THE ROLE OF REACTIVE OXYGEN SPECIES AND REDOX-SENSITIVE PROTEIN KINASES IN THE INFARCT-LIMITING EFFECT OF OPIOID PEPTIDE DELTORPHIN II IN CARDIAC REPERFUSION IN RATS

Popov S.V. [1],
Mukhomedzyanov A.V. [1],
Sirotina M. [1],
Kurbatov B.K. [1],
Azev V.N. [2],
Sufianova G.Z. [3],
Khlestkina M.S. [3],
Maslov L.N. [1]

[1] Cardiology Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences (Kievskaya str. 111A, Tomsk 634012, Russian Federation)
[2] Branch of Shemyakin – Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences (Nauki ave. 6, Pushchino 142290, Russian Federation)
[3] Tyumen State Medical University (Odesskaya str. 54, Tyumen 625023, Russian Federation)

Corresponding author:
Alexander V. Mukhomedzyanov,
e-mail: sasha_m91@mail.ru

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ABSTRACT

Background. *Mortality from acute myocardial infarction with ST-segment elevation in cardiac hospitals ranges from 4.5 to 7 %, and these data has not decreased in recent years. The most common cause of death in patients is cardiogenic shock, the likelihood of which directly depends on infarct size. It is quite clear that there is an urgent need to create drugs to limit the size of infarction and prevent the occurrence of cardiogenic shock.*

The aim. *To evaluate the role of reactive oxygen species and redox-sensitive protein kinases in the infarct-limiting effect of opioid peptide deltorphin II in cardiac reperfusion in rats.*

Materials and methods. *Coronary occlusion (45 min) and reperfusion (120 min) were performed in rats anesthetized with α-chloralose. The selective δ_2-opioid receptor agonist deltorphin II, a hydroxyl radical scavenger 2-mercaptoprpionyl glycine (2-MPG), a superoxide radical scavenger tempol, the protein kinase Cδ (PKCδ) inhibitor rottlerin, the PI3-kinase inhibitor wortmannin, the inhibitor of ERK1/2 kinase PD98059 were injected before of reperfusion of the heart.*

Results. *Deltorphin II contributed to a two-fold decrease in infarction size. Injection of 2-MPG, tempol, rottlerin, wortmannin, PD98059 alone had no effect on infarction size in rats. 2-MPG and tempol did not affect the infarction-reducing effect of deltorphin II. Rottlerin, wortmannin, and PD98059 eliminated the cardioprotective effect of deltorphin II.*

Conclusion. *The infarction-reducing effect of deltorphin II does not depend on the production of superoxide radical and hydroxyl radical. Superoxide radical and hydroxyl radical do not play a significant role in reperfusion injury of the heart after coronary occlusion (45 min). PKCδ, PI3-kinase, and ERK1/2 kinase are involved in the infarct-limiting effect of deltorphin II in myocardial reperfusion.*

Key words: *heart, ischemia, reperfusion, opioid receptors, reactive oxygen species, kinases*

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РОЛЬ АКТИВНЫХ ФОРМ КИСЛОРОДА И РЕДОКС-ЧУВСТВИТЕЛЬНЫХ ПРОТЕИНКИНАЗ В ИНФАРКТ-ЛИМИТИРУЮЩЕМ ЭФФЕКТЕ ОПИОИДНОГО ПЕПТИДА ДЕЛЬТОРФИНА II ПРИ РЕПЕРФУЗИИ СЕРДЦА У КРЫС

Попов С.В. [1],
Мухомедзянов А.В. [1],
Сиротина М. [1],
Курбатов Б.К. [1],
Азев В.Н. [2],
Суфианова Г.З. [3],
Хлёсткина М.С. [3],
Маслов Л.Н. [1]

[1] Научно-исследовательский институт кардиологии, ФГБНУ «Томский национальный исследовательский медицинский центр Российской академии наук» (634012, г. Томск, ул. Киевская, 111а, Россия)
[2] Филиал ФГБУН Института биоорганической химии им. академиков М.М. Шемякина и Ю.А. Овчинникова Российской академии наук (142290, г. Пущино, просп. Науки, 6, Россия)
[3] ФГБОУ ВО «Тюменский государственный медицинский университет» Минздрава России (625023, г. Тюмень, ул. Одесская, 54, Россия)

Автор, ответственный за переписку:
Мухомедзянов Александр Валерьевич,
e-mail: sasha_m91@mail.ru

РЕЗЮМЕ

Обоснование. *Смертность от острого инфаркта миокарда с подъёмом сегмента ST в кардиологических стационарах составляет от 4,5 до 7 %, и в последние годы этот показатель не снижается. Наиболее частой причиной гибели пациентов является кардиогенный шок, вероятность возникновения которого напрямую зависит от размера инфаркта. Вполне очевидно, что назрела настоятельная необходимость в создании препаратов, ограничивающих размер инфаркта и предотвращающих появление кардиогенного шока.*

Цель исследования. *Оценить роль активных форм кислорода и редокс-чувствительных протеинкиназ в инфаркт-лимитирующем эффекте опиоидного пептида дельторфина II при реперфузии сердца у крыс.*

Материалы и методы. *Коронароокклюзию (45 мин) и реперфузию (120 мин) воспроизводили у крыс, наркотизированных α-хлоралозой. Перед реперфузией животным вводили: селективный агонист δ_2-опиоидных рецепторов дельторфин II, «ловушку» гидроксильных радикалов 2-меркаптопрпионил глицин (2-МПГ), «ловушку» супероксидных радикалов темпол, ингибитор протеинкиназы Cδ (ПКСδ) роттлерин, ингибитор PI3-киназы вортманнин, ингибитор ERK1/2 киназы PD98059.*

Результаты. *Дельторфин II способствовал двукратному уменьшению размера инфаркта. Инъекция крысам одного 2-МПГ, темпола, роттлерина, вортманнина, PD98059 не влияла на размер инфаркта. 2-МПГ и темпол не влияли на инфаркт-лимитирующий эффект дельторфина II. Роттлерин, вортманнин и PD98059 устраняли кардиопротекторный эффект дельторфина II.*

Заключение. *Инфаркт-лимитирующий эффект дельторфина II не зависит от продукции супероксидного радикала и гидроксильного радикала. Супероксидный радикал и гидроксильный радикал не играют существенной роли в реперфузионном повреждении сердца после коронароокклюзии (45 мин). ПКСδ, PI3-киназа и ERK1/2 киназа вовлечены в инфаркт-лимитирующий эффект дельторфина II при реперфузии миокарда.*

Ключевые слова: *сердце, ишемия, реперфузия, опиоидные рецепторы, активные формы кислорода, киназы*

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INTRODUCTION

Mortality caused by acute myocardial infarction with ST-segment elevation in cardiological hospitals ranges from 4.5 % to 7 %, and in recent years this indicator has not decreased [1–3]. The most common cause of patient death is cardiogenic shock [4], the likelihood of which is directly related to the size of the infarct [5, 6]. Primary percutaneous coronary intervention provides almost 95 % recanalization of the infarct-related coronary artery [7], however, this still results in patients dying. One of the leading causes of death is reperfusion injury to the heart. It is quite obvious that there is an urgent need to develop drugs that can limit the size of the infarction and prevent the occurrence of cardiogenic shock.

According to our data, opioids have the ability to improve myocardial pumping function during cardiac reperfusion [8]. The opioid peptide deltorphin II is able to reduce the size of myocardial infarction when administered intravenously before reperfusion [9]. The infarct-limiting effect of this peptide has been found to be related to the activation of peripheral δ_2-opioid receptors (ORs) [9]. The intracellular signaling mechanism of the cardioprotective effect of deltorphin II has not yet been studied. It is generally accepted that mitochondrial K+channels (mitochondrial K^+channels (mitoK_{ATP}-channels) are the ultimate effector of the infarct-limiting effects of pre- and postconditioning [10, 11]. We have observed that the cardioprotective effect of deltorphin II is independent of the mitoK_{ATP} channel, but is mediated by activation of the sarcolemmal K_{ATP} channel (sarcK_{ATP} channel) [12]. In what way is the intracellular signal transmitted from δ_2-OR to the sarcK_{ATP} channel? We hypothesized that the role of intracellular messengers providing increased cardiac tolerance to reperfusion may be claimed by reactive oxygen intermediates (ROIs). What was this hypothesis based on?

In the 80s of the twentieth century, the prevailing assumption was that free radicals and ROIs play an exclusively negative role in cardiac reperfusion injury [13, 14]. Now a similar perspective is being held by some of the researchers [15–17]. The findings that free radical production in the myocardium increases manifold at the time of reperfusion compared to the preceding ischemic period were in favor of this view [18–20]. This perspective was supported by evidence of the infarct-limiting effect of antioxidants [21–23]. However, in these studies, antioxidants were generally used at high dosages that allow them to interact not only with free radicals but also with other molecules. As an example, the hydroxyl radical (•OH) "scavenger" 2-mercaptopropyl-glycine (2-MPG; 20 mg/kg) [24, 25] at a dose of 70 mg/kg injected intravenously can interact with peroxynitrite [26], and at a dose of 100 mg/kg limits the size of myocardial infarction by 2-MPG [27]. Consequently, the cardioprotective effect of 2-MPG may not be dependent on a decrease in •OH levels in myocardial tissue.

In the 90s of the XX century, the perception that free radicals and ROIs can not only be damaging but also protect the myocardium from the pathogenic effects of ischaemia and reperfusion was gradually formed. 2-MPG was found to eliminate the infarct-limiting effect of ischaemic preconditioning [11]. We have obtained evidence that ROIs play a key role in the cardioprotective effect of hypoxic preconditioning [28]. Free radicals and ROIs play the role of signaling molecules that activate redox-sensitive enzymes, primarily kinases [29]. For example, ROIs increase the activity of: protein kinase C (PKCδ and PKCε), PI3-kinase, and ERK1/2-kinase [29]. These kinases provide cardiac resistance to ischaemia and reperfusion [10]. There are reasons to believe that the role of such activators of kinases is claimed by: •OH, superoxide radical ($O_{2}^{-\bullet}$) and hydrogen peroxide [29].

THE AIM OF THE STUDY

To evaluate the role of reactive oxygen intermediates (ROIs) and redox-sensitive protein kinases in the infarct-limiting effect of the opioid peptide deltorphine II during cardiac reperfusion in rats.

MATERIALS AND METHODS

The study was performed on 144 male Wistar rats weighing 250–300 g. All procedures related to the housing and use of animals were undertaken in compliance with the European Parliament and Council of the European Union directives (2010/63/EU) governing the use of animals for scientific purposes. The study was approved by the Ethical Committee of the Cardiology Research Institute – branch of the Tomsk National Research Medical Center of the Russian Academy of Sciences (protocol No. 207 of 23.12.2020).

The animals were anesthetized with intraperitoneal administration of α-chloralose (60 mg/kg, intraperitoneal; Sigma) and connected to a SAR-830 Series artificial lung ventilation apparatus (CWE Inc., USA). Coronary occlusion (45 min) and reperfusion (120 min) were performed according to the method of J.E. Schultz et al. [30]. This procedure was performed by thoracotomy at the level of 2–3rd ribs and a ligature was applied to the left coronary artery a few millimeters below its exit from the aorta. After 45 minutes of ischemia, the ligature was removed to resume coronary blood flow. BP was recorded using a SS13L pressure-sensing means (Biopac System Inc., Goleta, USA) paired with an MP35 electrophysiological study device (Biopac System Inc., Goleta, USA). Blood pressure was measured by cannulation of the right carotid artery using a SS13L pressure-sensing means (Biopac System Inc., Goleta, USA) paired with an MP35 electrophysiological study device (Biopac System Inc., Goleta, USA) and a personal computer. This device was also used to register an electrocardiogram. After reperfusion, the heart was then removed from the thorax (chest) and flushed retrogradely through the aorta with physiological saline. To determine the area at risk (AAR), the ligature was retightened and the myocardium was stained by jet staining through the aorta with 5 % potassium permanganate. My-

ocardium subjected to ischemia-reperfusion is commonly referred to as the AAR. After being washed with physiological saline, 1 mm thick heart slices were made perpendicular to the longitudinal axis using an HSRA001-1 slicer (Zivic Instruments, USA). Visualisation of the necrosis zone from the area at risk was performed by staining with 1 % solution of 2,3,5-triphenyl tetrazolium chloride over a period of 30 minutes at 37 °C. The method is based on the ability of 2,3,5-triphenyl tetrazolium chloride to acquire a persistent colour when changing from the oxidized state to the reduced state under the action of dehydrogenases. Since no dehydrogenases were observed in the dead cardiomyocytes, the necrotic myocardium was not stained. After staining was completed, the slices were placed in 10% formaldehyde solution for 1 day. Slices were scanned on both sides using an HP Scanjet G4050 scanner. The size of the AAR and infarct size (IS) were determined by computerised planimetric method. The size of the infarct size was expressed as a percentage of the size of the hypoperfusion zone (area at risk) as the IS/AAR ratio.

Blockers were administered intravenously 10 min before reperfusion, and deltorphin II was administered 5 min before reperfusion. Each experimental group consisted of 12 specimens. Animals injected with physiological solution were included in the control group.

The following pharmacological agents were used in the experiment: δ_2-OR selective agonist deltorphin II – at a dose of 0.12 mg/kg [9]; hydroxyl radical "scavenger" 2-MPG – at a dose of 20 mg/kg [24]; superoxide radical "scavenger" tempol – at a dose of 30 mg/kg [31]; protein kinase Cδ (PKCδ) inhibitor rottlerin – at a dose of 0.3 mg/kg [32]; PI3-ki-

TABLE 1

HEART RATE (BEATS/MIN) AND SYSTOLIC BLOOD PRESSURE (MMHG) IN RATS WITH CORONARY OCCLUSION (45 MIN) AND REPERFUSION (120 MIN), Me [25%; 75%]

Group	Before ischemia	Before reperfusion	After 30 minutes of reperfusion	After 2 hours of reperfusion
		Heart rate		
Monitoring	367 [363; 371]	360 [358; 369]	354 [347; 360]	346 [340; 351]
Deltorphine II	364 [358; 369]	358 [353; 364]	352 [348; 355]	343 [338; 348]
2-MPG	361 [358; 366]	357 [352; 361]	353 [349; 358]	342 [337; 346]
Tempol	356 [351; 362]	351 [347; 355]	347 [344; 352]	339 [334; 343]
Rottlerin	370 [364; 374]	365 [360; 369]	358 [352; 363]	350 [343; 356]
Vortmannin	360 [356; 365]	354 [349; 360]	350 [345; 354]	340 [334; 345]
PD98059	363 [359; 368]	356 [352; 359]	352 [346; 358]	345 [341; 351]
		Systolic blood pressure		
Monitoring	124 [121; 127]	121 [117; 125]	118 [113; 121]	114 [109; 118]
Deltorphine II	121 [117; 125]	120 [118; 122]	116 [111; 119]	112 [107; 116]
2-MPG	125 [122; 129]	122 [119; 126]	119 [114; 123]	115 [111; 119]
Tempol	120 [116; 124]	116 [113; 121]	113 [110; 117]	107 [105; 112]
Rottlerin	125 [123; 129]	122 [119; 124]	117 [113; 120]	111 [108; 115]
Vortmannin	126 [122; 130]	121 [119; 126]	117 [114; 122]	113 [110; 117]
PD98059	128 [124; 132]	124 [120; 128]	120 [116; 125]	114 [109; 118]

nase inhibitor wortmannin – at a dose of 0.025 mg/kg [33]; ERK1/2 kinase inhibitor PD98059 – at a dose of 0.5 mg/kg [34].

Deltorphin II, 2-MPG, and tempol were dissolved in 0.9% NaCl, and the other inhibitors were dissolved in a mixture of DMSO/20% β-hydroxypropyl-cyclodextrin (1:9). As our preliminary experiments have demonstrated, a similar mixture that was infused at a dose of 1 ml/kg had no effect on infarction size.

Deltorphin II has been purchased from PolyPeptide Laboratories (USA), 2-MPG and rottlerin from Sigma-Aldrich (USA), tempol from Tocris (UK), wortmannin and PD98059 from LCLabs Company (USA).

Statistical data processing was performed with the use of "Statistica 13.0" software packages (StatSoft Inc., USA). The obtained data were verified for normality of distribution using the Shapiro-Wilk criterion; distributions that differed from normal were analyzed using the nonparametric Mann – Whitney criterion. Differences were considered statistically significant at $p < 0.05$. The results of all experiments are presented in the form of median and quartiles (Me [25 %; 75 %]).

RESULTS AND DISCUSSION

We have revealed that coronary occlusion and reperfusion as well as the selective δ_2-OR peptide agonist deltorphine II do not affect hemodynamic parameters (Table 1), which corresponds to our published data [9].

Rottlerin, wortmannin, PD98059, tempol, and 2-MPG also had no effect on hemodynamic parameters among rats with coronary occlusion and reperfusion (Table 1). The δ_2-OR agonist deltorphine II caused a two-fold reduction in the infarct size (Fig. 1).

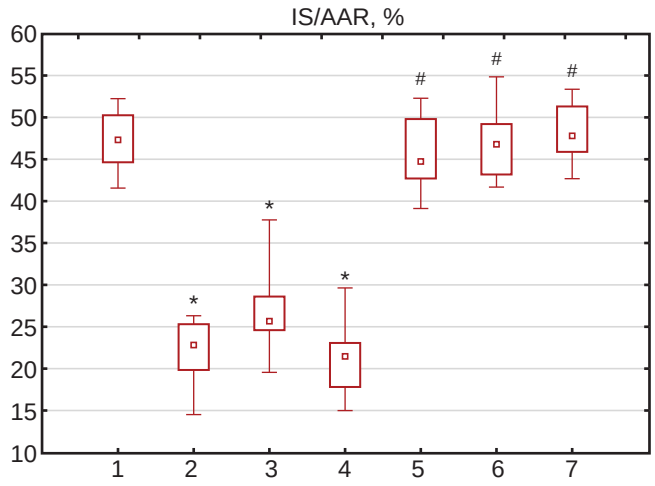

FIG. 1.

*The role of reactive oxygen species, the protein kinase Cδ, the PI3-kinase, and the ERK1/2 kinase in the mechanism of the cardioprotective effect of deltorphin II (Me [25%; 75%]). Groups: 1 – control; 2 – deltorphin II; 3 – deltorphin II + 2-MPG; 4 – deltorphin II + tempol; 5 – deltorphin II + rottlerin; 6 – deltorphin II + wortmannin; 7 – deltorphin II + PD098059. * – $p < 0.05$ vs control; # – $p < 0.05$ vs deltorphin II*

Injection of the PKCδ inhibitor rottlerin alone, the PI3-kinase inhibitor, or the ERK1/2-kinase inhibitor PD98059 had no effect on infarct size (Fig. 2).

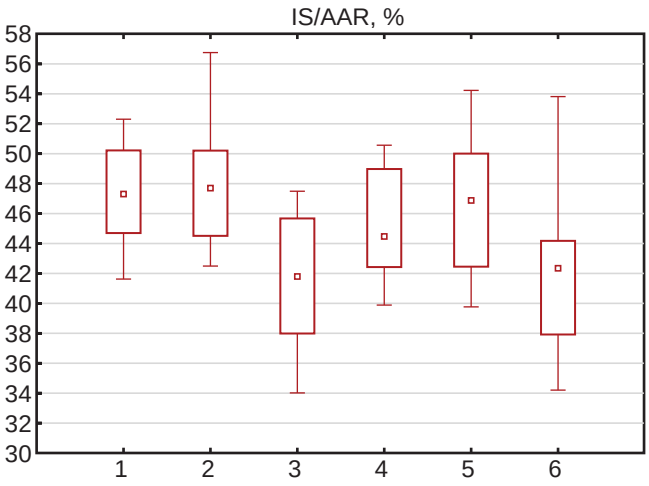

FIG. 2.

The effect of reactive oxygen species, inhibitors the protein kinase Cδ, the PI3-kinase, and the ERK1/2 kinase on infarct size as percentage of the area at risk after a 45-min ischemia and a 120-min reperfusion (Me [25%; 75%]). Groups: 1 – control; 2 – 2-MPG; 3 – tempol; 4 – rottlerin; 5 – wortmannin; 6 – PD098059

Consequently, these kinases are not involved in the formation of myocardial infarction in rats. An administration of the "scavenger" $^{\bullet}OH$ 2-mercaptopropionyl glycine or injection of the "scavenger" $O_{2}^{-\bullet}$ tempol also did not affect necrosis focus formation during cardiac reperfusion (Fig. 2). These data indicate that $^{\bullet}OH$ and $O_{2}^{-\bullet}$ are not involved in the pathogenesis of cardiac reperfusion injury.

We hypothesized that $^{\bullet}OH$ and $O_{2}^{-\bullet}$ do not damage the heart, but may increase cardiac resistance through activation of one of the isoforms of protein kinase C. PI3-kinase and ERK1/2-kinase may be involved in the cardioprotective effect of δ_2-OR agonist. Actually, we have previously observed that the infarct-limiting effect of deltorphin II is associated with the activation of protein kinases from group C; the inhibitor of all PKC isoforms chelerythrine eliminated the cardioprotective effect of the named peptide [12]. PKCs are known to be activated by ROIs [29], so it was reasonable to assume that ROIs are involved in the infarct-limiting effect of deltorphine II. However, it turned out that the "scavenger" $^{\bullet}OH$ 2-mercaptopropionyl glycine or the "scavenger" $O_{2}^{-\bullet}$ tempol did not affect the deltorphin-induced increase in cardiac reperfusion tolerance (Fig. 1). Consequently, $O_{2}^{-\bullet}$ and $^{\bullet}OH$ are not involved in the signaling mechanism of the protective effect of deltorphin II. It is possible that the activator of PKC and other redox-sensitive kinases is hydrogen peroxide, which is involved in intracellular and intercellular signaling [29].

Protein kinase C, PI3-kinase and ERK1/2-kinase are involved in the infarct-limiting effect of ischemic pre- and post-conditioning [10, 11]. These findings led us to sug-

gest that the above kinases are involved in the cardioprotective effect of deltorphin II. Indeed, the selective PKCδ inhibitor rottlerin was found to completely abolish the infarct-limiting effect of the named peptide (Fig. 1). After inhibition of PI3-kinase by wortmannin, we were unable to observe an infarct-limiting effect of deltorphine II (Fig. 1). After the blockade of ERK1/2 kinase with PD98059, we did not record the cardioprotective effect of the δ_2-OR agonist (Fig. 1). The presented data are consistent with the widespread viewpoint about the important role of protein kinase C, PI3-kinase and ERK1/2-kinase in ensuring the tolerance of the heart to the effects of ischemia and reperfusion [10, 11].

CONCLUSION

The presented data evidence that $O_{2}^{-\bullet}$ and $^{\bullet}OH$ are not involved in the pathogenesis of cardiac reperfusion injury after 45-minute coronary occlusion. These free radicals are not intracellular messengers mediating the cardioprotective effect of deltorphin II. PKCδ, PI3-kinase, and ERK1/2-kinase appear to play an important role in the formation of deltorphine-induced increase in cardiac tolerance to the pathogenic effects of reperfusion. Activation of the above kinases by deltorphin II occurs without the involvement of $O_{2}^{-\bullet}$ and $^{\bullet}OH$.

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Conflict of interest

The authors of this article declare the absence of a conflict of interest.

REFERENCES

1. Menees DS, Peterson ED, Wang Y, Curtis JP, Messenger JC, Rumsfeld JS, et al. Door-to-balloon time and mortality among patients undergoing primary PCI. *N Engl J Med*. 2013; 369(10): 901-909. doi: 10.1056/NEJMoa1208200

2. Fabris E, Kilic S, Schellings DAAM, Ten Berg JM, Kennedy MW, van Houwelingen KG, et al. Long-term mortality and prehospital tirofiban treatment in patients with ST elevation myocardial infarction. *Heart*. 2017; 103(19): 1515-1520. doi: 10.1136/heartjnl-2017-311181

3. Olier I, Sirker A, Hildick-Smith DJR, Kinnaird T, Ludman P, de Belder MA, et al. British Cardiovascular Intervention Society and the National Institute for Cardiovascular Outcomes Research. Association of different antiplatelet therapies with mortality after primary percutaneous coronary intervention. Association of different antiplatelet therapies with mortality after primary percutaneous coronary intervention. *Heart*. 2018; 104(20): 1683-1690. doi: 10.1136/hear tjnl-2017-312366

4. Basi MB, Lemor A, Gorgis S, Taylor AM, Tehrani B, Truesdell AG, et al. National Cardiogenic Shock Initiative Investigators. Vasopressors independently associated with mortality in acute myocardial infarction and cardiogenic shock. *Catheter Cardiovasc Interv*. 2022; 99(3): 650-657. doi: 10.1002/ccd.29895

5. Liakopoulos OJ, Schlachtenberger G, Wendt D, Choi YH, Slottosch I, Welp H, et al. Early clinical outcomes of surgical myocardial revascularization for acute coronary syndromes complicated by cardiogenic shock: A report from the North-Rhine-Westphalia Surgical Myocardial Infarction Registry. *J Am Heart Assoc*. 2019; 8(10): e012049. doi: 10.1161/JAHA.119.0 12049

6. Braile-Sternieri MCVB, Mustafa EM, Ferreira VRR, Braile Sabino S, Braile Sternieri G, Buffulin de Faria LA, et al. Main considerations of cardiogenic shock and its predictors: Systematic review. *Cardiol Res*. 2018; 9(2): 75-82. doi: 10.14740/cr715w

7. McCartney PJ, Berry C. Redefining successful primary PCI. *Eur Heart J Cardiovasc Imaging*. 2019; 20(2): 133-135. doi: 10.1093/ehjci/jey159

8. Mukhomedzyanov AV, Zhuk VV, Maslov LN, Shipunov AI, Andrienko OS, Gadirov RM. Cardioprotective effect of opioids, derivatives of amide N-methyl-2-(pirrolidin-1-yl)cyclohexyl-1-amine, under conditions of ischemia/reperfusion of the heart. *Bull Exp Biol Med*. 2021; 170(6): 710-713. doi: 10.1007/s10517-021-05138-y

9. Maslov LN, Mukhomedzyanov AV, Tsibulnikov SY, Suleiman MS, Khaliulin I, Oeltgen PR. Activation of peripheral δ_2-opioid receptor prevents reperfusion heart injury. *Eur J Pharmacol*. 2021; 907: 174302. doi: 10.1016/j.ejphar.2021.174302

10. Heusch G. Molecular basis of cardioprotection: signal transduction in ischemic pre-, post-, and remote conditioning. *Circ Res*. 2015; 116(4): 674-699. doi: 10.1161/CIRCRESAHA. 116.305348

11. Yellon DM, Downey JM. Preconditioning the myocardium: from cellular physiology to clinical cardiology. *Physiol Rev*. 2003; 83(4): 1113-1151. doi: 10.1152/physrev.00009.20 03

12. Mukhomedzyanov AV, Popov SV, Maslov LN. δ_2-opioid receptors as a target in designing new cardioprotective drugs: the role of protein kinase C, AMPK, and sarcolemmal K_{ATP} channels. *Bull Exp Biol Med*. 2022; 173(1): 33-36. doi: 10.1007/s10517-022-05487-2

13. Meyerson FZ. *Pathogenesis and prevention of stress and ischemic heart damage*. Moscow: Meditsina; 1984. (In Russ.).

14. Bilenko MV. *Ischemic and reperfusion injuries of organs*. Moscow: Meditsina; 1989. (In Russ.).

15. Matsushima S, Tsutsui H, Sadoshima J. Physiological and pathological functions of NADPH oxidases during myocardial ischemia-reperfusion. *Trends Cardiovasc Med*. 2014; 24(5): 202-205. doi: 10.1016/j.tcm.2014.03.003

16. Frangogiannis NG. Pathophysiology of myocardial infarction. *Compr Physiol*. 2015; 5(4): 1841-1875. doi: 10.1002/cphy.c150006

17. Granger DN, Kvietys PR. Reperfusion injury and reactive oxygen species: The evolution of a concept. *Redox Biol*. 2015; 6: 524-551. doi: 10.1016/j.redox.2015.08.020

18. Garlick PB, Davies MJ, Hearse DJ, Slater TF. Direct detection of free radicals in the reperfused rat heart using electron spin resonance spectroscopy. *Circ Res*. 1987; 61(5): 757-760. doi: 10.1161/01.res.61.5.757

19. Zweier JL, Rayburn BK, Flaherty JT, Weisfeldt ML. Recombinant superoxide dismutase reduces oxygen free radical concentrations in reperfused myocardium. *J Clin Invest*. 1987; 80(6): 1728-1734. doi: 10.1172/JCI113264

20. Bolli R, Patel BS, Jeroudi MO, Lai EK, McCay PB. Demonstration of free radical generation in "stunned" myocardium of intact dogs with the use of the spin tap alpha phenyl N-tert-butyl nitrone. *J Clin Invest*. 1988; 82(2): 476-485. doi: 10.1172/JCI113621

21. Näslund U, Häggmark S, Johansson G, Marklund SL, Reiz S, Oberg A. Superoxide dismutase and catalase reduce infarct size in a porcine myocardial occlusion-reperfusion model. *J Mol Cell Cardiol*. 1986; 18(10): 1077-1084. doi: 10.1016/s0022-2828(86)80294-2

22. Myers ML, Bolli R, Lekich RF, Hartley CJ, Roberts R. N-2-mercaptopropionylglycine improves recovery of myocardial function after reversible regional ischemia. *J Am Coll Cardiol*. 1986; 8(5): 1161-1168. doi: 10.1016/s0735-1097(86)80396-5

23. Bolli R, Zhu WX, Hartley CJ, Michael LH, Repine JE, Hess ML, et al. Attenuation of dysfunction in the postischemic 'stunned' myocardium by dimethylthiourea. *Circulation*. 1987; 76(2): 458-468. doi: 10.1161/01.cir.76.2.458

24. Tsutsumi YM, Yokoyama T, Horikawa Y, Roth DM, Patel HH. Reactive oxygen species trigger ischemic and pharmacological postconditioning: *In vivo* and *in vitro* characterization. *Life Sci*. 2007; 81(15): 1223-1227. doi: 10.1016/j.lfs.2007.08.031

25. Bolli R, Jeroudi MO, Patel BS, Aruoma OI, Halliwell B, Lai EK, et al. Marked reduction of free radical generation and contractile dysfunction by antioxidant therapy begun at the time of reperfusion. Evidence that myocardial "stunning" is a manifestation of reperfusion injury. *Circ Res*. 1989; 65(3): 607-622. doi: 10.1161/01.res.65.3.607

26. Tang XL, Takano H, Rizvi A, Turrens JF, Qiu Y, Wu WJ, et al. Oxidant species trigger late preconditioning against myocardial stunning in conscious rabbits. *Am J Physiol Heart Circ Physiol*. 2002; 282(1): H281-H291. doi: 10.1152/ajpheart.2002.282.1.H281

27. Sekili S, McCay PB, Li XY, Zughaib M, Sun JZ, Tang L, et al. Direct evidence that the hydroxyl radical plays a pathogenetic role in myocardial "stunning" in the conscious dog and demonstration that stunning can be markedly attenuated without subsequent adverse effects. *Circ Res*. 1993; 73(4): 705-723. doi: 10.1161/01.res.73.4.705

28. Sementsov AS, Naryzhnaya NV, Sirotina MA, Maslov LN. The role of reactive oxygen species in the infarct-limiting effect of hypoxic preconditioning. *Regional Blood Circulation and Microcirculation*. 2021; 20(2): 87-91. (In Russ.). doi: 10.24884/1682-6655-2021-20-2-87-91

29. Krylatov AV, Maslov LN, Voronkov NS, Boshchenko AA, Popov SV, Gomez L, et al. Reactive oxygen species as intracellular signaling molecules in the cardiovascular system. *Curr Cardiol Rev*. 2018; 14(4): 290-300. doi: 10.2174/1573403X14666180702152436

30. Schultz JEJ, Hsu AK, Gross GJJ. Ischemic preconditioning and morphine-induced cardioprotection involve the delta (δ)-opioid receptor in the intact rat heart. *Mol Cell Cardiol*. 1997; 29(8): 2187-2195. doi: 10.1006/jmcc.1997.0454

31. Pınar N, Kaplan M, Özgür T, Özcan O. Ameliorating effects of tempol on methotrexate-induced liver injury in rats. *Biomed Pharmacother*. 2018; 102: 758-764. doi: 10.1016/j.biopha.2018.03.147

32. Zatta AJ, Kin H, Lee G, Wang N, Jiang R, Lust R, et al. Infarct-sparing effect of myocardial postconditioning is dependent on protein kinase C signaling. *Cardiovasc Res*. 2006; 70: 315-334. doi: 10.10 16/j.cardiores.2005.11.030

33. Fettiplace MR, Kowal K, Ripper R, Young A, Lis K, Rubinstein I, et al. Insulin signaling in bupivacaine-induced cardiac toxicity: Sensitization during recovery and potentiation by lipid emulsion. *Anesthesiology*. 2016; 124: 428-442. doi: 10.1097/aln.0000000000000974

34. Lasley RD, Keith BJ, Kristo G, Yoshimura Y, Mentzer RM Jr. Delayed adenosine A1 receptor preconditioning in rat myocardium is MAPK dependent but iNOS independent. *Am J Physiol Heart Circ Physiol.* 2005; 289: H785-H791. doi: 10.1152/ajpheart.01008.2004

ЛИТЕРАТУРА

1. Menees DS, Peterson ED, Wang Y, Curtis JP, Messenger JC, Rumsfeld JS, et al. Door-to-balloon time and mortality among patients undergoing primary PCI. *N Engl J Med*. 2013; 369(10): 901-909. doi: 10.1056/NEJMoa1208200

2. Fabris E, Kilic S, Schellings DAAM, Ten Berg JM, Kennedy MW, van Houwelingen KG, et al. Long-term mortality and prehospital tirofiban treatment in patients with ST elevation myocardial infarction. *Heart*. 2017; 103(19): 1515-1520. doi: 10.1136/heartjnl-2017-311181

3. Olier I, Sirker A, Hildick-Smith DJR, Kinnaird T, Ludman P, de Belder MA, et al. British Cardiovascular Intervention Society and the National Institute for Cardiovascular Outcomes Research. Association of different antiplatelet therapies with mortality after primary percutaneous coronary intervention. Association of different antiplatelet therapies with mortality after primary percutaneous coronary intervention. *Heart*. 2018; 104(20): 1683-1690. doi: 10.1136/hear tjnl-2017-312366

4. Basi MB, Lemor A, Gorgis S, Taylor AM, Tehrani B, Truesdell AG, et al. National Cardiogenic Shock Initiative Investigators. Vasopressors independently associated with mortality in acute myocardial infarction and cardiogenic shock. *Catheter Cardiovasc Interv*. 2022; 99(3): 650-657. doi: 10.1002/ccd.29895

5. Liakopoulos OJ, Schlachtenberger G, Wendt D, Choi YH, Slottosch I, Welp H, et al. Early clinical outcomes of surgical myocardial revascularization for acute coronary syndromes complicated by cardiogenic shock: A report from the North-Rhine-Westphalia Surgical Myocardial Infarction Registry. *J Am Heart Assoc*. 2019; 8(10): e012049. doi: 10.1161/JAHA.119.0 12049

6. Braile-Sternieri MCVB, Mustafa EM, Ferreira VRR, Braile Sabino S, Braile Sternieri G, Buffulin de Faria LA, et al. Main considerations of cardiogenic shock and its predictors: Systematic review. *Cardiol Res*. 2018; 9(2): 75-82. doi: 10.14740/cr715w

7. McCartney PJ, Berry C. Redefining successful primary PCI. *Eur Heart J Cardiovasc Imaging*. 2019; 20(2): 133-135. doi: 10.1093/ehjci/jey159

8. Mukhomedzyanov AV, Zhuk VV, Maslov LN, Shipunov AI, Andrienko OS, Gadirov RM. Cardioprotective effect of opioids, derivatives of amide N-methyl-2-(pirrolidin-1-yl)cyclohexyl-1-amine, under conditions of ischemia/reperfusion of the heart. *Bull Exp Biol Med*. 2021; 170(6): 710-713. doi: 10.1007/s10517-021-05138-y

9. Maslov LN, Mukhomedzyanov AV, Tsibulnikov SY, Suleiman MS, Khaliulin I, Oeltgen PR. Activation of peripheral δ_2-opioid

receptor prevents reperfusion heart injury. *Eur J Pharmacol*. 2021; 907: 174302. doi: 10.1016/j.ejphar.2021.174302

10. Heusch G. Molecular basis of cardioprotection: signal transduction in ischemic pre-, post-, and remote conditioning. *Circ Res*. 2015; 116(4): 674-699. doi: 10.1161/CIRCRESAHA. 116.305348

11. Yellon DM, Downey JM. Preconditioning the myocardium: from cellular physiology to clinical cardiology. *Physiol Rev*. 2003; 83(4): 1113-1151. doi: 10.1152/physrev.00009.20 03

12. Mukhomedzyanov AV, Popov SV, Maslov LN. δ_2-opioid receptors as a target in designing new cardioprotective drugs: the role of protein kinase C, AMPK, and sarcolemmal K_{ATP} channels. *Bull Exp Biol Med*. 2022; 173(1): 33-36. doi: 10.1007/s10517-022-05487-2

13. Меерсон Ф.З. *Патогенез и предупреждение стрессорных и ишемических повреждений сердца*. М.: Медицина; 1984.

14. Биленко М.В. *Ишемические и реперфузионные повреждения органов*. М.: Медицина; 1989.

15. Matsushima S, Tsutsui H, Sadoshima J. Physiological and pathological functions of NADPH oxidases during myocardial ischemia-reperfusion. *Trends Cardiovasc Med*. 2014; 24(5): 202-205. doi: 10.1016/j.tcm.2014.03.003

16. Frangogiannis NG. Pathophysiology of myocardial infarction. *Compr Physiol*. 2015; 5(4): 1841-1875. doi: 10.1002/cphy.c150006

17. Granger DN, Kvietys PR. Reperfusion injury and reactive oxygen species: The evolution of a concept. *Redox Biol*. 2015; 6: 524-551. doi: 10.1016/j.redox.2015.08.020

18. Garlick PB, Davies MJ, Hearse DJ, Slater TF. Direct detection of free radicals in the reperfused rat heart using electron spin resonance spectroscopy. *Circ Res*. 1987; 61(5): 757-760. doi: 10.1161/01.res.61.5.757

19. Zweier JL, Rayburn BK, Flaherty JT, Weisfeldt ML. Recombinant superoxide dismutase reduces oxygen free radical concentrations in reperfused myocardium. *J Clin Invest*. 1987; 80(6): 1728-1734. doi: 10.1172/JCI113264

20. Bolli R, Patel BS, Jeroudi MO, Lai EK, McCay PB. Demonstration of free radical generation in "stunned" myocardium of intact dogs with the use of the spin tap alpha phenyl N-tert-butyl nitrone. *J Clin Invest*. 1988; 82(2): 476-485. doi: 10.1172/JCI113621

21. Näslund U, Häggmark S, Johansson G, Marklund SL, Reiz S, Oberg A. Superoxide dismutase and catalase reduce infarct size in a porcine myocardial occlusion-reperfusion model. *J Mol Cell Cardiol*. 1986; 18(10): 1077-1084. doi: 10.1016/s0022-2828(86)80294-2

22. Myers ML, Bolli R, Lekich RF, Hartley CJ, Roberts R. N-2-mercaptopropionylglycine improves recovery of myocardial function after reversible regional ischemia. *J Am Coll Cardiol*. 1986; 8(5): 1161-1168. doi: 10.1016/s0735-1097(86)80396-5

23. Bolli R, Zhu WX, Hartley CJ, Michael LH, Repine JE, Hess ML, et al. Attenuation of dysfunction in the postischemic 'stunned' myocardium by dimethylthiourea. *Circulation*. 1987; 76(2): 458-468. doi: 10.1161/01.cir.76.2.458

24. Tsutsumi YM, Yokoyama T, Horikawa Y, Roth DM, Patel HH. Reactive oxygen species trigger ischemic and pharmacological postconditioning: *In vivo* and *in vitro* characterization. *Life Sci*. 2007; 81(15): 1223-1227. doi: 10.1016/j.lfs.2007.08.031

25. Bolli R, Jeroudi MO, Patel BS, Aruoma OI, Halliwell B, Lai EK, et al. Marked reduction of free radical generation and contractile dysfunction by antioxidant therapy begun at the time of reperfusion. Evidence that myocardial "stunning" is a manifestation of reperfusion injury. *Circ Res*. 1989; 65(3): 607-622. doi: 10.1161/01.res.65.3.607

26. Tang XL, Takano H, Rizvi A, Turrens JF, Qiu Y, Wu WJ, et al. Oxidant species trigger late preconditioning against myocardial stunning in conscious rabbits. *Am J Physiol Heart Circ Physiol*. 2002; 282(1): H281-H291. doi: 10.1152/ajpheart.2002.282.1.H281

27. Sekili S, McCay PB, Li XY, Zughaib M, Sun JZ, Tang L, et al. Direct evidence that the hydroxyl radical plays a pathogenetic role in myocardial "stunning" in the conscious dog and demonstration that stunning can be markedly attenuated without subsequent adverse effects. *Circ Res*. 1993; 73(4): 705-723. doi: 10.1161/01.res.73.4.705

28. Семенцов А.С., Нарыжная Н.В., Сиротина М.А., Маслов Л.Н. Роль активных форм кислорода в инфаркт-лимитирующем эффекте гипоксического прекондиционирования. *Регионарное кровообращение и микроциркуляция*. 2021; 20(2): 87-91. doi: 10.24884/1682-6655-2021-20-2-87-91

29. Krylatov AV, Maslov LN, Voronkov NS, Boshchenko AA, Popov SV, Gomez L, et al. Reactive oxygen species as intracellular signaling molecules in the cardiovascular system. *Curr Cardiol Rev*. 2018; 14(4): 290-300. doi: 10.2174/1573403X14666180702152436

30. Schultz JEJ, Hsu AK, Gross GJJ. Ischemic preconditioning and morphine-induced cardioprotection involve the delta (δ)-opioid receptor in the intact rat heart. *Mol Cell Cardiol*. 1997; 29(8): 2187-2195. doi: 10.1006/jmcc.1997.0454

31. Pınar N, Kaplan M, Özgür T, Özcan O. Ameliorating effects of tempol on methotrexate-induced liver injury in rats. *Biomed Pharmacother*. 2018; 102: 758-764. doi: 10.1016/j.biopha.2018.03.147

32. Zatta AJ, Kin H, Lee G, Wang N, Jiang R, Lust R, et al. Infarct-sparing effect of myocardial postconditioning is dependent on protein kinase C signaling. *Cardiovasc Res*. 2006; 70: 315-334. doi: 10.10 16/j.cardiores.2005.11.030

33. Fettiplace MR, Kowal K, Ripper R, Young A, Lis K, Rubinstein I, et al. Insulin signaling in bupivacaine-induced cardiac toxicity: Sensitization during recovery and potentiation by lipid emulsion. *Anesthesiology*. 2016; 124: 428-442. doi: 10.1097/aln.0000000000000974

34. Lasley RD, Keith BJ, Kristo G, Yoshimura Y, Mentzer RM Jr. Delayed adenosine A1 receptor preconditioning in rat myocardium is MAPK dependent but iNOS independent. *Am J Physiol Heart Circ Physiol.* 2005; 289: H785-H791. doi: 10.1152/ajpheart.01008.2004

Information about the authors

Sergey V. Popov – Dr. Sc. (Med.), Professor, Member of RAS, Director, Cardiology Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, e-mail: psv@cardio-tomsk.ru, https://orcid.org/0000-0002-9050-4493

Alexander V. Mukhomedzyanov – Cand. Sc. (Med.), Research Officer at the Laboratory of Experimental Cardiology, Cardiology Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, e-mail: sasha_m91@mail.ru, https://orcid.org/0000-0003-1808-556X

Maria Sirotina – Junior Research Officer at the Laboratory of Experimental Cardiology, Cardiology Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, e-mail: sirotina_maria@mail.ru, https://orcid.org/0000-0002-4502-0836

Boris K. Kurbatov – Junior Research Officer at the Laboratory of Experimental Cardiology, Cardiology Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, e-mail: bobersanker@gmail.com, https://orcid.org/0000-0001-9603-822X

Viatcheslav N. Azev – Cand. Sc. (Chem.), Senior Research Officer, Branch of Shemyakin – Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, e-mail: viatcheslav.azev@bibch.ru, https://orcid.org/0000-0003-3275-4811

Galina Z. Sufianova – Dr. Sc. (Med.), Professor, Head of the Department of Pharmacology, Tyumen State Medical University, e-mail: sufianova@tyumsmu.ru, https://orcid.org/0000-0003-1291-0661

Maria S. Khlestkina – Cand. Sc. (Med.), Associate Professor at the Department of Pharmacology, Tyumen State Medical University, e-mail: hlestkina@tyumsmu.ru, https://orcid.org/0000-0002-5966-8916

Leonid N. Maslov – Dr. Sc. (Med.), Professor, Head of the Laboratory of Experimental Cardiology, Cardiology Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences, e-mail: maslov@cardio-tomsk.ru, https://orcid.org/0000-0002-6020-1598