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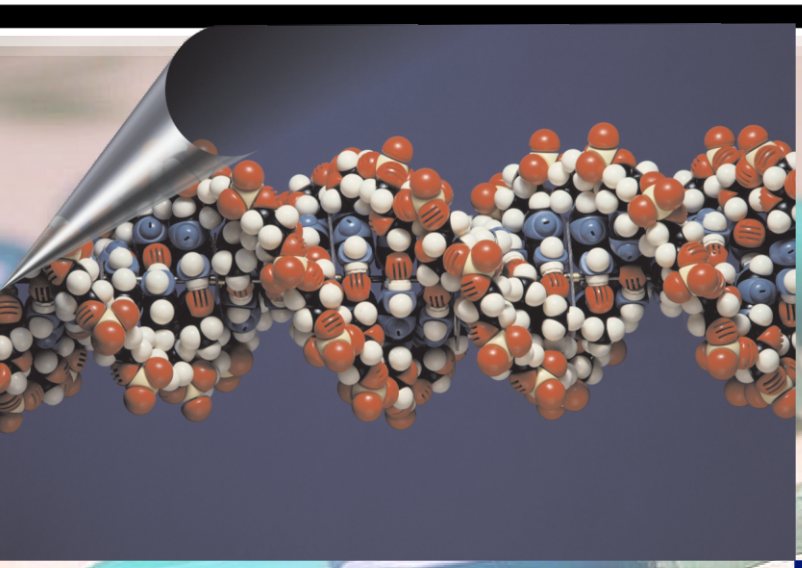

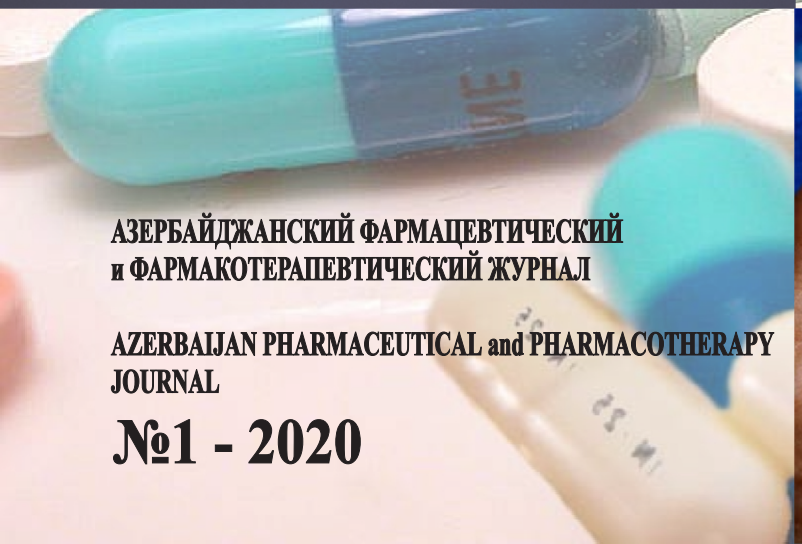

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THE EFFECT OF OVP-1 ON BLOOD PRESSURE AND PARAMETERS OF GENERAL HEMODYNAMICS IN ACUTE ARTERIAL HYPERTENSION IN RABBITS

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Ключевые слова: *OVP-1, arterial hypertension, rabbits, antihypertensive action*

Introduction

According to the WHO, arterial hypertension (AH) is a world leader among the most common cardiovascular diseases [1]. Despite the achievements of modern medicine, there are many genetic and other factors which determine the further increase in the prevalence of this pathology in our time, including hypodynamics, large-scale use of smartphones and other computer devices, chronic stress, malnutrition, etc. [2]. In addition, the difficulty of solving the problem of the prevalence of essential hypertension and secondary symptomatic increase in blood pressure (BP) is associated with the development of a significant number of concomitant cellular and subcellular pathological changes in most organs and systems which can lead to disability and mortality [3-4].

Modern pharmacotherapy of AH is associated with a significant number of adverse reactions due to the use of antihypertensive drugs, failure of patients to complex and long-term combination regimens, the presence of AH resistant forms [3]. Given the lack of efficacy and unsatisfactory tolerability of antihypertensive drugs, resulting in low motivation of patients to treat, the study of new compounds capable of antihypertensive effects is an important area of modern pharmacological science and practical pharmacy [5-7].

At the V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry of the National Academy of Sciences of Ukraine for the last 8 years it has been conducting the synthesis and study *in vitro* of the vasodilatory properties of oxazole derivatives [8]. Among them, one of the most promising groups of original compounds, which are able to reduce vascular tone, are phosphorylated oxazole derivatives, considering as a new class of potential antihypertensive drugs [9].

In the previous stages, the vasodilating activity presence of the group compound-leader OVP-1 *in vitro*, antihypertensive action *in vivo* was experimentally investigated and the safety of this compound was proved [10]. However, the mechanisms of the antihypertensive effect development of OVP-1 stays unclear. Analysis of foreign literature data shows that only one group of original compounds is known, which contain a hydrogenated oxazole ring in their structure and exhibit antihypertensive activity − C07D263 / 34 (USA), the vasodilating effect of which has been confirmed experimentally *in vivo* and *in vitro*, based on angiotensin II type 1 receptors blockage and neprilysin inhibition. Neprilysin is a neutral endopeptidase localized in the tissues of the heart and peripheral vessels, capable of inactivating natriuretic peptides, which are responsible for vasodilation [11].

Taking into account the above literature data and our previous experimental studies of phosphorylated oxazole derivatives, it was exprdient to continue the pharmacological study of the vasodilating effect of the leader compound OVP-1 in vivo.

The aim of work to evaluate the features of OVP-1 influence on the indicators of systemic hemodynamics under the conditions of experimental modeling of acute arterial hypertension in anesthetized rabbits.

Materials and methods

The original compound −phosphorylated 1,3-oxazole derivative (laboratory code OVP-1) was synthesized in Bioactive Nitrogen-Containing Heterocyclic Bases Chemistry Department of V.P. Kukhar Institute of Bioorganic Chemis-

try and Petrochemistry of the National Academy of Sciences of Ukraine. Melting point determination, IR spectroscopy and NMR spectroscopy were used to prove the composition and structure of the substance. The established results confirmed the compliance of the synthesized compounds with the claimed formulas [9].

Experimental studies were performed on 42 adult rabbits of the Chinchilla breed of the both sexes weighing 3-4 kg. Animals were cared for and euthanized in accordance with the principles of the European Convention for the Protection of Laboratory Animals (Strasbourg, 1986). The compliance with bioethical norms in conducting experimental research on the animals was confirmed by the Commission on Bioethical Expertise and Ethics of Scientific Research of the Bogomolets National Medical University (Minutes №118 of January 18, 2019).

The rabbits were randomly divided into a control pathology group (n=7), an experimental group (n=7), which OVP-1 was administered at a dose of 25 mg/kg (ED_{50}) [10] and a group of rabbits (n=7), which was administered comparison medicine − nebivolol ("Nebivolol hydrochloride", Hetero Drugs Limited, India) 10 mg/kg. Nebivolol was chosen as a comparator because it belongs to one of the main classes of modern antihypertensive drugs with vasodilating action and is a β-blocker of the third generation, able to prevent epinephrine-induced increase in blood pressure [12].

The animals were injected intravenously with a solution of OVP-1 25 mg/kg in a mixture of tween-80 and 0.9% NaCl solution for injection in a ratio of 1:10, after which 10 minutes later modeled acute hypertension by intravenous administration of epinephrine solution hydrotartrate ("Adrenaline-Darnitsa", solution for injection 0.18% 1 ml, CJSC "Pharmaceutical Company "Darnitsa", Ukraine) at a dose of 0.03 mg/kg [13]. The control group was administered placebo (a mixture of 0.9% NaCl solution for injection and twin-80 in a ratio of 10:1), and then modeled acute hypertension as described above. Nebivolol was pre-diluted in 0.9% NaCl solution for injection and administered intravenously.

Registration of the main parameters – systolic pressure (SP, mm Hg) and cardiac output (CO, ml/min) was performed after the introduction of OVP-1 solution for 10 minutes and on the background of OVP-1 after the introduction of the solution epinephrine hydrotartrate for at least 10 minutes using the hemodynamic system Hp Viridia Component Monitoring System ("Hewlett Packard", USA).

One of the significant factors influencing the BP level is the strength of the heart, which is characterized by the following indicators of cardiohemodynamics: heart rate (HR, ml/sec) and cardiac index (CI, ml/(m^2·min)). The last 2 parameters were calculated on the basis of the obtained values of CO according to formulas 1 and 2:

$$HR = CO / 60 \text{ sec}, \quad (1)$$

$$CI = CO / BSA, \quad (2)$$

where BSA – body surface area (m^2), which, in turn, was calculated as follows (formula 3):

$$BSA = 0.125\sqrt[3]{W^2}, \quad (3)$$

where W – body weight of the rabbit.

At the same time, any changes in the ultrastructure and metabolism of the left ventricle can cause a violation of its systolic and diastolic function, resulting in a change in BP [14]. The parameter which characterizes its functioning is a left ventricle working index (LVWI, kgm/ m^2· min), calculated by formula 4:

$$LVWI = CI \times SP \times 0{,}0135, \quad (4)$$

where 0,0135 – conversion factor mm Hg in kg·sec/m^2.

Another, no less important factor that determines the vascular component of the impact on BP is the total peripheral resistance (TPR, din/(sec·sm^5)), which depends mainly on the diameter of the precapillary vessels and calculated by the formula 5:

$$TPR = SP \times 1332 / HR, \quad (5)$$

where «1332» – conversion factor mm Hg in din/sec·sm^2.

Results

Investigation of OVP-1 influence on the parameters of general hemodynamics of rabbits under conditions of acute hypertension modeling was performed at a dose of 25 mg/kg (ED_{50}) in/v and compared with similar effects of nebivolol 10 mg/kg (Table 1). It was found that under the influence of placebo solution in the group of control pathology SP did not change, but in the modeling of acute hypertension with the introduction of epinephrine observed an increase in this indicator by 37.4% (182.57 ± 6.34 mm Hg; P <0,05) at the 1st min, 29.0% (171.43 ± 5.61 mm Hg; P <0.05) at the

5th min and 22.9% (163.29 ± 5.33) mm Hg; P <0.05) on the 10th min relative to baseline (132.86 ± 4.52 mm Hg).

The introduction of OVP-1 25 mg/kg resulted in a decrease in SP lasting 7 minutes. Statistically significant changes under the influence of oxazole derivative OVP-1 relative to baseline (154.14 ± 7.45 mm Hg) were observed on the 1st min - the decrease in SP was 15.9% (129.57 ± 6.19 mm Hg, P <0.05) and the 5th min. as a trend of 12.2% (135.29 ± 5.13 mm Hg; P> 0.05). After the introduction of epinephrine on the background of OVP-1 noted from the 1st min the beginning of the decrease in SP in the form of a trend, the peak of which was observed at the 10th min by 32.7% (109.86 ± 16.50 mm Hg; P<0.05) relative to the group of control pathology (163.29 ± 5.33 mm Hg). There were no statistically significant changes in SP between groups of rabbits injected with OVP-1 and nebivolol.

Table 1. *The effect of OVP-1 on the parameters of cardiohemodynamics of experimental rabbits before and after administration of epinephrine 0.03 mg/kg in the modeling of acute hypertension (n=7)*

Animal groups	Baseline	Time after administration of the test compound			Time after administration of epinephrine against the background of the test compound		
		1 min	5 min	10 min	1 min	5 min	10 min
SP, mm Hg							
CP (placebo)	132,86± 4,52	133,30± 4,97	143,71± 8,50	140,57± 4,99	182,57± 6,34*	171,43± 5,61*	163,29± 5,33*
OVP-1 25 mg/kg	154,14± 7,45	129,57± 6,19*	135,29± 5,13	164,57± 17,61	174,86± 17,93	118,57± 15,44#	109,86± 16,50*#
Nebivolol 10 mg/kg	150,43± 8,32	124,43± 7,81*	130,43± 6,30	142,57± 8,34	169,00± 14,67	112,43± 15,65#	107,29± 13,02*#
CO, ml/min							
CP (placebo)	1159,3± 121,4	1193,3± 122,7	1249,3± 123,5	1180,7± 133,5	893,7± 117,5*	1075,7± 184,1	1019,3± 60,6
OVP-1 25 mg/kg	755,6± 194,5	611,3± 177,0#	755,1± 113,0#	1140,0± 197,0	843,4± 143,1	1059,1± 88,6	1095,4± 95,5*
Nebivolol 10 mg/kg	676,1± 112,1	565,6± 96,8#	583,0± 86,4#	857,0± 101,6	756,6± 71,1	866,9± 124,2	936,4± 88,3
LVWI, kgm/ m^2· min							
CP (placebo)	3585,1± 391,8	3571,0± 357,8	3936,0± 372,7	3750,3± 327,9	3577,4± 307,2	4128,9± 583,6	3843,7± 465,5
OVP-1 25 mg/kg	2306,3± 384,8	1489,9± 457,5#	1975,1± 355,0#	3809,7± 904,6	2944,3± 634,6	2271,9± 715,1#	2255,1± 515,6#
Nebivolol 10 mg/kg	2345,9± 349,1	1345,0± 299,0#	1790,1± 317,5#	3831,4± 859,3	3256,9± 432,9	2653,3± 523,9#	2713,6± 556,0
TPR, din/ (sec· sm^5)							
CP (placebo)	8937,1± 1196,5	8902,53± 1012,0	9423,0± 938,8	9273,3± 1009,8	16640,3± 1523,8*	12955,1± 1770,0	12525,3± 1506,5
OVP-1 25 mg/kg	16591,1± 3518,1	17465,9± 1983,1#	15045,4± 2978,9#	13363,0± 2467,9	17371,9± 2901,1	9803,0± 1590,3*	9973,1± 901,4 *
Nebivolol 10 mg/kg	14631,3± 2212,1	12400,1± 1281,4	13083,9± 1740,9	13470,0± 2297,4	15552,3± 2578,9	9518,4± 1153,9*	9908,9± 901,3*

Note: *CP – control pathology; * – reliability relative to baseline, P<0,05; # – reliability relative to the corresponding value of the control pathology group, P<0,05; n – number of animals in the group.*

In the control pathology group, a decrease in CO at 1 minute after administration of epinephrine solution by 27.8% (893.7 ± 117.5 ml / min; P <0.05) relative to the baseline (1159,3±121,4 ml / min) was recorded. In the group of animals injected with OVP-1, the increase in CO at the 5th and 10th min after administration of a hypertensive agent on the background of oxazole derivative by 40.6% (1059.1 ± 88.6 ml / min; P < 0.05) and 45.0% (1095.4 ± 95.5 ml / min; P <0.05) relative to baseline (755.6 ± 94.5 ml / min). Changes in CO in rabbit groups injected

with OVP-1 and the reference drug were comparable.

In the control group on the 5th min after administration of epinephrine there was a tendency to increase LVWI by 15.2% (4128.9 ± 583.6 kgm / m^2 • min; P> 0.05) relative to baseline. (3585,1±391,8 kgm / m^2 • min) (Fig. 1).

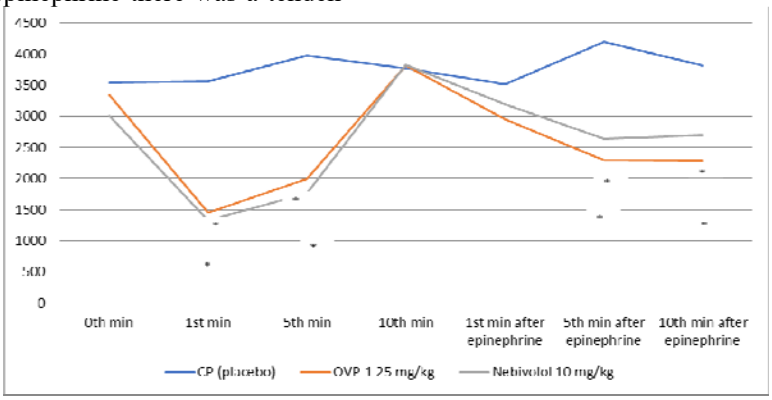

Figure 1. *Effect of OVP-1 25 mg/kg (ED_{50}) on LVWI of experimental rabbits before and after administration of epinephrine 0.03 mg/kg in the modeling of acute hypertension, kgm/(m^2*min) (n=7)*
Note: CP – control pathology group; * – reliability relative to baseline, P<0,05.

The effect of OVP-1 was manifested in the reduction of LVWI on the 1st min after administration by 58.3% (1489.9 ± 457.5 kgm / m^2 • min; P <0.05) and the 5th min - by 49.8 % (1975.1 ± 355.0 kgm / m^2 • min; P <0.05) relative to the corresponding values in the control group. A similar effect of reducing LVWI was observed on the 5th and 10th min after administration of epinephrine by 45%, respectively (2271.9 ± 715.1 kgm / m^2 • min; P <0.05) and 41.3% (2255.1 ± 515.6 kgm / m^2 • min; P <0.05) relative to the control pathology group. No statistically significant changes in LVWI were observed in the groups administered OVP-1 and nebivalol.

With the introduction of epinephrine in the control group of rabbits observed a maximum increase in TPR from the 1st min by 86.2% (16640.3 ± 1523.8 din/(sec· sm^5); P <0.05), at the 5th min this figure increased by 45% (12955.1 ± 1770.0 din/(sec· sm^5); P <0.05), by the 10th minute - by 40.1% (12525.3 ± 1506.5 din/(sec· sm^5)); P <0,05) relative to the initial value (8937,1 ± 1196,5 din/(sec· sm^5)) (Fig.2).

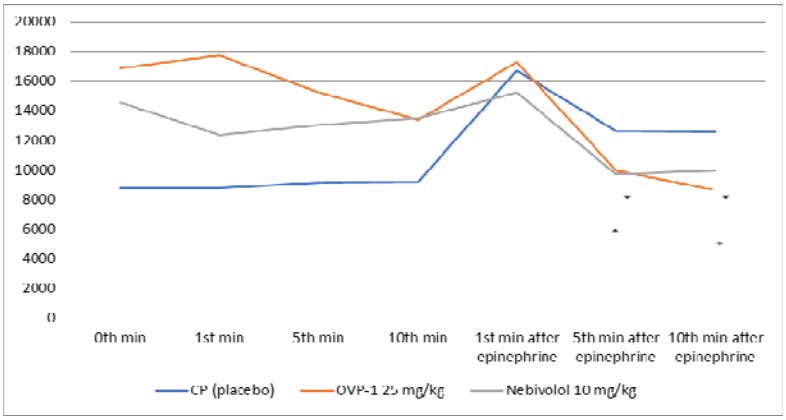

Figure 2. *Effect of OVP-1 25 mg/kg (ED_{50}) on TPR of experimental rabbits before and after administration of epinephrine 0.03 mg/kg in the modeling of acute hypertension, din/(sec*sm^5) (n=7)*
Note: *CP – control pathology group; * – reliability relative to baseline, P<0,05.*

In the group OVP-1 25 mg/kg after administration of epinephrine TPR under the influence of this compound decreased from the 5th min by 40.9% (9803.0 ± 1590.3 din/(sec· sm^5); P <0.05) relative to baseline values (16591.1 ± 3518.1 din/(sec· sm^5)). Changes in TPR in the rabbit groups administered OVP-1 and nebivolol were comparable.

Discussion and conclusion

In our experiment, the development of acute AH in rabbits was confirmed by an increase in SP for the 1st minute by an average of 1.4 times (P <0.05) compared with baseline. The antihypertensive effect of OVP-1 25 mg/kg was manifested by a decrease in SP by 32.7% with the introduction of epinephrine on the background of the test compound, which is consistent with previously obtained results of experimental studies of antihypertensive action of OVP-1 in models of acute and stable AH [10, 15-16].

A study of general hemodynamics in the modeling of acute AH suggests that the antihypertensive effect of OVP-1 may be due to a decrease in TPR, which under the influence of this compound at a dose of 25 mg/kg (ED_{50}) after administration of epinephrine decreased by 5 min by 40, 9% (P <0.05) relative to the baseline. The obtained result confirms the presence of vasodilating effect of this compound, found *in vitro* studies on isolated segments of the rat`s aorta [10].

Under the action of epinephrine on the background of OVP-1 there was an increase in CO on the 10th minute by 45% (P <0.05) relative to the baseline, which correlates with a decrease in TPR. At the same time, under the influence of OVP-1, there was a decrease in LVWI on the 1st min after administration by 58.3% (P <0.05) and on the 5th min - by 49.8% (P <0.05) relative to the corresponding indicator in control pathology group. A similar direction of the effect was observed on the 5th and 10th min on the background of epinephrine administration, respectively, by 45% (P <0.05) and 41.3% (P <0.05) relative to the control pathology group, which may be the result of slowing heart rate [10] and decreased SP.

The absence of statistically significant changes in the studied parameters of general hemodynamics between groups of rabbits injected with OVP-1 and the reference drug may indicate the identity of the mechanism of antihypertensive action of oxazole and nebivolol derivatives, which is realized by exposure to nitric oxide pattern [16]. At the same time, in contrast to OVP-1, among the side effects of nebivolol are bradycardia, bronchospasm and increased heart failure [17].

It was found that the original compound OVP-1 has an antihypertensive effect in the modeling of acute hypertension, which is associated with a decrease in SP due to TPR and LVWI. The obtained results are the basis for further in-depth preclinical studies of the mechanisms of OVP-1 action in order to develop a new original antihypertensive drug to prevent the development and treatment of AH.

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OVP-1-İN DOVŞANLARDA KƏSKİN ARTERİAL HİPERTENZİYA ZAMANI ARTERİAL TƏZYİQƏ VƏ ÜMUMİ HEMODİNAMİK PARAMETRLƏRƏ TƏSİRİ

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Açar sözlər: *OVP-1, arterial hipertansiyon, dovşan, antihipertenziv təsir*

Müalicə üçün xəstənin aşağı motivasiyasına səbəb olan antihipertenziv dərmanların effektivliyinin və qeyri-qənaətbəxş tolerantlığının nəzərə alınması, antihipertenziv təsir göstərə biləcək yeni birləşmələrin öyrənilməsi müasir farmakoloji elminin və praktik eczanənin vacib bir sahəsidir. İşin məqsədi, anesteziyalı dovşanlarda kəskin arterial hipertenziyanın eksperimental modelləşdirilməsi şəraitində sistem hemodinamikasının parametrlərinə OVP-1 təsirinin xüsusiyyətlərini qiymətləndirməkdir. Tədqiq edilən OVP-1 birləşməsinin, OPSS və LVEF səbəbiylə SBP səviyyəsinin azalması ilə əlaqəli kəskin arterial hipertansiyonun modelləşdirilməsində antihipertenziv təsir göstərdiyi aşkar edilmişdir. Alınan nəticələr, hipertansiyonun inkişafının və müalicəsinin qarşısını almaq üçün yeni bir orijinal antihipertensiv dərman hazırlamaq məqsədi ilə OVP-1-in təsir mexanizmlərinin daha da dərin preklinik tədqiqatları üçün əsasdır.

ВЛИЯНИЕ ОВП-1 НА АРТЕРИАЛЬНОЕ ДАВЛЕНИЕ И ПАРАМЕТРЫ ОБЩЕЙ ГЕМОДИНАМИКИ ПРИ ОСТРОЙ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ У КРОЛИКОВ

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Ключевые слова: *ОВП-1, артериальная гипертензия, кроли, антигипертензивное действие*

Учитывая недостаточную эффективность и неудовлетворительную переносимость антигипертензивных препаратов, что приводит к низкой мотивации пациентов к лечению, изучение новых соединений, способных оказывать антигипертензивное действие, является важным направлением современной фармакологической науки и практической фармации. Цель работы - оценить особенности влияния ОВП-1 на показатели системной гемодинамики в условиях экспериментального моделирования острой артериальной гипертензии у наркотизированных кролей. Было обнаружено, что исследуемое соединение ОВП-1 оказывает антигипертензивный эффект при моделировании острой артериальной гипертензии, что связано со снижением САД из-за ОПСС и РИЛЖ. Полученные результаты являются основой для дальнейших углубленных доклинических исследований механизмов действия ОВП-1 с целью разработки нового оригинального антигипертензивного препарата для предотвращения развития и лечения АГ.