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Functioning Of The Opiate Brain System.

Makhov AS, and Medvedev IN*.

Russian State Social University, st. V. Pika, 4, Moscow, Russia, 129226

ABSTRACT

The endogenous opioid system exhibits an extremely wide spectrum of biological activity, representing one of the most important systems of homeostasis regulation. Its components are capable of acting as neurotransmitters, hormones or modulators of many physiological functions. Opioid peptides and, in particular, the most polyfunctional peptide hormone β-endorphin, participate in the processes of neuroimmune interactions and show pronounced immunomodulatory activity. At present, it is considered that preparations of the opium group, and primarily morphine, cause significant structural and functional changes in the brain cells, including changes in synaptic plasticity. The reorganization of synapses leads to the realization of learning and memory processes. Morphine-induced pathological dependence is accompanied by a change in the functioning of a number of neurotransmitter receptors in the structures of the brain, followed by a change in the set of intracellular mechanisms, which eventually leads to a change in the functioning of a large number of synapses in certain parts of the central nervous system. In the case of drug addiction, complex disorders occur in brain brain neurons that are difficult to treat. At the microsocial level, the complex intrafamily relationship has a significant influence on a person's addiction to drug use. Macro-social factors contributing to the spread of drug abuse include moral degradation of society, a crisis of values and ideals, the destruction of traditional socialization institutions.

Keywords: brain, opiates, endorphins, enkephalins, drug addiction, drug addiction.

Corresponding author

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INTRODUCTION

The idea that there may be neurons in the brain of humans and animals that have the ability to somehow communicate with narcotic substances, primarily drugs of opiate origin, and under their influence to change their normal physiological functions, exists long ago [1].

In 1975, two Scottish researchers, H. Kosterlitz and R. Hughes, discovered in the brain extracts a substance with opiate activity [2]. Further studies have made it possible to establish the chemical structure of these substances. They turned out to be peptides called opioid neuropeptides (endogenous morphine-like compounds), and are divided into two main groups: enkephalins (short pentapeptides) and endorphins (peptides with a longer chain of 16-31 amino acids). In addition, in the brain extracts, several other neuropeptides not yet identified by their chemical structure, also possessing opiate activity (for example, striatum peptides, cerebrospinal fluid peptides, etc.) have been found in brain extracts [3].

The high density of opioidergic neurons is found in the nuclei of the thalamus, hypothalamus, black submentia, the nuclei of the tire, the nuclei of the seam, the gelatinous substance of the dorsal horns of the spinal cord, and the dorsal ganglia. The producers of enkephalins in the central nervous system are much larger. μ-opioid receptors are widely distributed in the central nervous system and on the periphery, including cells of the immune system [4].

Now opioid peptides are an actively studied class of pharmacological agents with stress limiting and, possibly, cardioprotective effects. In this regard, the study of the prospects for the clinical use of opioid peptides is extremely important [5]. The similarity of endogenous opioids and their exogenous analogs is confirmed by their influence on pain sensitivity. In recent years, there have been reports that endogenous opioids are most directly involved in the formation of motivations in the memory system [6].

Enkephalins, as well as endorphins, have many physiological functions. Among them, regulation of visceral reflexes and endocrine functions of the brain can be distinguished; they cause a short-term analgesic effect, activate the system of positive reinforcement, have an euphoric effect [7]. Opiates are produced in negligible quantities and are quickly deactivated by appropriate enzyme systems. In this regard, it gradually becomes clear that the central importance of the opiate system is the protection of orgasm from stress injuries, adequate analgesia and coordination of the functioning of organ and tissue systems at the level of the organism as a whole [8].

In this regard, the goal is set: to consider the most physiologically important effects of the opiate system in a person with reference to the available literature.

Endogenous opioid system

The endogenous opioid system exhibits an extremely wide spectrum of biological activity, representing one of the most important systems of homeostasis regulation. Its components, capable of acting as neurotransmitters, hormones or modulators of many physiological functions, are found in various tissues - in the nervous system, adrenal glands, digestive tract, and also in immunocompetent cells. Opioid peptides and, in particular, the most polyfunctional peptide hormone β-endorphin, participate in the processes of neuroimmune interactions and exhibit pronounced immunomodulatory activity, realizing their numerous regulatory effects through specific opiate binding sites of three main classes μ, δ, κ, expression of which on adaptive cells and innate immunity has been proven at transcriptional and translational levels [9].

Factors of natural resistance are a nonspecific form of protection against biological aggression and are formed in the body before the introduction of foreign agents, regardless of their antigen specificity. Myeloid monocyte cells, phagocytic granulocytes and monocytes, which have a pronounced secretory activity, can participate in the realization of the mechanisms of natural immunity and can participate in the processes of intercellular cooperation and regulation of the immune response [10].

One of the most important features of monocytes and neutrophils is the production of a number of antimicrobial factors - products of oxygen metabolism, formed during the activation of the cell. Active forms of oxygen show pronounced toxicity for somatic and microbial cells, interacting with substances containing

areas of increased electron density. Primary and secondary active forms of oxygen, as well as nitrogen metabolites, initiate peroxide oxidation of membrane lipids, destruction of proteins and nucleic acids of microorganisms. As a result, there is a violation of the integrity of microbial cells and the destruction of their biomolecules [11].

A particularly important role in this process is played by neutrophilic granulocytes. This cell population is 50-60% of peripheral blood cells and has powerful oxygen-dependent and oxygen-independent bactericidal systems. Previously, it was shown that β-endorphin enhanced phagocytic activity, modulated the secretory activity and bactericidal potential of monocytes and neutrophils. The ability of opioid peptides at low concentrations (10^{-7} M) to naloxone-dependently enhance the formation of reactive oxygen species by polymorphonuclear leukocytes and stimulate the metabolism of arachidonic acid in neutrophils (dinorphin A). At the same time, production of NO by neutrophils, on the other hand, can decrease when introducing into the cultures of β-endorphin and enkephalin at higher concentrations (10^{-3}-10^{-5} M). The purpose of this work is to investigate the effect of endogenous opioid peptide β-endorphin and synthetic agonists of μ- and δ-receptors on the production of reactive oxygen species by the fraction of leukocytes and neutrophils of peripheral blood [12].

Also, the protective effect of adaptation to hypoxia is not limited only to opioidergic neuroprotection and increased survival. It has been proved that adaptation to the hypoxic state is accompanied by activation of the endogenous opioid system, provides increased heart resistance to the main destructive consequences of acute oxygen deficiency. The manifestation of this protection is not only the reduction in the size of the infarction zone, but also the weakening of manifestations of postischemic contractile dysfunction and ventricular arrhythmias. The increase in electrical stability of the heart as a result of adaptation occurs with the participation of both central and peripheral opioid receptors.

Adaptation to cold increases the level of β-endorphin in blood plasma, the pituitary gland and the hypothalamus. Training and exercise did not affect the enkephalin content in the heart, but provided an increase in the level of β-endorphin in the hypothalamus and blood plasma. The combination of swimming and cold promoted an increase in the level of β-endorphin in the pituitary, hypothalamus and blood plasma, the content of meth-enkephalin in the myocardium increased almost 2-fold, and the level of leu-enkephalin remained unchanged [13].

Thus, opioid peptides are able to enhance the production of biologically significant substances by the body cells, changing the activity of their receptor and providing the conditions for maintaining homeostasis in the body as a whole.

Opium preparations

At present, it is considered that preparations of the opium group, and primarily morphine, cause significant structural and functional changes in the brain cells, including changes in synaptic plasticity. The reorganization of synapses, according to modern concepts, lies at the heart of learning and memory, and it is the morphine-induced disruption of the normal functioning of synapses that can lead to the appearance of pathological dependence. Morphine-induced pathological dependence is accompanied by a change in the functioning of a number of neurotransmitter receptors in the mesocorticolimbic structures of the brain, subsequent changes in the set of intracellular cascades, gene expression, ultimately leading to a change in the functioning of the synapse and the neuron as a whole in certain parts of the central nervous system [14].

An important element in altering the intracellular signal when exposed to psychoactive substances can be a change in the protein composition of the neuron and, in particular, post-translational modifications of intracellular polypeptides. Several versions of posttranslational modifications are known, some of which can be induced by morphine, for example, protein phosphorylation. However, to date, very little is known about morphine-induced proteolytic modifications of proteins in the nervous system. Nevertheless, limited proteolysis is a very common modification, and with great probability it can be assumed that when pharmacological effects of morphine are realized in the cell and in the extracellular space, proteolytic events essential for neuron function occur [15].

The data of the literature allow us to propose a hypothesis about the participation of proteolytic enzymes of the brain, in particular, the enzymes of the caspase family, in the realization of the pharmacological effects of opium group preparations [12].

Unfortunately, these drugs, in addition to the therapeutic analgesic effect, have one more feature: they are a means for abusing drug addicts who go to any offense to get the desired dose of "buzz". Therefore, public authorities need to balance the vital needs of sick people who really need anesthesia and the risk of leaking opioid analgesics from legal trafficking to illegal, especially since the number of drug users who are interested in such a leak is great. The high demand for opium drugs provokes a violation of the rules of their legal turnover.

Not so long ago, we have already witnessed what leads to the lack of proper control over the turnover of certain types of narcotic drugs. So, before June 1, 2012, on the free sale in Russia, there were codeine-containing medicines such as solpadein, pentalgin-H, sedalgin-neo, etc., in which the amount of codeine did not exceed 8 mg in one tablet. Making use of their availability, drug users bought these analgesics in large quantities and, with the help of household chemical products, made dezomorphine narcotic drug from them in artisanal conditions [16].

The availability of this type of drug and its low cost led to the fact that drug addicts who had previously used heroin and other opiate drugs began to switch to the use of desomorphine. In 2011, desomorphine was seized in the territory of most of the constituent entities of the Russian Federation. The weight of desemorfin withdrawn by law enforcement agencies from 2006 to 2011 increased more than 300 times: from 314 g in 2006 to 100.3 kg in 2011. In a number of constituent entities of the Russian Federation, out of the total number of people first registered in the connection with drug use, the proportion of desomorphine addicts reached ≥80%. So the popular analgesic, containing the minimum amount (only 8 mg in one tablet) of a narcotic codeine opioid, has caused massive abuse in illegal drug trafficking.

The influence of psychoactive substances on the human body

Significant factors are the indicators of neuroendocrine regulation of the reproductive system, there is a suppression of brain activity by psychoactive substances coming from outside the human body.

An important risk factor for the development of violations of the neuroendocrine regulation of the reproductive system is the high rate of craniocerebral trauma - in 57% of psychoactive substances-dependent adolescents, in particular, for every fifth alcohol-dependent and toxicomaniac, and poisoning with psychoactive substances. Toxic encephalopathies are significantly more often detected in toxic-drinkers (40%) than in girls who drink alcohol (22%) and drugs (9%). Given the role of the hepato-biliary complex in the production of steroids and globulin binding them, special attention should be paid to the high prevalence of liver diseases among psychoactive substances-dependent, especially viral hepatitis, which suffered 30% of drug addicts (hepatitis C) and 12% of alcohol-dependent girls (hepatitis A and B).

Mental disorders, behavioral disorders, suicidal attempts are revealed in every third (34%) of a girl who consumes psychoactive substances.

The study of the conditions and lifestyle of the surveyed cohort of teenage girls from the Moscow megapolis confirms the tendency characteristic of the last decade to increase the spread of bad habits among adolescents and the early start of the use of surfactants. According to the research, more than 70% of schoolchildren in Moscow smoke, about 90% drink alcohol, 18% use marijuana, 8.2% - inhalants, 2.2% use ecstasy and 5.4% - heroin.

There is a clear relationship between the presence of harmful habits and the early onset of sexual relations, especially in the group of girls, addicted to psychoactive substances, 81.7 per cent of whom are sexually active. The average age of sexual debut of adolescent girls in this group was 13.4±0.2 years, while the early sexual debut was observed among the consumers of alcohol (was 13.1±1.3 years), later - have drug addicts (14,0±0,4 years), which is significantly below the average age at first sex of girls of Russia is 15.8 to 16.1 years ($p<0.05$). While 22% of adolescents using psychoactive substances, sexual debut under the age of 13 years [4].

Emergency assistance with intoxication (overdose) of drugs

The task of effective emergency care for intoxication (overdose) of drugs is an important medical and social problem. In clinical addiction and toxicology, an antagonist of opioid receptors, naloxone hydrochloride, is widely used as an antidote for severe intoxication with opioids.

Now in the Russian Federation, naloxone is used in the form of an injection solution for intravenous and intramuscular administration. However, the injection route of administration, if necessary, of first and emergency medical care is not always available and technically complex [17].

In recent years, the subject of active experimental and clinical studies is the evaluation of the effectiveness of an alternative - intranasal route of naloxone administration for opioid overdosage oppression. It has been established that naloxone penetrates the systemic bloodstream through the mucous membrane of the nasal cavity almost as quickly as intravenously. The intranasal route of administration of naloxone most fully corresponds to the tasks of rapid relief of acute poisoning by opioids. This is due to the technical ease of application of the spray, the good bioavailability of the medicinal substances in intranasal administration, and also the intranasal route of administration is promising for substances that are easily destroyed by oral administration [18].

The active ingredient concentration of 1.2% and its dose of 100 µl were selected based on the results of a study of the bioavailability of naloxone in intranasal administration to rabbits compared with intramuscular and intravenous administration of the drug Naloxone injection 4 mg / ml.

It is shown that the absolute bioavailability of naloxone in intranasal administration is about 30% (when administered in equal doses) and increases proportionally with a double increase in the dose [19].

Thus, timely rendered qualified medical care can save a person's life. The obtained results allow to consider the developed preparation "Naloxone spray nasal" as an alternative to injection preparations of naloxone hydrochloride for use in emergency medicine as an antidote for opioid overdose.

CONCLUSION

The endogenous opioid system exhibits an extremely wide spectrum of biological activity, representing one of the most important systems of homeostasis regulation. Its components, capable of acting as neurotransmitters, hormones or modulators of many physiological functions, are found in various tissues - in the nervous system, adrenal glands, digestive tract, and also in immunocompetent cells. Opioid peptides and, in particular, the most polyfunctional peptide hormone β-endorphin, participate in the processes of neuroimmune interactions and exhibit pronounced immunomodulatory activity, realizing their numerous regulatory effects through specific opiate binding sites of three main classes µ, δ, κ, expression of which on adaptive cells and innate immunity is proven at the transcriptional and translational levels.

At present, it is considered that preparations of the opium group, and primarily morphine, cause significant structural and functional changes in the brain cells, including changes in synaptic plasticity. The reorganization of synapses, according to modern concepts, lies at the heart of learning and memory, and it is the morphine-induced disruption of the normal functioning of synapses that can lead to the appearance of pathological dependence. Morphine-induced pathological dependence is accompanied by a change in the functioning of a number of neurotransmitter receptors in the mesocorticolimbic structures of the brain, the subsequent change in the set of intracellular cascades, the expression of genes that ultimately leads to a change in the functioning of the synapse and the neuron as a whole in certain parts of the central nervous system.

Drug addiction is a serious and ill-treatable disease caused by a complex set of biological, psychological, social factors. Biological factors include genetic predisposition, lack of enzymes, congenital and acquired metabolic disorders, endocrine disorders, brain pathologies. At the microsocial level, the complex intrafamily relationship has a significant influence on a person's addiction to drug use. Macro-social factors contributing to the spread of drug abuse include moral degradation of society, a crisis of values and ideals, the destruction of traditional socialization institutions.

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