УДК 616.8-009.7-002.2-006-02:616.831-008.853.4]-092.9
https://doi.org/10.20538/1682-0363-2021-1-112-118

Effect of malignant growth and chronic neurogenic pain on neurotrophin levels in rat brain

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Aim. To determine neurotrophin levels in the gray and white matter of the brain in rats with tumor growth associated with chronic neurogenic pain (CNP).

Materials and methods. The study included white outbred male rats (n = 74). In the main group, the CNP model was created (by bilateral sciatic nerve ligation), and after 45 days, M1 sarcoma was transplanted subcutaneously (n = 11) or into the subclavian vein (n = 11). Two comparison groups (n = 13 each) consisted of sham-operated animals with M1 sarcoma transplanted subcutaneously and intravenously, but without CNP. Control groups included animals with CNP and sham-operated animals. Rats were euthanized on the 21st day of carcinogenesis. The enzyme-linked immunosorbent assay (ELISA) was used to determine brain levels of brain-derived neurotrophic factor (BDNF) (R&D System, USA & Canada), nerve growth factor (β-NGF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4) (RayBiotech, USA).

Results. CNP caused an increase in β-NGF levels in the cortex and white matter and a rise in BDNF levels only in white matter of the rat brain. Chronic pain stimulated M1 sarcoma growth in both subcutaneous and intravenous transplantation. The dynamics of neurotrophin levels in brain structures differed depending on the tumor site.

Conclusion. The results demonstrated that in both normal peripheral tumor growth and in tumor growth against the background of CNP, changes in neurotrophin levels in the brain of experimental animals can reflect the body reaction to chronic pain and stress caused by peripheral tumor growth.

Key words: M1 sarcoma, chronic neurogenic pain, brain, neurotrophins, nerve growth factor, brain-derived neurotrophic factor.

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

Source of financing. The authors state that they received no funding for the study.

Conformity with the principles of ethics. The study was approved by the Bioethics Committee for Working with Animals of Rostov Research Institute of Oncology (Protocol No. 2 of 29.05.2018).

For citation: Frantsiyants E.M., Bandovkina V.A., Kaplieva I.V., Cheryarina N.D., Neskubina I.V., Surikova E.I., Kotieva I.M., Trepitaki L.K. Effect of malignant growth and chronic neurogenic pain on neurotrophin levels in rat brain. *Bulletin of Siberian Medicine.* 2021; 20 (1): 112–118. https://doi.org/10.20538/1682-0363-2021-1-112-118.

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Влияние злокачественного роста и хронической нейрогенной боли на уровень нейротрофинов в мозге крыс

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РЕЗЮМЕ

Цель – изучить содержание нейротрофинов в сером и белом веществе головного мозга крыс при росте опухоли, сопряженном с хронической нейрогенной болью (ХНБ).

Материалы и методы. Работа выполнена на самцах белых беспородных крыс (n = 74). В основной группе животным моделировали состояние ХНБ (путем двусторонней перевязки седалищных нервов) и через 45 сут перевивали саркому М1 подкожно (n = 11) и в подключичную вену (n = 11). Две группы сравнения (в каждой по n = 13) – ложно оперированные животные с перевивкой саркомы М1 подкожно и внутривенно, но без ХНБ. Контрольные группы – животные с ХНБ и ложно оперированные животные. Забой производили на 21-е сут канцерогенеза. Методом иммуноферментного анализа в головном мозге определяли содержание нейротрофического фактора мозга (BDNF) (R&D System, США, Канада), фактора роста нервов (β-NGF), нейротрофина-3, нейротрофина 4/5 (RayBiotech, США).

Результаты. Показано, что ХНБ вызывает повышение уровня β-NGF в коре и белом веществе и BDNF только в белом веществе головного мозга крыс. Обнаружено, что хроническая боль стимулирует рост саркомы М1 в случае подкожной и внутривенной перевивки. При этом динамика уровня нейротрофинов в структурах мозга была различна в зависимости от локализации опухолевого роста.

Заключение. Полученные результаты свидетельствуют о том, что как при обычном росте опухоли на периферии, так и при росте опухоли на фоне состояния ХНБ изменение уровня нейротрофинов в мозге экспериментальных животных может быть отражением реакции организма на хроническую боль и стресс, сопровождающий рост опухоли на периферии.

Ключевые слова: саркома М1, хроническая нейрогенная боль, головной мозг, нейротрофины, фактор роста нервов, нейротрофический фактор мозга.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Исследование одобрено биоэтическим комитетом по работе с животными РНИОИ (протокол № 2 от 29.05.2018).

Для цитирования: Франциянц Е.М., Бандовкина В.А., Каплиева И.В., Черярина Н.Д., Нескубина И.В., Сурикова Е.И., Котиева И.М., Трепитаки Л.К. Влияние злокачественного роста и хронической нейрогенной боли на уровень нейротрофинов в мозге крыс. *Бюллетень сибирской медицины.* 2021; 20 (1): 112–118. https://doi.org/10.20538/1682-0363-2021-1-112-118.

INTRODUCTION

High prevalence and severity of chronic pain syndromes have caused significant intensification of fundamental and clinical research [1]. Nerve damage was discovered to result in complex molecular and biochemical changes in primary afferents, dorsal horn contours (neurons and especially microglia), as well as at higher levels of neuraxis [2]. The participation of neurotrophins in the processes associated with neuronal injury, chronic pain, and allodynia was revealed. The brain-derived neurotrophic factor (BDNF) has neuroprotective and growth-promoting effects on various populations of neurons after injury. However, data on the BDNF effect on pain and allodynia are contradictory [3]. The role of the nerve growth factor (β-NGF) in regulating synthesis of neurotransmitters and neu-

ropeptides of sympathetic and sensory nerve cells [4] and regeneration of primary nociceptive sensory pathways [5] was shown.

Other neurotrophins with β-NGF expression alter the lineages of primary sensory pathways *in vivo* [6]. Neurotrophin (NT-3) is currently being investigated in clinical trials for the treatment of peripheral neuropathies, which are often associated with chronic pain and allodynia [7]. Recently, neurotrophins and their Trk receptors have been found to be highly active in a variety of cancers, including breast, lung, rectal, pancreatic, prostate and liver cancer, myeloma, and lymphoid tumors [8].

In our previous studies, a violation of the mediator status in the mice brain under the influence of chronic neurogenic pain (CNP) and stimulation of malignant growth in the lungs of rats by chronic pain was demonstrated [9, 10]. The aim of this research was to study the content of neurotrophins in the gray and white matter of the brain of rats in a malignant process associated with chronic neurogenic pain.

MATERIALS AND METHODS

The work was carried out on 74 white outbred male rats weighing 180–220 g, which were bred in the vivarium of Rostov Research Institute of Oncology. The animal work was performed in accordance with the rules of the "European Convention for the Protection of Animals Used in Experiments" (Directive 86/609/EEC) and Order of the Ministry of Healthcare of the Russian Federation No. 267 of 19.06.03 "On Approval of Laboratory Practice Rules". The study was approved by the Bioethics Committee of Rostov Research Institute of Oncology.

In the experimental group, the animals were inoculated with a malignant tumor in the presence of CNP. The animals were anesthetized with Xylazine (Xila drug) at a dose of 0.05 ml / kg of body weight, and after 10 minutes – by Zoletil50 at a dose of 10 mg / 100 g of body weight. Then the CNP model was reproduced: the sciatic nerves were ligated on both sides, and the wounds were sutured. 45 days [10] after the CNP reproduction, 11 animals were subcutaneously (s/c) inoculated with M1 sarcoma according to the standard method, 11 animals were injected in the subclavian vein (i/v) with 0.3 ml of the M1sarcoma cell suspension in saline diluted as (1×10^{6}/l).

The comparison groups ($n = 13$ in each case) included sham-operated animals with inoculation of M1 sarcoma in the same area and at the same dose and volume as in the main groups, but without reproducing the CNP model.

The control groups consisted of 13 animals with reproduced CNP and 13 sham-operated animals, which were decapitated at the same time as the rats of the main and the comparison groups (on the 21st day of carcinogenesis).

After decapitation, the brain was quickly removed, the gray and white matter were isolated on ice and used for the preparation of 10% homogenates in 0.1 M potassium phosphate buffer of pH 7.4, containing 0.1% Tween-20 and 1% BSA. The brain neurotrophic factor (BDNF), as well as the nerve growth factor (β-NGF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4) (RayBiotech, USA) were determined by the ELISA method (R&D System, USA & Canada).

The results were statistically processed using the Statistica 10.0 software. All results were checked for compliance with the law of normal distribution (Shapiro – Wilk test). Data are presented as an arithmetic mean ± standard error of the mean ($M \pm \sigma$). The comparison of quantitative data in independent samples was carried out using the Kruskal – Wallis test; further a posteriori comparisons were performed using the Mann – Whitney test with an adjustment for the significance level.

RESULTS

The average survival of rats with subcutaneous injection of M1sarcoma was 79.2 ± 9.3 days, and with subcutaneous injection of M1 in the presence of CNP – 80 ± 11.8 days. The average tumor volume is shown in Table 1.

Table 1

The effect of chronic neurogenic pain on malignant process reproduction in the subcutaneous fatty tissue of male rats

Parameter	M1 s/c	CNP + M1 s/c
Dead rats from the total number of animals in the group, %	100	100
Tumor foci volume, cm^3, M ± σ	99.6 ± 5.2	145.5 ± 7.1[1]

[1] statistically significant in relation to the tumor volume with subcutaneous inoculation without chronic neurogenic pain ($p < 0.05$).

The average survival after intravenous administration of tumor suspension was 87 days, the maximum one was 128 days. Tumor foci in the lungs

in the presence of CNP appeared in almost all rats; they developed and resulted in the death of the animals (Table 2). In the group of animals with intravenous administration without CNP, one rat died. However, tumor nodes were not found in its lungs; the survival was 36 days longer than the average survival in the main group of animals with CNP.

Table 2

The effect of chronic neurogenic pain on malignant process reproduction in the lungs of male rats

Parameter	M1 i/v	Pain + M1 i/v
Dead rats from the total number of animals in the group, %	17	86
Presence of tumor foci in the lungs, volume, cm^3, $M \pm \sigma$	–	86 55.44 ± 6.2

The presented results unambiguously indicate that CNP not only stimulates malignant tumor growth, but also changes its biological aggressiveness, allowing it to develop in orthotopic inoculation. In this situation, it was interesting to determine the role of neurotrophins in the animals' brain in the manifestation of the altered aggressiveness of the neoplasm.

First of all, the CNP creation in rats was found to result in a change in some neurotrophins in the gray and white matter of animals without tumors (Table 3). Thus, the β-NGF levels increased by 1.5 times and 1.7 times, respectively. The BDNF content increased only in the white matter of the rat brain, by 1.6 times. Statistically significant changes in the content of NT-3 and NT-4 under the influence of CNP were not found.

Next, the content of neurotrophins in the brain of rats with traditional subcutaneous inoculation of M1 sarcoma, in an independent variant and in the presence of CNP was studied. When the tumor volume reached 99.6 ± 5.2 cm^3 (pre-terminal period of life), the level of β-NGF increased by 2.9 times relative to sham operated animals only in the gray matter of the brain, while in the white matter, its level reduced by 1.5 times (Table 3). The levels of BDNF and NT-4 had no statistically significant changes, and NT-3 exceeded the control values by 1.9 and 1.4 times in the gray and white matter of the brain, respectively.

With the growth of M1 sarcoma in the subcutaneous tissue in the presence of CNP, there was an increase in the level of β-NGF in the gray matter of the rat brain by 2.2 times relative to animals without CNP and by 4.1 times relative to rats without a tumor, but with CNP (Table 3). The level of BDNF in the gray matter of these rats was 1.4 times higher than in animals without CNP and 1.7 times higher than in animals with CNP alone.

Table 3

The level of neurotrophins in the brain of rats with different types of M1 sarcoma growth and in the presence of chronic neurogenic pain, $M \pm \sigma$

Parameter	NT-3 (pg/g of tissue)	NT-4 (pg/g of tissue)	BDNF (pg/g of tissue)	β-NGF (pg/g of tissue)
Control rats				
Gray matter	55.0 ± 5.1	11.3 ± 1.9	3,367.6 ± 352.9	362.1 ± 28.4
White matter	58.0 ± 6.3	7.4 ± 0.8	9,170.5 ± 861.7	886.0 ± 74.1
Rats with CNP				
Gray matter	56.1 ± 4.8	15.7±2.6	2,900.7 ± 276.3	553.9 ± 51.8[3]
White matter	67.0 ± 5.3	6.6±0.8	14,393.3 ± 1121.5[3]	1,501.7 ± 126.7[3]
Rats with s/c M1 sarcoma				
Gray matter	104.8 ± 9.2[3]	13.5 ± 1.4	3,511.0 ± 346.9	1,036.2 ± 92.4[3]
White matter	82.2 ± 7.1[3]	6.1 ± 0.7	10,287.7 ± 975.8	588.9 ± 55.3[3]
Rats with s/c M1 sarcoma + CNP				
Gray matter	62.3 ± 5.7[1]	12.7 ± 1.3	5,015.9 ± 423.6[1,2,3]	2,275.8 ± 214.1[1,2,3]
White matter	54.9 ± 4.6[1,2]	6.0 ± 0.7	3,440.6 ± 296.8[1,2,3]	1,452.4 ± 136.5[1,3]
Rats with i/v M1 sarcoma				
Gray matter	81.6 ± 7.9[3]	11.8 ± 1.3	4,534.6 ± 411.8[3]	1,747.3 ± 154.6[3]
White matter	147.7 ± 12.6[3]	6.9 ± 0.8	14,614.7 ± 926.7[3]	1,573.0 ± 168.1[3]
Rats with i/v M1 sarcoma + CNP				
Gray matter	44.4 ± 7.0[1]	12.6 ± 1.3	5,043.7 ± 396.7[2,3]	474.8 ± 49.6[1,3]
White matter	65.9 ± 6.3[1]	8.1 ± 1.0	22,073.7 ± 1654.8[1,2,3]	506.3 ± 45.9[1,2,3]

[1] statistically significant difference from the parameter in the group without CNP; [2] statistically significant difference from the parameter in the group with CNP; [3] statistically significant difference from the parameter in the group of control animals ($p < 0.0056$).

The NT-3 content in this sample was reduced compared to the M1 rats and did not have statistically significant differences from the corresponding control. In the white matter of the rat brain with the growth of M1 sarcoma in the subcutaneous tissue in the presence of CNP, there was an increased level of β-NGF, 2.5 times higher than the corresponding value for animals with the growth of M1 sarcoma in the subcutaneous tissue without CNP, and it did not differ significantly from the CNP values in the control. The BDNF level in the white matter of these rats was almost 3.0 times lower than the value in animals without CNP and 4.2 times lower than the CNP control value. Normalization of NT-3 was identified (Table 3).

In animals in which the tumor process in the lung did not develop after intravenous administration of the tumor suspension, in the gray and white matter of the brain, the β-NGF level increased by 4.8 times and 1.8 times, respectively, the BDNF level – by 1.3 times and 1.6 times, respectively, and the NT3 level – by 1.5 times and 2.5 times, respectively. In gray and white matter of the rats with a developed tumor process in the lung after administration of the tumor suspension in the presence of CNP, only the BDNF level increased by 1.7 times and 1.5 times, respectively, but the β-NGF level in the white matter only decreased by 3 times relative to control rats with CNP (Table 3).

DISCUSSION

This study showed that CNP reproduced by bilateral ligation of sciatic nerves causes an increase in the level of BDNF in the white matter and NGF-β in the cortex and white matter of the rat brain. This is consistent with numerous reference data.

NGF is considered to be a chronic pain mediator [11]. Anti-NGF therapy may be effective in reducing pain in experimental models [12]. BDNF is also involved in the mechanisms of neuropathic and inflammatory pain [13]. Neurotrophins mediate their biological functions through two transmembrane receptors: p75NTR (p75 pan-neurotrophin receptor) and TrkB receptor. Anti-NGF therapy may be useful for treating cancer pain, as it can suppress inflammation and then inhibit nerve sensitization [14]. In pain, BDNF is activated, among others, in the cerebral cortex [13, 15] and the spinal cord [16].

The authors of the present study have not found studies on neurotrophins in the brain of animals with the growth of a malignant tumor on the periphery, as it was shown in this research with the growth of M1 sarcoma in the subcutaneous tissue and the lung.

It was demonstrated that changes in the levels of some neurotrophins in therat brain tissue during subcutaneous growth of M1 were characterized by an increase in the NT-3 level in the cortex and white matter of the brain and a rise in the level of β-NGF in the cortex, while there was a decrease in β-NGF in the white matter. In the meantime, the intravenous administration of the tumor suspension, which did not result in tumor growth in the lung, had similar features in terms of the content of neurotrophins in the brain structures. Thus, an increase in the NT-3 level in the cortex and white matter and a rise in the β-NGF level in the cortex were found. Additionally, an increase in the BDNF content in the cortex and white matter and elevated β-NGF level in the white matter were discovered. It is possible that such changes in the level of neurotrophins in the brain of animals were caused bu the subcutaneous growth of M1 following stress accompanying tumor suspension administration and tumor growth. In case of intravenous administration of M1the changes may be caused not only by a stress response to the administration, but also by effective work of antitumor mechanisms that prevented tumor

BDNF is known to play a critical role in the stress response, as evidenced by its altered expression in the brains of stressed animals [17, 18]. Reports have shown that the functionality of the hypothalamus regions and the prefrontal cortex (PFC) of the brain is required for generation of the response to stress and pain [19]. BDNF is highly expressed in these regions, and its expression changes significantly in response to stress [18]. BDNF and β-NGF play an important role in the survival, differentiation, and plasticity of neurons during development and adulthood. When exposed to stress, they are good candidates for transmitting the influence of stress factors, causing changes in brain functioning [20]. β-NGF is required for the survival, proliferation, and differentiation of neurons in the peripheral and central nervous systems [21].

The comparative analysis of parameters in groups of animals with different variants of tumor growth in the presence of CNP is of great interest. This experiment combines chronic pain, tumor

growth, and stress from tumor suspension administration and further growth of the neoplasm. In case of the traditional subcutaneous growth of M1 sarcoma in the presence of CNP, the change in the NGF level reflected the CNP state, while the change in the BDNF level rather reflected the stress response [22].

Everything is more complicated in case of a tumor in the lung in the presence of CNP. A drastic decrease in the NGF level in the cortex and white matter, as opposed to the group of animals with administered tumor suspension, not accompanied by tumor growth in the lung, rather indicates depletion of this protein in the brain structures. The BDNF content in the gray and white matter indicates a pronounced response to stress, which is confirmed by a change in its expression in the brain of stressed animals [17, 18].

CONCLUSION

Thus, the obtained results indicate that during normal tumor growth both on the periphery and in the presence of CNP, changes in the level of neurotrophins in the brain of experimental animals may reflect the body response to chronic pain and stress accompanying tumor growth on at the periphery.

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Authors contribution

Frantsiyants E.M., Kaplieva I.V. – conception and design of the experiment. Frantsiyants E.M., Kaplieva I.V., Bandovkina V.A. – analysis and interpretation of the obtained results. Bandovkina V.A., Surikova E.I. – drafting and editing of the manuscript, critical revision of the manuscript for important intellectual content. Trepitaki L.K., Neskubina I.V. – carrying out of the experiment. Cheryarina N.D., Surikova E.I. – performance of the enzyme immunoassay. Frantsiyants E.M., Kotieva I.M. – final approval of the manuscript for publication.

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Received: 18.11.2019
Accepted: 30.04.2020