

NEUROTROPHIC FACTORS AND INFLAMMATORY CYTOKINES IN THE MOTHER-PLACENTA-FETUS SYSTEM IN EXPERIMENTAL HYPERHOMOCYSTEINEMIA

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НЕЙРОТРОФИЧЕСКИЕ ФАКТОРЫ И ПРОВОСПАЛИТЕЛЬНЫЕ ЦИТОКИНЫ В СИСТЕМЕ «МАТЬ – ПЛАЦЕНТА – ПЛОД» ПРИ ЭКСПЕРИМЕНТАЛЬНОЙ ГИПЕРГОМОЦИСТЕИНЕМИИ

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An essential aspect of metabolic imbalance of L-homocysteine and its accumulation in blood (hyperhomocysteinemia) is its aggravating effect in pregnancy. However, little is known about the effects of maternal increased L-homocysteine levels on brain development of fetuses. In the development of the fetus, accompanied by changes in metabolism in the placenta, an important role belongs to neurotrophic factors and apoptosis. This study investigated the effects of chronic L-methionine administration on some parameters of inflammation and on neurotrophic factor levels in the brain of embryos, as well as in the placenta and serum of pregnant rats. The observed disturbances can be resulted from both a direct impact of L-homocysteine and its metabolites on the fetal CNS, and hyperhomocysteinemia-caused changes in normal state of the placenta.

Keywords: hyperhomocysteinemia; placenta; cytokines; neurotrophic factors.

Существенным аспектом метаболического дисбаланса L-гомоцистеина и его накопления в крови (гипергомоцистеинемия) является его негативные эффекты при беременности. Тем не менее, мало что известно о влиянии повышенного уровня L-гомоцистеина у матери на развитие мозга плода. В развитии плода, сопровождающемся изменениями обмена веществ в плаценте, важная роль принадлежит нейротрофическим факторам и апоптозу. В этом исследовании изучалось влияние хронического введения L-метионина на изменение некоторых показателей воспаления и уровней нейротрофических факторов в головном мозге эмбрионов, плаценте и сыворотке крови беременных крыс. Выявленные нарушения могут быть следствием как прямого воздействия L-гомоцистеина и его метаболитов на ЦНС плода, так и результатом изменений под влиянием гипергомоцистеинемии нормального функционального состояния плаценты.

Ключевые слова: гипергомоцистеинемия; плацента; цитокины; нейротрофические факторы.

Introduction. In the development of the fetus, accompanied by changes in metabolism in the placenta, an important role belongs to neurotrophic factors and apoptosis. Recently, certain adverse effects on the further development in the course of embryogenesis have been actively studied. It was shown that maternal hyperhomocysteinemia (HHC) is one of the pathological factors that can disrupt fetal brain development and cause persistent long-term effects in various systems of the growing organism (Shcherbitskaya et al., 2017).

In the literature, many investigations described the mechanisms of L-homocysteine (HC) effect causing the death of neurons. In addition, several authors demonstrated a pro-inflammatory state associated with HHC (Gori et al., 2005). Additionally, acute HC administration was reported to increase proinflammatory cytokine levels in the rat brain

and serum (da Cunha et al., 2010). The signaling pathways of cytokines, growth factors, and hormones are vital to the interchange between maternal and fetal cells in the placenta. Present in both the brain and periphery, neurotrophins play critical roles in placental and fetal development. IL-1 β was demonstrated to block induction of brain-derived neurotrophic factor (BDNF) (Barrientos et al., 2004), which is a critical player in normal neurodevelopment. Although mainly expressed in the nervous system, BDNF and its receptors, tropomyosin-related kinase B and p75NTR are localized in the placenta and have important functions during pregnancy (Briana et al., 2018).

This study aimed to examine associations of prenatal exposure to maternal HHC with levels of neurotrophic factors and inflammatory cytokines.

Materials and methods. Wistar rats were housed in a room with controlled conditions of temperature, humidity, and illumination (12/12h light/dark cycle). The animals were given ad libitum access to food and water. These animal studies were performed in accordance with the Directive No. 86/609 of the Council of European Communities. In our study, we created prenatal HHC by daily administration of L-methionine (0.6 mg/kg b.w.) to pregnant Wistar rats from the 4th day of pregnancy (E4) to delivery. We assessed the effects of maternal HHC on brain tissue of fetuses on 20th day of pregnancy (E20), as well as on the placentas and serum of the pregnant rats. BDNF and neuregulin-1 (NRG-1) levels were analyzed using Western blotting, the data obtained being normalized with use of β -actin. Cytokine (TNF- α , IL-1 β , and IL-6) measurement was performed with a commercial ELISA kit (R&D systems, USA).

Results. Decreased body and placenta weight characterized HHC embryos. The development of HHC was confirmed by increased HC serum level in rats at various stages of pregnancy. We also found increased HC level in the serum and brain of fetuses subjected to prenatal HHC on E20.

Additionally, we showed an increase in brain NRG1 and caspase-3 levels on E20, as well as in the level of proBDNF in the brain of fetuses subjected to prenatal HHC. This indicates the activation of

apoptosis in the brain of experimental rats during embryonic development. At the same time, despite the observed increase in IL-1 β level in the mothers' blood, there was found no increase in the level of proinflammatory cytokines in the pups' brain.

On E20 in the experimental group, we did not detect caspase-3 activation in the placenta. However, we could observe decrease in NRG-1 level and monoamine oxidase activity. In addition, we showed a high proBDNF expression level and an increase in the levels of pro-inflammatory cytokines including IL-1 β in the placenta of experimental pregnant rats. Being an inhibitor of methyltransferase, HC is known to be able to disrupt catechol-O-methyltransferase. The decrease in the placental activity of monoamine oxidase suggests the possibility of disturbance of the placental barrier for maternal biogenic amines, which can also cause disorders of fetal development, in particular the nervous system of the fetus.

Conclusion. The data obtained indicate that proposed HC-induced apoptosis of neuronal cells results in early developmental impairments of brain maturation, which might underlie long-term deficits in the offspring learning and memory processes. Metabolic changes observed may be due to the disturbances of placental functioning caused by increased HC content in the maternal organism.

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