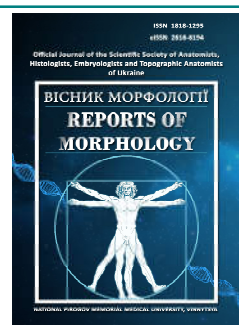




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# Morphometric study of angioarchitectonic under the effect of opioid (experimental study)

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*Opioids are potent drugs that are widely used to combat pain in severe wounds and in cancer patients. The professional literature provides a limited amount of data on the morphometric analysis of the links of the hemomicrocirculatory bed of the cerebellar cortex and choroid of the eyeball under the influence of an opioid in the experiment. The aim of the work was to establish the features and conduct morphometric studies of the links of the hemomicrocirculatory bed of the cerebellar cortex and choroid in normal conditions and under conditions of 6-week exposure to an opioid in the experiment. The experimental study was carried out on 24 male white rats, 3 months old and weighing 160-180 g. The material for the study is represented by preparations of the choroid and cerebellum with an injected vascular bed. Compared with the control group of animals, profound destructive changes in the angioarchitectonics of the choroid and cerebellar cortex were found under the influence of Nalbuphine. The capillary component is destroyed, the arterioles are tortuous, sclerosed, their lumen is uneven, the wall is thickened, the venules are dilated and deformed. A decrease in comparison with the norm in the diameter of arterioles, the density of the network of exchange vessels, arterio-venular coefficient, as well as an increase in the diameter of venules and an indicator of trophic activity of the tissue. Expansion of arterio-venular anastomoses indicates the discharge of blood from the arterioles into the venous bed, bypassing the destroyed capillaries. A pronounced relationship was established between the depth of structural transformations of the hemomicrocirculatory bed of the cerebellar cortex, choroid of the white rat's eye and morphometric parameters. It has been confirmed that the triggering mechanism of destructive changes under the influence of narcotic analgesics is the development of angiopathy.*

**Keywords:** morphometry, opioids, experiment, eyeball, cerebellum, vascular tunic.

### Introduction

It is well-recognized that, despite similar pain characteristics, some people with chronic pain recover, whereas others do not [1]. Opioids are potent drugs that are widely used to control cancer pain and are routinely used analgesics in patients with chronic wounds [17, 21]. Increasing evidence suggest that opioids mediate clinically relevant effects that go beyond their classical role as analgesics [5, 16]. However, it is undeniable that the long-term and systematic use of opioids can cause structural changes of organs and systems [11, 24].

The significant metabolic and structural changes, early disability, and mortality in opioid-dependent patients require the study of pathogenetic mechanisms of the development and progression of multiple polyorganic comorbid conditions [9, 10]. Nowadays, a number of unresolved

issues regarding the features of the hemomicrocirculatory bed of cerebellar cortex and eyeball in norm and after long-term opioid influence remain, what makes the current study relevant.

Nalbuphine is a synthetic kappa-receptor (KOR) agonist opioid and partial mu-receptor (MOR) antagonist which has been synthesized in an attempt to provide analgesia without the undesirable side effects of pure agonists. The central and peripheral analgesic action and the lower risk of addiction/dependence potential seems to be related to the agonist action on KOR, while its MOR antagonist action would be responsible for its lower risk of respiratory depression [3, 25].

It is used to treat moderate to severe pain and provide preoperative and postoperative analgesia and sedation

[4, 20]. Endothelial cells (human arterial and rat microvascular) contain a high affinity, saturable opiate binding site [22].

The aim of the work was to establish the features and conduct morphometric studies of the links of the hemomicrocirculatory bed of the cerebellar cortex and choroid in normal conditions and under conditions of 6-week exposure to an opioid in the experiment.

### Material and methods

The study was carried out on 24 mature white male rats aged 3.0 months and body weight 160-180 g. The injection of Nalbuphine hydrochloride (Rusanpharma LTD., India) was done intramuscularly with a gradual weekly increase in dosage: from 8 mg/kg to 35 mg/kg. Sampling of the material was carried out after 6 weeks of drug injection. The control group consisted of 9 white rats to which saline solution (Indar, Kyiv, Ukraine) was injected. The experiments were conducted in compliance with the provisions of the "Guide for the care and use of laboratory animals, 8th edition, 2011". Euthanasia was performed by way of overdosing intraperitoneal anesthesia using Thiopental sodium (Kyivmedpreparat, Kyiv, Ukraine).

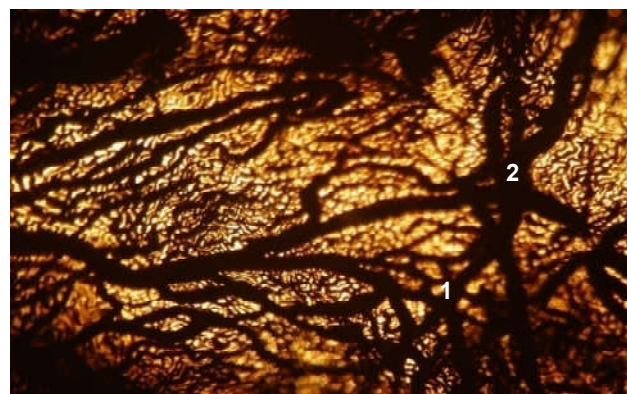
The material is represented by the preparations of eyeballs and cerebellum of rats with injected vascular way. An injection mass consisting of a mixture of 20% solution of collargol and glycerol in a 2 : 1 ratio was used for the injection of the bloodstream.

For morphometric analysis of the vessels of hemomicrocirculatory bed of the eyeball and cerebellar cortex, the following quantitative criteria were used: microvascular diameter, arteriolar-venular coefficient, tortuosity coefficient, density of mesh of exchange vessels, index of trophic tissue activity. Statistical analysis of the results of the study was performed by a computer program "InStat" for biomedical and epidemiological studies.

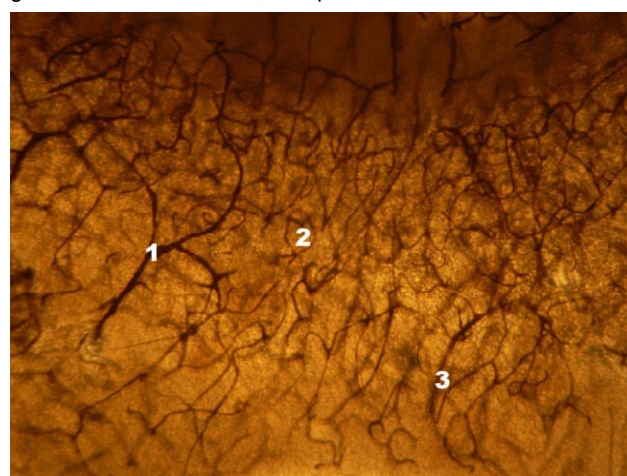
### Results

The layer of veins, the layer of arteries, and the capillary layer are clearly distinguished in the choroid of the rat (Fig. 1). Arterial branches of the annular arteries of the iris are included in the ciliary processes, branching into numerous anastomosing microvessels, which form a thick mesh of broad capillaries. Capillary nets occupy almost the entire volume of ciliary processes. Along the edges of the ciliary processes, veins extend through which the venous blood drains into the venous plexus which is behind the ciliary muscle. The blood supply of the ciliary muscle is provided by the branches of the iris vessels and the choroid, which anastomoses with each other.

In the iris of the white rat clearly visible are annular arteries of the iris, which, arcuately arched, go towards each other and, anastomosing with each other in the anterior and posterior regions of the iris, form a large arterial circle of the iris. From the large arterial circle of the iris, many branches are going both to the ciliary body and the iris.



**Fig. 1.** The angioarchitectonic of the choroid of the control animal (rat) eye ball. Microphoto. x200. Injection of blood vessels by ink gelatin mass. 1 - arteriole; 2 - capillaries.



**Fig. 2.** Vascularization of the cerebellar cortex of the white rat in norm. Microphoto. x160. Injection of blood vessels by ink gelatin mass. 1 - arteriole; 2 - capillary net; 3 - venules.

Arterioles of the iris go radially to the pupil margin, where a capillary loop mesh surrounding the pupil is formed. Capillary loop mesh of the pupillary edge of the iris is gentle, the loops are thin.

Under morphometric study of angioarchitectonic in norm - the diameter of arterioles -  $(21.80 \pm 2.30) \mu\text{m}$ , the diameter of venules -  $(27.09 \pm 1.44) \mu\text{m}$ , capillaries of ciliary processes -  $(6.40 \pm 0.34) \mu\text{m}$ .

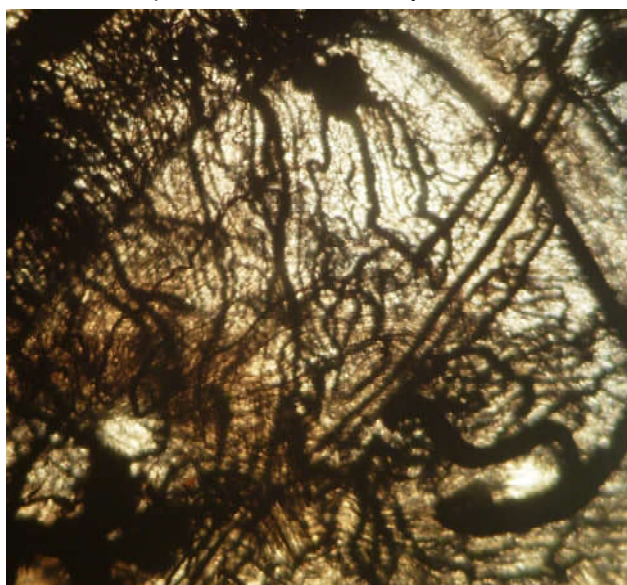
The vascularization of the cerebellum of the white rat is mainly provided by the right and left nasal and right and left caudal ventral arteries, which are the branches of the basilar artery, and the caudal dorsal arteries, which are branches of the vertebral arteries. The cerebellar arteries, penetrating into the cerebellum, separate and form in the cerebellar cortex a hemomicrocirculatory bed containing classically arterioles, precapillary arterioles, capillaries, postcapillary venules and venules. Anastomosing capillaries form a capillary net in the cerebellar cortex (Fig. 2).

According to the results of morphometric studies of the vessels of the hemomicrocirculatory bed of the cerebellar cortex of the white rat, the following values of morphometric





**Fig. 3.** Expansion of the arteriolar component of the cerebellar cortex of the white rat after 6 weeks of injection of Nalbuphine. Injection of blood vessels by ink gelatin mass. Microphoto. x160. 1 - arteriolar component; 2 - cerebellar artery.



**Fig. 4.** Deep destructive changes of the links of the hemomicrocirculatory bed of the iris of the eyeball of white rat under conditions of 6-week administration of Nalbuphine. Microphoto. x100.

parameters were obtained in norm: the diameter of arterioles -  $(20.58 \pm 0.32) \mu\text{m}$ , venules -  $(29.00 \pm 0.20) \mu\text{m}$ , respectively, arteriolar-venular coefficient is  $0.71 \pm 0.01$ . The diameter of the capillaries of the cerebellar cortex of the white rat in norm -  $(5.81 \pm 0.01) \mu\text{m}$ , the density of the mesh of the exchange vessels is  $62.20 \pm 2.19$ , the trophic activity of the cerebellar cortex tissue is  $(45.62 \pm 0.97) \mu\text{m}$ .

After 6 weeks of experimental study, deep destructive changes of vessels of hemomicrocirculatory bed of the vascular tunic of the eyeball and cerebellar cortex are observed.

The arteriolar component of the cerebellar cortex is significantly enlarged (Fig. 3). The diameter of the arterioles at this time of the experiment is  $(35.46 \pm 2.14) \mu\text{m}$ , the control

is  $(20.40 \pm 0.68) \mu\text{m}$ . During this period arteriolar-venular anastomoses widen in the cerebellar cortex. Vascular loops of the cerebellar cortex lose a delicate, tortuous pattern, often breaking off.

The diameter of the cerebellar cortex capillary after 6 weeks of administration of Nalbuphine is  $(8.25 \pm 0.94) \mu\text{m}$ , control -  $(5.80 \pm 0.10) \mu\text{m}$ . Increased vascular permeability, hemorrhage, microaneurysms were detected.

It is quite natural that stagnation and disturbance of outflow of venous blood cause expansion of the venular component, which is confirmed by a significant increase in the diameter of venules to  $(48.34 \pm 2.42) \mu\text{m}$ , control -  $(28.24 \pm 0.19) \mu\text{m}$  in morphometric analysis. The change in the arteriolar-venular coefficient is evident, which at this stage of the study is  $0.74 \pm 0.01$ . There is a change in the density of vessels, violation of their integrity, which is confirmed by the following changes in morphometric parameters. The density of the mesh of the exchanged vessels decreases sharply, this can be explained by the development of significant destruction, mainly of the cerebellar cortex capillaries, and is  $33.80 \pm 4.42$  (control -  $62.10 \pm 0.36$ ). The index of tissue trophic activity increases to  $(67.70 \pm 2.34) \mu\text{m}$  control -  $(47.64 \pm 0.78) \mu\text{m}$ . Responsive destructive changes in the vessels of the hemomicrocirculatory bed are observed in the choroid of the eyeball after 6 weeks of the experiment (Fig. 4).

According to morphometric parameters: the diameter of the arterioles is  $(28.42 \pm 0.41) \mu\text{m}$ , control  $(21.80 \pm 2.30) \mu\text{m}$ ; the diameter of the venules increased to  $(48.74 \pm 2.59) \mu\text{m}$ , the control -  $(27.09 \pm 1.44) \mu\text{m}$ , which led to a probable decrease of the arteriolar-venular coefficient to  $0.58 \pm 0.03$ , the control -  $0.8 \pm 0.07$ . The density of the mesh of the exchange vessels was reduced to  $64.00 \pm 5.82$ , the control was  $120.40 \pm 7.53$ , and the index of tissue trophic activity increased to  $(31.94 \pm 2.61) \mu\text{m}$ , the control -  $(18.15 \pm 0.74)$ . The diameter of the capillaries of the ciliary processes is  $(9.76 \pm 0.51) \mu\text{m}$ , control -  $(6.40 \pm 0.34) \mu\text{m}$ .

In both described organs there is an expansion of arteriolar-venular anastomoses, which indicates the discharge of blood from the arterioles into the venous way, bypassing the destroyed capillaries.

## Discussion

The results of the present work are a fragment of the scientific research project "The structure of organs and their bloodstream in ontogenesis under the effect of laser irradiation and pharmaceutical agents in cases of blood supply disorders, reconstructive surgeries and diabetes mellitus" (State Registration Number 0110U001854), being conducted at the Department of Normal Anatomy, Danylo Halytsky Lviv National Medical University.

The number of people consuming narcotic analgesics does not decrease, but on the contrary tends to increase [5, 16]. Nalbuphine is an agonist of  $\kappa$ -opioid receptors and a partial antagonist of  $\mu$ -opioid receptors, which can stimulate  $\kappa$ -receptors and antagonize the acute rewarding

effects of morphine, has a short duration of action and rapid clearance compared with other opioids and is less likely to cause side effects [15]. It is widely used either as an analgesic or as an adjuvant with morphine [4, 12, 19]. For this reason, the number of requests for opioids in Pubmed has traditionally remained the same. The relevance of the topic of drug use and drug dependence has led to numerous animal experiments (white Wistar rats) to study the macro-, micro- and ultrastructure of organs and systems under the influence of opioids [8, 13]. The study of microscopic and electron microscopic level revealed the pattern of primary lesion of the vascular component. This prompted the study of angioarchitectonics to evaluate the microcirculatory bed [7, 14].

A number of authors describe that vessels of the hemomicrocirculatory bed are most likely to respond to the influence of environmental factors, and therefore one of the first to undergo structural restructuring, which is the basis for the development of the pathological process [2, 6, 18, 23]. Since no numerical values of morphometric indices of white rats of different ages were found in the analysis of professional literature, a model for comparing long-term opioid (Nalbuphine) versus control was selected.

Expansion of arterioles and venules during this study period, compared to control, is due to the inability of these vessels to cope with significant blood flow. In our opinion, the dilation of the veins of the choroid of the eyeball at this time of the experiment contributes to the increasing in the capacity of the venular part of the hemomicrocirculatory bed, tortuosity of arterioles provides a decrease in the force of the pulse impulse in these vessels, the appearance of additional arteriolar-venular anastomoses and its activation leads to increasing of capillar bloodflow. Dilation of arteriolar-venular anastomoses of the vascular membrane of the eyeball and cerebellar cortex indicates the discharge of blood from the arterioles into the venous way, bypassing the ruptured capillaries. Additional anastomoses are opened. We consider this as a compensatory mechanism that enhances the flow and, accordingly, provides the unloading of the destroyed capillary nets of both us and other organs [26]. Therefore, the preparations clearly visualize "empty" areas where there is no capillary

component. Actually, these changes in angioarchitectonics determine the nature and features of clinical manifestations of the pathological process.

The presented experimental study article differs from the one published in this field in that it describes new data on the effect of opioids on the features of angioarchitecture of two organs: the vascular sheath of the eyeball and the cerebellar cortex of the white rat. Mathematical analysis allowed to systematize the obtained experimental data and represent a comparative characteristic of angioarchitectonics of the studied structures in normal and pathological conditions. It is valuable that morphometric data from control animals can be used as a norm in future studies. The findings allow us to broaden our knowledge and address the conflicting issues of the effects of opioids on the eyeball and cerebellum. The structure of the hemomicrocirculatory way creates a morphological basis for understanding the pathogenesis of ophthalmic and neurological diseases of drug users and patients who have to take opioids for a long time and to decide on optimal treatment tactics. The findings are important for both morphologists and clinicians.

### Conclusions

Thus, the morphometric analysis of the vessels of the hemomicrocirculatory bed of the eyeball and the cerebellar cortex of the white rat allowed us to estimate the degree of vascularization in norm and under prolonged exposure to Nalbuphine. There is a clear relationship between the depth of structural transformations of the vessels of hemomicrocirculatory bed of the cerebellar cortex and the choroid of the eyeball and morphometric parameters in the experiment.

The deformation of the arterioles and the irregularity of their lumen, the destruction of the capillary component, significant dilation and deformation of the venules were revealed. Reduction, in comparison with control, diameter of arterioles, density of a net of exchange vessels, arteriolar-venular coefficient. An increasing of the diameter of venules, of trophic activity of the tissue testify to the destructive changes of the hemomicrocirculatory bed of the cerebellar cortex and the choroid of the eyeball under the influence of Nalbuphine.

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#### МОРФОМЕТРИЧНЕ ВИВЧЕННЯ АНГІОАРХІТЕКТОНІКИ ПІД ВПЛИВОМ ОПІОЇДУ (ЕКСПЕРИМЕНТАЛЬНЕ ДОСЛІДЖЕННЯ)

**Матешук-Вацеба Л.Р., Підвальна У.Є., Бекесевич А.М.**

Опіоїди - сильнодіючі препарати, що широко застосовуються у боротьбі з болем при важких пораненнях та в онкохворих. Фахова література наводить обмежену кількість даних морфометричного аналізу ланок гемомікроциркуляторного русла кори мозочка та судинної оболонки очного яблука під впливом опіоїду в експерименті. Метою дослідження було встановити особливості та провести морфометричне дослідження ланок гемомікроциркуляторного русла судинної оболонки очного яблука і кори мозочка в нормі за умов 6-тижневого впливу опіоїду в експерименті. Експериментальне дослідження проведено на 24 білих щурах самцях віком 3 міс і вагою 160-180 г. Матеріал для дослідження представлений препаратами судинної оболонки ока і мозочка з ін'єктованим судинним руслом. У порівнянні з контрольною групою тварин виявлено глибокі деструктивні зміни ангіоархітектоніки судинної оболонки очного яблука та кори мозочка під впливом налбуфіну. Капілярний компонент зруйнований, артеріоли звивисті, просвіт їх нерівномірний, стінка їх потовщена, склерозована, венули розширені та деформовані. Встановлено зменшення, порівняно з нормою, діаметра артеріол, щільності сітки обмінних судин, артеріоло-венулярного коефіцієнта, а також збільшення діаметра венул та показника трофічної активності тканини. Розширення артеріоло-венулярних анастомозів свідчить про скидання крові з артеріол до венозного русла, минаючи зруйновані капіляри. Виявлено виражений зв'язок між глибиною морфологічних змін ланок гемомікроциркуляторного русла кори мозочка, судинної оболонки ока білого щура та морфометричними показниками. Підтверджено, що пусковим механізмом деструктивних змін під впливом наркотичних анальгетиків є розвиток ангіопатії.

**Ключові слова:** морфометрія, опіоїди, експеримент, око, мозочок, судинна оболонка.

**МОРФОМЕТРИЧЕСКОЕ ИЗУЧЕНИЕ АНГИОАРХИТЕКТониКИ ПОД ВОЗДЕЙСТВИЕМ ОПИОИДА (ЭКСПЕРИМЕНТАЛЬНОЕ ИССЛЕДОВАНИЕ)**

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Опиоиды - сильнодействующие препараты, широко применяемые в борьбе с болью при тяжелых ранениях и у онкобольных. Профессиональная литература приводит ограниченное количество данных морфометрического анализа звеньев гемомикроциркуляторного русла коры мозжечка и сосудистой оболочки глазного яблока под влиянием опиоида в эксперименте. Целью работы было установить особенности и провести морфометрические исследования звеньев гемомикроциркуляторного русла коры мозжечка и сосудистой оболочки глазного яблока в норме и в условиях 6-недельного воздействия опиоида в эксперименте. Экспериментальное исследование проведено на 24 белых крысах-самцах возрастом 3 мес и весом 160-180 г. Материал для исследования представлен препаратами сосудистой оболочки глаза и мозжечка с инъецированным сосудистым руслом. По сравнению с контрольной группой животных обнаружены глубокие деструктивные изменения ангиоархитектоники сосудистой оболочки глазного яблока и коры мозжечка под влиянием налбуфина. Капиллярный компонент разрушен, артериолы извилистые, склерозированные, просвет их неравномерный, стенка утолщена, венулы расширенные и деформированные. Установлено уменьшение, по сравнению с нормой, диаметра артериол, плотности сетки обменных сосудов, артериоло-венулярного коэффициента, а также увеличение диаметра венул и показателя трофической активности ткани. Расширение артериоло-венулярных анастомозов свидетельствует о сбросе крови из артериол в венозное русло, минуя разрушенные капилляры. Установлена выраженная связь между глубиной структурных преобразований гемомикроциркуляторного русла коры мозжечка, сосудистой оболочки глаза белой крысы и морфометрическими показателями. Подтверждено, что пусковым механизмом деструктивных изменений под воздействием наркотических анальгетиков является развитие ангиопатии.

**Ключевые слова:** морфометрия, опиоиды, эксперимент, глаз, мозжечок, сосудистая оболочка.

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