Opioid system and its role in the organisms

Opioid system is represented by opioid receptors, their endogenous agonists (opioid peptides) and enzymes, the synthesis and inactivation of these agonists [1]. In humans and animals only agonists called receptors have been identified, which represent real properties of the peptide at birth (endorphins, enkefalins, dynorphins, endomorphines) [1]. At present, biochemical and pharmacological methods have identified several types of opioid receptors: (μ) mu; (δ), delta; (κ), kappa [1, 2].

Opioid receptors (OR) are a lipoprotein complex that can be found in cytoplasmic membranes of target cells [3]. Most high density noted above is in the brain structures responsible for the proconduiting and the perception of pain: back horns of the spinal cord gray matter of the nucleus of the thalamus and hypothalamus, and some torye department limbic system [4, 5]. In addition, OR can be found in the brain stem, which determines their involvement in the regulation of the life important centers, especially it concerns the medulla oblongata. They can also be found in the endocrine glands and other organs [1, 6, 7]. Revealed opioid receptors localized in the wall of the intestine, with the highest concentration are presented in the δ-opioid receptors localized initial parts of the intestine, whereas the γ-opioid receptors are predominantly found in neurons and submucous mezentericheskih nodes [8, 9]. It was established that cardiomyocytes synthesize enkefalins, dynorphins and endorphins [10, 11], and the content of opioid peptides in the myocard is comparable to their concentration are presented in the δ-opioid receptors coupled through G-proteins to K+- and Ca2+-channels.

Key words: opioid receptors, opioid system, Kαβ3- channels, cAMP, cGMP, inositoltriphosphate, nitric oxide, hypoxia, adaptation.

Interaction of opioid receptors with ion channels and intracelluar Signaling systems

Opioid receptors belong to superfamilly by applying G-protein-coupled receptors [3]. All OR-helix, consisting α-sections of the polypeptide chains kidney rolled into of hydrophobic residues s nokislot [9], which is closely integrated rovany in the cell membrane. On the outer and inner one hundred membrane are receptor sites, with standing of the hydrophilic amino acids. By the extracellular to the domains to valence attached oligosacharidy, so the OR is glycoproteins. Extracellular loop and the NH2-terminal the receptors interactions exist with ligands and intracelluar sites perform intermodeyst condition receptors and G-proteins and proteininase that phosphorylation of serine, threonine and tyrosine, modulate activity of the OR [3]. Cell response to activation opioid receptors depends on whether G-proteins and effectors, it induces rapid [21]. In neuronal tissue these are μ- and δ-opioid receptors coupled through G-proteins to Kαβ3-channels [22–24], while the k-receptors interact with Ca2+-channels.

Localized at the sarcolemma of cardiomyocytes κ- and δ-opioid receptors inhibits adenyl cyclase via activation of Gi-proteins [25]. The κ-receptors may be absent at the sarcolemma of cardiomyocytes ver, same researchers note that as a selective agonist of κ-receptors U-50, 488H does not inhibit sarcolemma adenyl cyclase and has no impact on asset sion of G-proteins [25]. There κ-receptor agonist bremazocin does not affect theirs some evidence and that the level
of cAMP in the myocardium [26]. There is evidence that activation of all three types of opioid receptors leads to reduced activity adenyl cyclase and reduces the level of cAMP in the cell [25–28]. Effects of δ- and κ-agonists may be associated with a change in phosphoinositol exchange, realized with the participation of inositoltriphosphate [19, 29–33]. For example, in model experiments on isolated cardiomocytes of rats activation of δ1-opioid receptors found that ditch causes inositol-1,4,5-triphosphat-mediated mobilization of Ca2+ [32]. It was established that opioids can induce recovery of cGMP content in the myocardium [34, 35]. It is well known that cAMP, cGMP and inositoltriphosphate are an intracellular regulator of calcium transport. Hence indeed, there is a reason to believe that the inotropic and chronotropic effects of opioids have by changing the synthesis of these intracellular messengers in cardiomocyte. However, some electrophysiological studies suggest that opioid receptors regular ion channels by interacting with G-proteins no secondary by messendgers [36]. This is evidenced by data on the ability μ- and δ-agonists increase of K+-current, and κ-agonists modulate Ca2+-channels [36].

As mentioned above, the opioid receptors through G-proteins linked to K+-channels [37–39]. It is known that neuronal KATP-channels mediate the analgesia induced by stimulation of μ- and δ-opioid receptors [38–40]. The results obtained by K. D. Wild et al. [40] showed that a selective inhibitor of KATP-channel glibenklamid completely δ1-agonist DPDE eliminates the antinociceptive effect of the peptide. However, the analgesic effect δ1-agonist deltorphin II is not blocked by glibenclamide, but not eliminated for tetraethylammonium, which inhibits the potential-dependent K+-channels [40]. It follows that the δ1-receptors associated with KATP-channel and δ2-receptors are associated with voltage-dependent K+-channels. Interacting with different receptors how many types of KATP-channels and potential-dependent K+-channels not known [41, 42]. In cardiac muscle three types of KATP-channels, the localized in the smooth muscle of the arteries, the sarcolemma and in mitochondria of cardiac myocytes were identified [41, 42]. At present time δ1-opioidergic activation is evidence of in there mitochondrial exponentially KATP-channels in heart cells [42]. The question of the topological opioidergic regulation efficiency sarcoklemmal KATP-channels and voltage-dependent K+-channels are not shown.

The vasodilator effects for μ- and δ1-agonists that associated with activation of KATP-channels, and had no this effect after pretreatment of glibenclamide [43]. However, there is evidence that the expansion of peripheral arteries after injection of the selective μ-agonists endomorphin is the result increased activity of NO-synthase [44]. Established that the vasodilator effect of morphine is accompanied by an increase synthesis of NO [18].

Since δ1-opioid receptors are located on the sarcolemmal and mitochondrial KATP-channels in the inner mitochondrial membrane, it was unclear how δ1-agonists gained activated K+ current in these organelles. However, evidence was obtained that the role of an intracellular mediator in this process is to qualify nitric oxide. It was found that NO can activate mitochondrial exponentially KATP-channels without changing the K+-current in the sarcolemma of cardiomocytes. However, rigorous proof that it is nitric oxide transmits the signal from the cardiac opioid receptors to mitochondrial KATP-channels unavailable. Thus, the mechanisms of action of opioids on cells of very diverse and include: reducing the level of cAMP, increased production of NO, increased synthesis of cGMP elevation of inositoltriphosphate, activation of K+-channels and inhibition of Ca2+-current. The following discussion focuses on the basic biological effects associated with activation of opioid receptors.

**Biological effects of opioid receptors activity**

The major known effects in the spectrum of biological activity of the endogenous agonists of opioid receptors can be considered as part enkephalins and enorphins in the regulation of pain reflexes of cardiovascular, respiratory and endocrine systems, functions of the gastrointestinal tract, behavior and psychoemotional processes [1, 45–49]. In response to the stimulation of opioid receptors occurs attenuation of adrenergic influence on the heart [6], decreased cardiac output [34], marked inotropic, chronotropic and haemodynamic effects [45]. Such a variety of cardiovascular effects of opioid peptides can consider treat them as endogenous modulators of physiological and pathologi- cal processes in the myocardium, opening prospects for practical use of kinetic skin synthetic analogs of endogenous opioids. In recent years, a positive role of opioids in the formation of adaptive stability of the heart to ischaemia-reperfusion has been increasingly described [50, 51]. There is evidence of adaptive role of opioids (enkephalins and endorphins) to increase the stability of the brain to hypoxia [52–54].

**Opioids and adaptation to hypoxia**

The term “hypoxia” means not enough oxygen in the body. Under normal conditions, the intensity of oxidative phosphorylation corresponds to the functional needs of tissues and organs. If you violate this correlation of a state of energy deficit, leading to a variety of functional and morphological changes, aimed at forming increased body resistance to hypoxia, while the deep degree of fine hypoxia and high exposure to destructive (until the death of the organism) from variation [55, 56]. The ability of organisms to ad-
adaptation to a lack of oxygen is one of the most popular and ancient forms of adaptation, at which, along with an increase in the potential of the oxygen systems ensuring radiation body is formed increased stability of the myocardium to the damaging effect of various extreme factors [57, 58]. Currently, a large number of published data on the protective effects of chronic hypoxia and the molecular mechanisms of these effects. Next, we shall dwell briefly remain existing in the literature on this subject.

In experiments on mice, examined the effect of acute hypoxia (oxygen content 10.8 % within 30 min). It was found that 2 hours after hypoxic excitation action is a 2-fold increase in the level of leu-enkephalin in the hypothalamus. At the same time, in the case of acute hypoxia ment with oxygen content 8.2 %, the same authors observed a decrease in the level of leu- and met-enkephalin [59]. In the experiments on the isolated rat heart for fixed, it was found that 5-min total ischemia leads to a significant increase from content in the myocard opioid peptides – leu- and met-enkephalin [60]. Consequently, in conditions of acute hypoxia is activation of endogenous opioid systems.

Near the author conducted research antihypoxic properties of morphine and naloxone [61, 62]. Criterion was the lifetime of the mice were placed in a chamber with the oxygen content of 5 % and 95 % nitrogen. In the case of a blockade of opioid receptors naloxone 5 mg / kg, no effect has been recorded, increasing the dose to 10 mg / kg was associated with decreased survival of animals. On the contrary, the introduction of morphine in doses of 2 and 5 mg / kg increased the lifetime of the mice. The authors managed to obtain evidence that the use of morphine at the dose of 5 mg / kg reduces the consumption of oxygen by the body [62]. Later it was shown that in the implementation of morphine-induced resistance to hypoxia is involved protein kinase C (nPKC\(\epsilon\)) [63]. Russian scientists were also obtained data on the presence antihypoxic properties of the peptide agonists of \(\mu\)-opioid receptors [64, 65]. From these data it followed that the protective effect of opioids in acute hypoxia is associated with \(\mu\)-receptors and does not depend on activation of \(\delta\)-receptors [64].

However, in studies on mechanisms of action of leaks action of adaptation to hypoxia, data were obtained witness responding to the leading role of \(\delta\)-receptors in the protective effect of endogenous opioids [66, 67]. Studies were conducted on mice, adapted to hypoxia (4.5 % oxygen for 1.5, 2.0, 2.5 min, after each episode followed by 5 min normoxia). After this adaptation estimated survival under conditions of acute hypoxia. To evaluate the role of endogenous opioids naloxone (0.1 and 1 mg / kg) 5 min before exposure were administered. At a dose of 1 mg/kg naloxone blocks the effect of adaptation to hypoxia, introduction of morphine in doses of 1, 5, 10, 20 mg / kg had no effect, and 50 mg / kg - reduced the protective effect of hypoxia. The use of selective antagonist of \(\delta\)-receptors naltrindol eliminated the protective effect of to adaptation [67], which allowed the authors to draw conclusions about the key role of endogenous \(\delta\)-agonist [66]. There are data and the prolonged effect of synthetic \(\delta\)-agonists BW373U86 in the lifetime of the mice under conditions of acute hypoxia [61]. In recent years, data were obtained in favor of this view. On the model of hypoxic preconditioning (8–9 sessions at an oxygen content of 1 % in those for 30 min and 30 min normoxia) investigated the stability of cortical neurons of mice to the toxic action of glutamate [68]. It was found that hypoxic preconditioning significantly reduces the damage of these neurons in the application of glutamate at a concentration of 100 \(\mu\)M/L (4 hours). At the same time increase creases the binding of these structures of brain \(\delta\)-agonist, DADLE, which authors by radioreceptor analysis determined [68, 69].

It should be noted that the protective effect of adaptation to hypoxia is not limited to opioidergic neuroprotection and improved survival. Significantly mustache established that adaptation to the hypoxic condition, activating the endogenous opioid system provides increased tolerance of the heart to the main harmful effects of acute hypoxia [27, 50, 57, 60]. Manifestation of this protection is not only a reduction in the size of the infarction, but also the weakening of the manifestations of postishemic contractile dysfunction and ventricular arrhythmias [27, 50, 57, 60].

Improved electrical stability in cardiac adaptation ented animals occurs as a result of activation of both central and periphery opioid receptors [57, 60].

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ОПИОИДНАЯ СИСТЕМА И АДАПТАЦИЯ К ГИПОКСИИ

Обзор посвящен анализу роли опиоидных рецепторов, их эндогенных и синтетических агонистов в формировании устойчивости организма к действию острой гипоксии. Приводятся данные о том, что стимуляция опиоидных рецепторов сопровождается нейропротекторным эффектом при острой гипоксии. Рассматривается роль различных типов опиоидных рецепторов в реализации защитного действия адаптации к гипоксии. Анализируются сведения о механизмах действия опиоидов, роли цАМФ, цГМФ, оксида азота, инозитолтрифосфата, К⁺ - и Са²⁺ - каналов в реализации эффектов агонистов опиоидных рецепторов. Обсуждаются опиоидергические механизмы, обеспечивающие повышенную устойчивость сердца к последствиям острой кислородной нехваточности.

Ключевые слова: опиоидные рецепторы, опиоидная система, КАТР-каналы, цАМФ, цГМФ, инозитолтрифосфат, оксид азота, гипоксия, адаптация.