REVIEWS

Opioid Receptors and Heart Resistance to Arrhythmogenic Factors

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We present detailed data on the role of central and peripheral opioid receptors in the regulation of heart resistance to arrhythmogenic factors. Stimulation of peripheral δ_2- and κ_1-receptors increases heart resistance to the arrhythmogenic effect of acute ischemia and reperfusion. Activation of peripheral μ- and δ_1-opioid receptors improves electrical stability of the heart in animals with postinfarction cardiosclerosis. Possible mechanisms for opioidergic regulation of heart resistance to arrhythmogenic factors are discussed.

Key Words: *arrhythmogenesis; opioid receptors; cardiac ischemia/reperfusion*

Much attention was given to electrophysiological mechanisms of arrhythmia. The autonomic nervous system plays an important role in the pathogenesis of ventricular and atrial arrhythmias. However, the involvement of various biologically active substances circulating in the blood or *in situ* synthesized in the myocardium in the regulation of electrical stability of the heart is poorly understood. These substances include opioid peptides.

Reviews were made on the structure and interaction of opioid receptor (OR) ligands with intracellular signaling systems [12,15,22]. Recent publications provide data on the permeability of the blood-brain barrier (BBB) for OR ligands [6] and the role of the opioid system in the regulation of hemodynamics [4]. Here we briefly characterized the opioid system.

The opioid system includes OR, opioid peptides (agonists of OR), enzymes involved in the synthesis of opioid peptides from high-molecular-weight precursors, and enzymes that cleave these peptides. According to the classification of the International Union of Pharmacologists, there are 4 types of OR: OR_1 (δ), OR_2 (κ), OR_3 (μ), and OR_4 (opioid receptor-like, ORL1). These receptors are divided into subtypes (*e.g.*, δ_1 and δ_2, κ_1 and κ_2). OR are localized on the cell membrane. G proteins couple these receptors with enzymes for intracellular signaling (adenylate cyclase, phospholipase C, tyrosine kinase, NO synthase, guanylate cyclase, and protein kinases). Stimulation of OR increases the synthesis of NO, cGMP, inositol triphosphate, and diacylglycerol. By contrast, cAMP production is suppressed after activation of OR. These changes are usually observed during activation of β-adrenoceptors with exogenous or endogenous catecholamines. We found that administration of isoproterenol to animals is followed by an opioid-induced decrease in cAMP concentration in the myocardium [2]. Pretreatment of rats with Ala^2,Leu^5,Arg^6-enkephalin abolished the increase in myocardial cAMP concentration during coronary occlusion [26]. However, dalargin increased cGMP concentration in the myocardium of animals [26]. The δ_1-OR agonist TAN-67 has cardioprotective activity associated with activation of protein kinase C, tyrosine kinase, and ATP-sensitive K^+ channels (K_{ATP} channels) [31], which plays a role in intracellular signaling.

Opioid peptides enkephalins, endorphins, endomorphins, dynorphins, and nociceptin act as endoge-

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nous agonists of OR [12,15,22]. Endomorphins are selective ligands of μ-OR. Nociceptin is a selective agonist of ORL1-receptors. Other endogenous opioid peptides can interact with several types of OR. Most opioid peptides have high affinity for a certain type of OR. Enkephalins act as primary agonists of δ-OR, but also activate μ-OR. Primary agonists of κ-OR dynorphins can stimulate μ- and δ-receptors.

OR are present practically in all organs and tissues that differ in the number of their subtypes. The role of the opioid system in the regulation of central hemodynamics was described in details [4]. The sarcolemma of cardiomyocytes contains δ-, κ_1-, κ_2-, and ORL1-receptors, but not μ-receptors. However, μ-receptors were identified on endotheliocytes in coronary vessels. Exogenous opioid peptides produce cardioprotective and antiadrenergic postsynaptic effects, which is probably related to inhibition of adenylate cyclase in cardiomyocytes. The antiadrenergic effect of opioid peptides can be realized at the presynaptic level due to suppression of catecholamine release from sympathetic terminals in the myocardium.

The amount of opioid peptides in myocardial tissue surpasses their concentration in the blood by several times, but does not differ from that in neuronal tissue [27]. Our previous studies showed that the content of leu-enkephalin and met-enkephalin in isolated heart increases by 2 times after 15-min global ischemia [2]. These data suggest that the opioid system plays an important role in the regulation of heart activity during ischemia and reperfusion. Activation of OR increases heart resistance to the cardiotoxic effect of the β-adrenoceptor agonist isoproterenol [2]. The observed changes probably result from opioidergic inhibition of adenylate cyclase in cardiomyocytes.

It can be hypothesized that activation of OR should provide heart resistance to the cardiotoxic and arrhythmogenic effect of catecholamines.

Activation of central and peripheral OR modulates heart resistance to the arrhythmogenic effect of catecholamines, aconitine, and $CaCl_2$. Intravenous injection of selective peptide μ-OR agonists DALDA and PL017 increases heart resistance to the arrhythmogenic effect of epinephrine [9]. DALDA produced a dose-dependent antiarrhythmic effect (U_{50} 40 μg/kg), but was ineffective during selective blockade of μ-OR [9]. These data indicate that μ-OR improve heart resistance to the arrhythmogenic effect of epinephrine. The opioid peptide DALDA does not cross BBB [6]. Probably, the antiarrhythmic effect of DALDA is associated with binding to peripheral μ-OR. Central μ-OR play an important role in arrhythmogenesis. Intracerebroventricular infusion of the selective μ-receptor agonist DAMGO increases heart resistance to the arrhythmogenic effect of epinephrine [2]. Therefore, activation of central and peripheral μ-OR improves electrical stability of the heart.

Other results were obtained after intravenous injection of peptide δ_2-OR agonists DSLET and DTLET. These peptides even in high dose (0.5 mg/kg) had no effect on heart resistance to the arrhythmogenic effect of epinephrine [16]. However, the nonpeptide δ-OR agonist BW373U86 decreased the incidence of epinephrine-induced ventricular tachycardia [16]. As distinct from DSLET and DTLET, BW373U86 crosses BBB [6]. We assumed that the antiarrhythmic effect is associated with activation of central δ-OR. Further studies showed that intracerebroventricular infusion of selective peptide agonists of δ_1- and δ_2-OR DPDPE, DSLET, and DTLET decreases the incidence of epinephrine-induced ventricular arrhythmias [16]. The antiarrhythmic effect of δ-OR agonists was not observed during blockade of OR with naloxone or selective δ-OR antagonist ICI 174,864 [16]. It can be hypothesized that activation of peripheral δ-OR has no effect on heart resistance to the arrhythmogenic effect of epinephrine, whereas binding of agonists to central δ_1- and δ_2-OR significantly increases heart resistance to the arrhythmogenic effect of this catecholamine.

In rats changes were revealed after intracerebroventricular treatment with agonists of κ_1-receptors (U-50,488 and [D-Ala^2]-dynorphin A_{1-13}) and κ_2-receptors (bremazocine) potentiating the arrhythmogenic effect of epinephrine [24,25]. Selective blockade of κ_1-receptors abolished the arrhythmogenic effect of κ-OR agonists [24,25]. By contrast, intravenous injection of selective κ_1-OR agonists decreased the incidence of epinephrine-induced arrhythmias [24]. Thus, activation of peripheral κ_1-OR increases heart resistance to the arrhythmogenic effect of epinephrine, whereas stimulation of central κ-OR produces electrical instability of the heart.

We showed that intravenous injection of the ORL1-receptor agonist nociceptin potentiates the arrhythmogenic effect of epinephrine [10]. Nociceptin acts as a selective ORL1-receptor agonist and cannot cross BBB [6]. Therefore, activation of peripheral OR_4 increases cardiac sensitivity to the arrhythmogenic effect of catecholamines.

These data illustrate that activation of μ- and κ_1-OR improves heart resistance to the arrhythmogenic effect of epinephrine. Stimulation of peripheral ORL1-receptors increases cardiac sensitivity to the arrhythmogenic effect of catecholamines. Stimulation of peripheral δ-OR has no effect on this characteristic. Binding of agonists to central μ- and δ-OR increases heart resistance to epinephrine, while stimulation of κ-OR in the brain potentiates the arrhythmogenic effect of this catecholamine.

Activation of OR affects myocardial sensitivity to the arrhythmogenic effect of not only catecholamines, but also $CaCl_2$ and aconitine. Our studies showed that selective peptide μ-OR agonists DALDA and PL017 increase heart resistance to the arrhythmogenic effect of $CaCl_2$ [9]. Under these conditions the antiarrhythmic effect of peptides was less significant compared to that observed during epinephrine-induced arrhythmias. The arrhythmogenic effect of epinephrine and $CaCl_2$ in rats was abolished by treatment with DALDA in doses of 50 and 500 кg/kg, respectively [9]. Systemic administration of selective κ-OR agonist spiradoline increases heart resistance to the arrhythmogenic effect of $CaCl_2$ [24]. Activation of peripheral ORL1-receptors had no effect on the incidence of ventricular arrhythmias produced by $CaCl_2$ in toxic doses [10]. It should be emphasized that the antiarrhythmic effect of OR agonists on the model of $CaCl_2$-induced arrhythmias was less pronounced compared to that observed during epinephrine-induced arrhythmias. These differences are probably related to antiadrenergic activity of opioid peptides manifested in competition with catecholamines for adenylate cyclase in cardiomyocytes. Catecholamines activate adenylate cyclase, while opioid peptides inhibit this enzyme.

Stimulation of peripheral μ-, κ-, and ORL1-receptors increases heart resistance to the arrhythmogenic effect of aconitine. The μ-OR agonist DALDA (0.1 mg/kg) and ORL1-receptor agonist nociceptin (0.4 mg/kg) possessed the highest antiarrhythmic activity [5,10]. The toxic effect of aconitine on the heart is associated with disturbances in inactivation of fast Na^+ channels, overload of cardiomyocytes with Na^+, intensification of Na^+/Ca^{2+} exchange, accumulation of excess Ca^{2+}, and electrical instability of the heart . Therefore, blockers of fast Na^+ channels are most potent during aconitine-induced arrhythmias. There is little likelihood that opioid peptides inhibit Na^+ channels (similarly to tetrodotoxin). The antiarrhythmic effect of these peptides is probably associated with the decrease in Ca^{2+} overload of cardiomyocytes due to inhibition of Na^+/Ca^{2+} exchange. This hypothesis requires further investigations.

Thus, our findings suggest that activation of peripheral OR significantly increases heart resistance to the arrhythmogenic effect of epinephrine and aconitine. The sympathoadrenal system plays an important role in the pathogenesis of arrhythmias during coronary occlusion and reperfusion. Adrenoceptor blockers prevent the development of arrhythmias under conditions of ischemia and reperfusion. Blockers of fast Na^+ channels have similar activity and increase heart resistance to the toxic effect of aconitine. We assumed that peptide μ-OR agonists possess maximum antiarrhythmic activity during coronary occlusion. For example, DALDA in a dose of 0.1 mg/kg increases heart resistance to the arrhythmogenic effect of epinephrine and aconitine. Agonists of κ-OR are less potent in this respect. In doses of 1 and 8 mg/kg they prevent the development of arrhythmias induced by epinephrine and aconitine, respectively. Probably, activation of δ- and ORL1-receptors does not modulate cardiac sensitivity to the arrhythmogenic effect of coronary occlusion and reperfusion, because activation of δ-OR has no effect, while nociceptin potentiates the arrhythmogenic influence of epinephrine.

Stimulation of OR increases heart resistance to the arrhythmogenic effect of acute coronary occlusion and reperfusion. At first glance the results of experiments with the mixed agonist of μ- and δ-OR Ala^2, Leu^5,Arg^6-enkephalin (dalargin) are consistent with our hypothesis that OR play a role in the regulation of heart resistance to the arrhythmogenic effect of ischemia and reperfusion. However, this peptide in a dose of 0.1 mg/kg prevented the development of ventricular fibrillation (VF) during coronary occlusion and reperfusion [26]. Dalargin crosses >0.5 mg/kg BBB in doses [6]. It could be suggested that the antiarrhythmic effect of Ala^2,Leu^5,Arg^6-enkephalin in this dose is related to activation of peripheral OR. However, dalargin acts as an agonist of μ- and δ-OR. It was unclear which subtype of receptors is responsible for the antiarrhythmic effect of dalargin. Experiments with selective agonists of OR were performed to solve this problem. Opioid peptides were used in equimolar concentrations, since the molecular weight of peptide OR agonists can differ by several times. The selective peptide μ-OR agonist DALDA served as the standard. Published data show that this peptide in a dose of 0.1 mg/kg (146 nmol/kg) increases heart resistance to the arrhythmogenic effect of epinephrine and aconitine [9]. We hypothesized that DALDA will exhibit the highest antiarrhythmic activity during acute ischemia and reperfusion.

This agonist of μ-OR had no effect on the incidence and type of arrhythmias in ketamine-narcotized rats exposed to 10-min coronary occlusion and reperfusion [28]. Selective δ_1-OR agonists TAN-67 and DPDPE in a dose of 146 nmol/kg did not modulate heart resistance to the arrhythmogenic effect of coronary occlusion and reperfusion [28]. However, selective δ_2-OR agonists deltorphin II and deltorphin D in the same dose decreased the incidence of ventricular arrhythmias during coronary occlusion and reperfusion. Selective blockade of δ_2-OR abolished the antiarrhythmic effect of deltorphin II [28]. We hypothesize that activation of δ_2-OR increases heart resistance to the arrhythmogenic effect of acute ischemia and reperfusion. Permeability of BBB for various compounds is in inverse proportion to their molecular weight

[6]. The molecular weight of deltorphins 2-fold surpasses that of dalargin. It can be assumed that peripheral δ_2-OR determine heart resistance to the arrhythmogenic effect of ischemia and reperfusion.

There are no selective peptide agonists of κ-OR characterized by high resistance to enzymatic hydrolysis and pronounced biological activity. Therefore, the role of κ-OR in arrhythmogenesis was studied using nonpeptide κ-OR ligands. The selective agonist of κ_1-OR (-)-U-50,488 in a dose of 2200 nmol/kg was potent in preventing the development of arrhythmias in rats produced by 10-min coronary occlusion and reperfusion [19]. The enantiomer of (+)-U-50,488 differing from (-)-U-50,488 by low affinity for κ-OR had no effect on the incidence and type of ischemic and reperfusion arrhythmias [19]. The antiarrhythmic effect of (-)-U-50,488 was abolished under conditions of selective κ_1-OR blockade [254], but persisted during the inhibition of κ_2-OR [25]. Activation of κ_2-OR after intravenous injection of the selective κ_2-OR agonist GR-89696 did not modulate the incidence and type of ischemic and reperfusion arrhythmias [25]. These data suggest that activation of κ_1-OR increases heart resistance to the arrhythmogenic effect of acute ischemia and reperfusion. It is difficult to evaluate the site of these receptors in the organism, since (-)-U-50,488 easily crosses BBB and activates both central and peripheral κ_1-OR [6]. Intracerebroventricular infusion of (-)-U-50,488 decreased heart resistance to the arrhythmogenic effect of epinephrine. By contrast, intravenous injection of (-)-U-50,488 increased heart resistance to this catecholamine [24,25]. Activation of peripheral κ_1-OR probably increases electrical stability of the heart. By antiarrhythmic activity, (-)-U-50,488 is less potent than δ_2-OR agonists (deltorphins) by 15 times. However, we cannot conclude that δ_2-OR play a more important role in arrhythmogenesis than κ_1-OR. (-)-U-50,488 has low affinity for OR. By contrast, deltorphins are characterized by a higher affinity for OR than other opioid peptides [15].

Nociceptin (orphanin FQ) increases heart resistance to the arrhythmogenic effect of aconitine. However, nociceptin potentiates the arrhythmogenic effect of epinephrine on the myocardium. It was unclear whether activation of ORL1-receptors affects the incidence and type of ischemic and reperfusion arrhythmias. Studies showed that intravenous pretreatment with orphanin FQ in a dose of 285 nmol/kg has no effect on the incidence of arrhythmias produced by 10-min coronary occlusion and reperfusion [16]. Antiarrhythmic activity of the selective ORL1-receptor agonist nociceptin is probably associated with activation of ORL1-receptors. Orphanin has high molecular weight. It is unlikely that this peptide enter the brain after systemic administration. These data suggest that activation of peripheral nociceptin receptors does not modulate heart resistance to the arrhythmogenic effect of 10-min ischemia and reperfusion.

Therefore, activation of peripheral δ_2-, κ_1-, and ORL1-receptors contributes to the increase in heart resistance to the arrhythmogenic effect of acute ischemia and reperfusion (10 min). However, μ-, δ_1-, and κ_2-receptors play a less important role in the regulation of electrical stability of the heart during acute ischemia. Special attention must be given to the increase in heart resistance to acute ischemia after activation of OR. It is well known that 10-min ischemia produces reversible changes in the myocardium. However, prolonged ischemia is followed by the development of irreversible changes in most cardiomyocytes. Therefore, arrhythmias developed after acute coronary occlusion and long-term ischemia have different pathogenetic mechanisms [1]. The role of OR in arrhythmogenesis during long-term ischemia requires detailed investigations. It cannot be excluded that activation of several subtypes of OR during long-term ischemia can potentiate its arrhythmogenic effect. This hypothesis is confirmed by published data that OR antagonists exhibit antiarrhythmic activity during 30-40-min coronary occlusion [3]. We did not reveal the antiarrhythmic effect of naloxone and selective OR blockers during acute ischemia/reperfusion and arrhythmias produced by epinephrine or aconitine [9,11,16,19]. These data suggest that endogenous agonists of OR play minor role in the regulation of electrical stability of the heart during 10-min coronary occlusion, reperfusion, and administration of epinephrine or aconitine in toxic doses. We believe that endogenous opioid peptides are involved in the regulation of electrical stability of the heart in adapted or experimental animals exposed to chronic stress. Our studies showed that high resistance of hypoxia-adapted animals to the arrhythmogenic effect of epinephrine is associated with activation of δ-OR with endogenous agonists [8]. The resistance of adapted animals to arrhythmias under conditions of coronary occlusion and reperfusion depends on stimulation of μ-OR [7].

Increase in electrical stability of the heart after stimulation of peripheral μ- and δ-OR. Our previous studies showed that the μ-receptor agonist morphine and mixed agonist of μ- and δ-receptors dalargin increase VF threshold (VFT) in rats with postinfarction cardiosclerosis [23]. Therefore, these compounds possess antifibrillation activity. We assumed that stimulation of μ- and δ-OR can prevent electrical instability of the heart during postinfarction cardiac fibrosis. Intravenous injection of the selective peptide μ-receptor agonist DALDA in a dose of 0.1 mg/kg increased VFT in animals with postinfarction cardiosclerosis [11]. The antifibrillation effect of DALDA was not obser-

ved during selective blockade of μ-receptors. However, selective blockade of δ-OR did not modulate the influence of DALDA [11]. Published data show that DALDA crosses BBB and produces a central effect only after intravenous injection in a dose of 5 mg/kg or higher [6]. It can be hypothesized that activation of peripheral μ-receptors improves electrical stability of the heart during postinfarction cardiosclerosis.

Intravenous injection of selective δ_1-OR agonists TAN-67 (0.5 mg/kg) and/or DPDPE (0.1 mg/kg) also increased VFT in rats with postinfarction cardiosclerosis [18,28]. However, δ_2-OR agonist DSLET promoted a decrease in VFT [31]. The antifibrillation effect of DPDPE was not observed during blockade of peripheral OR with methyl naloxone not crossing BBB [3,28]. Selective blockade of δ-OR completely abolished the antifibrillation effect of DPDPE. However, the effect of DPDPE persisted during selective blockade of μ-OR [28]. Therefore, activation of peripheral δ_1-OR increases electrical stability of the heart in rats with postinfarction cardiac fibrosis.

Selective blockers of μ- and δ-OR (CTAP and ICI-174,864) and nonselective blockers of OR (naloxone and methyl naloxone) had no effect on VFT in rats with postinfarction myocardial scars [11,18,28]. The data suggest that OR are not involved in the regulation of electrical stability of the heart in nonadapted animals with postinfarction cardiosclerosis.

The role of δ_1- and κ-OR in the regulation of electrical stability of the heart in animals with this disorder remains unclear. Our studies showed that activation of peripheral m and δ_1-OR increases VFT in rats with postinfarction myocardial scars. At first glance these results seem to contradict published data that activation of OR during coronary occlusion and reperfusion has no effect on the incidence and type of arrhythmias.

We gave attention to the results of experiments performed by I. Baczko *et al*. [20]. These investigators showed that the incidence of VF is highest in rats narcotized with barbiturates, but maximum in animals under ketamine anesthesia [20]. Our studies revealed that the incidence of VF in ketamine-narcotized rats exposed to 10-min coronary occlusion and 10-min reperfusion does not exceed 10% and 25%, respectively [16]. It can be hypothesized that activation of μ- and δ_1-OR prevents VF, but does not modulate the incidence of ventricular extrasystoles or tachycardia. The antiarrhythmic effect of selective agonists of μ- and δ_1-receptors can be observed during experimental arrhythmias accompanied by VF. Our previous experiments showed that the primary agonist of μ-receptors dalargin significantly decreases the incidence of VF, but has no effect on ventricular extrasystoles or tachycardia under conditions of coronary occlusion and reperfusion [26].

Mechanism of opioid-induced increase in heart resistance to arrhythmogenic factors. There is no agreement regarding the mechanism of opioid-induced increase in heart resistance to arrhythmogenic factors. Some investigators believe that the autonomic nervous system plays an important role in the antiarrhythmic effect of opioid peptides [17]. This conclusion is derived from the data that stimulation of the vagus nerve, sympathectomy, and adrenoceptor blockade increase heart resistance to the arrhythmogenic effect of coronary occlusion and reperfusion. The cardiovascular effect of intravenous opioid peptides is related to activation of OR on peripheral afferent terminals of the vagus nerve [4]. Activation of these receptors modulates functional activity of the autonomic nervous system (increase in vagal tone and suppression of the sympathetic nervous system) [4]. This effect of opioid peptides provides the increase in heart resistance to arrhythmogenic factors. As differentiated from other researchers [17], we did not find any evidence that the autonomic nervous system plays a role in the opioid-induced increase in heart resistance during stimulation of peripheral of OR [13,14]. However, it cannot be excluded that this system is involved in the opioid-induced increase in heart resistance to arrhythmogenic factors (*e.g.*, intracerebroventricular infusion of OR agonists) [10,16]. On the other hand the antiarrhythmic effect of opioid peptides can be related to activation of presynaptic OR on myocardial adrenergic terminals [4]. Activation of these receptors suppresses epinephrine release [4], which plays an important role in the pathogenesis of arrhythmias produced by ischemia and reperfusion of the heart. The role of the autonomic nervous system in the antiarrhythmic effect of opioid peptides requires further detailed investigations.

The antiarrhythmic effect of opioid peptides can be associated with activation of cardiac OR coupled with adenylate cyclase, which is followed by inhibition of cAMP synthesis. Some authors reported that this nucleotide acts as an endogenous arrhythmogenic factor [21]. The antiarrhythmic effect of β-adrenoblockers results from suppression of cAMP synthesis [21]. Dalargin decreases cardiac cAMP concentration during experimental coronary occlusion [26]. This is only the working hypothesis, since no correlation was found between the decrease in myocardial cAMP concentration and antiarrhythmic effect of opioid peptides *in vivo*. Comparative studies on the isolated heart under conditions of experimental ischemia and reperfusion were not conducted.

Functions of OR in the endothelium of coronary vessels are associated with NO synthase activity [4]. Activation of these receptors stimulates NO synthesis [4], which also increases electrical stability of the

heart [30]. Opioid peptides produce a direct effect on cardiomyocytes by activating phospholipase C. These changes are followed by activation of protein kinase C and tyrosine kinase and stimulation of ion current in mitochondrial K_{ATP} channels [31]. Activation of these channels contributes to opioid-induced increase in cardiomyocyte resistance to the adverse effect of ischemia and reperfusion [31]. We showed that blockade of K_{ATP} channels with glybenclamide or selective blockade of mitochondrial K_{ATP} channels with 5-hydroxydecanoate abolishes the antiarrhythmic effect of opioid peptides [18,28]. However, selective blockade of sarcolemmal K_{ATP} channels did not modulate the antiarrhythmic effect of opioid peptides [28]. At first glance these results seem to be paradoxical. Antiarrhythmic activity of preparations is believed to be associated with changes in ion transport in cardiomyocyte sarcolemma. However, opening of mitochondrial K_{ATP} channels also increases the resistance of cardiomyocytes to ischemia and reperfusion [29,32]. Activation of OR and functionally related mitochondrial K_{ATP} channels delays the formation of irreversible damage to cardiomyocytes during coronary occlusion [31]. Delayed appearance of pathological changes in cardiocytes reduces the probability of arrhythmias during coronary occlusion and perfusion, which increases heart resistance to the arrhythmogenic effect of ischemia and reperfusion. It is necessary to test the validity of this working hypothesis. Opioid peptides increase the resistance not only to ischemia/reperfusion, but also to treatment with epinephrine and aconitine. These changes and increase in VFT in rats with postinfarction cardiosclerosis cannot be explained by activation of mitochondrial K_{ATP} channels. The events occurring from activation of OR to the increase in heart resistance to arrhythmogenic factors remain unclear.

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