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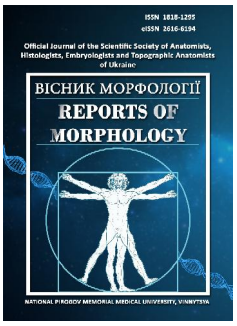

Morphometric assessment of the effects of monosodium glutamate on the carotid sinus wall: an experimental study

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The increase in global burden of stroke is hard to overestimate. Every year it continues to be a leading cause of mortality worldwide. Extracranial pathology of the carotid arteries is a major underlying reason of stroke. Given the role of alimentary factors in the development of atherosclerosis of the carotid arteries, possible influence of food additives on the carotid sinus structure is of special interest. Monosodium glutamate is one of the most common food additives that is allowed for consumption in many countries due to it being considered relatively safe. Recent scientific research however points towards the possible adverse effects of monosodium glutamate on the living organism. The aim of this study was to analyze qualitative and quantitative parameters of carotid sinus structural organization of white male albino rats under normal conditions, in the setting of oral monosodium glutamate consumption and after its withdrawal. Carotid sinuses of 30 white male albino rats that had been daily consuming 10 mg/kg of monosodium glutamate for 4 or 8 weeks with subsequent withdrawal for 2 weeks were subjected to qualitative and quantitative analysis at different time-points of the experiment. The data obtained was compared with the results of morphologic and morphometric study of carotid sinuses of 9 rats of the control group. For morphometric analysis, the following parameters were considered: intima thickness, media thickness, adventitia thickness, diameters of the arterioles, venules and capillaries of the carotid sinus vasa vasorum. Summarizing the morphometric analysis results, it is worth noting that, for the duration of 8 weeks of the experiment, steady increase in the thickness of all layers of the vascular wall, but especially intima and adventitia, was observed in the study group. At the same time, the diameter of the arterioles located in the carotid sinus adventitia was decreasing, while venules and capillaries demonstrated invariable increase of their lumen diameter. After 2 weeks of monosodium glutamate withdrawal, the thickness of intima and adventitia continued to increase, while media thickness had somewhat decreased, probably due to fibrosis and dystrophy. The tendency towards narrowing of the arterioles' lumen and widening of the venules and capillaries persisted for at least 2 weeks despite discontinuation of monosodium glutamate. Therefore, systematic consumption of monosodium glutamate may lead to impairment of carotid sinus structural organization, particularly endothelial proliferation, fibrotic and dystrophic changes of media, adventitia thickening as well as microcirculatory vessels damage, that continue to persist despite the food additive withdrawal.

Keywords: *monosodium glutamate, carotid sinus, internal carotid artery, intima, media, adventitia.*

Introduction

Cardiovascular diseases, due to their prevalence, as well as a prominent place in the structure of mortality, are a significant medical and social problem [1, 9]. Cerebral stroke ranks 5th among the causes of death and is the leading cause of disability [26]. The pathogenetic basis for the occurrence of morphological changes in tissues and organs is often micro- and macroangiopathy, which cause tissue trophic disorders and, as a result, their structural rearrangement [12]. Approximately 85 % of all strokes are ischemic strokes, about 20 % of which are caused by extracranial pathology of the internal carotid arteries [21]. Atherosclerotic plaque often occurs in the area of bifurcation

of the carotid arteries, especially in the area of the carotid sinus - a small expansion of the internal carotid artery, which is most often located just cranial to their bifurcation and is an important structure involved in the regulation of hemodynamics. Morphological changes in the area of the carotid sinus can accelerate the formation of atherosclerotic plaque, which, in turn, most often leads to strokes in patients without other known cardiovascular risks [10].

Among all the factors that influence the development of carotid artery pathology, food plays a prominent role, and both the quantitative and qualitative composition of food are of significant importance. In this context, monosodium glutamate is of particular interest - a common food additive that is approved for use in many countries, is considered relatively safe and is widely used to improve the organoleptic properties of food for both adults and children. According to the data of the European Food Safety Authority (EFSA), the acceptable group daily dose of monosodium glutamate was set at the level of 30 mg/kg in terms of glutamic acid, however, in most population groups, the daily consumption of monosodium glutamate not only significantly exceeds this level, but in some of them are even higher than the doses that cause unwanted effects in humans [11]. At this time, the European Commission plans to revise the maximum daily doses of monosodium glutamate allowed for consumption.

Despite the important role of monosodium glutamate in the development of certain pathological conditions, its influence on the structure and function of the vascular bed, in particular the carotid arteries and the carotid sinus, has not been sufficiently studied. However, the role of monosodium glutamate in the development of obesity and hypertension [25], Alzheimer's disease [13], abnormalities in the development of the nervous system [1] and gastric erosions [8] is described in the scientific literature. The relationship between monosodium glutamate consumption and manifestations of toxic effects in tissues of lymph nodes [15], colon [16], liver [6] and reproductive system [20] was also shown. The ability of monosodium glutamate to cause oxidative stress in myocardial cells was also reported, which was characterized by an increase in the levels of marker enzymes [7]. It is also known that monosodium glutamate is capable of inducing obesity and an increase in cholesterol levels, which can lead to an increased risk of cardiovascular events [4]. In view of this, the study of the ways of influence of monosodium glutamate on the morphology of the vascular wall, in particular the wall of the carotid sinus, is important for establishing the mechanisms of its action, the nature of structural changes, as well as identifying possible modifying factors that weaken or modulate this influence.

The purpose of the study: to analyze the qualitative and quantitative parameters of the structural organization of the carotid sinus of white male laboratory rats in normal conditions, under the influence of monosodium glutamate in the experiment, as well as when it is withdrawn.

Materials and methods

39 male white laboratory rats aged 3.5-5.0 months with an initial body weight of 180-200 g were involved in the study, which were equally divided into experimental groups (subgroup 1, n=10; subgroup 2, n=10; subgroup 3, n= 10) and control (n=9) groups. Experimental group animals received 10 mg/kg/day orally administered monosodium glutamate for 4 (subgroup 1) or 8 weeks (subgroup 2), while control group animals received no dietary supplements. After 8 weeks of the experiment, monosodium glutamate administration was discontinued, instead, the experimental animals were transferred to a standard vivarium diet with an assessment of the morphological structure of the wall of their carotid sinus 2 weeks after withdrawal (subgroup 3).

The animals were kept in cages of 4 individuals each, in a well-ventilated and lighted room of the vivarium, and had unlimited access to food that corresponded to the standard diet of the vivarium. Throughout the experiment, the principles of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986), the norms of the Law of Ukraine No. 3447-IV "On the Protection of Animals from Cruelty Treatment", general ethical principles of experiments on animals, adopted by the First National Congress of Ukraine on Bioethics (2001), which was confirmed by the commission on the ethics of scientific research, experimental developments and scientific works of Danylo Halitskiy Lviv National Medical University (protocol No. 3 dated 11.3.2022).

4 weeks after the beginning of the study, 10 animals of the research group (subgroup 1) were removed from the experiment by overdose of ether anesthesia; another 10 animals of the experimental group were removed from the experiment at the end of 8 (subgroup 2) and 10 (subgroup 3) weeks, respectively. The research material is represented by histological preparations of the carotid sinus of white rats, made by making sections of the tissue of the bifurcation of the carotid arteries from previously prepared paraffin blocks. For histological examination, the sections were stained with methylene blue and hematoxylin-eosin. The preparations were studied and photographed at magnifications of the microscope: x200, x400, x1000. The "Aver Media" computer system was used to photograph micropreparations. The ImageJ program was used for morphometric analysis. In order to evaluate the morphometric indicators, the following parameters were analyzed: the thickness of the intima of the carotid sinus wall, the thickness of the media of the carotid sinus wall, the thickness of the adventitia of the carotid sinus wall, the diameter of the vessels of the microcirculatory bed (vasa vasorum) located in the adventitia of the carotid sinus.

Statistical data processing was performed using MS Excel 2007 software. Experimental data are presented as the average value of the sample parameter and its standard deviation (M±σ). Since the general variances of the studied values are unknown, the sample means are subject to the Student's t-distribution.

Results

During the morphological study of the studied area of the carotid sinus of a white rat, it was found that the internal and external carotid arteries originated from the common carotid artery, the bifurcation of the common carotid artery was located behind the posterior angle (large horn) of the hyoid bone, 2-4 mm below the latter in both animals groups The diameter of the internal carotid artery practically corresponded to that of the external carotid artery. During histological examination (staining with methylene blue and hematoxylin-eosin), the wall of both carotid arteries consisted of clearly defined three layers: inner - intima, middle - media, and outer - adventitia, in which small blood vessels, known as vasa vasorum, were visible.

The structural organization of the carotid sinus wall in animals of the control group was characterized by the following parameters: intimal thickness 4.362±0.494 μm, media thickness 47.17±0.99 μm, adventitia thickness 75.36±0.68 μm. As for vasa vasorum, the diameter of arterioles in the control group was 20.73±0.71 μm, venules 32.27±0.63 μm, capillaries 6.249±0.391 μm.

At the end of the 4 week of monosodium glutamate use, moderate swelling of the carotid sinus wall in the area directly above the bifurcation was observed in the experimental animals of subgroup 1 when compared with the control group, as well as fibrosis and hyperemia of the adventitia capillaries. The wall of individual capillaries was damaged, isolated diapedesis hemorrhages were also detected (Fig. 1). The pronounced multiplication and folding of the intima attracted attention (Fig. 2). Morphological changes at the end of the 4th week of the experiment were characterized by the following morphometric parameters: intima thickness 6.873±0.668 μm (control 4.322±0.524 μm, $p<0.05$), media thickness 60.68±0.91 μm (control 46.81±1.12 μm, $p<0.05$), adventitia thickness 81.13±1.93 μm (control 75.22±0.71 μm, $p<0.05$). Regarding the vasa vasorum, the diameter of the arteriole in the experimental group was 16.67±0.51 μm (control 21.21±0.67 μm, $p<0.05$), venules 42.22±0.78 μm (control 32.714±0.576 μm, $p<0.05$), capillary 8.247±0.231 μm (control 6.224±0.324 μm, $p<0.05$).

After 8 weeks of consumption of monosodium glutamate by experimental animals of subgroup 2, the wall of their carotid sinus was disorganized, the intimal layer of endotheliocytes was deformed, often without clear contours, in some places interrupted, protrusions of the endothelium, proliferation of endotheliocytes, and in some places - exfoliation of endotheliocytes into the lumen of the carotid sinus were observed (Fig. 3). Bundles of smooth myocytes of the muscle media were separated by wide layers - thickened elastic membranes, often deformed. Perivascular edema, dilatation of vasa vasorum, thickening of arteriole walls were observed, formation of wall thrombi occurred in lumens (Fig. 4). At the end of the 8th week of the experiment, the morphometric parameters were: intima thickness 9.552±0.724 μm (control 4.337±0.564 μm, $p<0.05$), media thickness 81.52±2.31 μm (control 46.92±0.98 μm, $p<0.05$), adventitia thickness 126.1±0.7 μm (control 74.98±0.64 μm, $p<0.05$). Regarding the vasa vasorum, the diameter of the arteriole in the experimental group was 13.04±0.45 μm

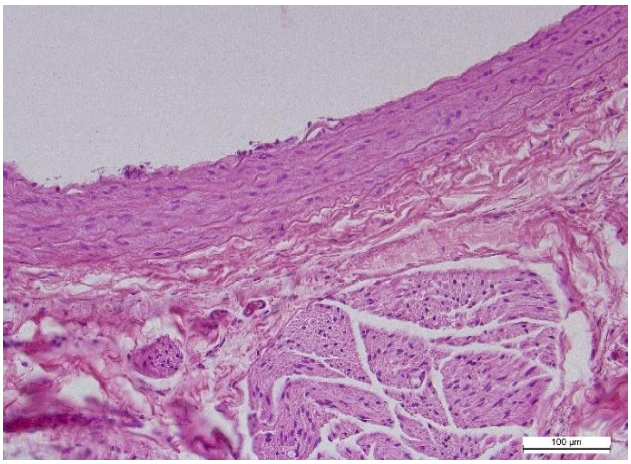

Fig. 1. A fragment of the carotid sinus wall of a white rat after 4 weeks of monosodium glutamate consumption. Hematoxylin-eosin staining. x200.

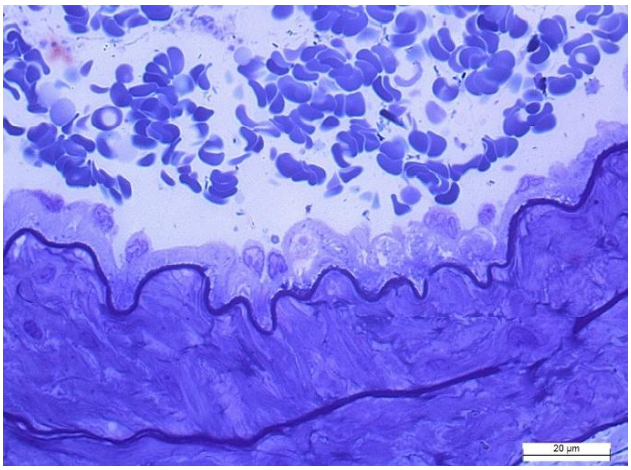

Fig. 2. A fragment of the carotid sinus wall of a white rat after 4 weeks of monosodium glutamate consumption. Staining with methylene blue. x1000.

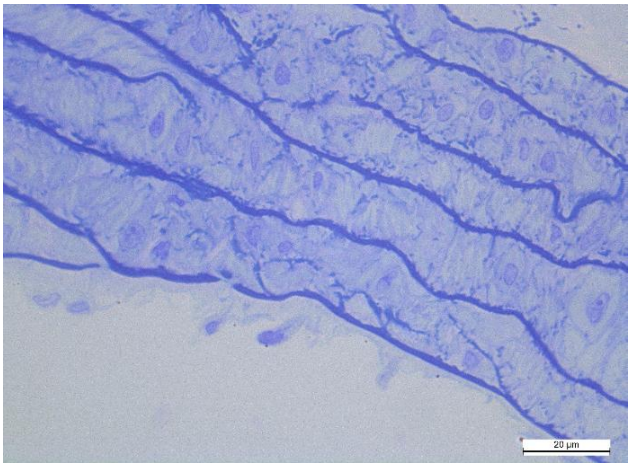

Fig. 3. A fragment of the wall of the carotid sinus of a white rat after 8 weeks of monosodium glutamate consumption. Staining with methylene blue. x1000.

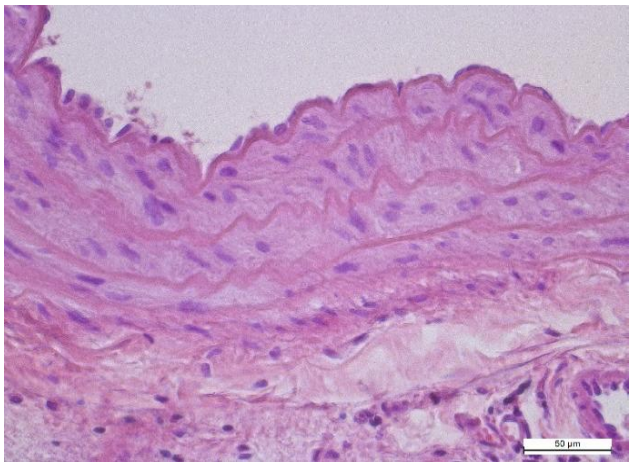

Fig. 4. A fragment of the wall of the carotid sinus of a white rat after 8 weeks of monosodium glutamate consumption. Hematoxylin-eosin staining. x400.

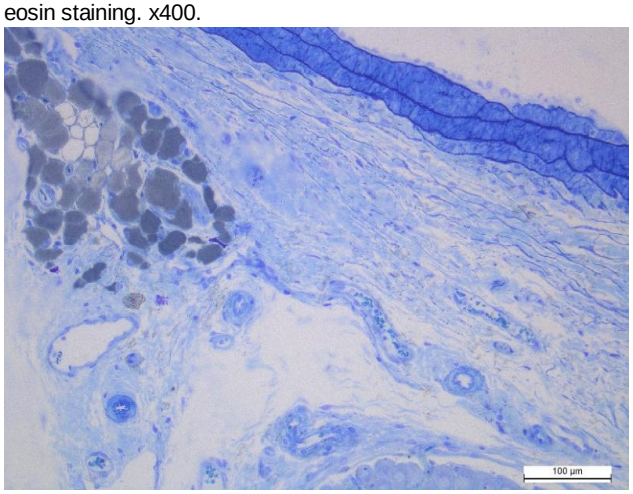

Fig. 5. A fragment of the carotid sinus wall of a white rat after 8 weeks of monosodium glutamate consumption and 2 weeks of its withdrawal. Staining with methylene blue. x200.

(control 20.86±0.74 μm, p<0.05), venules 63.26±1.50 μm (control 32.68±0.62 μm, p<0.05), capillary 9.044±0.338 μm (control 6.142±0.443 μm, p<0.05).

At the end of the 10 week of the experiment, that is, at the end of 2 weeks from the moment of discontinuation of monosodium glutamate, compensatory processes in the wall of the carotid sinus were practically not observed in animals of subgroup 3, which previously received it orally for 8 weeks. Thickening of the wall of the carotid sinus due to adventitia and, to a lesser extent, intima was noted, signs of exudative-proliferative inflammatory process prevailed, vacuolar dystrophy of myocytes and fibro-sclerotic changes, deformation of elastic membranes, which led to a relative decrease in its thickness, were observed in the media. In the significantly thickened adventitia, with interspersed fat, structural changes were detected on the part of all vessels of the vasa vasorum: hyperemia of capillaries, reduction of the lumen of arterioles due to thickening and swelling of their walls, formation of paramural thrombi, expansion and thinning of venule walls, perivascular edema (Fig. 5). The morphometric parameters of subgroup 3 were: intimal thickness 14.71±0.88 μm (control 4.352±0.478 μm, p<0.05), media thickness 57.33±1.34 μm (control 46.63±0.96 μm, p<0.05), adventitia thickness 236.6±1.3 μm (control 75.43±0.76 μm, p<0.05). Regarding the vasa vasorum, the diameter of the arteriole in the experimental group was 11.12±0.89 μm (control 20.47±0.58 μm, p<0.05), venules 102.1±1.3 μm (control 32.35±0.62 μm, p<0.05), capillary 10.03±0.56 μm (control 6.319±0.442 μm, p<0.05).

The dynamics of changes in the thickness of the layers of the carotid sinus wall are shown in the graphs (Figs. 6, 7 and 8).

The dynamics of changes in blood vessels of the hemomicrocirculatory bed (vasa vasorum) are shown in the graphs (Figs. 9, 10 and 11).

Summarizing the results of the morphometric study, it should be noted that during the 8 weeks of the experiment in the experimental group, the thickness of all layers of the vascular wall, especially the intima and adventitia, decreased, the diameter of arterioles decreased, and the diameter of venules and capillaries of the hemomicrocirculatory channel increased. After withdrawal of sodium glutamate, the thickness of the adventitia and intima continued to increase, but the thickness of the media decreased slightly, presumably

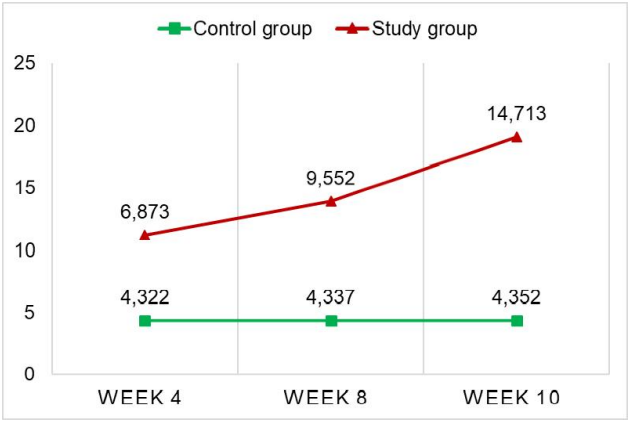

Fig. 6. The thickness of the carotid sinus intima wall of a white laboratory rat (μm).

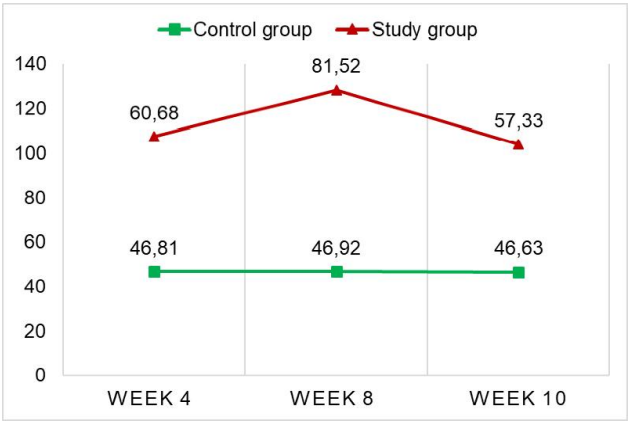

Fig. 7. The thickness of the carotid sinus media wall of a white laboratory rat (μm).

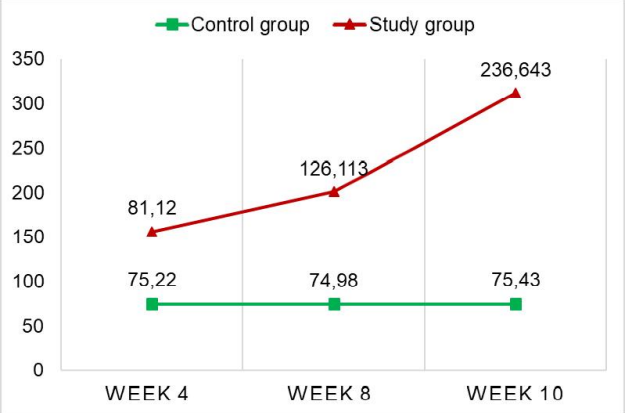

Fig. 8. The thickness of the carotid sinus adventitia wall of a white laboratory rat (μm).

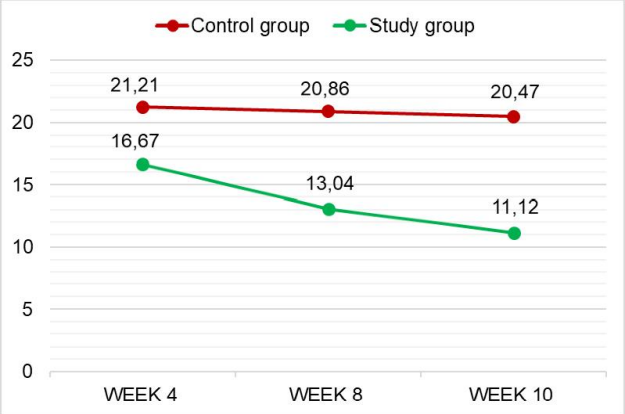

Fig. 9. The diameter of the carotid sinus arterioles wall of a white laboratory rat (μm).

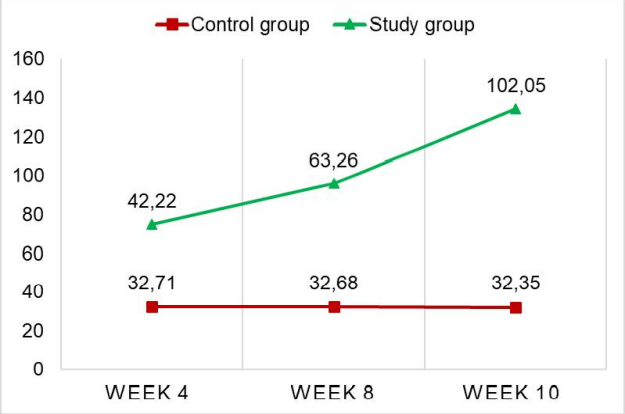

Fig. 10. The diameter of the carotid sinus venules wall of a white laboratory rat (μm).

due to fibro-dystrophic changes. The tendency to narrowing of the lumen of arterioles and expansion of the lumen of venules and capillaries persisted 2 weeks after withdrawal of monosodium glutamate.

Discussion

Extracranial pathology of the carotid arteries is an important risk factor for the development of brain perfusion

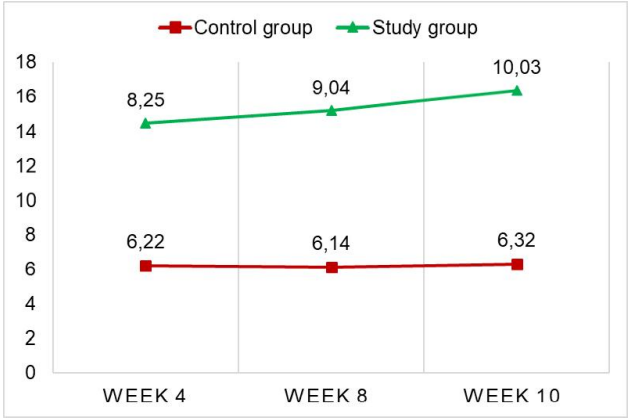

Fig. 11. The diameter of the carotid sinus capillaries wall of a white laboratory rat (μm).

disorders, which can be manifested by a wide range of pathological conditions, from cognitive disorders to cerebral stroke [18]. In this context, the attention of the scientific community has been focused on the study of the mechanisms of influence of the most common food additive - monosodium glutamate, on the living organism for several decades. Scientific studies have proven that its long-term use is associated with the development of a number of pathological conditions, including metabolic syndrome, diabetes, dyslipidemia and obesity, hypertension and other diseases of the cardiovascular system, neuroendocrine disorders, depression and anxiety [17, 19], disorders of the urinary and reproductive systems [23], liver diseases [5].

The results of our research indicate that the adverse effect of monosodium glutamate on the structural organization of the carotid sinus is noticeable after four weeks of its consumption and increases in dynamics. These effects do not diminish with withdrawal of glutamate. Thus, after 4 and 8 weeks of the experiment, histological examination reveals significant changes in the structure of the wall of the carotid arteries in the area of the carotid sinus at the microscopic level, which can be directly related to the harmful effect of monosodium glutamate. In particular, the changes we discovered on the part of the endothelium may indicate the ability of monosodium glutamate to cause its proliferation with subsequent violations of the structure of the inner layer of the vascular wall, which may in turn contribute to the development of atherosclerotic plaques and thrombus formation in dynamics.

The mechanisms and role of endothelial dysfunction are actively studied and described in the specialized literature [24, 28], in particular in the context of the ability of monosodium glutamate to provoke endothelial damage [2]. In our study, special attention was paid to the progressive thickening of the carotid sinus wall, especially due to the adventitia, which can potentially play a significant role in the development of atherosclerotic lesions of the carotid artery wall. Our data are confirmed in the professional literature, where it was reported, in particular, about the thickening of the adventitia of the carotid arteries and the thickening of

collagen, which is part of the wall of the carotid artery, in an experiment under the influence of dietary factors, in particular under the conditions of consumption of a high-salt diet [14]. In turn, the consumption of monosodium glutamate in combination with a high-fat diet led to an increase in nitric oxide levels and, as a result, the development of oxidative stress, which, in turn, increased the area of damage during myocardial infarction in the experiment [3].

The structural changes in myocytes of the middle layer of the carotid sinus wall that we discovered were similar to the described damage to cardiomyocytes in ischemia or diabetes [22, 27].

An important pathogenetic factor in the development of damage to the vascular wall is a violation of its microcirculation. The changes in the blood vessels of the hemomicrocirculatory channel that we discovered indicate the probable ability of monosodium glutamate to lead to structural disorders of arterioles, venules and capillaries of the vasa vasorum, and therefore to create conditions for the development of hypoxic-ischemic and stagnant changes in the wall of the carotid sinus. Of particular interest is the fact that the above-described morphological disorders, presumably related to the influence of monosodium glutamate, increased even two weeks after its withdrawal. This may indicate the ability of monosodium glutamate to trigger a cascade of vascular wall damage processes, which are potentially significant risk factors in the context of the development of cerebrovascular disorders.

Taking into account the possible adverse effect of even low doses of monosodium glutamate on the structural organization of the carotid sinus, which has a tendency to progress and the absence of positive dynamics after the withdrawal of the mentioned food additive, further research is needed to find the possibilities of correcting or leveling this effect, as well as studying the degree of severity and duration pathological effects of applied doses of glutamate.

Conclusion

Monosodium glutamate with systematic oral use can lead to a violation of the structural organization of the wall of the carotid sinus, in particular to the proliferation of the endothelium, fibro-dystrophic changes in the media, thickening of the adventitia, and damage to the vessels of the microcirculatory channel, which continue to increase even after its withdrawal.

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МОРФОМЕТРИЧНА ХАРАКТЕРИСТИКА СТІНКИ СОННОЇ ПАЗУХИ ЗА УМОВ ВПЛИВУ ГЛУТАМАТУ НАТРІЮ В ЕКСПЕРИМЕНТІ

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Значення мозкового інсульту важко переоцінити: з року в рік він залишається одним із лідерів в структурі смертності. Екстракраніальна патологія сонних артерій, зокрема ділянки сонної пазухи, є однією з провідних причин мозкового інсульту. З огляду на роль аліментарних чинників в розвитку атеросклерозу сонних артерій, особливий інтерес становить вивчення впливу поширених харчових добавок на структурну організацію сонної пазухи. Глутамат натрію - одна із найпоширеніших харчових добавок, яка вважається безпечною і часто застосовується в харчовій промисловості. Однак сучасні наукові дослідження вказують на можливий несприятливий вплив глутамату натрію на структуру і функції органів і тканин живого організму. Метою дослідження було проаналізувати якісні і кількісні параметри структурної організації ділянки сонної пазухи білих лабораторних щурів-самців в нормі, під впливом глутамату натрію в експерименті, а також при його відміні. Досліджено ділянку сонної пазухи і виконано морфометричний аналіз її стінки у 30 лабораторних білих щурів самців, котрі впродовж 4 або 8 тижнів отримували глутамат натрію перорально в дозі 10 мг/кг/добу з подальшою його відміною, що тривала 2 тижні, морфологічним і морфометричним методами на макро- та мікроструктурному рівнях через 4, 8 і 10 тижнів експерименту. Отримані дані порівняні з результатами морфологічного і морфометричного дослідження аналогічної ділянки у 9 тварин контрольної групи. Для оцінки морфометричних показників проаналізовано наступні параметри: товщина інтими стінки сонної пазухи, товщина медії стінки сонної пазухи, товщина адвентиції стінки сонnної пазухи, діаметр судин мікроциркуляторного русла (vasa vasorum), розташованих в адвентиції сонної пазухи. Підсумовуючи результати морфометричного аналізу, слід зазначити, що протягом 8 тижнів експерименту в дослідній групі збільшувалась товщина всіх шарів судинної стінки, особливо інтими і адвентиції, зменшувався діаметр артеріол і збільшувався діаметр венул і капілярів гемомікроциркуляторного русла. Через 2 тижні після відміни глутамату натрію товщина адвентиції та інтими продовжувала зростати, однак товщина медії дещо зменшилася, імовірно за рахунок фіброзно-дистрофічних змін. Тенденція до звуження просвіту артеріол і розширення просвіту венул і капілярів зберігалася і через 2 тижні після відміни глутамату. Таким чином, глутамат натрію при систематичному пероральному вживанні може призводити до порушення структурної організації стінки сонної пазухи, зокрема до проліферації ендотелію, фіброзно-дистрофічних змін медії, потовщення адвентиції та пошкодження судин мікроциркуляторного русла, які продовжують наростати навіть після його відміни.

Ключові слова: *глутамат натрію, сонна пазуха, внутрішня сонна артерія, інтима, медія, адвентиція.*