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THE EFFECT OF THYMOSIN β_4 ON THE FUNCTIONAL ACTIVITY OF THE IMMUNE AND NERVOUS SYSTEM COMPONENTS

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ДЕЙСТВИЕ ТИМОЗИНА β_4 НА ФУНКЦИОНАЛЬНУЮ АКТИВНОСТЬ КОМПОНЕНТОВ ИММУННОЙ И НЕРВНОЙ СИСТЕМ

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The data on properties of thymosin β_4, a conserved multifunctional polypeptide of mammals is summarized. Attention has been focused on regulatory activity of thymosin β_4 in regard to immune and nervous system components. In these systems thymosin β_4 is present in different cell types both stationary and mobile ones. Besides intracellular localization thymosin β_4 is also located in extracellular fluids. Inside cells, thymosin β_4 has been postulated to regulate actin polymerization as a G-actin-sequestering molecule. But molecular mechanisms of thymosin β_4 located extra cells on cell functions remain unclear. The structural-functional organization of thymosin β_4 is also discussed. Thymosin β_4 is a perspective medicine preparation for the therapy of diseases related to immune and neurological disturbances in patients.

Keywords: thymosin β_4; thymosin β_4-derived peptides; immune and nervous systems.

В работе суммированы данные о свойствах тимозина β_4, консервативного многофункционального полипептида млекопитающих. Внимание акцентируется на регуляторных свойствах тимозина β_4 в отношении компонентов иммунной и нервной систем. В обеих системах тимозин β_4 обнаружен в клетках различного типа как стационарных, так и подвижных. Кроме внутриклеточной локализации тимозин β_4 также обнаружен во внеклеточных средах. Существует устойчивое мнение, что внутриклеточная активность тимозина β_4 определяется его способностью регулировать полимеризацию актина посредством секвестирования G-актина. Вместе с тем, до сих пор не установлены молекулярные механизмы действия внеклеточного тимозина β_4 на функции клеток. Обсуждается также вопрос о структурно-функциональной организации тимозина β_4. Тимозин β_4 можно рассматривать в качестве перспективного лекарственного препарата для лечения заболеваний, связанных с нарушениями иммунного и неврологического статуса больных.

Ключевые слова: тимозин β_4; пептидные фрагменты тимозина β_4; иммунная и нервная системы.

Introduction. Pathogenesis of many infectious and autoimmune diseases as well as neurodegenerative disorders is related to the functional disbalance of basic cells in both systems. To correct the immune and neuronal status, changed or damaged during various pathological processes, the natural double-duty peptide preparations regulating functions both immunocompetent and neuronal cells can be used. Among such agents is thymosin β_4.

Structure and functions of thymosin β_4. Thymosin β_4 (Figure 1) is a member of a family consisting of highly conserved polypeptides, primarily isolated from thymus and characterized as a compound regulating the maturation and differentiation processes of T cells [2].

Thymosin β_4 is the most abundant β-thymosins both in the immune and nervous systems of mammals. Thymosin β_4 realizes numerous different functions including its participation in the regulation of the immune and nervous system activity (Table 1) [2, 5]. It has been observed that thymosin β_4 regulates functions of various cells such as lymphocytes, neutrophils, macrophages, mast cells (immune system); neurons, astrocytes, oligodendrocytes, microglial cells (nervous system). Wherein, thymosin β_4 affects activity both stationary and migratory cells, changing biochemical and morphological characteristics of cells.

Thymosin β_4: *structural-functional relationships*. The data accumulated indicates that peptide fragments of thymosin β_4 may exhibit biological activity. N-terminal tetrapeptide Ac-SDKP, representing the fragment 1–4 of thymosin β_4, inhibits the proliferation of lymphocytes, as well as pluripotent hematopoietic stem cells, induces the degranulation of mast cells, inhibits a collagen syn-

Ac-SDKP DMAEI EKFDK SKLKK TETQE KNPLP SKETI EQEKQ AGES
5 10 15 20 25 30 35 40

Fig. 1. Amino acid sequence of thymosin β_4

Table 1

Effect of thymosin β_4 on the activity of the immune and nervous systems

Immune system	Nervous system
activates maturation and differentiation of T cells	activates synaptogenesis, viability and migration of neurons
restores reduced level of T-helper cells in patients with lupus nephritis	participates in formation of the midbrain structures (in chickens and mice)
inhibits the inflammatory response	decreases apoptosis in neurons
inhibits macrophage migration	stimulates axon growth and neuron regeneration
stimulates release of chemokines by neutrophils and accelerates their migration	stimulates oligodendrogenesis and microglial cells activity
stimulates the production of IL-2 and γ-interferon by lymphocytes	reduces the toxic effect of ethanol on astrocytes in culture
promotes lymphocyte proliferation	decreases the Glu-induced toxic effect on cultured cortical neurons
inhibits the proliferation of mast cells and induces their degranulation	improves functions of damaged neural tissue (stroke, brain injury)

thesis by fibroblasts and reduces the TGF_β activity. This tetrapeptide has been shown to be generated by a prolyl-oligopeptidase [7].

The pentapeptide fragment 10–14 of thymosin β_4, EKFDK, has immunoregulatory activity. The pentapeptide has been shown to stimulate the mitogen-induced proliferative response of human T-lymphocytes, as well as antibody genesis at the secondary immune response to T-dependent antigen in mice [3]. Besides, this peptide influences functions of phagocytic cells in particular it stimulates migration and oxidative metabolism of human granulocytes [4].

The main function of the hexapeptide fragment 17–22 of thymosin β_4, LKKTET, is a primarily binding with actin monomers. The heptapeptide 17–23 of thymosin β_4, isolated from wound fluid, regulates mast cell functions inducing exocytosis of compounds normalizing the wound healing processes [7].

In human T-lymphocytes the thymosin β_4 fragments 16–26 and 31–39 induce expression of CD2 antigens which are important for the acceleration of adhesion between T-lymphocytes and other immunocompetent cells [1].

It is wide-spread opinion that the intracellular functions of thymosin β_4 are connected with its ability to regulate the processes of actin polymerization through G-actin monomer sequestration. Binding with G-actin, thymosin β_4 prevents actin filament formation [6]. However, there are reports concerning the participation of thymosin β_4 in physiological events, not connected with sequestration of actin, such as inflammation, apoptosis, angiogenesis and wound healing. In some cases the extracellular location of thymosin β_4 has been revealed although pathways of thymosin β_4 releasing from cells are still not discovered. It remains unclear, what kinds of cell surface receptors participate in mediating of thymosin β_4 functions.

It should be noted that thymosin β_4 has great therapeutic potential. Thymosin β_4 and its peptide fragments could be useful for the therapy of diseases related to immune dysfunctions and neurological disturbances.

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