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The Effect of Cryopreserved Cord Blood Nucleated Cells on Pathological Processes in the Progressive Aging of the Brain (Experimental Study)

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Abstract—This work presents data on morphometric indices of the vascular bed and brain substance of spontaneously hypertensive *SHR* rats, which may be considered evidence of the developing pathological brain aging processes in these animals. Chronic alcohol intoxication aggravates the neurodegeneration, significantly reducing the indices of the neuroglial index, the number of functioning vessels and activating the LPO processes. A single intraperitoneal administration of cryopreserved human cord blood nucleated cells in a dose of (1–5) × 10^7/kg promoted the regeneration of neurocells, the stimulation of angiogenesis and an increased level and quality of neurotissue metabolism, reducing the signs of dystrophic, destructive and pathologically altered compensatory adaptive processes in the rat's brain as a result of the restoration of its microhemocirculation and cytoarchitecture.

Keywords: progressive aging of brain, arterial hypertension, chronic alcohol intoxication, cord blood

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INTRODUCTION

The leading mechanism of aging of the whole organism is age-related changes in the brain. Cerebrovascular diseases occupy the leading position in the development of progressive aging processes of the brain (from molecular genetic to systemic-functional diseases), which are diagnosed in 20-30% of cases in working-age people, and the mortality from this pathology reaches 11-12% in economically developed countries [7].

Arterial hypertension (AH), alcohol abuse, diabetes, smoking and other factors of the external and internal environment of the body are modifying effects that promote the development of the brain's progressive aging processes.

Disorders of cerebral blood flow with hypoxia of brain matter and a cascade of metabolic changes involve in the aging process the functional structures of all levels of nervous regulation of the organs and systems of the body, which leads to the development of diseases associated with age [5, 7, 8].

A complex and diverse combination of primary
1 destructive and secondary reparative changes and adaptive processes is formed on all structural and functional levels of the cerebral vascular system in the process of AH development and progression.

Resistant AH leads to a change in the architectonics of the vascular bed and a violation of the microcirculation of the brain, increasing the degree of ischemia and degenerative-dystrophic lesions of its tissue, which can be seen as evidence of a breakdown in the autoregulation of cerebral blood flow.

As a result, AOF accumulation, depletion of endogenous antioxidant stocks and activation of lipid peroxidation of cell membranes occur, which lead to brain cell death [7, 8].

Alcohol intake as an emotional and psychological compensation for an unfavorable external and/or internal environmental factor also contributes to the disruption of the functional and morphological parameters of the brain tissues. Chronic alcohol intoxication (HAI) causes neurodegeneration of the brain, affecting a decrease in the intensity of neurogenesis and the number of functioning vessels, neuronal death and increased intensity of LPO. The combination of persistent AH and HAI aggravates the progressive organic lesion of the central nervous system [17, 19].

Considering the severity of the consequences of the development of cerebrovascular diseases and the impossibility of changing the progressive course of the vascular process by traditional methods of treatment, a search is under way for fundamentally new therapies [5, 8]. These methods include stem cell therapy, which serves as a valuable source of both neuron-like cells and neurotrophic factors and is used to treat a number of neurodegenerative and cerebrovascular diseases [1, 12, 14, 15].

The goal of our study was to evaluate morphological and morphometric parameters and LPO in brain tissue of *SHR* rats with a model of progressive brain aging 30 days after the administration of cryopreserved human cord blood nucleated cells.

MATERIALS AND METHODS

All studies were performed on 28 mature (12–13 months) spontaneously hypertensive male rats of the *SHR* line. As a normotensive control, we used 7 white non-native male rats of the corresponding age.

The animals of the *SHR* line were divided into four groups (7 each): first – intact (*SHR*); second – animals with HAI (*SHRalk*); third – rats after administration of cryopreserved cord blood (CB) nucleated cells (NCc) (*SHR* + CB); fourth – rats with HAI after the administration of NCc CB (*SHRalk* + CB).

HAI was performed in rats in accordance with model [4] for 10 months, starting from the age of two months, without interrupting this process until the animals were withdrawn from the experiment. All rats were withdrawn from the experiment on time, corresponding to the 30th day after the administration of the PCK PC.

Cryopreserved human NSC CB was obtained in a low-temperature bank of the Institute for Problems of Cryobiology and Cryomedicine of National Academy of Sciences of Ukraine (Kharkov) [2]. Unfrozen samples of the NSC CB were injected once intraperitoneally at a dose of $(1–5) \times 10^7$ cells per 1 kg of body weight in a volume of 1 ml of CB plasma.

The material for morphological and morphometric studies was the rat brain, fixed in a 10% neutral formalin, from which we excised samples from the 0.4 cm anterior central convolution, including the pia mater, gray and white matter of the brain, cortex and subcortical structures.

The preparations were stained with hematoxylin and eosin (for a general assessment of the state of the pia mater and brain matter), picrofuxin according to Van Gieson (for the detection and evaluation of the degree of development of collagen fibers in the stroma of the pia mater and in the vessel wall), toluidine blue according to Nissl (for studying the state of the neuronal population and the glial component of the cell population and morphometric studies). The density of neurons, gliocytes, functioning (open) capillaries (in 1 mm^2) in the III-V layers of the cerebral cortex and the value of the neuroglial index (the number of glial cells per neuron) were determined. All morphometric and morphological studies were performed on an Olympus BX-41 ("Olympus Corporetion", Japan) microscope using the Olympus DP-Soft computer program (Version 3: 1).

LPO intensity was determined by spectrophotometry, according to the rate of accumulation of its final MDA product. The MDA level in the homogenate of the brain tissue was calculated in the presence of prooxidants (Mora salt and ascorbic acid) (induced by LPO) and in their absence (spontaneous LPO) on the 30th day after the administration of NCc CB.

We used Excel Microsoft (2007) for the statistical processing of the data. The obtained digital data were presented as the arithmetic mean (M) and the error of the arithmetic mean (m). Based on the Mann-Whitney U-test, the probability of differences (p) was calculated between groups.

Differences were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

Genetically determined spontaneously hypertensive *SHR* rats, characterized by elevated blood pressure [9, 10], are a promising model for the study of a number of cerebrovascular diseases and vascular dementia [12, 17].

As a result of a microscopic study of the arterial vessels of the pia mater and the brain matter of brain tissue preparations in intact spontaneously hypertensive *SHR* rats of the first group, we detected morphological changes characteristic of hypertension: hypertrophy and hyperplasia of smooth muscle cells, spasm and hyalinosis of the part of the walls of arteries and arterioles, and plasma impregnation of the blood vessel walls.

There were signs of congestion and a decrease in tone of venous vessels. Some of the capillaries in the brain tissue were in a collapsed state with slightly discernible lumens, some dilated and with signs of stasis.

The density of functioning capillaries was 170.23 ± 7.01 sp/mm^2, which is significantly lower than in the normotensive rats (Table 1).

In all the observations of the cortex and subcortical structures, foci of ganglion-cell rarefaction and desolation with an unevenly expressed decrease in the density of neurons were detected.

The density of neurons in the III-V layers of the cortex was 1116.15 ± 41.97 sp/mm^2, which is significantly lower compared with the corresponding index in normotensive rats. A diffuse increase in the density of gliocytes was observed in the fine-grained, pale neuropil. The density of neuroglia cells in the III-V layers of the cortex on the average was 1655.68 ± 52.26 sp/mm^2 in the first *SHR* group, the value of the neuroglial index was 1.48 ± 0.04, which also significantly exceeded the corresponding parameters in normotensive animals (see Table 1). The observed morphological and morphometric changes in the vascular component of brain tissue, degenerative changes in neurons, their selective atrophy and activation of proliferation of neuroglia cells can be considered as evidence of the development of pathological aging processes in *SHR* rat brain.

A number of morphological changes were detected in all studied structural components of the brain tissue

Table 1. Parameters of compensatory processes in brain tissue of experimental animals

Group	Neuroglial index	Density, sp/mm^2		
		neurons	gliocytes	functioning capillaries
Normotensive	0.85 ± 0.02	1473.09 ± 41.46	1253.43 ± 45.33	228.81 ± 9.61
1	1.48 ± 0.04*	1116.15 ± 41.97*	1655.68 ± 52.26*	170.23 ± 7.01*
2	2.27 ± 0.06*, **	829.21 ± 30.20*, **	1879.46 ± 73.02*, **	113.95 ± 8.79*, **
3	1.17 ± 0.03**	1263.04 ± 38.28	1474.47 ± 62.14**	201.81 ± 11.30**
4	1.26 ± 0.04***	1202.64 ± 34.97***	1521.14 ± 65.30***	192.20 ± 9.15***

* Differences are significant between the normotensive control group and the first, second groups, $p < 0.05$; ** the differences are significant between the first group and the second, third group, $p < 0.05$; *** differences are significant between the second and fourth group, $p < 0.05$.

in the rats from the second group, indicating the negative effect of HAI, – signs of dystrophic, destructive and compensatory-adaptive processes were observed. In pia mater, these changes were characterized by pronounced compensatory hypertrophy and hyperplasia of the smooth muscle cells and the development of sclerotic changes in the wall of the arterial vessels, congestive veins with the formation of focal extravazates. We noted the proliferation of functionally active fibroblasts with the development of an unevenly expressed diffuse fibrosis in the stroma. The neuronal population of the cortex and subcortical structures was characterized by degenerative changes in neurons followed by necrosis and neuronophagy, the formation of numerous foci of ganglion cell rarefaction and depletion of brain matter. The average density of neurons in the III-V layers of the cortex for the second group was 829.21 × 0.20 sp/mm^2, which is significantly below the corresponding indices in normotensive animals and rats from the first group (see Table 1).

In the neuroglia of the rats from the second *SHR*alk group, diffuse-focal gliosis was observed, due to hyperplasia and hypertrophy of astrocytes with the formation of numerous glial nodules in the nerve cell depletion foci of the cortex and subcortical formations. The density of neuroglia cells in III–V layers of the cortex in the *SHR*alk group was 1879.46 ± 73.02 sp/mm^2 on average, the value of the neuroglial index – 2.27 ± 0.06, which is significantly higher than the corresponding indices in intact animals of this line and normotensive control (see Table 1). Small caliber arteries and most capillaries of the cortex, white matter and subcortical formations had poorly discernible lumens, with a decrease in tone and signs of stasis. Morphometrically, the density of functioning capillaries was 113.95 ± 8.79 sp/mm^2, which is significantly lower than in normotensive control and in intact spontaneously hypertensive rats from the first group (see Table 1).

Thirty days after the intraperitoneal injection of NSC CB into *SHR* rats, changes formed under the influence of the preceding hypertension were detected in arterial vessels of pia matter. At the same time, there was a decrease in the degree of hypertrophy and hyperplasia of smooth myocytes and intermuscular sclerosis in the arteries of the muscle type, the absence of destruction of the vascular wall with a significant increase in the content of functionally active capillaries compared to hypertensive animals from the first group without cell therapy (see Table 1). The observed changes in blood vessels caused a decrease in the effect of the ischemic factor on the neuronal population of the cortex and subcortical structures, and as a result, degenerative changes in nerve cells were less often detected than in intact hypertensive animals. The average density of neurons in the III–V layers of the cortex was 1263.04 × 8.28 sp/ mm^2 in the third group.

The density of functioning capillaries was significantly higher compared to the data of the first group and amounted to 201.81 ± 11.30 sp/mm^2, and the density values of gliocytes and the neuronoglial index were 1474.47 ± 62.14 and 1.17 ± 0.03 respectively, which is significantly lower in comparison with the indices in intact animals (see table 1). Acute focal destructive changes in brain tissue (*SHR* + PC) were not seen in the third group.

As a result of a microscopic and morphometric study of brain preparations from the region of the precentral gyrus in the animals of the 4th group (*SHR*alk + PC), we obtained the data indicating the morphological changes in the studied structural components.

In the pia matter, signs of moderate arterio- and arteriolosclerosis with a thickening of their walls and a narrowing of the lumen, venous plethora with fine-focal perivascular hemorrhages, edema of the sclerotized stroma were observed, but the severity and prevalence of the detected changes was reduced in comparison with the animals from the second group (*SHR*alk).

In the cortex and subcortical formations, foci of ganglionic cell desolation and rarefaction with diffuse focal proliferation of neuroglia cells were detected on brain preparations of rats of the fourth group in 60% of observations, while in the second comparison group these changes were recorded in all observations. Neuronal population is heterogeneous, – in addition to

Table 2. The level of MDA in brain tissue of experimental animals

Group	Nmol MDA/mg of brain tissue		
	initial reaction	spontaneous reaction	induced reaction
Normotensive	0.10 ± 0.01	0.43 ± 0.08	0.51 ± 0.04
1	0.26 ± 0.02*	0.64 ± 0.05*	0.91 ± 0.12*
2	0.40 ± 0.05*, **	0.97 ± 0.15*, **	2.32 ± 0.36*, **
3	0.25 ± 0.04	0.66 ± 0.07	0.88 ± 0.05
4	0.31 ± 0.03***	0.78 ± 0.07***	1.63 ± 0.26***

* Differences are significant between the normotensive control group and the first, second groups, $p < 0.05$; ** the differences are significant between the first group and the second, third group, $p < 0.05$; *** differences are significant between the second and fourth group, $p < 0.05$.

normal neurons, individual cells or their groups with degenerative changes, chromatolysis, karyolysis and neuronophagy were observed less often than in the second comparison group, that was morphometrically confirmed by a significant increase in the density of neurons (1202.64 ± 34.97 sp/mm^2), a decrease in the gliocyte density (1521.14 ± 65.30) and the value of the neuronoglial index (1.26 ± 0.04), $p < 0.05$.

Intracerebral vessels were characterized by mild arteriosclerosis and hyalinosis, sometimes with signs of spasm and plasma impregnation, not clearly expressed venous fullness, stasis in separate capillaries and an increase in the content of functioning capillaries, which was characterized morphometrically by a significant increase in their density (192.20 ± 9.15) compared with the third group.

Focal destructive changes in the acute period were not found in the brain tissue of animals of the fourth group.

In *SHR* rats with signs of progressive aging of the brain, in the etiology of development of which AH dominates as an independent factor, and in combination with intoxication with alcohol substitutes, intraperitoneal injection of NSC CB stimulates neuro- and angiogenesis, reducing the signs of dystrophic and destructive processes in brain tissue, which affects the formation of compensatory-adaptive reactions. The successful use of NSC CB for the treatment of neurological diseases in the experiment is not in doubt [1, 12, 14, 15].

The work published by J. M. Castellano et al. in 2017 confirmed the presence of factors in CB contributing to the revitalization of age-related brain tissue disorders [13]. Interesting data were obtained by the scientists of Stanford University and published in the "Nature" journal in 2018 [20]. It was shown that the injection of blood from old mice to young mice led to premature aging of the brain.

It transpired that under these conditions a specific protein is activated, the suppression of which can halt the age-related changes in the CNS [20].

The question of the mechanisms of action and the fate of donor cells is still unresolved and there are different opinions on the matter. Moreover, the administration method does not always play a decisive role: the best neurotherapeutic result can be obtained not only with intracerebral or intravenous transplantation of CB cells, but also with intraperitoneal and intramuscular injection [1, 13, 16, 21]. The increase in the number of markers of transplanted cells in the examined organs described by A. O Solovieva et al. [11], in particular in the brain, after 1 and 3 months indicates plasticity, proliferation and differentiation of transplanted stem cells in recipient organs. Another mechanism involves the therapeutic effect of stem cells through their soluble endogenous factors and biologically active substances that provide suitable conditions for the regeneration of neural cells, angiogenesis, and improving the level and quality of metabolism of nervous tissue. This contributes to the recovery of microhemocirculation and cytoarchitectonics of the brain [16].

Since the activation of LPO takes place in the pathogenesis of cerebrovascular diseases, and oxidative stress is one of the factors in the development of premature aging [8, 12, 22], it was of interest to elucidate the intensity of LPO in the brain tissue of the first group of rats with progressive aging of the brain and the effect of the NSC CB administration on this process. The obtained results showed that in all three investigated reactions, the level of MDA in brain tissue homogenate in the first group of intact rats was 160; 48 and 78% higher than in normotensive control, $p < 0.05$ (Table 2).

HAI was accompanied by further activation of LPO processes.

The MDA level in the rats of the second group significantly exceeded this index in intact rats by 53 and 51% for the initial and spontaneous LPO reactions, respectively. The introduction of the NSC CB in intact rats of the third group caused a decrease in MDA level in all three reactions after 30 days of follow-up, but these changes were statistically insignificant (see Table. 2). The introduction of NSC CB in rats with HAI of the fourth group led to a significant

decrease in the MDA content in all LPO reactions (see Table 2).

It was shown in works [12, 18, 22] that LPO processes occupy a central place in the development of pathologies associated with cerebrovascular diseases, which can be the cause of structural and functional damage to the brain. The intensity of lipid peroxidation (determined by MDA level) in the brain tissue of spontaneously hypertensive rats (as compared to normotensive control) that we observed may indicate a decrease in antioxidant protection in these animals, which is one of the reasons for the change in the structure of brain tissue in hypertension and cerebral circulation [12, 22]. The obtained results on the influence of HAI on the LPO processes in brain tissue of *SHR* rats can be explained by the fact that the neurotoxic effects of alcohol and its metabolite (acetaldehyde) are realized through general pathogenetic mechanisms such as oxidative stress and enhanced formation of free radicals and nitric oxide.

Summarizing the obtained data on the intraperitoneal injection of NSC CB concerning the POL processes, we can speculate on their ambiguous effect on the prooxidant-antioxidant balance in the brain of experimental rats. CB cells can exhibit pronounced antioxidant properties, activating the antioxidant defense system and inhibiting excessive manifestation of ethanol-dependent oxidative stress (data for the fourth group). The results obtained agree with the data presented in paper [3]. The authors showed the possibility of stem cells (allogeneic mononuclear bone marrow cells were used in the work) influencing LPO processes, reducing the level of the final product of oxidative reactions in the brain tissue in comparison with the control.

The antioxidant properties of NSC CB are shown in [6] on the model of ischemic stroke in rats. The authors attribute the therapeutic effect of the PC both to its direct antioxidant activity and to the stabilizing effect of the PCK SC on biomacromolecules capable of activating the antioxidant defense system in experimental animals. In our work, NSC CB did not affect the activity of LPO processes in the initial and spontaneous reactions in intact spontaneously hypertensive rats of the *SHR* line. It is possible that cryopreserved CB cells cannot affect the genetically determined level of LPO. Given the above, LPO processes do not dominate the list of causes that cause structural changes in brain tissue in *SHR* rats.

CONCLUSIONS

The observed morphological and morphometric changes in the vascular component of brain tissue, degenerative changes of neurons, their selective atrophy and the activation of proliferation of neuroglia cells can be considered evidence for the development of processes of pathological brain aging in intact *SHR* rats. In this situation, the progressive aging of the brain is only potentiated by chronic alcohol intoxication.

Intraperitoneal administration of cryopreserved cord blood nucleated cells to *SHR* rats with progressive brain aging (against a background of genetically determined arterial hypertension and intoxication by alcohol substitutes) promotes the regeneration of neural cells, stimulation of angiogenesis and an increase in the level and quality of metabolism in nervous tissue, reducing the signs of dystrophic, destructive and pathologically altered compensatory -adaptive processes in the brain as a result of the restoration of its microhemocirculation and cytoarchitecture.

The introduction of cryopreserved cord blood nucleated cells helps to reduce the MDA level in the brain tissue of rats with chronic alcohol intoxication, but does not affect the genetically determined process of LPO in the brain of control spontaneously hypertensive rats.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests. The authors declare that they have no conflict of interest.

Statement on the welfare of animals. The experiments were performed according to regulations approved by the Committee on Bioethics of the Institute for Problems of Cryobiology and Cryomedicine of the National Academy of Sciences of Ukraine and coordinated with the regulations of the "European Convention for the Protection of Vertebrates Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986).

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SPELL: 1. reparative