**UDC 616.831-008.9:577.121.7:616.12-008.331.1-085.225]-092.9**
**DOI https://doi.org/10.32782/2226-2008-2025-4-1**

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# FEATURES OF CEREBRAL ENERGY METABOLISM IN CHRONIC ARTERIAL HYPERTENSION AND UNDER CORRECTION WITH BETA-BLOCKERS OF DIFFERENT GENERATIONS

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Given the high prevalence of arterial hypertension in the world and in our country in particular, as well as the tendency to increase in the number of younger patients, it becomes important to examine in greater depth the characteristic alterations in organs and tissues that occur under prolonged blood pressure elevation and pathogenetic treatment.

**The aim of the study** is to examine the characteristic changes in neuronal parameters related to energy metabolism in animals with spontaneous arterial hypertension and in correction with beta-blockers of different generations.

**Materials and methods.** The study involved 40 male rats with spontaneous arterial hypertension (SHR) and 10 normotensive control normotensive Wistar-Kyoto rats (WKR). The animals were divided into 5 experimental groups of 10 rats each. Different groups of experimental animals with spontaneous arterial hypertension were administered propranolol, carvedilol, and hypertril in therapeutic doses (groups 3, 4 and 5). In the experimental study, massometric, biochemical and statistical methods were used. The levels of ATP, malate, COX, and mitochondrial enzymes in animal brain homogenates were studied biochemically.

**Results.** In groups of rats that received beta-blockers with different properties (groups 3, 4 and 5), blood pressure was quickly stabilized to target values. Propranolol has showed a negative effect on both the content of ATP and malate as compared to the SHR results. Carvedilol has not changed the total pool of macroergic compounds ATP and malate concentrations, leaving the values at the levels of hypertensive rats. Both beta-blockers have shown no significant differences in the reduced activity of COX, mt-AsT and mt-CK. The hypertril administration has helped to completely restore the ATP and malate production, mt-AsT and mt-CK activity to normative values along with partially restored COX, in particular, the activity of mt-AsT and mt-CK enzymes was increased as compared to the SHR values.

**Keywords:** arterial hypertension, energy metabolism, beta-blockers, hippocampus, SHR.

**УДК 616.831-008.9:577.121.7:616.12-008.331.1-085.225]-092.9**

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**ОСОБЛИВОСТІ ЦЕРЕБРАЛЬНОГО ЕНЕРГООБМІНУ ПРИ ТРИВАЛІЙ АРТЕРІАЛЬНІЙ ГІПЕРТЕНЗІЇ ТА ЗА УМОВ КОРЕКЦІЇ SS-БЛОКАТОРАМИ РІЗНИХ ПОКОЛІНЬ**

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Проводилась оцінка стану церебрального енергообміну в умовах артеріальної гіпертензії та тривалого лікування ß-блокаторами різних поколінь. Різним групам експериментальних тварин зі спонтанною артеріальною гіпертензією вводили анаприлін, карведилол та гіпертрил у терапевтичних дозах. Біохімічно досліджували показники енергообміну в гомогенатах головного мозку тварин. Встановлено, що артеріальна гіпертензія супроводжується значним енергетичним дефіцитом. Тривала корекція підвищеного тиску анаприліном або карведилолом не дає позитивного впливу на енергозабезпечення нервових клітин, введення гіпертрилу сприяє повному відновленню показників енергообміну до рівня нормотензивних тварин.

**Ключові слова:** артеріальна гіпертензія, енергетичний обмін, ß-блокатори, гіпокамп, щури SHR.

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## Introduction

Hypertensive disease (HD) is currently one of the most common cardiovascular diseases. According to the WHO study results, over 1.28 billion adults aged 30–79 years are affected by HD worldwide, and the number is progressively growing [1]. In 2019, the mean age-standardized prevalence of HD among adults aged 30–79 years was 34% in men and 32% in women [2].

The disease progression results in target organ damage with significant complications, such as retinopathy, chronic heart failure, myocardial infarction, that is characteristic of hypertension pathogenesis [3]. The brain is among the first organs affected by elevated blood pressure (BP) [4]. The chronic hypertension-mediated cascade of functional and morphological changes in brain structures is manifested by microaneurysms, atherosclerotic changes, vascular remodeling, white matter damage (demyelination and lacunar lesions), eventually leading to the development of vascular dementia or stroke [5]. From a clinical standpoint, an important attribute of brain damage in HD is a long asymptomatic period or minor cognitive and memory disorders in the initial period.

Viewed in pathogenetic way, damage to the brain in HD primarily results from alterations in the small peripheral vascular walls and ischemia, giving rise to destructive processes that are caused by an imbalance between intensive energy metabolism with a high brain tissue demand for oxygen and glucose as well as blood supply impairments [6]. Glucose is the main metabolic substrate to meet high brain energy requirements due to its easy transport across the blood-brain barrier (BBB) into neurons. Glucose is converted to pyruvate during aerobic glycolysis, which is further irreversibly transformed to acetyl-coenzyme A regulated by the pyruvate dehydrogenase complex. Acetyl-coenzyme A, in turn, reacts to begin the tricarboxylic acid cycle, providing the production of reducing equivalents required for oxidative phosphorylation and ATP generation. Accordingly, inadequate oxygen and glucose supply to brain tissue mediates energy deficit worsening due to the processes mentioned above [7].

Energy deficiency due to impaired ATP-producing mitochondrial function initiates mechanisms of chronic excitotoxicity which is maintained for a long time owing to excessive calcium influx into neurons and the induction of cascade intracellular neurodegenerative reactions. Decreased activity of ATP-dependent enzymes (Na+/K+-ATPases), which maintain the cell membrane potential, is a key point to cell depolarization and attenuation of the NMDA receptor blockage by magnesium even at normal concentrations and activity of excitatory amino acids [8].

A principal component of excitotoxicity in the ischemic brain is considered to be insufficient astrocyte glutamate uptake, which entails its high extracellular concentrations, while a high density of NMDA and non-NMDA receptors in neurons and oligodendrocytes makes them extremely sensitive to glutamate. Excitotoxicity contributes to neuronal cell death through energy depletion (due to $Na^+$ extrusion after mediated influx into the channel) in combination with calcium-mediated mitochondrial damage and generation of reactive oxygen species (ROS). This mechanism is responsible for neuronal death in Alzheimer's disease and other neurodegenerative processes accompanied by cerebral ischemia [9].

The association between the occurrence of energy deficiency in brain tissues and arterial hypertension (AH) provokes the question as to how the treatment of this disease affects the energy production processes in neurons. This is especially true for beta-blockers, which are considered valuable agents and first-line therapy for AH management [10]. Of note, notwithstanding a decade-long use in various treatment regimens, insights into the effect of beta-blockers on the neuronal energy homeostasis remain imperfect [11; 12].

**The aim of the study** is to examine the characteristic changes in neuronal parameters related to energy metabolism in animals with spontaneous arterial hypertension and in correction with beta-blockers of different generations.

## Materials and methods

The studies used 8-month-old 40 male second generation spontaneously hypertensive rats (SHRs) with an original weight of 280–300 g and 10 normotensive control age-matched male Wistar-Kyoto rats (WKRs) with a mean weight of 200–220 g (8-month-old). BP (BP systolic/BP diastolic) values in SHRs were within a range of 178.1 ± 2.61/96.5 ± 2.51 mm Hg, while the control values were 118.1 ± 10.9/66.9 ± 2.1 mm Hg. Experimental studies were carried out on the basis of the Educational and Scientific Medical Laboratory Center with a vivarium of Zaporizhzhia State Medical and Pharmaceutical University strictly according to Ukrainian National Standard "General Ethical Principles for Animal Experiments" (Ukraine, 2001) aligned with the Council Directive 2010/63EU provisions of Directive 2010/63/EU of the European Parliament and the Council of 22 September 2010 on the protection of animals used for scientific purposes. The Bioethics Commission of Zaporizhzhia State Medical and Pharmaceutical University of the Ministry of Health of Ukraine has not found any violations of moral and ethical norms in conducting scientific research (Protocol No. 2, March 15, 2023).

The present study was carried out within the framework of the dissertation entitled "Pathogenetic Features of Morphofunctional Alterations of the Hippocampus in Essential Arterial Hypertension and its Correction with B-Blockers of Different Classes", which was approved at the meeting of the Department of Pathological Physiology with the Course of Normal Physiology, Zaporizhzhia State Medical and Pharmaceutical University (Protocol No. 9, March 30, 2023).

The experimental study plan involved a set of parallel instrumental, functional, and statistical methods and included body weight measurements and BP monitoring using a non-invasive BP analyzer BP-2000 Blood Pressure Analysis System™, Series II (Visitech Systems, USA) when forming groups, on the 7th day and before the experimental animal sacrifice (on the 31st day).

The animals were assigned to 5 experimental groups of 10 rats each. Group 1 (control) – normotensive WKRs (normotensive Wistar-Kyoto rats). Group 2 – spontaneously hypertensive rats (SHRs). SHR groups 3, 4 and 5 were given one of beta-blocker test drugs orally with 1% starch mucilage daily for 30 days: group 3 – daily for 30 days:

group 3 – propranolol ("Anaprilin-Zdorovya", "Zdorovya Pharmaceutical Company", Ukraine), non-selective beta1, beta2-blocker, lipophilic with high neuroavailability) at a dose of 50 mg/kg of animal body weight; group 4 – carvedilol ("Carvedilol-KV", JSC "Kyiv Vitamin Plant JSC", Ukraine), mixed alpha1, beta1, beta2, hybrid alpha-beta – adrenoblocker with antioxidant activity, at a dose of 50 mg/kg body weight; group 5 – hypertril (bromide 1-(b-phenylethyl)-4-amino-1,2,4-triazolium, LLC "SPA "Pharmatron", Ukraine), superselective beta-adrenoblocker with NO-modeling effect, at a dose of 20 mg/kg body weight.

At the end of the experiment, the animals were sacrificed by single-stage decapitation under anesthesia (thiopental sodium 40 mg/kg intraperitoneally). The brains were washed with ice-cold 0.15M KCl (4°C) 1:10 and homogenized using a Potter-Elvehjem homogenizer (DWK Life Sciences, GmbH, Germany) at a temperature of +2°C in ten volumes of a medium, which consisted of (mmol): sucrose – 250, Tris-HCl buffer – 20, EDTA-1 (pH 7.4). At a temperature of +4°C, large cell fragments were isolated by differential centrifugation on a Sigma 3–30k refrigerated centrifuge (Germany) for 7 minutes at 1000 x g, and then the supernatant was removed and centrifuged again for 20 minutes at 17.000 x g. The supernatant was removed completely and stored at -80°C.

The mitochondrial pellet was resuspended in isolation medium containing bovine serum albumin (0.5 mg/ml, the suspension contained 40–60 mg protein/ml) and pelleted again for 10 minutes at 17.000 x g. The mitochondrial samples were kept frozen at -80°C until the time of analysis. A suspension of 0.5–1.0 mg protein/ml was used to determine the opening rate of the mitochondrial permeability transition pore (mPTP). A protein-free extract was obtained by adding a precise volume of mitochondrial suspension, cytosol to perchloric acid (0.6M) followed by neutralization with 5.0M potassium carbonate. The specificity of energy metabolism changes was identified by ATP concentrations based on thin-layer chromatography, malate content – using the Hohorst method, mitochondrial creatine kinase (mt-CK) activity – after purification via DEAE Sephadex A50 by the Warburg optical test, mitochondrial aspartate aminotransferase (mt-AsT) and cytochrome C oxidase (COX) in the obtained mitochondrial fraction – through spectrophotometry [13].

The normality of variables was assessed with the Kolmogorov–Smirnov (D) test with Lilliefors correction and Shapiro–Wilk (W) criteria. In case of non-normal distribution or analysis of ordinal variables, Mann–Whitney U tests were applied for 2 unrelated samples; for a larger number of samples – the Kruskal–Wallis H and Friedman tests followed by post-hoc analysis by Games–Howell or Tukey. The Wilcoxon test was used to compare groups before and after the drug administrations. The chi-square test was utilized to compare qualitative characteristics between groups with a contingency table analysis. The study results were processed using the statistical package "SPSS 16", "Microsoft Excel 2003", "STATISTICA® for Windows 7.0" (StatSoft Inc.). A p-value of less than 0.05 was considered statistically significant for all calculations.

## Results and discussion

Biochemical analyses have shown an association between brain energy deficit and chronic AH, as evidenced by depleted amounts of ATP and the Krebs cycle intermediate malate (Table 1).

Based on the findings, a collapse in the macroergic compounds represented by a significant decrease in ATP by 26.8% and malate by 28.9% has been revealed in animals with spontaneous AH (Table 1).

In this regard, a clear parallelism between decreased levels of energy metabolism substrates and suppressed activity of mitochondrial enzymes regulating the mitochondrial-cytosolic transport of electrons and protons has been shown. Chronic AH in SHRs has been found to cause a more than twofold reduced neuronal activity of mt-CK, COX and mt-AsT (Table 2).

Pharmacological correction of AH by administration of beta-blockers from different generations has resulted in reliably stabilized BP to 110.0 ± 2.882/72.3 ± 1.8 mm Hg after propranolol administration, 109.6 ± 1.82/71.7 ± 2.1 mm Hg – after carvedilol, and to 110.4 ± 2.12 / 69.5 ± 1.7 mm Hg after using hypertril. As expected, the results have confirmed a high effectiveness of these medications for normalizing AH.

Propranolol and carvedilol have been found to exert more mixed effects on the neuronal bioenergetics. It is also noteworthy the absence of a positive effect after long-term administration of both drugs compared to normotensive control. Indicatively, the amounts of ATP and malate were 37.9% and 42% lower, respectively, after correction with propranolol and 25.2% and 31.6% less, respectively, after long-term administration of carvedilol, as compared to the control values (Group 1). Drug correction has shown no positive effects on the activity of mitochondrial enzymes regulating energy metabolism, leaving it low without significant intergroup differences (Table 2).

Table 1

**Concentrations of substrates for energy metabolism in the brain of animals with arterial hypertension (M±m)**

| Animal groups (n=10) | ATP, μM/g | Malate, μM/g |
|---|---|---|
| Normotensive rats (WKRs) | 3.17±0.05 | 0.38±0.02 |
| SHRs | 2.32±0.01[1] | 0.27±0.01[1] |
| SHR+ propranolol, 50 mg/kg | 1.97±0.01[1,2,3] | 0.22±0.01[1,2,3] |
| SHR+ carvedilol, 50 mg/kg | 2.37±0.02 [1,3] | 0.26±0.03[1,3] |
| SHR+ hypertril, 20 mg/kg | 3.10±0.01[2] | 0.44±0.01[1,2] |

Note: ([1]) – significance of differences (p<0,05) as compared to Group 1 (WKR);

([2]) – significance of differences (p<0,05) as compared to Group 2 (SHR);

([3]) – significance of differences (p<0,05) as compared to Group 5 (SHR+ hypertril).

Table 2

**Enzymatic activity values of the mitochondrial energy metabolism in the brain of animals with arterial hypertension (M±m)**

| Animal groups (n=10) | COX, μM/mg/min | mt-AsT, μM/mg/min | mt-CK, μM/mg/min |
|---|---|---|---|
| Normotensive rats (WKRs) | 13.7±1.5 | 2.77±0.15 | 2.00±0.11 |
| SHRs | 6.17±1.0[1] | 1.21±0.11[1] | 0.81±0.07[1] |
| SHR+ propranolol, 50 mg/kg | 6.00±0.7[1] | 1.11±0.08[1,3] | 0.71±0.05[1,3] |
| SHR+ carvedilol, 50 mg/kg | 6.25±0.8[1] | 1.23±0.15[1,3] | 0.90±0.08[1,3] |
| SHR+ hypertril, 20 mg/kg | 8.2±1.2[1] | 3.12±0.10[2] | 1.87±0.10[2] |

Note: ([1]) – significance of differences (p<0,05) as compared to Group 1 (WKR);

([2]) – significance of differences (p<0,05) as compared to Group 2 (SHR);

([3]) – significance of differences (p<0,05) as compared to Group 5 (SHR+ hypertril).

Comparison of these values with the data of spontaneously hypertensive SHRs has revealed negative effects of propranolol on the amount of both ATP (15.1% decrease) and malate (18.5% decrease), while the total content of macroergic compounds and the Krebs cycle intermediate malate concentration remained at a level of SHR values after the carvedilol use (Table 2). Such a pattern of propranolol and carvedilol effects has been seen in the studied complex of enzymes regulating energy metabolism, manifested by the absence of significant differences in the reduced activity of COX, mt-AsT and mt-CK as compared to the SHR values (Table 2).

A major achievement of the experimental study has been the identification of hypertril (superselective β-adrenoblocker with NO-modeling properties) positive effects on neuronal energy production in rats with essential hypertension. The hypertril use has restored ATP and malate generation to normative values with partially reactivated mitochondrial enzymes. This was evident in mt-AsT and mt-CK completely restored activity, although COX was 40% lower (Table 2).

A reducing effect of hypertril on energy substrates and the malate-aspartate shunt enzymes as well as the creatine kinase/phosphocreatine system involved in ATP resynthesis has been revealed, which was manifested in increased contents of ATP and malate by 33.6% and 63%, respectively, and a higher activity of mt-AsT 2.57 times and mt-CK – 2.3 times when comparing the obtained results with the SHR values (Group 2) (Table 2).

The findings on energy metabolism impairments in the brain of spontaneously hypertensive rats have been obtained for the first time, not being a contradiction to the concept of target organ damage in hypertension. These data indicate the development of secondary brain mitochondrial dysfunction. Apparently, intermediate metabolites generating the oxidative stress system – carbonylated and nitrosylated peptides, which are second messengers, initiate a cascade of metabolic disorders, in particular, modulate the mPTP opening. Mitochondrial disorders are a primary cause of cellular degeneration, being actively involved in a complex network of metabolic process intracellular regulation, from the exchange of specific and exclusive mitochondrial matrix metabolites to the release of apoptogenic factors initiating cell death. Preservation of the mitochondrial functional activity largely depends on the state of the active and passive ion channels. Energy dissipation during the mPTP opening, is apparently due to the uncoupling of mitochondrial oxidative phosphorylation processes [14]. AH-induced mitochondrial dysfunction in rats caused abnormalities of energy production in the brain, which was characterized by a high level of energy metabolism and a critical dependence on energy supply. So, downregulation of aerobic ATP production, energy deficit, activation of glycolysis and inhibition of compensatory cytosolic-mitochondrial energy shunts have been observed in the cytosolic and mitochondrial fractions of the control group animal brain. This confirms our data on the anaerobic glycolysis activation and inhibition of not only aerobic oxidation, but also the compensatory malate-aspartate shuttle system in the SHR brain. There are data demonstrating the prospects of activating a new malate-oxaloacetate shunt that utilizes NADH and produces ATP in SHRs. Energy deficit at the cellular level has been considered the main cause of the primary BP elevation since the last decades. The driving factor of energy deficiency in AH is increasingly purported to be the secondary mitochondrial dysfunction triggering, and one of its mechanisms is calcium overload due an excessive cytosolic calcium influx into mitochondria. Other mechanisms are ROS hyperproduction, deficiency of NO and release of its cytotoxic compounds [15].

The SHR case implies the possibility of genetically determined properties of mitochondrial membranes, initiating membrane-related dysregulations of intracellular calcium handling with the cytoplasmic accumulation of free calcium ions in high concentrations. The observed elevated BP in SHRs occurs both with mitochondrial ATP synthesis inhibition and increased rate of the mPTP opening. Deregulation of ATP synthesis processes in mitochondria and the mPTP opening rate are heavily interlinked and greatly relies on the mitochondrial ROS generation as well as concentrations of calcium and products of oxidative protein modification. Impaired electron transport chain activity due to iron binding and inhibition of cytochrome C oxidase in complex IV has been shown as a consequence of mitochondrial NO level depletion caused by superoxide-induced inactivation. Hyperproduction of ROS with a multitude of redox protein modifications, low- and very low-density lipoproteins along with calcium overload in AH are responsible for a damaging effect on mitochondrial membranes. The most significant stage of reducing myocardial energy supply in

AH is the ROS-induced deleterious effects on the inner mitochondrial membrane permeability with the mPTP opening and a consequent release of various matrix proteins, many of which induce programmed cell death [16]. It is believed that AH-associated mitochondrial dysfunction and energy deficiency in the brain are considerably aggravating factors and result in memory loss and cognitive function impairments. Analyzing the obtained results of biochemical studies on energy metabolism before and after hypertril administrations, it can be concluded that the initiating mechanism of the anti-ischemic hypertril action is its effect on mitochondrial dysfunction. Apparently, hypertril, prevents the mPTP opening and maintains the mitochondrial functional activity followed by energy metabolism improvements during ischemia by reducing harmful effects of ROS and free radicals on the SH-groups of the cysteine-dependent site of the mitochondrial inner membrane protein. Such a mechanism of hypertril for influencing energy metabolism parameters is probably realized through additional effects identified earlier, namely antioxidant and NO-mimetic [17]. The validity of such assumptions is based on various studies demonstrating NO deficiency in patients with mitochondrial diseases and improvements in mitochondrial functions and energy metabolism after administration of NO-mimetics [15].

There is information about effects of carvedilol on mitochondrial bioenergetic functions and ROS generation. Thus, carvedilol is capable of reducing $H_2O_2$ production, increasing reduced glutathione levels and restoring mitochondrial respiration due to its antioxidant effects. Carvedilol exhibits ROS scavenging activity and also lowers the ROS production in mitochondria through “soft uncoupling” and a slight decrease in the mitochondrial membrane potential. In addition, it can directly protect the mitochondrial ultrastructure and reduce mitochondrial calcium overload. Explicit mitoprotective properties of carvedilol has been shown to be associated with its effects to diminish ROS generation through the medium of mitochondrial xanthine oxidase activity and enhance the activity of cytosolic Cu, copper-zinc superoxide dismutase and mitochondrial manganese superoxide dismutase as well as catalase [18].

## Conclusions

1. Sustained arterial hypertension-induced brain abnormalities are characterized by a significantly depleted mitochondrial pool of macroergic compounds ATP and malate by almost a third with a depressed activity of mitochondrial enzymes mt-CK, COX and mt-AsT by more than twofold.

2. Long-term correction of elevated blood pressure with propranolol or carvedilol has not resulted in positive effects on the energy supply for nerve cells despite blood pressure stabilized. The values of ATP and malate as well as the activity of mitochondrial regulatory enzymes of energy metabolism have been below the control ones.

3. Propranolol has shown a negative effect on both the content of ATP and malate (15.1% and 18.5% decrease, respectively) as compared to the SHR results. Carvedilol has not changed the total pool of macroergic compounds ATP and malate concentrations, leaving the values at the levels of hypertensive rats. Both beta-blockers have shown no significant differences in the reduced activity of COX, mt-AsT and mt-CK.

4. The hypertril administration has helped to completely restore the ATP and malate production, mt-AsT and mt-CK activity to normative values along with partially restored COX, in particular, the activity of mt-AsT and mt-CK enzymes was 2.57 and 2.3 times increased, respectively, as compared to the SHR values.

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*Надійшла до редакції 15.06.2025 р.*
*Прийнята до друку 01.09.2025 р.*
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