Nonopioid Effect of β-Endorphin

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Abstract—This review presents the generalized literature data and the results of our own research of the nonopioid effect of β-endorphin, an opioid neuropeptide interacting not only with opioid but also with nonopioid (insensitive to the opioid antagonist naloxone) receptors. The roles of the hormone and its receptors in regulation of the immune, nervous, and endocrine systems are discussed. The effect of neuromediator on the immune system mediated by both opioid and nonopioid receptors is considered in detail. The data on distribution and function of the nonopioid β-endorphin receptor in human and animal organisms are presented. All available data on the characteristics of the nonopioid β-endorphin receptor obtained by means of radioligand analysis are given. The discussed information is supposed to extend our conceptions of the role of β-endorphin in mammals and to be of extensive use in medicine and pharmacology.

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β-Endorphin is a neuropeptide consisting of 31 amino acids and formed in the hypophysis as a result of cleavage of proopiomelanocortin (POMC). The peptide interacts with two types of opioid receptors: μ and δ [1]. The ability of β-endorphin to bind to several types of receptors is due to its structural peculiarities. It is considered that the molecule of this hormone contains two different sites: the N- and C-terminal fragments needed for the binding to opioid receptors (μ- and δ-, respectively) [2]. Opioid receptors have been found in the brain and spinal cord [3], on cells of the immune system, and on adrenal glands, enabling it to perform its hormonal functions. It was shown that the anesthetic effect of β-endorphin, regulation of respiration, control of the cardiovascular system, and eating behavior were mediated through the δ- and μ-opioid receptors [2]. The δ-receptors play an important role in peptide regulated motion activity, sense of smell, cognitive functions, and emotional behavior [2, 4], while μ-opioid receptors are important for controlling thermoregulation, learning, and memory by β-endorphin [2, 5].

Previously it was shown that cells of the immune system not only contain opioid receptors but also express the β-endorphin precursor (POMC) gene and secrete active β-endorphin. The mRNA of the precursor and the peptide itself were found in T- and B-lymphocytes, monocytes, and macrophages [6]. Besides, immunohistochemical analysis shows that macrophages, monocytes, granulocytes, and lymphocytes contain a complete enzyme complex necessary for β-endorphin synthesis and secretion [7]. In this case, the role of β-endorphin consists in regulation of cell activity of the immune system and anesthetization in an inflammatory focus [6, 8]. The effect of this opioid neuropeptide on cells of the immune system is mediated by the μ- and δ-opioid receptors found on these cells [9-12]. It should be noted that all the above effects are blocked by specific opioid antagonist naloxone.

However, some physiological activities of the hormone are not blocked by opioid antagonists and, consequently, cannot be mediated by interaction with opioid receptors. Up to now, nonopioid receptors are little studied and the relevant data are fragmentary. The goal of this review is to generalize the results of available studies of the nonopioid effect of β-endorphin and its nonopioid receptor.

EFFECT OF β-ENDORPHIN ON THE IMMUNE SYSTEM

The effect of β-endorphin as a hormone has been studied most completely in cells of the immune system: T-lymphocytes, monocytes, macrophages, and B-lym-

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phocytes. Three types of opioid receptors are expressed on the surface of immunocytes: \( \mu \), \( \delta \), and \( \kappa \) [9-13]. \( \beta \)-Endorphin has a dual effect on immune cells: the suppressing effect of \( \beta \)-endorphin on phagocytosis of macrophages mediated through opioid receptors is described [14]; in accordance with other investigations, the hormone has an inhibitory effect on proliferation of the donor T-lymphocytes [15]. Besides, \( \beta \)-endorphin was shown to decrease proliferation of T-lymphocytes of peripheral human blood \textit{in vitro} activated by hemagglutinin [16]. This effect is typical of many endogenous opioids (endorphins, enkephalins) and morphine, the alkaloid opioid having an inhibitory effect on cells of the immune system [17]. This review [17] presents solid evidence of the fact that morphine inhibits the functions of natural killers, B-cells, T-cells, and phagocytizing cells when introduced \textit{in vivo}. The direct suppressing effect of the narcotic has been shown \textit{in vitro} in phagocytizing cells. The effect of morphine disappears in the presence of opioid blockers. This means that the inhibitory effect is realized through classical opioid receptors. The action of opioids may be direct (immediately on immunocytes) or indirect (via neuronal signals or other neuromediators). The results of the above works suggest that opioids, including \( \beta \)-endorphin, have an inhibitory effect on immunocytes by interacting with opioid receptors.

This suggestion is favored by the work of Refojo [18], where \( \beta \)-endorphin knockout mice were obtained. These mice were tested for the level of cytokines in plasma and the activity of cells of the immune system. The knockout mice were shown to have enhanced splenocyte proliferation, production of cytokines IL-2, IL-6, and TNF-\( \alpha \) by macrophages, and the IL-6 level in plasma after the treatment with lipopolysaccharide. All tests showed the increase in immune response. These data may be indisputable evidence of the inhibitory effect of endogenous \( \beta \)-endorphin on the immune system at all levels.

Inhibitory effect of the hormone is confirmed by the modern data obtained in the study of the influence of the agonists of opioid receptors (\( \mu \), \( \delta \), \( \kappa \)) on regulation of the expression of chemokines, cytokines, and their receptors, the central component of immunomodulating activity of opioids [19]. It has been shown that \( \beta \)-endorphin inhibits the transcription of IL-2 and the transcription factors transactivating IL-2 in activated human T-lymphocytes. Incubation of T-lymphocytes with opioids reduced the level of cAMP in the cells. Thus, \( \beta \)-endorphin had an inhibitory effect on physiological regulation of the activation of T-cells [20].

However, quite a number of studies are devoted to the stimulating effect of \( \beta \)-endorphin on T-lymphocytes [21-23] and on macrophages and monocytes [24, 25]. This problem has to be clarified.

The existence in an organism of nonopioid receptors (i.e. insensitive to the opioid blocker naloxone) is known. The term “nonopioid” receptor was first introduced by the American scientist Hazum in 1979 [26]. It was shown that specific binding of \( ^{125} \text{I}-\text{I-labeled} \beta-[D-Ala^\text{\text{2}}] \) endorphin with transformed human lymphocytes was inhibited neither by naloxone (the antagonist of opioid receptors) nor by morphine, enkephalins, \( \alpha \)-endorphin, \( \beta \)-lipotropin, \( \alpha \)-melanocyte-stimulating hormone, ACTH, insulin, and glucagon [26]. However, the binding was completely inhibited by \( \beta \)-endorphin and \( \beta \)-[D-Ala\text{\text{2}}] endorphin. The dissociation constant \( (K_d) \), the major characteristic describing the interaction between the ligand and the receptor, was 3 nM.

This discovery suggested the presence on human lymphocytes of unknown specific \( \beta \)-endorphin binding sites of nonopioid nature. It was shown that the C-terminal region of the \( \beta \)-endorphin molecule was necessary for the binding with this receptor, because no binding of \( \alpha \)-endorphin with this receptor was revealed. Thus, the receptor studies proved the existence of nonopioid \( \beta \)-endorphin receptors on human T-lymphocytes, making it possible to explain the immunomodulating effect of the hormone.

The studies of Heijnen et al. imparted clearness to investigation of the problem of \( \beta \)-endorphin action on T-lymphocytes [15]. It was ascertained that \( \beta \)-endorphin has a modulating effect on T-lymphocytes. The study of the influence of the hormone on concanavalin A (Con A) induced T-lymphocytes of two donors showed that the effect of this peptide was exactly the opposite: the hormone increased the proliferation of T-lymphocytes of one donor and inhibited the proliferation of lymphocytes of the other donor in the same range of concentrations \((10^{-14}-10^{-9} \text{ M})\). The influence of different fragments of \( \beta \)-endorphin on the proliferation of Con A activated T-lymphocytes of these donors was investigated. According to the data of Heijnen et al. [15], \( \beta \)-endorphin fragments 10-16 and 2-31 had the same activity as the intact molecule. The findings suggest that the modulating effect of \( \beta \)-endorphin on human T-lymphocytes is associated with the level of expression of the nonopioid receptor on cell surface.

Further studies in this field confirmed the presence of nonopioid \( \beta \)-endorphin receptors on T-lymphocytes. Gilman was the first to establish the influence of \( \beta \)-endorphin on the functional activity of immune cells [27]. In the presence of \( \beta \)-endorphin, the production of mitogens by human T-lymphocytes increased. The hormone also contributed to the proliferation of T-cells \textit{in vitro}. Later it was shown that the stimulating effect of \( \beta \)-endorphin on T-lymphocytes was associated with its ability to enhance IL-2 production by these cells, and the subsequent interaction between cytokine and receptors resulted in cell division. This effect was not inhibited by naloxone; consequently, it was mediated by the naloxone-insensitive receptor [28].

The research of van der Bergh et al. [21] plays a special role in investigation of the effect of \( \beta \)-endorphin on