DOI 10.1007/s11055-016-0252-7
Neuroscience and Behavioral Physiology, Vol. 46, No. 4, May, 2016

Expression of the *FGF2* and *TIMP1* Genes in the Adult Rat Brain after Administration of Interleukin-1β during Early Postnatal Ontogeny

A. N. Trofimov,[1] O. E. Zubareva,[1] A. P. Shvarts,[1] A. M. Ishchenko,[2] and V. M. Klimenko[1]

Translated from Rossiiskii Fiziologicheskii Zhurnal imeni I. M. Sechenova, Vol. 100, No. 9, pp. 1025–1037, September, 2014. Original article submitted July 4, 2014.

Hypotheses relating to the developmental nature of cognitive impairments in schizophrenia and other neuropathologies propose that the development of stable cognitive deficit involves important roles for hypoxia, trauma, and infections operating during the prenatal and early postnatal periods. These pathological states are accompanied by increases in the production of proinflammatory cytokine interleukin-1β (IL-1β) in cells of the nervous and immune systems. We report here studies of the characteristics of the expression of the *Fgf1* and *Timp1* genes, which are involved in regulating the cerebral mechanisms of neuroplasticity, in cells of the medial prefrontal cortex and the dorsal and ventral areas of the hippocampus in adult rats given IL-1β during early postnatal ontogeny. Experiments were performed in standard conditions and on acquisition of a conditioned active avoidance reflex. Learning impairments in experimental animals were accompanied by decreased production of FGF-2 mRNA in cells of the medial prefrontal cortex and ventral hippocampus. There were no differences between groups in conditions without cognitive loading.

Keywords: interleukin-1β, FGF-2, TIMP-1, early ontogeny, conditioned active avoidance reflex, learning.

Proinflammatory cytokines – interleukin-1β, interleukin-6 (IL-1β, IL-6) and tumor necrosis factor α (TNF-α) – play a key role in the processes of neuroimmune integration and the regulation of motivational states and homeostatic reactions [4, 5]. Studies in recent years have demonstrated that these substances also have effects on cerebral neuroplasticity processes [39]. IL-1 receptors are present in the hypophysis and cerebral cortex, with maximal densities in the dentate fascia of the hippocampus [8]. IL-1β alters long-term potentiation in hippocampal field CA1 neurons [10] and field CA3 neurons [36] and has dose-dependent effects on learning and memory in adult animals [27]. Less is known about the effects of proinflammatory cytokines on the formation of cognitive functions and the cerebral mechanisms of neuroplasticity in early postnatal ontogeny. The relevance of this question arises from the fact that impairments to cognitive functions in children, adolescents, and even adults are often due to various pathological states experienced in early childhood and accompanied by increases in blood and urine IL-1β, IL-6, and TNF-α levels (perinatal hypoxia, infections, birth traumas) [7, 20]. Results of studies using administration of IL-1β, IL-6, and TNF-α synthesis inducers in early ontogeny (bacterial lipopolysaccharide (LPS), polyinosinic:polycytidylic acid (poly I:C)) have led various authors to propose a hypothesis for the role of proinflammatory cytokines acting in the brain at the early stages of development in the formation of cognitive deficit in schizophrenia [41]. However, this hypothesis as yet lacks experimental confirmation.

We have previously described impairments to conditioned reflex activity and spatial memory in rats with increased IL-1β levels during the third week of life [3, 6].

[1] Research Institute of Experimental Medicine, North-Western Branch, Russian Academy of Medical Sciences, St. Petersburg, Russia; e-mail: alexander.n.trofimov@gmail.com.
[2] State Research Institute of Specially Pure Biopreparations, Russian Federal Medical-Biological Agency, St. Petersburg, Russia.

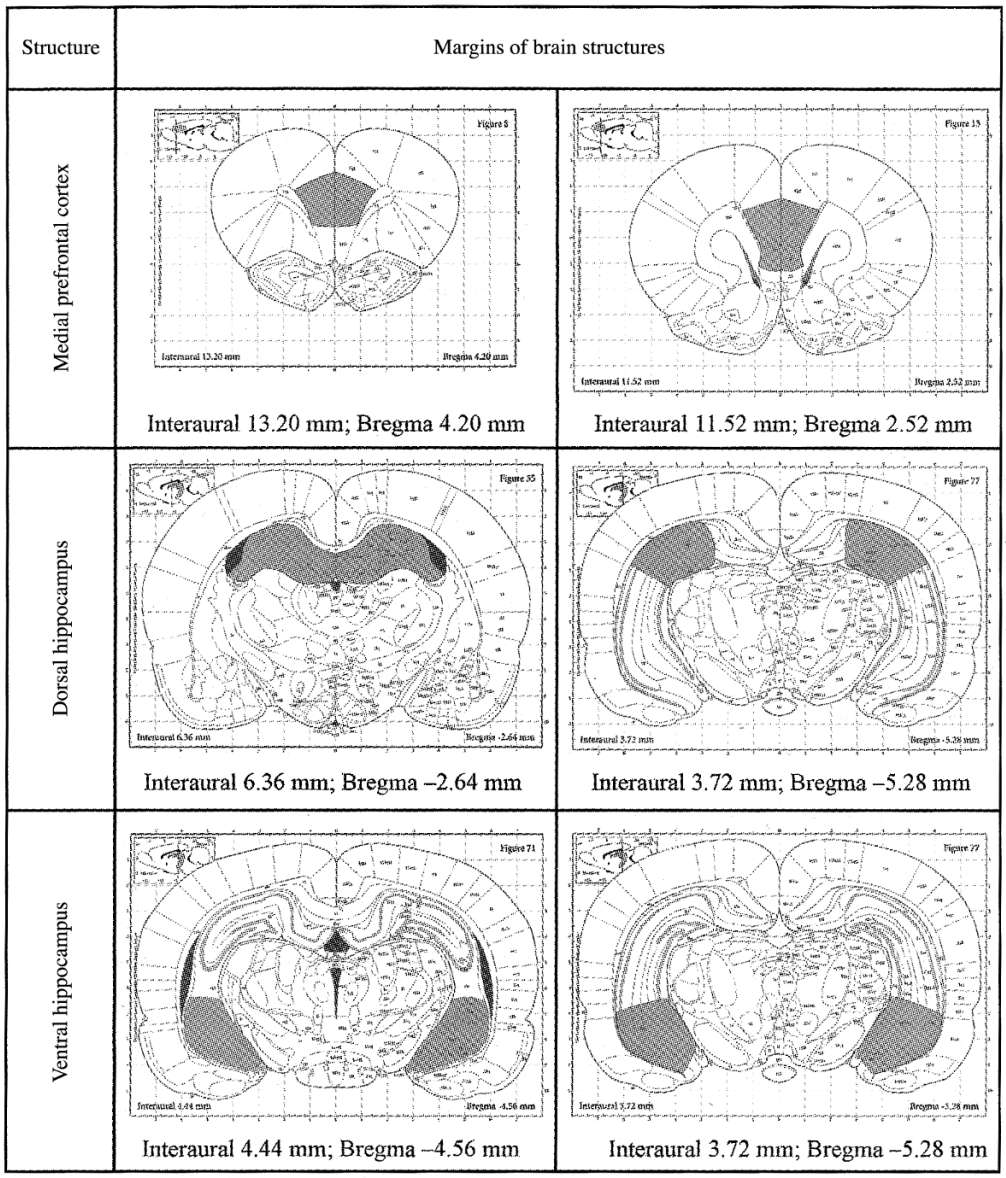

Fig. 1. Diagram showing the brain structures studied (gray areas) [43].

It was suggested that one of the mechanisms of these impairments may consist of changes in the expression of genes involved in regulating neuroplasticity processes in cells in brain structures with key roles in performing cognitive functions. With the aim of verifying this hypothesis, we report here our studies of the expression the gene for fibroblast growth factor 2 (FGF 2) – a growth factor playing a key role in the differentiation and proliferation of central nervous system cells – and the gene for the extracellular matrix protein tissue metalloprotease type 1 (TIMP-1). Both of these proteins are involved in the regulation of learning and memory processes [13, 28, 34, 52]. The synthesis of these proteins, like IL-1β production, increases in brain cells in response to infectious diseases [12, 37, 46] and hypoxia [9, 25], though in contrast to the proinflammatory cytokines involved in neurodegenerative processes, FGF-2 and TIMP-1 operate as neuroprotectors in these states [25, 49]. IL-1β has been shown to have a direct stimulatory action on FGF-2 production in hippocampal cells [45] and on TIMP-1 production in astrocytes [50]. Finally, both of these proteins have been discussed in relation to possible roles in the pathogenesis of schizophrenia [14].

Methods

Experiments were performed on 26 male Wistar rats in compliance with humanitarian principles (European Community Directives No. 86/609 EC) and were approved by the local ethics committee of the Research Institute of Experimental Medicine, North-Western Branch, Russian

TABLE 1. Nucleotide Sequences of Primers and Probes for Polymer Chain Reactions

Gene	Oligonucleotide	Sequence
Gapdh	Direct primer	5′-TGCACCACCAACTGCTTAG-3′
	Reverse primer	5′-GGATGCAGGGATGATGTTC-3′
	Probe	5′-R6G-ATCACGCCACAGCTTTCCAGA-BHQ2-3′
Timp1	Direct primer	5′-CTGGCATAATCTGAGCCCTG-3′
	Reverse primer	5′-GCAAAGTGATCGCTCTGGTAG-3′
Fgf2	Direct primer	5′-TCAAGGATCCCAAGCGGCTCTACT-3′
	Reverse primer	5′-CACTCCCTTGATGGACACAAC-3′

Academy of Medical Sciences. Animals were kept in standard conditions with free access to food and water. The light regime was operated automatically: day was from 10:00 to 22:00 and night was from 22:00 to 10:00. Litters contained equal numbers of rats. Animals of each litter were divided into groups which received recombinant human IL-1β (Institute of Specially Pure Biopreparations) at the moderately pyrogenic dose of 1 μg/kg (experimental group, $n = 13$) or apyrogenic physiological saline (control group, $n = 13$). Doses were given as daily courses from day 15 to day 21 of life. The treatment periods was selected as the period critical for the action of IL-1β on the forming cognitive functions of the brain [2, 3].

The animals' learning ability and biochemical parameters were studied at age 70–80 days. Two series of experiments were performed. The first series compared the levels of FGF-2 and TIMP-1 mRNA production in cells of brain structures in control and experimental animals not subjected to cognitive loading. In the second series, the same parameters were measured in rats trained to a conditioned active avoidance reflex (CAAR).

The CAAR was developed in a shuttle box of size 40 × 30 × 55 cm consisting of two identical sectors with electrode floors at different levels. Animals received electrocutaneous shocks (the unconditioned stimulus) 5 sec after exposure to the conditioned signal (a light), causing the animal to move into the other sector. Currents of 0.4–0.6 mA were used (selected individually on the basis of the animal's reaction). Intertrial intervals were 20–40 sec. Reactions were regarded as correct when animals moved in response to the conditioned stimulus before onset of the painful stimulus. On experimental day 1, rats were given the opportunity to explore the chamber for 5 min and were then presented with 10 combinations of the conditioned and unconditioned stimuli. Animals were presented with 20 combinations on each of the next four days. The number of correct reactions was assessed on each experimental day. At the processing stage of the model, most intact animals trained using this scheme were found to achieve the learning criterion (70% correct responses) by training days 6–7. As the study task was to identified differences in the expression of the *Fgf2* and *Timp1* genes during learning in control and experimental rats, analyses were performed on training day 5, when formation of the conditioned reflex was still continuing.

Brains were harvested from a number of randomly selected animals 2 h after the last training session; brains were quickly frozen and stored at a temperature of –70°C. The medial prefrontal cortex (mPFC) and the dorsal and ventral parts of the hippocampus (DH, VH) were identified on slices prepared using a Thermo Scientific MICROM HM 525 cryostat microtome using a scheme based on the *Atlas of the Rat Brain in Stereotaxic Coordinates* [43] and shown in Fig. 1. The need for differential analysis of these two areas of the hippocampus arose from their different roles in the learning process [18] and the greater LPS sensitivity of cells in the dorsal hippocampus than the ventral [32].

Total RNA was extracted from brain structures using TRI reagent (Molecular Research Center, Inc., USA) on ice in sterile conditions.

Levels of gene expression were assessed using the real-time polymerase chain reaction on a CFX96 Touch™ Real-Time PCR Detection System (Bio-Rad, USA) amplifier. SYBR Green technology was used to identify expression of the *Timp1* gene (GenBank NM_053819) and *Fgf2* (GenBank NM_019305) and TaqMan technology to identify the level of mRNA for the reference gene *Gapdh* (GenBank NM_017008). Primer and probe sequences are shown in Table 1 and were synthesized by Alkor-Bio company (St. Petersburg, Russia). Each sample was analyzed in duplicate. When using the SYBR Green method, the polymerase chain reaction was followed by analysis of melting curves. Relative *Fgf2* and *Timp1* expression was calculated using the $2^{-\Delta\Delta Ct}$ method [38].

Data were analyzed statistically in SPSS 20. Normality of distributions was confirmed using the Shapiro–Wilks test. Measures of learning in the CAAR test were found to have normal distributions, while measures of gene expression did not. Thus, statistical processing of behavioral data was performed using Student's t test (the Figure shows means and standard errors, while molecular data were processed using the nonparametric Mann and Whitney U test (data are presented as point spread diagrams showing medians and interquartile intervals). Differences were regarded as significant at $p < 0.05$.

Results

Analysis of the expression of the *Fgf2* and *Timp1* genes without cognitive loading did not identify any significant differences in the levels of FGF-2 and TIMP-1 mRNA in brain

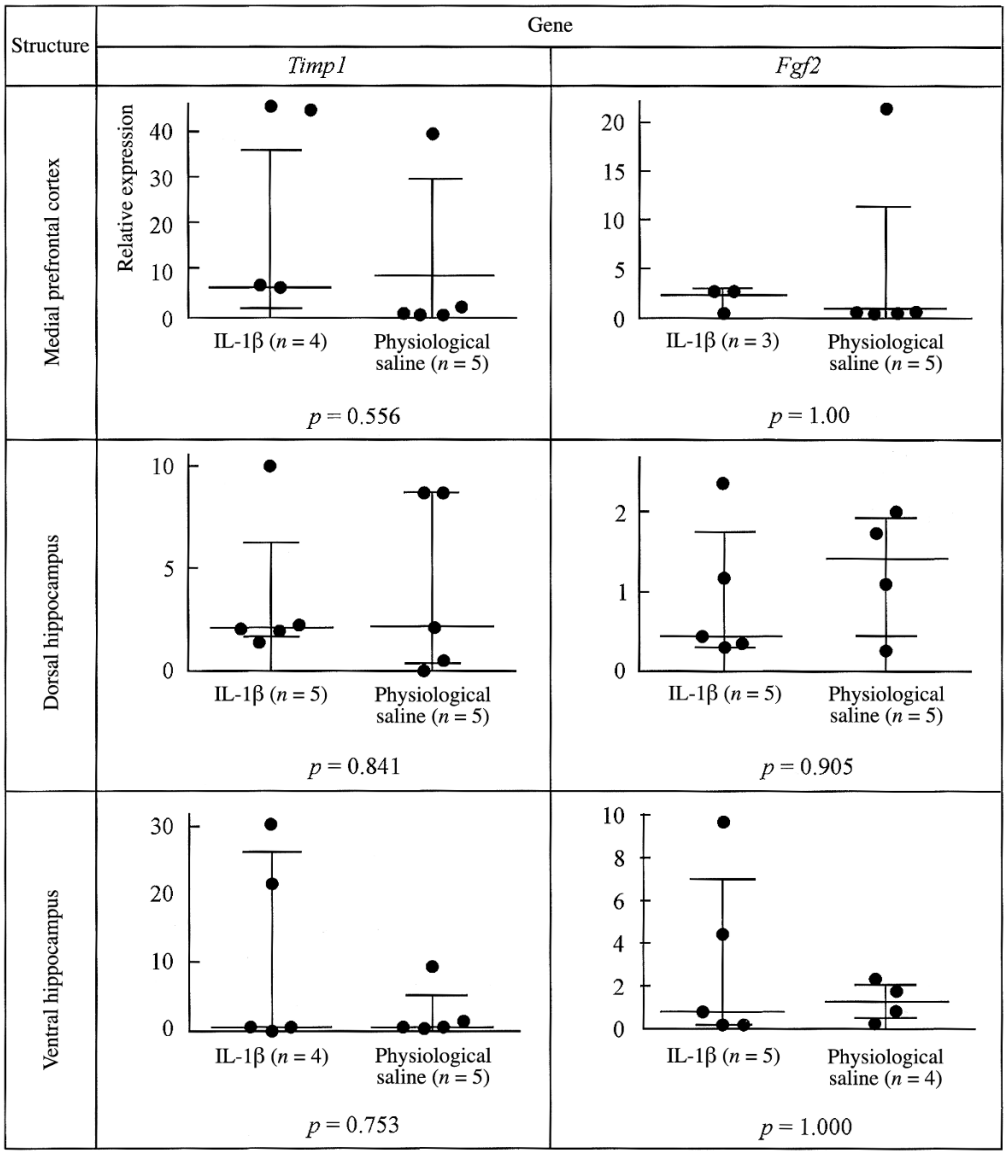

Fig. 2. Levels of expression of the *Timp1* and *Fgf2* genes in brain structures in adult rats not subjected to cognitive loading. Plots show quantities of mRNA calculated using the $2^{-\Delta\Delta Ct}$ method relative to the level of reference gene *Gapdh* mRNA. Data are shown as point plots illustrating spreads, showing medians and interquartile intervals; *n* is the number of animals in the group.

structures in experimental and control rats (for TIMP-1: in the mPFC: $U = 7.0$; $p = 0.556$; in the DH: $U = 11.0$, $p = 0.841$; in the VH: $U = 10.5$, $p = 0.753$; for FGF-2: in the mPFC: $U = 7.0$; $p = 1.000$; in the DH: $U = 9.0$, $p = 0.905$; in the VH: $U = 10.0$, $p = 1.000$).

In the CAAR test (Fig. 3), learning dynamics in experimental rats did not show any significant difference from control rats in the first three days of the experiment (means: day 1: 0.23 ± 0.17 correct excursions in experimental animals and 0.46 ± 0.24 in controls, $t = 0.783$, $p = 0.441$); day 2: 1.62 ± 0.49 correct excursions in experimental animals and 3.69 ± 0.90 in controls, $t = 2.027$, $p = 0.054$); day 3: 4.15 ± 1.01 correct excursions in experimental animals and 5.62 ± 0.82 in controls, $t = 1.126$, $p = 0.271$).

However, on training days 4 and 5, when the learning effect had started to appear, rats given IL-1β during the third week of life made fewer correct excursions than controls, pointing to impairment in conditioned reflex activity (means: day 4: 4.92 ± 1.03 correct excursions in experimental animals and 8.31 ± 1.27 correct excursions in control animals, $t = 2.068$, $p = 0.049$; day 5: 5.00 ± 1.01 correct excursions in experimental animals and 8.38 ± 1.15 correct excursions in control animals, $t = 2.212$, $p = 0.037$). By training day 5 (at the moment of harvesting the brain), the learning criterion (70% correct responses) in the 26 animals tested was achieved by only one animal – from the control group – indicating that animals were already in the process of acquiring the CAAR.

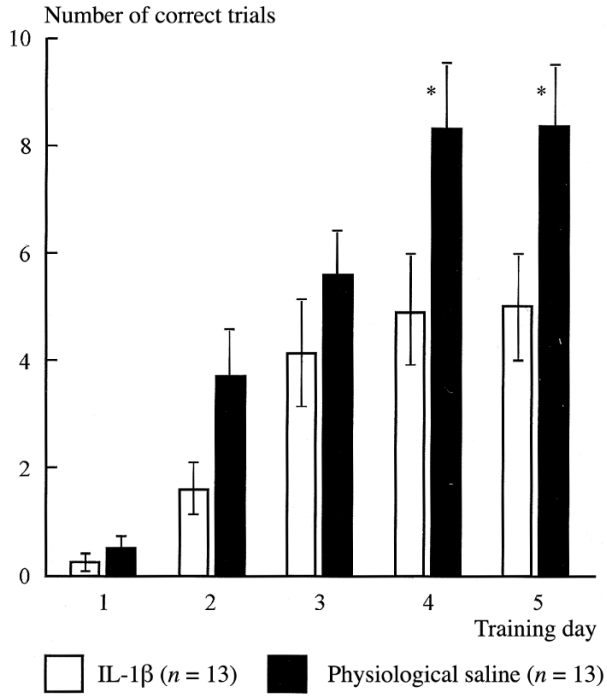

Fig. 3. Numbers of correct trials in the CAAR test. Data are shown as means and standard errors. *Significant differences, Student's t test, $p < 0.05$; n is the number of animals in the group.

In conditions of training (Fig. 4), the relative levels of FGF-2 mRNA in mPFC and ventral but not dorsal hippocampus cells from rats given IL-1β when young were significantly lower than in animals given physiological saline (in the mPFC: $U = 0$, $p = 0.009$; in the DH: $U = 4.0$, $p = = 0.762$; in the VH: $U = 2.0$, $p = 0.038$). In the case of TIMP-1 mRNA, the difference between groups was statistically insignificant (in the mPFC: $U = 3.0$, $p = 0.067$; in the DH: $U = 8.0$, $p = 0.476$; in the VH: $U = 10.0$, $p = 0.410$).

Discussion

The problem of the effects of immune factors on the establishment of cognitive brain functions at early age has attracted extensive attention from researchers. It is actively addressed in the framework of the "fetal programming" and "development-related" ("neurodevelopmental") hypotheses of the formation of several neuromental illnesses, including Alzheimer's disease, schizophrenia, and autism [30, 41]. It has been suggested that increases in the levels of proinflammatory cytokines, particularly IL-1β, at early ages (intrauterine and neonatal infections, perinatal hypoxia, etc.), lead to impairment to the normal development of the integrative systems of the brain (the hippocampus, frontal cortex, tec.), leading to increased predisposition to cognitive psychopathology. This suggestion is supported by data indicating that IL-1β suppresses axon growth and branching [42], has antiproliferative properties [29], and impairs differentiation of neural precursor cells [15].

The effects of exposure to IL-1β on developing glial cells and neurons may include impairment to memory and cerebral neuroplasticity mechanisms. We have previously demonstrated degradation of conditioned reflex activity and spatial memory induced by IL-1β at early ages [3, 6]. Memory impairments in a new object recognition test were seen in adult rats given the IL-1β synthesis inducer bacterial LPS on days 7 and 9 of life. [33]. Testing of the offspring of rats given lipopolysaccharide during pregnancy revealed changes in the processes of long-term depression in hippocampal field CA1 and impairments to various stages of neurogenesis (proliferation, survival, differentiation) in the dentate fascia [17, 21]. Decreased survival of neurons in the dorsal part of the hippocampus was demonstrated in rats given lipopolysaccharide during the neonatal period [32].

However, there is little information on the characteristics of the production of proteins controlling cerebral neuroplasticity processes in animals with increased IL-1β levels at early age. This is suggested by some studies, particularly those of Cui et al. [16], showing that administration of bacterial lipopolysaccharide to pregnant females decreased the concentration of BDNF (brain-derived neurotrophic factor) protein, a powerful regulator of neurogenesis, in the hippocampus of their offspring.

The present study addressed the production of the mRNA for two proteins involved in controlling cerebral neuroplasticity mechanisms in animals which had had increased IL-1β levels in early postnatal ontogeny.

Our interest in TIMP-1 arose because of ongoing discussion of the role of extracellular matrix proteins – tissue metalloproteases and their inhibitors – in controlling cerebral neuroplasticity mechanisms [51], learning [13], and impaired cognitive functions, including those linked with inflammatory processes in the body [19]. Contrary to expectation, we were unable to identify long-term impairments to TIMP-1 mRNA production in cells in brain structures in rats given IL-1β in early postnatal ontogeny, which contrasted to the situation with FGF-2, where significant changes were demonstrated. Rats given IL-1β in early postnatal ontogeny were shown to have decreased expression of the *Fgf2* gene in mPFC and VH cells on learning in the CAAR test.

Pathological states accompanied by high levels of IL-1β production affect the development of cells producing FGF-2. Flores et al. [23] observed a decrease in the number of FGF-2-immunoreactive cells in the ventral tegmental area and substantia nigra in adult rats subjected to prenatal hypoxia. In the nucleus accumbens, the number of these cells, conversely, increased, while no analysis was performed in the hippocampus. Theoretically, impairment to FGF-2 mRNA production could occur in both neurons and glial cells, though it probably mostly affects astrocytes – its major producers [44].

Decreases in FGF-2 mRNA production in rats with high IL-1β levels in early postnatal ontogeny may be mediated by changes in the activity of the dopaminergic system.

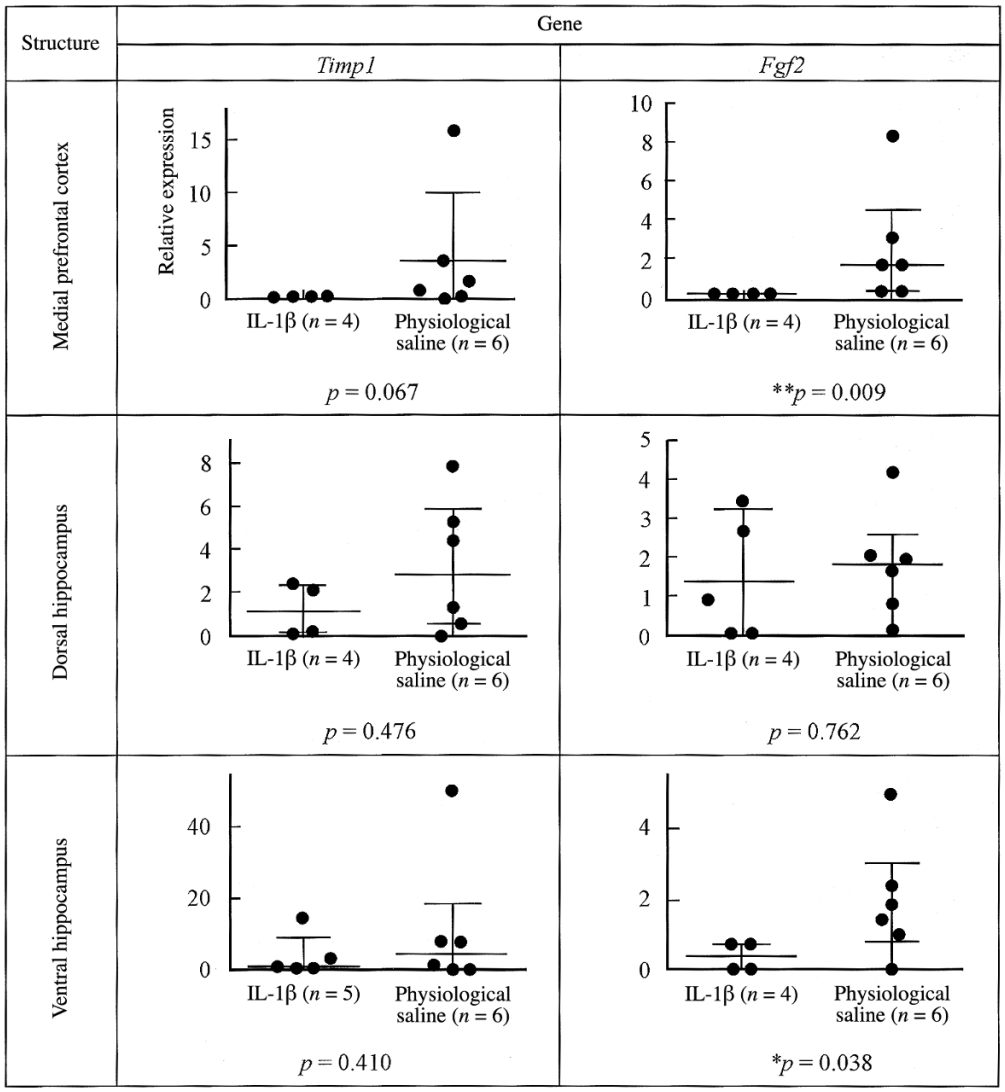

Fig. 4. Levels of expression of the *Timp1* and *Fgf2* genes in brain structures in adult rats on formation of the CAAR. Plots show quantities of mRNA calculated using the $2^{-\Delta\Delta Ct}$ method relative to the level of reference gene *Gapdh* mRNA. Data are shown as point plots illustrating spreads, showing medians and interquartile intervals. Significant differences, Mann–Whitney *U* test: $*p < 0.05$; $**p < 0.01$; *n* is the number of animals.

A tight functional connection between FGF-2 and dopamine neurons has been demonstrated in many studies; changes in these interactions occur in schizophrenia [48]. Increases in FGF-2 mRNA production in cells in the hippocampus and prefrontal cortex are seen after administration of the selective dopamine D_2 receptor agonist quinpirole [24]. On the other hand, impairments to the activity of the brain dopaminergic system after neonatal elevation of IL-1β levels were demonstrated by Kabiersch et al. [35].

The changes in FGF-2 mRNA production seen here in rats given IL-1β in early postnatal ontogeny occurred only in conditions of cognitive loading. It is interesting that similar data were obtained by Bilbo et al., [11] in relation to the brain neurotrophic factor BDNF. Using administration of live cultures of *E. coli* (an inducer of IL-1β synthesis) to for-day-old rats as a model, these authors found that experimental animals at age 21 days showed increased BDNF mRNA production in hippocampal fields CA1 and CA3 in learning associated with fear but not in learning not involving fear. These data, along with our results, suggest that neonatal increases in IL-1β levels do not simply alter the production of particular proteins, but lead to impairments to various systems mechanisms of neuroplasticity.

The decreases in *Fgf-2* gene expression found here in mPFC and VH cells in experimental rats were accompanied by impairment to learning in the CAAR test. The involvement of FGF-2 in the regulation of cerebral learning and memory mechanisms has been demonstrated repeatedly.

FGF-2 stimulates long-term potentiation in dentate fascia neurons in the hippocampus [31], and serious impairments to this are seen in mice with knockout of the type 1 FGF-2 receptor gene [52]. Mice with knockout of the type 2 FGF-2 receptor gene have reduced hippocampal volume and impairments to spatial memory [47]. Increased production of FGF-2 mRNA was found in the hippocampus in learning in a Morris water maze [26]. These data are consistent with our results from animals trained in an active avoidance test.

The decreases in FGF-2 mRNA production seen on training of the experimental animals occurred in the mPFC and ventral part of the hippocampus, but not in the dorsal hippocampus. The key role of the mPFC in the mechanisms of memory and learning, including those associated with fear, have been described in tens of reviews [40]. It is also known that the ventral part of the hippocampus is involved in the formation of anxiety states and stress reactions [1], so it is expected that the decrease in *Fgf2* gene expression seen here in cells of the mPFC and ventral part of the hippocampus in experimental rats will be accompanied by impairment to learning in stressful conditions.

The link between FGF-2 and memory mechanisms points to the potential for using this protein to treat cognitive impairments. Studies in this direction have already given initial results: intranasal administration of FGF-2 has been shown to improve memory in an experimental model of Alzheimer's disease [22]. Taking cognizance of the results obtained here, this approach also appears to have potential for correcting cognitive deficit induced by increased IL-1β levels at early age.

REFERENCES

1. N. V. Gulyaeva, "Effects of stress factors on the functioning of the hippocampus in the adult brain: molecular-cellular mechanisms and the dorsoventral gradient," *Ros. Fiziol. Zh.*, **99**, No. 1, 3–16 (2013).
2. O. E. Zubareva, A. P. Eliseeva, A. S. Simbirtsev, and V. M. Klimenko, "Effects of proinflammatory cytokines on the establishment of behavior in early postnatal ontogeny," *Ros. Fiziol. Zh.*, **91**, No. 4, 374–784 (2005).
3. O. E. Zubareva, K. P. Shcherbakova, S. V. Kalemenev, et al., "Impairments to conditioned reflex activity in adult rats after administration of IL-1β in early postnatal ontogeny," *Zh. Vyssh. Nerv. Deyat.*, **61**, No. 6, 736–741 (2011).
4. V. M. Klimenko, O. E. Zubareva, and I. N. Krasnova, "The role of intracerebral IL-1 receptors in modulating the body's homeostatic reactions," *Neirokhimiya*, **12**, No. 2, 16–22 (1995).
5. V. M. Klimenko and O. E. Zubareva, "The neurobiology of cytokines, behavior, and adaptive reactions," *Ros. Fiziol. Zh.*, **85**, No. 9, 1244–1254 (1999).
6. A. N. Trofimov, O. E. Zubareva, A. S. Simbirtsev, and V. M. Klimenko, "Effects of neonatal increases in IL-1β levels on the formation of spatial memory in adult rats," *Ros. Fiziol. Zh.*, **98**, No. 6, 782–792 (2012).
7. H. Aly, L. Abd-Rabboh, M. El-Dib, et al., "Ascorbic acid combined with ibuprofen in hypoxic ischemic encephalopathy: a randomized controlled trial," *J. Perinatol.*, **29**, No. 6, 438–443 (2009).
8. E. Ban, G. Milon, N. Prudhomme, et al., "Receptors for interleukin-1 (alpha and beta) in mouse brain: mapping and neuronal localization in hippocampus," *Neuroscience*, **43**, No. 1, 21–30 (1991).
9. N. Bednarek, P. Svedin, R. Garnotel, et al., "Increased MMP-9 and TIMP-1 in mouse neonatal brain and plasma and in human neonatal plasma after hypoxia-ischemia: a potential marker of neonatal encephalopathy," *Pediatr. Res.*, **71**, No. 1, 63–70 (2012).
10. F. P. Bellinger, S. Madamba, and G. R. Siggins, "Interleukin-1 beta inhibits synaptic strength and long-term potentiation in the rat CA I hippocampus," *Brain Res.*, **628**, No. 1–2, 227–234 (1993).
11. S. D. Bilbo, R. M. Barrientos, A. S. Eads, et al., "Early-life infection leads to altered BDNF and IL-1 beta mRNA expression in rat hippocampus following learning in adulthood," *Brain Behav. Immun.*, **22**, No. 4, 451–455 (2008).
12. G. Bregola, L. Frigati, S. Zucchini, and M. Simonato, "Different patterns of induction of fibroblast growth factor-2 and brain-derived neurotrophic factor messenger RNAs during kindling epileptogenesis and development of a herpes simplex vector for fibroblast growth factor-2 gene transfer in vivo," *Epilepsia*, **41**, No. 6, S122–126 (2000).
13. F. A. Chaillan, S. Rivera, E. Marchetti, et al., "Involvement of tissue inhibition of metalloproteinases-1 in learning and memory in mice," *Behav. Brain Res.*, **173**, No. 2, 191–198 (2006).
14. M. K. Chan, P. C. Guest, Y. Levin, et al., "Biomarkers of Neurological and Psychiatric Disease," *Int. Rev. Neurobiol.*, **101**, 95–144 (2011).
15. S. J. Crampton, L. M. Collins, A. Toulouse, et al., "Exposure of foetal neural progenitor cells to IL-1β impairs their proliferation and alters their differentiation – a role for maternal inflammation?" *J. Neurochem.*, **120**, No. 6, 964–973 (2012).
16. Q. J. Cui, L. Y. Wang, Z. X. Wei, and W. S. Qu, "Continual naringin treatment benefits the recovery of traumatic brain injury in rats through reducing oxidative and inflammatory alterations," *Neurochem. Res.* [Epub ahead of print] (2014).
17. K. Cui, H. Ashdown, G. N. Luheshi, and P. Boksa, "Effects of prenatal immune activation on hippocampal neurogenesis in the rat," *Schizophr. Res.*, **113**, 288–297 (2009).
18. J. Czerniawski, T. Yoon, and T. Otto, "Dissociating space and trace in dorsal and ventral hippocampus," *Hippocampus*, **19**, No. 1, 20–32 (2009).
19. F. Dal-Pizzol, H. A. Rojas, E. M. Dos Santos, et al., "Matrix metalloproteinase-2 and metalloproteinase-9 activities are associated with blood-brain barrier dysfunction in an animal model of severe sepsis," *Mol. Neurobiol.*, **48**, No. 1, 62–70 (2013).
20. E. S. J. M. De Bont, A. M. Martens, J. Van Raan, et al., "Tumor necrosis factor-α, interleukin-1β, and interleukin-6 plasma levels in neonatal sepsis," *Pediatr. Res.*, **33**, 380–383 (1993).
21. M. Escobar, N. Crouzin, M. Cavalier, et al., "Early, time-dependent disturbances of hippocampal synaptic transmission and plasticity after in utero immune challenge," *Biol. Psychiatry*, **70**, 992–999 (2011).
22. C. Feng, C. Zhang, X. Shao, et al., "Enhancement of nose-to-brain delivery of basic fibroblast growth factor for improving rat memory impairments induced by co-injection of β-amyloid and ibotenic acid into the bilateral hippocampus," *Int. J. Pharm.*, **423**, No. 2, 226–234 (2012).
23. C. Flores, J. Stewart, N. Salmaso, et al., "Astrocytic basic fibroblast growth factor expression in dopaminergic regions after perinatal anoxia," *Biol. Psychiatry*, **52**, No. 4, 362–370 (2002).
24. F. Fumagalli, F. Bedogni, M. E. Maragnoli, et al., "Dopaminergic D2 receptor activation modulates FGF-2 gene expression in rat prefrontal cortex and hippocampus," *J. Neurosci. Res.*, **74**, No. 1, 74–80 (2003).
25. Y. Ganat, S. Soni, M. Chacon, et al., "Chronic hypoxia up-regulates fibroblast growth factor ligands in the perinatal brain and induces fibroblast growth factor responsive radial glial cells in the sub-ependymal zone," *Neuroscience*, **112**, No. 4, 977–991 (2002).
26. F. Gómez-Pinilla, V. So, and J. P. Kesslak, "Spatial learning and physical activity contribute to the induction of fibroblast growth factor: neural substrates for increased cognition associated with exercise," *Neuroscience*, **85**, No. 1, 53–61 (1998).

27. I. Goshen, T. Kreisel, H. Ounallah-Saad, et al., "A dual role for interleukin-1 in hippocampal-dependent memory processes," *Psychoneuroendocrinology*, **32**, No. 8–10, 1106–1115 (2007).
28. B. M. Graham and R. Richardson, "Memory of fearful events: the role of fibroblast growth factor-2 in fear acquisition and extinction," *Neuroscience*, **189**, 156–169 (2011).
29. H. F. Green, E. Treacy, A. K. Keohane, et al., "A role for interleukin-1β in determining the lineage fate of embryonic rat hippocampal neural precursor cells," *Mol. Cell. Neurosci.*, **49**, No. 3, 311–321 (2012).
30. H. Hagberg, P. Gressens, and C. Mallard, "Inflammation during fetal and neonatal life: implications for neurologic and neuropsychiatric disease in children and adults," *Ann. Neurol.*, **71**, No. 4, 444–457 (2012).
31. J. Ishiyama, H. Saito, and K. Abe, "Epidermal growth factor and basic fibroblast growth factor promote the generation of long-term potentiation in the dentate gyrus of anaesthetized rats," *Neurosci. Res.*, **12**, No. 3, 403–411 (1991).
32. K. Järlestedt, A. S. Naylor, J. Dean, et al., "Decreased survival of newborn neurons in the dorsal hippocampus after neonatal LPS exposure in mice," *Neuroscience*, **253**, 21–28 (2013).
33. T. A. Jenkins, M. K. Harte, G. Stenson, and G. P. Reynolds, "Neonatal lipopolysaccharide induces pathological changes in parvalbumin immunoreactivity in the hippocampus of the rat," *Behav. Brain Res.*, **205**, No. 2, 355–359 (2009).
34. J. Jourquin, E. Tremblay, A. Bernard, et al., "Tissue inhibitor of metalloproteinases-1 (TIMP-1) modulates neuronal death, axonal plasticity and learning and memory," *Eur. J. Neurosci.*, **22**, No. 10, 2569–2578 (2005).
35. A. Kabiersch, H. Furukawa, A. del Rey, and H. O. Besedovsky, "Administration of interleukin-1 at birth affects dopaminergic neurons in adult mice," *Ann. NY Acad. Sci.*, **840**, 123–127 (1998).
36. H. Katsuki, S. Nakai, Y. Hirai, et al., "Interleukin-1β inhibits long-term potentiation in the CA3 region of mouse hippocampal slices," *Eur. J. Pharmacol.*, **181**, No. 3, 323–326 (1990).
37. H. M. Liu, H. B. Yang, and R. M. Chen, "Expression of basic fibroblast growth factor, nerve growth factor, platelet-derived growth factor and transforming growth factor-beta in human brain abscess," *Acta Neuropathol.*, **88**, No. 2, 143–150 (1994).
38. K. J. Livak and T. D. Schmittgen, "Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) method," *Methods*, **25**, No. 4, 402–408 (2001).
39. J. McAfoose and B. T. Baune, "Evidence for a cytokine model of cognitive function," *Neurosci. Biobehav. Rev.*, **33**, 355–366 (2009).
40. R. Marek, C. Strobel, T. W. Bredy, and P. Sah, "The amygdala and medial prefrontal cortex: partners in the fear circuit," *J. Physiol.*, **591**, No. 10, 2381–2391 (2013).
41. U. Meyer, "Developmental neuroinflammation and schizophrenia Developmental," *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **42**, 20–34 (2013).
42 A. M. Nolan, Y. M. Nolan, and G. W. O'Keeffe, "IL-1β inhibits axonal growth of developing sympathetic neurons," *Mol. Cell. Neurosci.*, **48**, No. 2, 142–150 (2011).
43. G. Paxinos and C. Watson, *The Rat Brain in Stereotaxic Coordinates*, Academic Press Elsevier, Burlington (2005), 5th ed.
44. B. Reuss, von Bohlen, and O. Halbach, "Fibroblast growth factors and their receptors in the central nervous system," *Cell Tiss. Res.*, **313**, No. 2, 139–157 (2003).
45. S. Rivera, S. J. Gold, and C. M. Gall, "Interleukin-1 beta increases basic fibroblast growth factor mRNA expression in adult rat brain and organotypic hippocampal cultures," *Brain Res. Mol. Brain Res.*, **27**, No. 1, 12–26 (1994).
46. V. Shukla, S. A. Kumar, T. N. Dhole, and U. K. Misra, "Upregulated expression of matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases in BALB/c mouse brain challenged with Japanese encephalitis virus," *Neuroimmunomodulation*, **19**, No. 4, 241–254 (2012).
47. H. E. Stevens, G. Y. Jiang, M. L. Schwartz, and F. M. Vaccarino, "Learning and memory depend on fibroblast growth factor receptor 2 functioning in hippocampus," *Biol. Psychiatry*, **71**, No. 12, 1090–1098 (2012).
48. A. F. Terwisscha van Scheltinga, S. C. Bakker, and R. S. Kahn, "Fibroblast growth factors in schizophrenia," *Schizophr. Bull.*, **36**, No. 6, 1157–1166 (2010).
49. L. Tong and W. Zhang, "Fetal hypoxia and programming of matrix metalloproteinases," *Drug Discov. Today*, **17**, No. 3–4, 124–134 (2012).
50. K. M. Wilczynska, S. M. Gopalan, M. Bugno, et al., "A novel mechanism of tissue inhibitor of metalloproteinases-1 activation by interleukin-1 in primary human astrocytes," *J. Biol. Chem.*, **281**, No. 46, 34,955–34,964 (2006).
51. J. W. Wright and J. W. Harding, "Contributions of matrix metalloproteinases to neural plasticity, habituation, associative learning and drug addiction," *Neural Plast.*, Article ID 579382 (2009).
52. M. Zhao, D. Li, K. Shimazu, Y. X. Zhou, et al., "Fibroblast growth factor receptor-1 is required for long-term potentiation, memory consolidation and neurogenesis," *Biol. Psychiatry*, **62**, No. 5, 381–390 (2007).