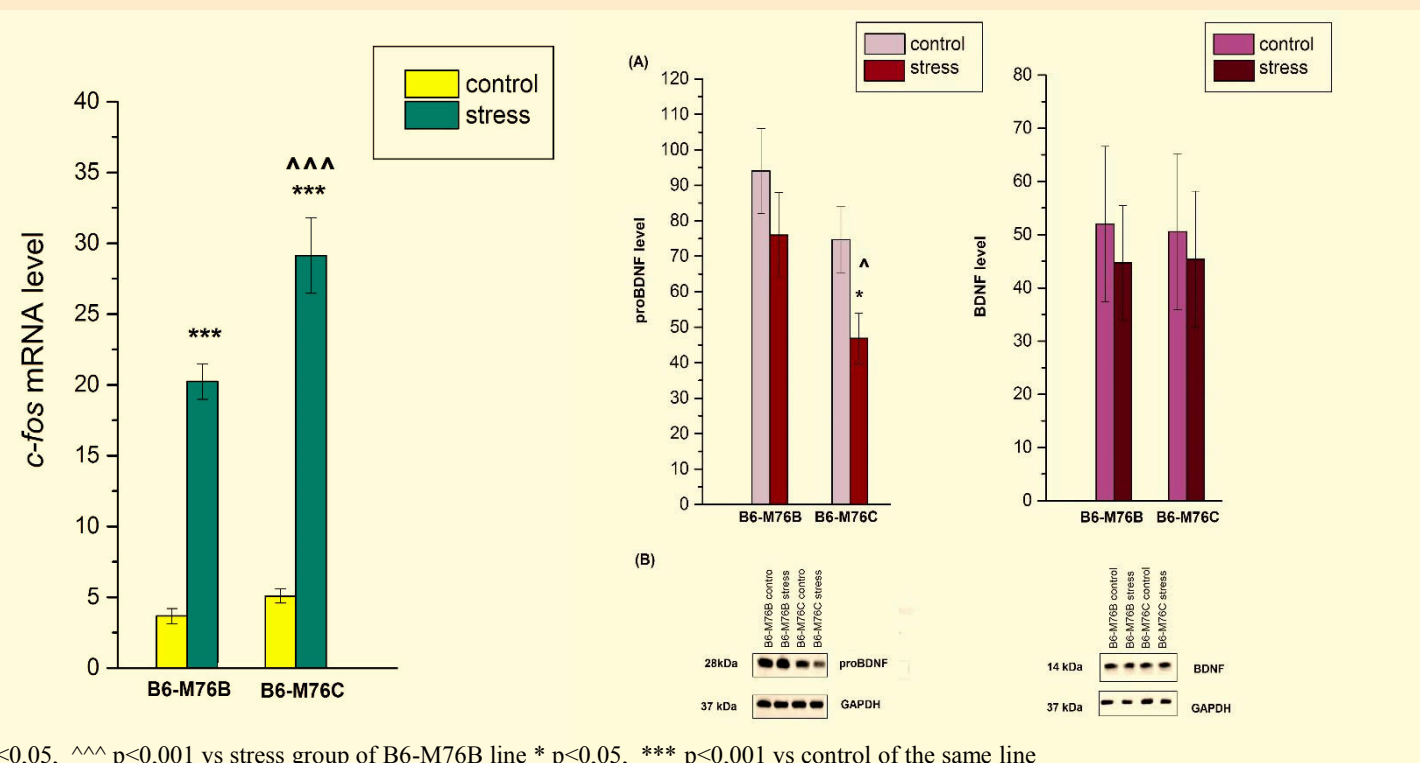
Results

Adrenal response to acute stress

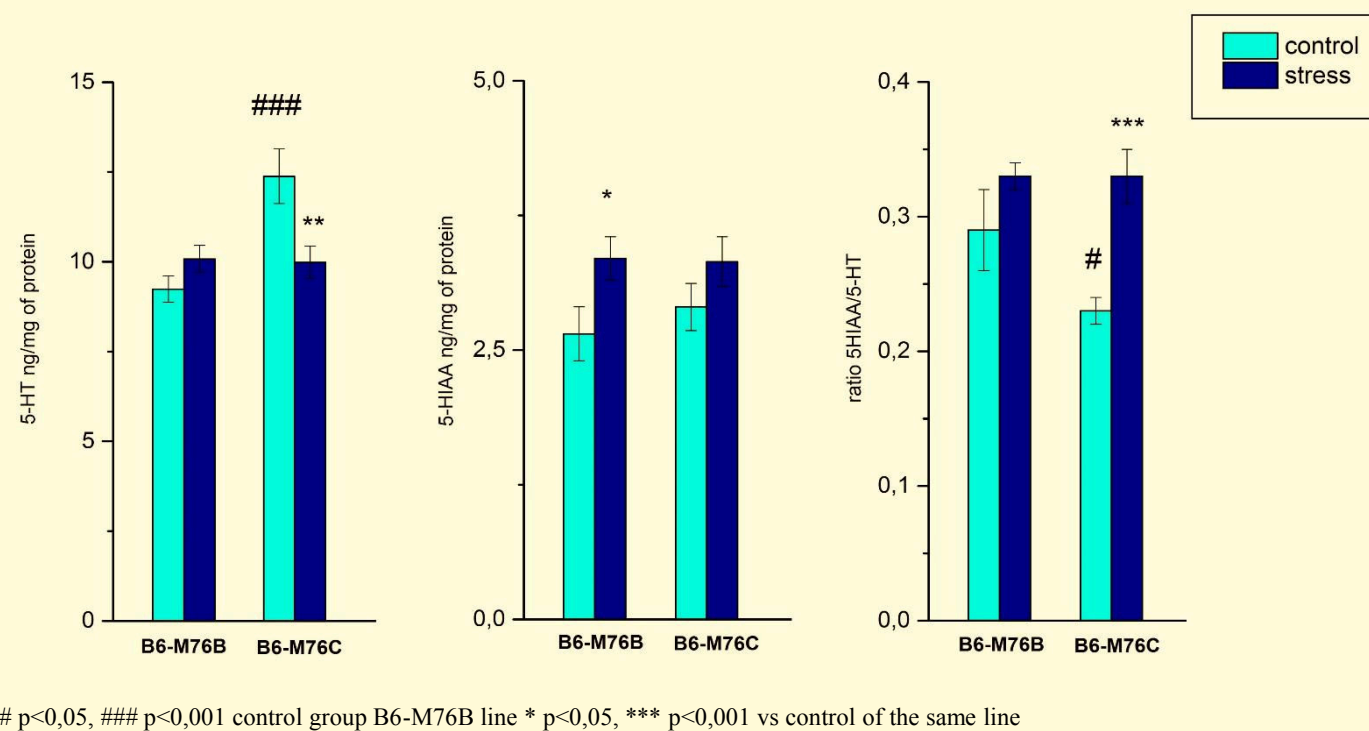


Acute restriction stress led to increase in the levels of dopamine (DA), norepinephrine (NE), epinephrine (E) and DA/NE ratio in the adrenal medulla only in B6.CBA-D13Mit76C mice compared with the corresponding control group. These differences are probably related to rapid conversion of NE into E in B6.CBA-D13Mit76C. Such changes in B6.CBA-D13Mit76C mice followed by stress probably indicate a higher sympathetic innervation of the adrenal gland.

Hypothalamus response to acute stress



Expression of *c-fos* gene was increased under stress condition in both lines compared with corresponding control groups but the B6.CBA-D13Mit76C mice after stress exposure demonstrated augmented expression of *c-fos* gene compared with B6.CBA-D13Mit76B mice. The proBDNF protein level was decreased in stressed B6.CBA-D13Mit76C but not in B6.CBA-D13Mit76B mice.



Acute restriction stress also led to increase of the 5-HIAA/5-HT ratio in the B6.CBA-D13Mit76C but not in B6.CBA-D13Mit76B mice.

The present study showed that the catecholamines of adrenal glands as well as BDNF and 5-HT systems in the hypothalamus were more susceptible to acute stress in the B6.CBA-D13Mit76C mice compared with B6.CBA-D13Mit76B. The B6.CBA-D13Mit76C mice represent considerable interest in the prospect of study of hypothalamic pituitary adrenal axis with hyperactive response to stress.

Conflict of Interests: the authors declare that there is no conflict of interests

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