DELAYED COGNITIVE DEFICIT AS A RESULT OF NEONATAL LIPOPOLYSACCHARIDE EXPOSURE: A PRESUMABLE IMPLICATION OF LONG-LASTING CHANGES OF NEUROPLASTIC GENE EXPRESSION

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Disorders of the CNS development at an early age caused by various types of perinatal pathology, such as infectious diseases, trauma, hypoxia and ischemia, often lead to the development of cognitive brain dysfunctions in adulthood. Proinflammatory cytokines play key role in these pathological processes and can affect the expression of genes involved in the regulation of neuroplasticity. This article describes the changes in the expression of fibroblast growth factor-2 (Fgf2), as well as genes encoding matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of matrix metalloproteinases-1 (TIMP-1), proteins that by intercellular matrix re-modeling are involved in the regulation of neuroplasticity.

Keywords: neonatal pathology; brain development; cognitive deficit; lipopolysaccharide; neuroplasticity.
is one of most widely used and comprehensively studied models of the cognitive and behavioural effects of early-life systemic inflammation [2, 3]. Low-dose postnatal LPS treatment is known to increase cytokine production, inhibit hippocampal long-term potentiation and impair various forms of memory and learning in adulthood [4, 5]. Yet, particular molecular mechanisms of the action of pro-inflammatory factors on the cells of CNS need more investigation to be fully elucidated.

One of possible mechanisms of long-term cognitive impairments evoked by early-life inflammation is an altered production of proteins that are involved in the regulation of brain neuroplasticity. In our previous studies on Wistar rats that were treated with moderately pyrogenic doses of LPS during the 3rd week of postnatal development, we focused on the prefrontal and hippocampal gene expression of fibroblast growth factor-2 (Fgf2) as well as matrix metalloproteinase-9 (Mmp9) and tissue inhibitor of metalloproteinases-1 (Timp1). As these particular genes are known to be implicated in both the development of CNS and memory formation, as well as their expression was described to be affected by inflammation-related events, we hypothesized these genes to react on the LPS treatment and serve as molecular mechanisms for abnormal brain maturation. We have found the LPS-treated animals to show decreased exploratory activity and increased static movement, impaired active avoidance learning and spatial memory formation compared to the control animals that were injected with saline [6, 7]. Impaired behavior was associated with decreased Fgf2 expression in the medial prefrontal cortex in comparison with vehicle-treated control. Adolescent and adult LPS-treated animals demonstrated increased anxiety-like behavior and decreased exploratory behavior in the open field arena. Gene expression of Mmp9 and Timp1 was differentially altered in the cortex and hippocampus of pups vs. adult untrained rats and remained unchanged in rats trained in either learning task, revealing that prolonged pro-inflammatory challenge during early postnatal development negatively affects the plasticity factors involved in memory acquisition in adulthood. These results suggest that an increase in cognitive stimulation might be an effective approach to reduce the negative effects of neonatal immune challenges on brain functioning. Supported by RFBR 17-04-02116.

References