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NEW SHORT-RANGE AUTO-PARACRINE MECHANISMS UNDERLYING THE FUNCTIONAL ACTIVITY OF TISSUE BASOPHILS IN MAMMALS.

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Abstract

This report presents modern literary information and the results of own research on the biological role of a number of endogenous biologically active factors of peptide nature produced in tissue basophils: melatonin, thymalin, and ACTH. So, in addition to numerous biologically active substances, tissue basophils of the mammalian organism produce melatonin, ACTH, and corticotropin releasing factor.

The provided information according to which the field of activity of thymic mediators - thymosin β4 and thymalin is not limited exclusively within the frame of the immune system, but is also implemented within the APUD system. So, mediators of the brain layer of the thymus are involved in the processes of stimulation and / or inhibition of histamine and serotonin, as well as degranulation and release of these factors into the perivascular space.

Through our studies, we have found that under a number of extreme conditions in tissue basophils, the processes of "transformation" of serotonin into melatonin (the only source from which melatonin is synthesized) are activated. The authors of this publication come to the conclusion that, with certain stimulation of tissue basophils (in vivo experiments, under the conditions of injections of physiological concentrations of E. Coli lipopolysaccharide to laboratory animals), the processes of intracellular synthesis of melatonin from serotonin are sharply activated in tissue basophils.

According to the authors, except histamine, an important role should be played not by serotonin, but by melatonin produced in tissue basophils, in the regulation of transcapillary metabolism, and in a particular vascular permeability. Facts discovered during the recent years regarding the synthesis of ACTH in tissue basophils, receptors for the corticotropin-releasing factor on the membrane of these cells allow the authors to consider the role of extrahypophysial ACTH in the regulation of many integrative functions of the organism from a completely new perspective, and, in particular, steroidogenesis and insulinogenesis in the adrenal gland and pancreas, respectively. Apparently, under the conditions of "specific" stimulation of tissue basophils, the latter begin to selectively produce ACTH, which has a modulating effect on target cells localized, at least, in the peripheral glands of internal and mixed secretion.

Keywords: *tissue basophils, synthesis, stimulation, ACTH, melatonin, thymosin, thymalin*

Many cellular associations of mammalian organisms are endowed with multifaceted potencies depending on the bio-object of their realization in the functioning of specific integrative systems. From our point of view, the concept of "association", is exclusively arbitrary, since specific stages of their effects on target cells are singled out of the entire spectrum of polyfunctional activities of parenchymatous and stromal cells. Such analytical approach in biology and medicine can be rather justified, because it is aimed at identifying specific mechanisms underlying the formation and course of specific processes in specific organs and tissues.

Similar examples of various branches development in fundamental medicine are more than

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enough. Several of them are suffice for elucidation.

Early in 1969, famous English pathologist A. Pearse proposed a concept about the organism's "specialized, highly organized cellular system with a distinctive capability of producing peptide hormones and biogenic amines" [*Pearse AG, 1969*]. According to this concept, certain cells throughout an entire organism are capable of synthesizing biogenic amines by preliminary uptake of their precursors. The author designated these cellular "associations" by the term of amine precursor uptake and decarboxylation.

The system of amine precursor uptake and decarboxylation includes over 60 types of cells localized in various organs and systems [*Andrew A, 1982; Raikhlin N et al., 1993; Raikhlin NT, Kvetnoy IM, Yuzhakov V.V. 1994; Kvetnoy I et al., 1999*].

Within the frame of the APUD-systems in the body of mammals, both tissue basophils and basophilic granulocytes of blood function. Despite the fact that almost a century and a half has passed, since Paul Ehrlich described mast cells in 1877, numerous aspects related to the activity of tissue basophils have been so far studied insufficiently.

During this period, tissue basophils appeared under a variety of names: mast cell, mast cell, mast blood cell, basophilic leukocyte, heparinocyte, histaminocyte. Currently, researchers use the term "tissue basophil", i.e. adhered to the terminology adopted in 1975 at the International Congress of Anatomists in Tokyo. [*Kopaeva YuN*, 1980].

In the middle of the last century, biologically active substances were found in the mast cells during the period when they were divided into two groups. The first group included heparin, histamine, eosinophilic chemotactic anaphylaxis factor, the second is a slow-reacting substance of anaphylaxis, prostaglandins, platelet activating factor, neutrophilic chemotactic factor of anaphylaxis, etc. [*Protsenko VA et al., 1987*].

Numerous informative data are currently available and continue to be received regarding the pleiotropic potencies of tissue basophils, both in terms of the synthesis and absorption of endogenous biologically active substances of the most diverse nature and the presence on their membrane of numerous receptors for a wide range of endogenously active factors produced in the central nervous system, central and peripheral endocrine glands, immunogenesis organs and in the reproductive system.

So, in tissue basophils, more and more endogenously active factors such as melatonin, thymosin β4, thymosin β10, ACTH, corticotropin releasing factor continue to be detected. Numerous receptors for various molecules were found on the surface of tissue basophils, including acetylcholine, corticosteroids, corticotropin releasing factor, adrenaline, parathyroid hormone, substance P, vasoactive interstitial peptide, ACTH, somatotropin, endorphins, melatonin, leptin, etc. (2017).

There is unique but very informative information, according to which individual mediators (hormones) of the thymus medulla are actively involved in the regulation of a number of cellular associations, united by a single concept - the APUD system (AminoPrecursors Uptake and Decarboxylation).

Recent studies have shown that thymosin β-4 dose-dependently induces degranulation of tissue basophils. Particular attention, in our opinion, deserves the scientific development of a range of researchers, which specifically established the stimulating and inhibitory effect of thymosin on tissue basophils, depending on the doses. Thus, thymosin β-4 at a dose of 10^{-14} M causes the maximum suppression of proliferation of tissue basophils, and the use of a mediator at a dose of 10^{-8} M is accompanied by maximum degranulation (up to 89%) of tissue basophils [*Leeanansaksiri W, et al., 2004*]. In studies [*Labunets IF, 2007*], a sharp increase in the level of melatonin in blood serum was recorded 3 hours after a single injection of thymalin in adult mice, which carried a permanent character, since the melatonin content was significantly reduced after 24 hours. The supernatant obtained from thymus homogenates (thymalin) induces the production

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

Table 4

The effect of thymalin on the degranulation process and the level of serotonin and melatonin in tissue basophils

Indicators \ Groups	Control (n=16)		Experimental (n=16)		p
	M	±m	M	±m	
Degrees of degranulation					
without signs	24.3	3.6	50.1	10.7	0.025>p>0.01
partial	23.9	5.2	38.6	5.3	0.05>p>0.025
expressed	16.3	2.9	5.4	1.7	0.005>p>0.0005
Indicators of serotonin and melatonin (in UEFA)					
Serotonin	34.8	4.5	51.3	6.8	0.05>p>0.025
Melatonin	23.6	3.4	10.25	3.9	0.025>p>0.01

***Note**: p - in relation to the indicators of the experimental group to the corresponding indicators of the control group. UEF - Conventional Fluorescence Units.*

of melatonin by the pineal gland. Conducted by our own research [*Zilfyan AV, 2019*], it was found that a single intraperitoneal injection of thymalin (a drug created on the basis of thymarin) in experimental rats leads to a complete delay in the secretory process in mesenteric basophils.

The results of the morphometric and fluorescence microscopic analysis are shown in table 1.

As can be seen from the table, in rat mesentery, under the conditions of a therapeutic dose of thymalin injection, tissue basophils dominated either without signs of degranulation, or at the stage of partial degranulation.

Thus, the number of the above mentioned tissue basophils was twice higher than the level of tissue basophils in the mesentery of rats of the control group. Under the conditions of thymalin injection, the cells looked somewhat shriveled and were characterized by a very compact orientation of the granules along the entire perimeter of the cytoplasm.

Leading the quantitative fluorescence-microscopic research, it was found that a single injection of thymalin to laboratory animals was accompanied by excessive cumulation in serotonin tissue basophils, the content of which was 1.5 times higher than of animals in the control group. It is important to mention that an increase in the content of intracellular serotonin occurred against the background of a decrease in the content of melatonin in tissue basophils. Thus, the melatonin content in mesenteric tissue basophils under the conditions of thymalin injection decreased by 2.3 times, compared with the same indicator in rats of the control group. Apparently, the mediator produced in the thymus, thymalin, directly and / or indirectly affects the synthesis and secretion of serotonin and melatonin in tissue basophils by “selective” cumulation of serotonin in them. In this aspect, it is not excluded that in this particular case, the physiologically involved intracellular processes of “transformation” of serotonin into melatonin are disrupted. Thus, based on the analysis of literary sources, we can conclude that mediators (thymus hormones) take an active part in the functional activity of tissue basophils, which are considered in the context of their modulating effect on many integrative systems of the body, and as well as the entire set of cell associations involved in the APUD system.

In the pineal gland, a biologically active substance was found to have a direct effect on frog melanophores [*Lerner A, et al.*, 1958]. The synthetic and metabolic aspects associated with the melatonin produced in the pineal gland were studied by Axelrod J. and Weissbach H. (1960), for which, one of the authors was awarded the Nobel Prize in 1970 for discovering the biological role of pineal melatonin and a number of other hormones.

As you know, melatonin is considered as a unique neurotransmitter, which is subject to circadian, ultradian, monthly and seasonal fluctuations. Melatonin produced in the pineal gland has a selective modulating effect on the synthesis and secretion of a number of releasing factors, neurohormones and neurotransmitters of the hypothalamus and pituitary gland.

At the same time, it should be noted that the biological effects of extra pineal melatonin were not the subject of special discussion. Most authors tried to confine themselves to the mere fact of synthesizing melatonin in several organs of the digestive, respiratory, cardiovascular systems, as well as in isolated cells of the APUD system scattered throughout the body.

As mentioned [*Kvetnoy IM et al.*, 1999] in his

review, "extrapineal melatonin should be considered as a key paracrine molecule for local coordination of cellular functions".

At the present stage of development of "theoretical and clinical endocrinology" sporadically new, too informative information appears about the biological purpose of extra pineal melatonin in the integrative activity of the mammalian organism and new levels of its structural organization.

The important fact is, that the under experimental conditions, during epiphysectomy, optimal concentrations of melatonin continue to be determined in the blood serum and urine of laboratory animals, which, according to [*Kvetnoy IM et al., 1999*], indicates the important role of extra pineal melatonin in the integrative mammalian activities. Apparently, the synthesis of melatonin in specific organs and tissues on the periphery is intended to maintain the function of precisely those organs in which the synthesis of this hormone occurs.

So, in a number of studies [*Zargaryan AL, et al, 2008; Kyalyan GP, et al., 2010; Zilfyan AV, 2019*], it was found that under the experimental conditions, under the certain extreme conditions (immobilization stress at different stages of development, as well as under conditions of injection of endotoxin (E. Coli) and melatonin to laboratory animals, in mesenteric and loose connective tissue basophils occurred redistribution of endogenously active substances - histamine, serotonin and melatonin, which significantly affected the morphological and functional state of the hemomicrocirculation pathways, and, first of all, the degree of vascular permeability. Thus, by the method of immunomorphology (under the conditions of introducing a minimum concentration of LPS in experimental animals) in tissue basophils, there was a redistribution of the levels of endogenously active substances, that play an important role in the regulation of transcapillary metabolism: against the background of a significant decrease in the level of serotonin, the content of melatonin increased. Considering a number of facts: the presence of melatonin receptors on the surface of tissue basophils, the potential for synthesis of melatonin in the same basophils, the presence of serotonin in the latter, we came to the conclusion, that under the conditions of the introduction of E. Coli LPS in tissue basophils, the transition of serotonin to melatonin occurs. It should be emphasized that these processes occurring in tissue basophils (meaning an increase in the level of melatonin against the background of a significant decrease in the content of serotonin) correlated very clearly with the processes that were played out on the territory of the hemomicrocirculatory source. Under the conditions of E. Coli endotoxin injection to experimental animals, the process of increased degranulation of tissue basophils with the release of granules with a rich content of melatonin and, to a less extent, histamine into them in the pericapillary space was accompanied by signs of increased permeability of blood capillaries.

So far, it was considered that among the biologically active substances produced by tissue basophils, histamine and serotonin play a leading role in the regulation of vascular permeability and transcapillary metabolism. It was also established that these serotonin-induced effects are strictly dose-dependent. Even a slight increase in their concentrations in the pericapillary space begins to have a toxic effect on the cellular and extracellular components of the walls of microvessels, and, first of all, on endotheliocytes. Within the frames of these studies we concluded that the biological purpose of serotonin produced in tissue basophils is dictated not so much by its effects on the walls of microvessels as by its potential for intracellular transformation into melatonin. In our point of view, melatonin should play an important role (in addition to histamine) in the mechanisms of increased permeability of microvessels, whose increased synthesis in extreme situations occurs in the cytoplasm of tissue basophils from its predecessor, serotonin. Apparently, the processes of enhanced intracellular synthesis of melatonin from serotonin are largely associated with the nature of the effect on the organism of various provocative factors. So, in our studies, it was found that with immobilization stress at all stages of its course - the stages of anxiety, tension, resolution (including exhaustion), there were no signs of an increased melatonin content in tissue basophils.

Based on our studies, the role of tissue basophils in the mechanisms of regulation of transcap-

illary metabolism should be considered from a qualitatively new point of view, in terms of the direct effect on the vascular wall of melatonin produced in tissue basophils. It is possible that in a number of extreme situations, mutually transitive translational processes of tryptophan-serotonin-melatonin begin to function in the same tissue basophils, but at a different qualitative level, with intensification of melatonin synthesis. The information available in the literature regarding also the effect of ACTH and / or its synthetic analogues on the functional state of tissue basophils is worthy. Thus, according to [*Irman-Florjanc T, Erjavec F, 1984*], ACTH in a dose-dependent manner ($1x10^{-4}$ M - $1x10^{-3}$ M) stimulates the secretion of histamine and serotonin from tissue basophils. A number of authors [*Hashimoto M,* et *al., 2015*] studied the effect of ACTH on plasma histamine levels and the content of tissue basophils in the lymphoid tissue of the nasal mucosa with polyposis. It was found that intraperitoneal administration of ACTH lowers the level of IL-10, IgE and histamine in blood plasma, as well as the number of tissue basophils in lymphoid tissue. The introduction of a synthetic analogue of ACTH (1-24) in a daily dose of 0.01 *mg / kg* reduces the number and volumetric parameters of tissue basophils with a simultaneous increase in serotonin content in cells. Also noteworthy is the fact that, under the conditions of the introduction of corticotropin releasing factor, tissue basophils dominated in the tissues without signs of degranulation with a high histamine content in the cytoplasm [*Eutamene H, et al., 2003*].

It is also controversy evidence, according to which the intraperitoneal administration of corticotropin releasing factor induces degranulation of tissue basophils by the receptor mechanism (involving GRF (1) and GRF (2) receptors). It is possible that the opposite effects of corticotropin releasing factor, to a certain extent, depend on the tested doses of this stimulant *[Larauche M, et al., 2009*].

At present, very convincing facts have been discovered according to which synthesis of ACTH and cortitropin releasing factor occur in tissue basophils [*Teoharides TC, 2017*]. Moreover, the same author found receptors for cortitropin releasing factor on tissue basophils. We also consider that it is necessary to dwell on studies published earlier [*Csaba G, et al, 2004; 2006; 2015*]. The authors lead a search aimed at the presence or absence of ACTH, growth hormone, triiodothyronine and progesterone in the nucleus and cytoplasm of tissue basophils. Pronounced fluorescence (immunomorphological analysis) of ACTH and growth hormone was found in the nuclei of tissue basophils. ACTH fluorescence was also detected by the authors in the cytoplasm and intracellular matrix of these cells.

Thus, a number of researchers obtained very convincing facts indicating the synthesis of ACTH in tissue basophils [*Csaba G, Kovacs P, 2009; Theoharides TC, 2017*].

The results obtained by the authors were based on the following objective facts.

In tissue basophils, the presence of ACTH is detected in the cytoplasm and in the intracellular granules themselves.

The first important tool indicative of the synthesis of ACTH in tissue basophils is the fact that ACTH is detected in the nuclei of tissue basophils themselves.

The second important help indicative of the synthesis of ACTH in tissue basophils is the discovery of a stimulating ACTH mediator, the corticotropin releasing factor in their cytoplasm, as well as the presence of specific receptors for this releasing factor on the surface of tissue basophils. From a qualitatively new position we can evaluate the functional purpose of tissue basophils, which in mammals act as a component of the APUD system. In this regard, the pleiotropic synthetic potencies of tissue basophils are comparable, in our opinion, with the pleiotropic potencies that are endowed with cells of the lymphoid series of the mammalian organism. It should be specially noted that the subtle mechanisms underlying the directed synthesis of specific mediators by tissue basophils, and, first of all, the hormonal spectrum of action (melatonin, ACTH, corticotropin releasing factor) have not been completely studied up to date. Moreover, general and, especially, regional mechanisms have not been established, which, in each case, selectively trigger intracellular mechanisms that pro-

vide a pure synthesis of individual active substances in tissue basophils. A situation is created similar to that of an attempt to interpret the very wide pleiotropic potencies of lymphocytic cells. It is these two cell populations, in our opinion, that should serve, first of all, as the subject of a special study, the implementation of which should involve advanced scientists of the current and, especially, future generation. The subject of special research should also be the "mast cells" of blood - basophilic granulocytes of blood. We, however, confine ourselves to the interpretation of a recently discovered fact, which, in our opinion, is of great scientific and practical significance. In this particular case, we are talking about the ability of tissue basophils to synthesize ACTH and the factor that stimulates its synthesis is corticotropin releasing factor. In our opinion, directed synthesis of extrahypophasic ACTH occurs exclusively in all parenchymal organs and organs of immunogenesis, since all internal organs of mammals are also characterized by a rich content of tissue basophils.

In addition to tissue basophils, apparently, many mediator functions, including during the production of melatonin and ACTH, are carried out by blood basophils. In this case, the delivery of the aforementioned hormones to target organs can occur in two ways: 1) through the migration of tissue basophils from the blood into tissues, in which they begin to act as tissue basophils; 2) by "excretion" of hormones into the blood, with their subsequent entry into the tissues through the microvasculature. Of particular note is the fact that the secretory potencies of tissue basophils in various organs are far from equivalent. So, the maximum content of histamine and serotonin was found in tissue basophils of the thymus, mesenteric lymph nodes. Their insignificant content was found in the basophils of the myocardium, lungs and thyroid gland. Tissue basophils of the intestine are characterized by the absence of heparin [*Protsenko BA, et al., 1987*]. Unfortunately, with respect to other synthesis products in tissue basophils in specific organs and tissues, we do not have such information.

It is possible that such selective activity of tissue basophils is due to their "gradation" for various subpopulations, the functional activity of which in each particular organ is strictly aimed at providing specific functions assigned to specific organs.

A similar "historical case" has already occurred in biology, medicine, and molecular biology, when lymphocytes (small lymphocytes) were previously described as monomorphic structures, and many years later they were identified "in new quality" as subpopulations. Moreover, each lymphocytic subpopulation is endowed with the most specific functional activity strictly characteristic of it, in particular, in terms of their synthesis of immunocytokines, pro- and anti-inflammatory spectrum of action.

A similar gradation of tissue basophils on secretory cells of various structural and functional activities should be the subject of a special study.

In this aspect, there are wide prospects, in terms of studying the directed synthesis of ACTH specifically in tissue basophils of the adrenal gland and pancreas, since the "postulate" put forward by us about the participation of only extra hypophyseal ACTH in the secretory activity of the adrenal glands is more convincing, if not final it's confirmation [*Zilfyan AV, 2019*]. It is necessary to attract the attention of readers to one more circumstance. The mesentery of mammals is literally "flooded" with tissue basophils. It even creates a somewhat illusory impression that the mesentery acts as a "depot" of tissue basophils. It is unlikely that such an abundance of mast cells is necessary to maintain tissue homeostasis only of its connective tissue base. Of course, the activity of tissue basophils of the mesentery is directly and / or indirectly also associated with digestion processes. Due to the abundance of tissue basophils located around numerous microvessels, the mesentery acts as a bridgehead, on the territory of which secretory processes of synthesis and / or cumulation of biologically active substances in tissue basophils occur, with their subsequent entry into the regional bloodstream and, ultimately, into target organs.

In particular, it is possible that melatonin and ACTH are also admitted to the adrenal gland and pancreas by tissue basophils located exclusively in the pericapillary space of the connective tissue base of the mesentery. It is also possible that structurally "unified" tissue basophils and blood baso-

phils are represented by associations that are functionally different, each of which is endowed with relatively limited secretory activity depending on the nature of endogenous stimulation.

Thus, the functional activity of tissue and blood basophils should, in our opinion, be considered from a qualitatively new perspective - in terms of their pleiotropic potencies, when specific endogenously active modulators in each case stimulate a specific "bouquet" of mediators and hormones.

The assumption seems to be very justified. "Tissue basophils can synthesize, store and secrete hormones, which is characteristic of endocrine glands, transport them to popular foci, or produce them locally.

The effect of tissue basophils on a particular organ or process is very controversial and often has a dual stimulating or inhibitory character. This is explained by the morphological variety of tissue basophils and the content of cells in target tissues. Tissue basophils in the target tissue are transported in immature form and, when exposed to the surrounding microflora, mature " [*Csaba G, 2015*].

In the final section of this article, I consider, it necessary to draw the reader's attention to the following key points:

1. Tissue basophils act as a source of synthesis, deposition and secretion of a wide range of biologically active substances, including the hormonal spectrum of action.
2. The effect of tissue basophils on the structural components of target organs is far from unidirectional and depends both on the functional purpose of the target cells in a particular (separate) organ and on the functional state of the tissue basophils themselves.
3. Tissue basophils from the blood migrate to the target organs in an immature form. Their maturation occurs already in situ - in the target tissue itself.

With respect to the first paragraph. The polypotent function of tissue basophils in terms of the possible synthesis of numerous endogenously active factors (hormonal and mediator spectrum of action) does not, in our opinion, testify to their simultaneous synthesis and secretion into the microenvironment of the target tissue.

With respect to the second paragraph. In each specific situation (in a specific target organ), it is precisely the spectrum of biologically active substances that is needed to provide in situ local, tissue, and cellular homeostasis. And finally, with regard to the third paragraph. Tissue basophils, possessing wide secretory potencies, as they differentiate in specific target organs, only a strictly limited range of biologically active factors are produced, cumulated and secreted, which are necessary exclusively to maintain regional tissue homeostasis.

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