ГИПОКСИЕЙ ИНДУЦИРОВАННЫЙ ФАКТОР-1α И МАРКЕРЫ ВОСПАЛЕНИЯ У ПАЦИЕНТОВ С ИШЕМИЧЕСКИМ ИНСУЛЬТОМ

Пивоварова Л.П.[1], Вознюк И.А.[2], Осипова И.В.[1], Арискина О.Б.[1], Гоголева Е.А.[1], Прохорова М.В.[1], Карпова Н.Г.[1]

[1] ГБУ «Санкт-Петербургский научно-исследовательский институт скорой помощи имени И.И. Джанелидзе», Санкт-Петербург, Россия
[2] ФГБОУ ВО «Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова» Министерства здравоохранения РФ, Санкт-Петербург, Россия

Резюме. Ишемический инсульт (ИИ) возникает в результате локального нарушения гемоциркуляции и гипоксии в ткани головного мозга. Индуцируемый гипоксией фактор-1α (HIF-1α), участвующий в регуляции уровня кислорода в тканях, играет важную роль в патофизиологии инсульта, включая выживаемость нейронов, нейровоспаление, ангиогенез, метаболизм глюкозы, проницаемость гематоэнцефалического барьера (ГЭБ), и имеет значение в исходах ишемического инсульта. Сведения о роли HIF-1α в развитии инсульта разноречивы. Эффекты влияния HIF-1α связаны с длительностью и тяжестью ишемии. Известно о роли HIF-1α в ишемическом повреждении головного мозга, включая воспалительную реакцию и потерю целостности ГЭБ после инсульта. Цель исследования – определение связи содержания гипоксией индуцированного фактора-1α в крови пациентов со степенью неврологического дефицита в остром периоде ишемического инсульта и исходом заболевания. Обследованы 58 человек с ишемическим инсультом в возрасте 73 (67-81) лет. Пациенты были разделены на две группы – выписанные и умершие. Определяли тяжесть инсульта (NIHSS), неврологический дефицит, индекс коморбидности, содержание в крови HIF-1α, белка p53, интерлейкина-6, цистатина С, СРБ, креатинина, гематологические показатели при поступлении, на 3-и и 10-е сутки заболевания. Содержание HIF-1α в крови пациентов с ИИ при поступлении было ниже, чем в группе сравнения и оставалось сниженным до 10-го дня наблюдения. На 10-е сутки определялась связь HIF-1α с NIHSS, неврологическим дефицитом, индексом коморбидности и исходом заболевания. Наблюдали обратную связь HIF-1α с содержанием эритроцитов, гемоглобина и гематокрита что можно расценивать как отражение гемической составляющей смешанной гипоксии. Также у пациентов с неблагоприятным исходом ИИ выявлено повышенное содержание цистатина С в крови, которое было связано с концентраций HIF-1α. Во все сроки наблюдения церебральной катастрофы была отмечена корреляционная связь цистатина С с содержанием креатинина и СРБ. Эти результаты могут свидетельствовать о дисфункции эндотелиоцитов, нарушении клубочковой фильтрации, воспалении, ассоциированными с гипоксией при ИИ. Прогностическая значимость уровня HIF-1α в

Адрес для переписки:

Осипова Ирина Викторовна
ГБУ «Санкт-Петербургский научно-исследовательский институт скорой помощи имени И.И. Джанелидзе»
192242, Россия, Санкт-Петербург, ул. Будапештская, 3.
Тел.: 8 (812) 384-46-68.
Факс: 8 (812) 384-46-46.
E-mail: ivosipova@yandex.ru

Address for correspondence:

Irina V. Osipova
I. Dzhanelidze Research Institute of Emergency Medicine
3 Budapestkaya St
St. Petersburg
192242 Russian Federation
Phone: +7 (812) 384-46-68.
Fax: +7 (812) 384-46-46.
E-mail: ivosipova@yandex.ru

Образец цитирования:

Л.П. Пивоварова, И.А. Вознюк, И.В. Осипова, О.Б. Арискина, Е.А. Гоголева, М.В. Прохорова, Н.Г. Карпова «Гипоксией индуцированный фактор-1α и маркеры воспаления у пациентов с ишемическим инсультом» // Медицинская иммунология, 2023. Т. 25, № 4. С. 991-996.
doi: 10.15789/1563-0625-HIF-2740

For citation:

L.P. Pivovarova, I.A. Voznyuk, I.V. Osipova, O.B. Ariskina, E.A. Gogoleva, M.V. Prokhorova, N.G. Karpova "Hypoxia-induced factor-1α and markers of inflammation in patients with ischemic stroke", Medical Immunology (Russia)/ Meditsinskaya Immunologiya, 2023, Vol. 25, no. 4, pp. 991-996.
doi: 10.15789/1563-0625-HIF-2740

DOI: 10.15789/1563-0625-HIF-2740

крови на 10-е сутки заболевания для исхода ИИ составила AUC = 0,900. Содержание HIF-1α в крови в остром периоде связано с тяжестью ишемического инсульта и исходом заболевания.

Ключевые слова: гипоксией индуцированный фактор-1α, апоптоз, маркеры воспаления, цистатин С, ишемический инсульт, исход

HYPOXIA-INDUCED FACTOR-1α AND MARKERS OF INFLAMMATION IN PATIENTS WITH ISCHEMIC STROKE

Pivovarova L.P.[a], Voznyuk I.A.[b], Osipova I.V.[a], Ariskina O.B.[a], Gogoleva E.A.[a], Prokhorova M.V.[a], Karpova N.G.[a]

[a] *I. Dzhanelidze Research Institute of Emergency Medicine, St. Petersburg, Russian Federation*
[b] *First St. Petersburg State I. Pavlov Medical University, St. Petersburg, Russian Federation*

Abstract. Ischemic stroke (IS) occurs as a result of local disturbance of hemocirculation and hypoxia in the brain tissue. Hypoxia-inducible factor-1α (HIF-1α), which is involved in the regulation of tissue oxygen levels, plays an important role in the pathophysiology of stroke, including neuronal survival, neuroinflammation, angiogenesis, glucose metabolism, blood-brain barrier permeability, and is important in IS outcomes. The purpose of the study was to determine the relationship between blood levels of HIF-1α and the degree of neurological deficit in the acute period of IS and the outcome of the disease. We examined 58 people with IS aged 73 (67-81) years. Patients were divided into two groups – discharged and dead. The severity of stroke (NIHSS), neurological deficit, comorbidity index, blood levels of HIF-1α, p53 protein, interleukin-6, cystatin C, CRP, creatinine, hematological parameters were determined at admission, on days 3 and 10 of the disease. At admission the blood levels of HIF-1α was lower than in the comparison group and remained reduced until the 10th day. On day 10 the association of HIF-1α with neurological deficit, comorbidity index and disease outcome was determined. We observed a feedback of HIF-1α with the content of erythrocytes, hemoglobin and hematocrit, which can be regarded as a reflection of the hemic component of mixed hypoxia. In dead patients, an increased blood level of cystatin C was detected, which was associated with HIF-1α concentrations. In all periods of observation of IS, a correlation between cystatin C and creatinine and CRP levels was noted. These results may indicate dysfunction of endotheliocytes, inflammation associated with hypoxia in IS. The prognostic significance of the blood level of HIF-1α on the 10th day for the outcome of IS was AUC = 0.900. Blood levels of HIF-1α in the acute period was associated with the severity of IS and the outcome of the disease.

Keywords: hypoxia-induced factor-1α, apoptosis, markers of inflammation, cystatin C, ischemic stroke, outcome

Introduction

Ischemic stroke (IS) occurs as a result of a local disturbance of hemocirculation in the brain tissue, which causes the development of hypoxia. Hypoxia-inducible factor 1α (HIF-1α), which is involved in the regulation of tissue oxygen levels, has been shown to play an important role in the pathophysiology of stroke, including neuroinflammation, regulation of blood-brain barrier permeability, glucose metabolism, neuronal survival, and angiogenesis [4].

HIF-1 (hypoxia inducible factor) is a transcription factor that allows the cell to survive in hypoxia; it was discovered more than 20 years ago when studying the mechanisms of adaptation of living organisms to changes in the oxygen content in the environment; found in various cells and tissues subject to hypoxia.

HIF is a heterodimer containing two protein subunits, HIF-1α (73-120 kDa) and HIF-1β (91-94 kDa) [11]. HIF-1α is a DNA-binding protein that undergoes hydroxylation in the presence of oxygen and binds to the conservative protein ubiquitin, which is involved in the regulation of intracellular proteasome degradation of other proteins [5]. With a decrease in the level of oxygen in the cell, hydroxylation does not occur, HIF-1α stabilizes and dimerizes with the second subunit of the HIF transcription factor, HIFβ, which is insensitive to oxygen. The resulting complex is translocated to the nucleus, where it binds to hypoxia response elements, HREs, thus launching the genetic program for cell survival under conditions of oxygen deficiency.

HIF-1α mediates the expression of many genes that are involved in neurogenesis, angiogenesis, cell proliferation, erythropoiesis, and cell metabolism, increasing the adaptation of nervous tissue to ischemic stress and, therefore, exhibiting a neuroprotective role [5]. Other studies have reported a detrimental role for HIF-1α in ischemic brain injury, including the inflammatory response and loss of blood-brain barrier (BBB) integrity following ischemic stroke. This indicates that HIF-1α is likely to be a mediator of neuroinflammation or a factor that determines BBB permeability [4]. Pan Z. et al. (2021) described

the mechanisms of regulation of HIF-1 production in stroke, when an elevated level of reactive oxygen species promotes HIF-1 expression by inhibiting prolyl hydrolase (PHD) activity and the NF-κB pathway. HIF-1 increases glucose uptake by regulating glucose transport proteins and glycolytic enzymes. Also, HIF-1 induces the production of pro-inflammatory cytokines IL-6, TNF, IL-20, MCP-1.

HIF-1 is involved in the regulation of expression of BNIP3, a pro-apoptotic member of the Bcl-2 and p53 family, to activate autophagy and inhibit the anti-apoptotic Bcl-2 protein, thus activating apoptotic signaling pathways and apoptosis. Increased production of erythropoietin (EPO) and vascular endothelial growth factor (VEGF) under the influence of HIF-1 contributes to the weakening of apoptosis. At the same time, the production of VEGF leads to disruption of the BBB [15]. The main structural component of the BBB is the endothelial cells of the walls of blood vessels that provide exchange in the blood-CNS system. Proliferation and migration of endothelial cells are largely dependent on VEGF. In addition, VEGF increases vascular permeability by initiating angiogenesis and neovascularization in ischemia-damaged tissue. After a stroke, the formation of a new vasculature is vital to compensate for the function of an occluded vessel in the penumbra. However, structural changes and an increase in vascular basement membrane permeability during activation of angiogenesis can lead to cerebral edema or hemorrhagic transformation in the acute phase of a stroke.

Information about the role of HIF-1 in the development of stroke is contradictory. In a mouse stroke model deficient in HIF1α/HIF2α, early neuronal death and neurological damage were reduced. At 24 h after stroke, cell death and edema were significantly reduced, but after 72 h, cerebral edema increased, accompanied by activation of apoptosis and a decrease in angiogenesis [1].

In another study, suppression of HIF-1α production after 0.5 h of ischemia in rats attenuated cerebral edema and apoptosis, while after 8 h of ischemia, neuronal damage increased and VEGF expression decreased [14]. It is likely that the effects of HIF-1 are associated with the duration and severity of ischemia. Chen C.H. et al. (2010) reported that HIF-1 inhibition can reduce BBB damage after stroke in adult and neonatal rats, which may be due in part to blocking the HIF-1α signaling pathway in neuronal apoptosis and suppressing VEGF activity to protect the BBB. Baranova O. et al. (2007) in an experiment showed that the expression of HIF-1 α is associated with the outcome of ischemic stroke.

Purpose of the study – to determine the relationship between the content of hypoxia-induced factor (HIF-1α) in the blood of patients with the degree of neurological deficit in the acute period of ischemic stroke and the outcome of the disease.

Materials and methods

We examined 58 people with ischemic stroke (IS), aged 73 (67-81) years, including 34 women, 24 men. The examination was carried out in accordance with the Procedure for the provision of medical care to patients with stroke of the Ministry of Health of the Russian Federation No. 928n, 2012. The condition of patients was assessed using the National Institutes of Health Stroke Scale (NIHSS), a modified Rankin scale for assessing the degree of disability and functional patient independence, Rivermead mobility index, Charlson comorbidity index (Table 1). The comparison group consisted of 25 volunteers aged 65.0 (62.0-67.0) years.

Blood levels of hypoxia-induced factor (Hypoxia-inducible factor 1-alpha, HIF-1α, R&D Systems, Inc, USA), p53 protein (Human p53 ELISA Kit, Invitrogen, ThermoFisher Scientific), interleukin-6 (IL-6), cystatin C (ELISA, Vector-Best, Russia) by ELISA; CRP by immunoturbidimetric method, creatinine (Roche, Cobas c501, Roche Diagnostics, Switzerland); hematological parameters (Sysmex XN1000, Japan) at admission, on days 3 and 10 of the disease was determined.

Statistical processing of the results was carried out using the Statistica 6.0 software package; the median (Me) and percentiles ($Q_{0.25}$-$Q_{0.75}$), Spearman's correlation coefficients were determined; the prognostic significance of the indicators was assessed using ROC analysis. In the correlation analysis of indicators with the outcome of the disease, discharged

TABLE 1. CHARACTERISTICS OF NEUROLOGICAL DEFICIT IN PATIENTS WITH ISCHEMIC STROKE

Groups	Age	NIHSS	Rivermead Index	Rankin Scale	Charlson Index	n
All patients with IS	73 (67-81)	9.5 (5-13)	2.0 (1.0-7.0)	4.0 (3.0-4.0)	6.0 (4.0-7.0)	58
Discharged	71 (66-79)	7.3 (4.3-12.8)	2.5 (1.0-6.5)	4.0 (3.0-4.0)	5.0 (4.0-7.0)	44
Dead	80 (72-81)	16.0 (11.0-21.0) p = 0.022	1.0 (0.0-2.0)	4.0 (4.0-5.0)	7.5 (6.0-9.0) p = 0.004	14

Note. p, significance of differences between groups of patients discharged and dead.

patients were assigned 1 point, and those who died – 0 points. Statistical significance was taken for $p < 0.05$.

Results and discussion

Patients with IS were divided into two groups – a group of discharged patients and a group of dead patients. Patients of the selected groups significantly differed in the severity of stroke at admission and the value of the Charlson comorbidity index (Table 1). NIHSS scores and comorbidity index were associated with disease outcome ($r = -0.497$; $p < 0.001$ and $r = -0.394$; $p < 0.001$, respectively).

It is known from the literature that the level of HIF-1α in the blood of patients increases during hypoxia, which is associated with cerebral ischemia [4]. In our study, we observed a decrease in the content of HIF-1α in the blood both in discharged patients (by 2 times) and in dead patients (by 2.8 times) during all periods of observation (Table 2). It is not yet clear what mechanisms are responsible for the inhibition of HIF-1α production in the acute period of stroke.

A decrease in the content of the apoptotic protein p-53 by 3 times by the 3rd day of observation was also noted in discharged patients and 8 times in the dead. The concentration of HIF-1α was associated with the level of p-53 in the blood serum of patients on the 10th day of observation ($r = 0.999$, $p < 0.001$). We observed inhibition of apoptosis with a decrease in HIF-1α in the blood, while in the literature, inhibition of apoptosis is described with an increase in HIF-1α expression [7].

Recently, cystatin C has been considered as a biomarker of endothelial dysfunction in cerebrovascular pathology, as well as an adequate indicator of the state of renal functions, including those with normal renal function, but diagnosed with ischemic stroke [6]. The content of cystatin C in patients with IS is associated with the severity of stroke and its consequences [8]. Cystatin C is a non-glycosylated protein with a molecular weight of 13.4 kDa, an inhibitor of cysteine proteinases, synthesized by all cells containing nuclei, freely filtered through the glomerular membrane, and completely metabolized in the kidneys.

Wang Y. et al. (2019) in a meta-analysis that included nine studies involving 3773 patients with ischemic stroke, showed an association between cystatin C and the risk of ischemic stroke: it turned out that patients with ischemic stroke had significantly higher serum cystatin C concentrations compared with participants without ischemic stroke.

Our results also demonstrated a more pronounced increase in the level of cystatin C in the blood in patients with an unfavorable outcome of ischemic stroke (Table 2). On the 10th day of observation, a relationship was found between the concentrations of HIF-1α and cystatin C ($r = 0.927$; $p < 0.001$). In all periods of observation of cerebral catastrophe, a medium and strong correlation was noted between cystatin C and creatinine and CRP levels. These results may indicate dysfunction of endotheliocytes, impaired glomerular filtration, inflammation associated with hypoxia in IS.

At the same time, the feedback of HIF-1α with the content of erythrocytes, hemoglobin and hematocrit was observed ($r = -0.648$, $p < 0.05$; $r = -0.586$, $p < 0.05$; $r = -0.579$, $p < 0.05$ respectively), which can be regarded as a reflection of the hemic component of mixed hypoxia.

An experiment [12] showed that pro-inflammatory cytokines, including IL-6, are involved in the activation of HIF-1α in the rat hippocampus and contribute to cerebral damage caused by transient global ischemia. Xu S. et al., 2020 found that under hypoxic conditions, IL-6 enhances the expression of

TABLE 2. BLOOD LEVELS OF HIF-1α, p53, AND CYSTATIN C IN IS PATIENTS DISCHARGED AND DEAD

Patients with IS	Days after IS	HIF-1α, pg/mL	p53, E/mL	Cystatin C, mkg/mL
Comparison group		114 (44-116)	2.54 (1.08-4.06)	0.64 (0.62-1.17)
Discharged	1	56 (47.5-67.0) p = 0.015	1.16 (0.41-6.66)	0.87 (0.71-1.04)
	3	58.0 (48.0-66.0) p = 0.040	0.71 (0.31-3.95)	0.85 (0.76-1.02)
	10	52.0 (48.0-58.0) p = 0.033	0.5 (0.4-0.9)	1.0 (0.8-1.4)
Dead	1	42.0 (39.0-44.0) p = 0.012	2.2 (1.8- 2.5)	0.9 (0.9-1.1)
	3	40.0 (40.0-40.0) p = 0.041	0.3 (0.29-0.31)	1.22 (1.18-1.42) p = 0.027
	10	–	0.34 (0.34-0.34)	1.4 (1.3-1.6)

Note. p, significance of differences compared with data from the comparison group.

TABLE 3. BLOOD LEVELS OF IL-6 AND CRP IN IS PATIENTS DISCHARGED AND DEAD

Patients with IS	Days after IS	IL-6, pg/mL	CRP, mg/L
Comparison group		2.2 (2.0-2.7)	1.3 (1.0-4.8)
Discharged	1	10.1 (4.6-29.4)	5.0 (3.1-18.0)
	3	10.4 (2.7-30.1) $p_1 = 0.000$	10.6 (4.4-25.9) $p = 0.007$ $p_1 = 0.000$
	10	13.9 (4.6-35.7) $p = 0.058$ $p_1 = 0.000$	12.9 (4.9-40.7) $p = 0.025$ $p_1 = 0.000$
Dead	1	32.3 (24-180) $p_1 = 0.003$	19.1 (10.6-44.8) $p = 0.000$
	3	84.7 (48.9-239.7) $p = 0.011$	130 (75.8-193.0) $p = 0.000$
	10	91.9 (64.6-117) $p = 0.003$	172 (165-195) $p = 0.000$

Note. p, significance of differences compared to data from the comparison group; p_1, significance of differences between groups discharged and dead.

HIF-1α through a signal protein and transcription activator 3 (STAT3). In our study, an increase in the content of IL-6 compared with the norm by 5-6 times in discharged patients and by 14-42 times in patients with a lethal outcome was noted (Table 3). Although we did not find a direct relationship between HIF-1α and IL-6 concentrations, there was a correlation between HIF-1α and CRP levels ($r = 0.978$; $p < 0.001$). Previously, we showed [9] that in patients with IS, an increase in the concentration of IL-6 in the blood preceded an increase in the concentration of CRP; changes in indicators were interrelated and reflected the severity of ischemic stroke. We can assume an indirect effect of IL-6 on the level of HIF-1α in IS.

The content of HIF-1α in the blood of all patients with IS decreased upon admission to the hospital and remained at the same level during 10 days of observation, but only on the 10th day was the relationship of HIF-1α with the severity of neurological deficit, with the Rankin and Rivermead scale, with the index comorbidity and disease outcome ($r = 0.982$, $p < 0.001$; $r = 0.670$; $p < 0.05$; $r = -0.694$; $p < 0.05$; $r = 0.684$, $p < 0.01$; $r = -0.674$, $p < 0.001$, respectively). The prognostic significance of the level of HIF-1α in the blood on the 10th day of the disease for the outcome of IS according to the ROC analysis was AUC = 0.900, sensitivity 80%, specificity 100%.

Thus, HIF-1α plays a key role in the development of the compensatory and adaptive response of cells and tissues to ischemia and hypoxia, and is associated with endotheliocyte dysfunction, impaired glomerular filtration, and the development of inflammation in patients with ischemic stroke. The content of HIF-1α in the blood in the acute period is associated with the severity of ischemic stroke and the outcome of the disease.

References

1. Barteczek P., Li L., Ernst A.S., Böhler L.I., Marti H.H., Kunze R. Neuronal HIF-1α and HIF-2α deficiency improves neuronal survival and sensorimotor function in the early acute phase after ischemic stroke. *J. Cereb. Blood Flow Metab., 2017, Vol. 37, no. 1, pp. 291-306.*
2. Baranova O., Miranda L.F., Pichiule P., Dragatsis I., Johnson R.S., Chavez J.C. Neuron-specific inactivation of the hypoxia inducible factor 1 alpha increases brain injury in a mouse model of transient focal cerebral ischemia. *J. Neurosci., 2007, Vol. 27, no. 23, pp. 6320-6332.*
3. Chen C.H., Ostrowski R.P., Zhou C.M., Tang J.P., Zhang J.H. Suppression of hypoxia-inducible factor-1α and its downstream genes reduces acute hyperglycemia-enhanced hemorrhagic transformation in a rat model of cerebral ischemia. *J. Neurosci. Res., 2010, Vol. 88, no. 9, pp. 2046-2055.*
4. He Q., Ma Y., Liu J., Zhang D., Ren J., Zhao R., Chang J., Guo Z.N., Yang Y. Biological functions and regulatory mechanisms of hypoxia-inducible factor-1α in ischemic stroke. *Front. Immunol., 2021, Vol. 12, 801985.* doi: 10.3389/fimmu.2021.801985.
5. Ivan M., Kaelin W.G. Jr. The EGLN-HIF O_2-sensing system: multiple inputs and feedbacks. *Mol. Cell, 2017, Vol. 66, no. 6, pp. 772-779.*
6. Kim T.J., Kang M.K., Jeong H.G., Kim C.K., Kim Y., Nam K.W., Mo H., An S.J., Ko S.B., Yoon B.W. Cystatin C is a useful predictor of early neurological deterioration following ischaemic stroke in elderly patients with normal renal function. *Eur. Stroke J., 2017, Vol. 2, no. 1, pp. 23-30.*
7. Pan Z., Ma G., Kong L., Du G. Hypoxia-inducible factor-1: Regulatory mechanisms and drug development in stroke. *Pharmacol. Res., 2021, Vol. 170, 105742.* doi: 10.1016/j.phrs.2021.105742.

8. Su M., Zhou Y., Chen Z., Pu M., Li Z., Du H., Xu G. Cystatin C predicts futile recanalization in patients with acute ischemic stroke after endovascular treatment. *J. Neurol., 2022, Vol. 269, no. 2, pp. 966-972.*
9. Voznyuk I.A., Pivovarova L.P., Gogoleva E.A., Osipova I.V., Ariskina O.B., Morozova E.M., Chernyavsky I.V., Markelova E.V. Biomarkers of brain damage and inflammation in patients with acute cerebral ischemia. *S. Korsakov Journal of Neurology and Psychiatry, 2022, Vol. 122, no. 8, Iss. 2, pp. 54-60.* (In Russ.)
10. Wang Y., Li W., Yang J., Zhang M., Tian C., Ma M., Zhang Q. Association between cystatin C and the risk of ischemic stroke: a systematic review and meta-analysis. *J. Mol. Neurosci., 2019, Vol. 69, no. 3, pp. 444-449.*
11. Weidemann A., Johnson R.S. Biology of HIF-1alpha. *Cell Death Differ., 2008, Vol. 15, no. 4, pp. 621-627.*
12. Xing J., Lu J. HIF-1α activation attenuates IL-6 and TNF-α pathways in hippocampus of rats following transient global ischemia. *Cell. Physiol. Biochem., 2016, Vol. 39, no. 2, pp. 511-520.*
13. Xu S., Yu C., Ma X., Li Y., Shen Y., Chen Y., Huang S., Zhang T., Deng W., Wang Y. IL-6 promotes nuclear translocation of HIF-1α to aggravate chemoresistance of ovarian cancer cells. *Eur. J. Pharmacol., 2021, Vol. 894, 173817.* doi: 10.1016/j.ejphar.2020.173817.
14. Yeh S.H., Ou L.C., Gean P.W., Hung J.J., Chang W.C. Selective inhibition of early-but not late-expressed HIF-1α is neuroprotective in rats after focal ischemic brain damage. *Brain Pathol., 2011, Vol. 21, no. 3, pp. 249-262.*
15. Yeh W.L., Lu D.Y., Lin C.J., Liou H.C., Fu W.M. Inhibition of hypoxia-induced increase of blood-brain barrier permeability by YC-1 through the antagonism of HIF-1alpha accumulation and VEGF expression. *Mol. Pharmacol., 2007, Vol. 72, no. 2, pp. 440-449.*

Авторы:

Пивоварова Л.П. *— д.м.н., руководитель отдела лабораторной диагностики ГБУ «Санкт-Петербургский научно-исследовательский институт скорой помощи имени И.И. Джанелидзе», Санкт-Петербург, Россия*

Вознюк И.А. *— д.м.н., профессор, главный внештатный специалист-невролог Комитета по здравоохранению Санкт-Петербурга и Министерства здравоохранения по Северо-Западному федеральному округу, профессор кафедры неврологии, заместитель главного врача по неврологии ФГБОУ ВО «Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова» Министерства здравоохранения РФ, Санкт-Петербург, Россия*

Осипова И.В. *— к.м.н., старший научный сотрудник отдела лабораторной диагностики ГБУ «Санкт-Петербургский научно-исследовательский институт скорой помощи имени И.И. Джанелидзе», Санкт-Петербург, Россия*

Арискина О.Б. *— к.б.н., научный сотрудник отдела лабораторной диагностики ГБУ «Санкт-Петербургский научно-исследовательский институт скорой помощи имени И.И. Джанелидзе», Санкт-Петербург, Россия*

Гоголева Е.А. *— к.м.н., старший научный сотрудник, заведующая неврологическим отделением для пациентов с ОНМК ГБУ «Санкт-Петербургский научно-исследовательский институт скорой помощи имени И.И. Джанелидзе», Санкт-Петербург, Россия*

Прохорова М.В. *— младший научный сотрудник неврологического отделения для пациентов с ОНМК ГБУ «Санкт-Петербургский научно-исследовательский институт скорой помощи имени И.И. Джанелидзе», Санкт-Петербург, Россия*

Карпова Н.Г. *— врач клинической лабораторной диагностики, клинико-диагностическая лаборатория ГБУ «Санкт-Петербургский научно-исследовательский институт скорой помощи имени И.И. Джанелидзе», Санкт-Петербург, Россия*

Authors:

Pivovarova L.P., *PhD, MD (Medicine), Head, Laboratory Diagnostics Department, I. Dzhanelidze Research Institute of Emergency Medicine, St. Petersburg, Russian Federation*

Voznyuk I.A., *PhD, MD (Medicine), Professor, Chief Freelance Specialist-Neurologist of the Health Committee of St. Petersburg and the Ministry of Health in the North-Western Federal District, Professor of the Department of Neurology, Deputy Chief Physician for Neurology, First St. Petersburg State I. Pavlov Medical University, St. Petersburg, Russian Federation*

Osipova I.V., *PhD (Medicine), Senior Research Associate, Laboratory Diagnostics Department, I. Dzhanelidze Research Institute of Emergency Medicine, St. Petersburg, Russian Federation*

Ariskina O.B., *PhD (Biology), Research Associate, Laboratory Diagnostics Department, I. Dzhanelidze Research Institute of Emergency Medicine, St. Petersburg, Russian Federation*

Gogoleva E.A., *PhD (Medicine), Senior Research Associate, Head, Neurological Department for Patients with Stroke, I. Dzhanelidze Research Institute of Emergency Medicine, St. Petersburg, Russian Federation*

Prokhorova M.V., *Junior Research Associate, Neurological Department for Patients with Stroke, I. Dzhanelidze Research Institute of Emergency Medicine, St. Petersburg, Russian Federation*

Karpova N.G., *Doctor of Clinical Laboratory Diagnostics, Clinical Diagnostic Laboratory, I. Dzhanelidze Research Institute of Emergency Medicine, St. Petersburg, Russian Federation*

Поступила 13.04.2023
Отправлена на доработку 14.04.2023
Принята к печати 20.04.2023

Received 13.04.2023
Revision received 14.04.2023
Accepted 20.04.2023