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IS THE HYPOTHALAMIC-PITUITARY SYSTEM INVOLVED IN THE PROCESSES OF ADRENAL GLUCOSTEROIDOGENESIS? THE ROLE OF EXTRAPITUITARY ACTH IN THE SECRETORY ACTIVITY OF THE ADRENAL GLAND, PANCREAS AND TISSUE BASOPHILS (OWN CONCEPT)

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Abstract

At present, it is generally accepted that the glucocorticoid function of adrenal glands is realized due to the functioning of the hypothalamic-pituitary-adrenal system in mammals.

At the same time, over the years, informative data have appeared that according to which biological effects of peripheral ACTH are not limited to the activities of this system. Thus, by in vivo and in vitro experimental studies, it was found that ACTH in dose-dependent way has a direct stimulating effect on the insulin synthesis processes in the pancreas of a number of laboratory animals. Our own in vivo and in vitro studies, it was also found that ACTH in a dose-dependent way has a direct stimulating effect on the processes of lipase release by pancreatic acinar cells.

By our own in vivo and in vitro studies, it was also possible to establish that "Synachten" commercial syntactic preparation, an ACTH analog with a similar amino acid sequence (1-24), has a direct dose-dependent effect on the processes of lipase release by acinar cells of the pancreas.

In our opinion, new data, according to which ACTH actively participates in the processes of tissue basophil activity, ensuring the release of histamine and serotonin from cells into the perivascular space is of considerable interest.

Thus, ACTH takes an active part in the incretory and alkaline secretory activities of the pancreas and the selective secretory function of tissue basophils. There is literary information in which, in our opinion, very important data are given, according to which, in addition to the pituitary gland, extracerebral sources of ACTH synthesis were found.

So, leukocyte-lymphocytic cells and tissue basophils act as sources of ACTH synthesis.Moreover, leukocyte cells also act as a source of thyroid hormone synthesis, which in its structural and biological characteristics is similar to the thyroid hormone produced in the central nervous system. The syntactic potency of tissue basophils, in terms of their selective production of ACTH, was established in a series of experimental studies in which ACTH was detected in the cytoplasm and nucleus, and corticotropin releasing factor on the membrane of the same tissue basophils.

Based on the analysis of available informative literary data and our own studies, we hypothesize that the biological effects of perpipheral ACTH are realized not due to pituitary ACTH, but ACTH produced in leukocyte-lymphocytic cells and tissue basophils. The similar conclusion goes for thyroid hormone.

In our opinion, the biological effects of peripheral ACTH are not realized on the principles of vertical compounds (through the central nervous system), but due to the presence of horizontal compounds between peripheral organs and systems, among which new, more ancient, evolutionarily formed sources of ACTH synthesis are found.

KEYWORDS: *hypothalamic-pituitary-adrenal system, extrahypophysial synthesis, ACTH, pancreas, tissue basophils, own concept.*

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Adrenocorticotropic hormone (ACTH) belongs to the family of natural melanocortins. The family of melanocortins, in addition to ACTH, is represented by melanostimulating hormones and their fragments. The ACTH synthesis is carried out in neurosecretory

cells of the anterior pituitary gland. In brain tissue, ACTH high concentrations are found in the lower nuclei of the brain stem, in the periaqueductal grey matter, the dorsal nucleus of the suture, in the locus cerebellum, in the parabrachial nuclei, in the magnus raphe nucleus and in the nucleus of the solitary tract. It has been long established that the main role of pituitary ACTH is to control adrenal function. Other hormone functions are considered side effects, in particular, their effect on lipid metabolism by lipase activation. It was also established that ACTH corticotropic activity is approximately an order of magnitude higher than that of melanostimulating hormones.

The neurotrophic and neuroprotective effects of these hormones have long been demonstrated in many in vitro and in vivo experiments. Melanocortins, including ACTH, increase the survival of neurons, increase the number of germinating processes, and enhance protein synthesis. ACTH has a modulating effect on the growth and differentiation of neurons, which leads to an increase in neuronal connections. ACTH also accelerates axon regeneration after peripheral nerve damage and muscle reinnervation. In relation to ACTH mediator functions in the central nervous system, there is abundant literary information according to which, ACTH in very low concentrations interacts with dopamine, opiate, cholinergic, serotonergic and glutamatergic neurons.

The role of pituitary ACTH in the secretory activity of the adrenal gland, pancreas and tissue basophils: According to a long-established fact, the main function of pituitary ACTH is its stimulating effect on the processes of adrenal glucosteroidogenesis involved in the functioning of the hypothalamic-pituitary-adrenal system. At least two more compounds have a similar effect: beta-endorphin and alpha-melanocyte-stimulating hormone. Both biologically active compounds are known to be formed from the precursor that is common with ACTH – proopiocortin.

In addition to the cerebral factors involved in steroidogenesis processes along with ACTH, the adrenal glands themselves produce a factor from the family of opioid peptides, which also has a stimulating effect on the production of steroid hormones. Thus, chromaffin cells of the adrenal medulla, in addition to catecholamines, also produce met-enkephalin, which is formed in situ from proenkephalin [*Lewis J et al., 1982; 1984; Van Loon G et al., 1985*].

In our opinion, the available literary information regarding also the ACTH effect and/or its synthetic analogues on the functional state of tissue basophils is noteworthy. Thus, according to Irman-Florjanc T. and Erjavec F., (1984), ACTH in a dose-dependent way (1×10^{-4} M - 1×10^{-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 in case of polyposis.

It was found that the 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 corticotropin releasing factor introduction, tissue basophils dominated in the tissues without signs of degranulation with a high content of histamine in the cytoplasm [*Eutamene H et al., 2003*]. There is also opposite information, 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*]. Recent studies [*Theoharides T, 2017*] also confirm the fact that the targeted effects of corticotropin releasing factor on tissue basophils are realized due to the presence of receptors on their surface for the indicated releasing factor. There is also individual information of an experimental orientation, according to which ACTH affects plasma levels of melatonin. Moreover, depending on the timing of the melatonin determination, a number of

authors obtained diametrically opposite results [*Barsotti A et al., 2017*]. So, according to the authors, an hour after the ACTH administration, the level of melatonin in the blood plasma decreases, and six hours after the hormone administration in the blood plasma of experimental animals, rather high levels of melatonin are determined.

In addition to ACTH effect on synthetic and secretory processes in tissue basophils, the incretory and secretory apparatus of the pancreas act as "points of application" of the hormone. A prerequisite for conducting targeted studies on the role of ACTH in the secretory activity of pancreas were the studies [*Levobitz H et al., 1965; 1966*], which indicated in the form of "reports" that ACTH caused hypoglycemia, which allowed the author to make an assumption according to which the pancreas may also serve as a "target" in the implementation of peripheral ACTH effects. After that, already in a relatively short period (from 1967 to 1998), followed studies in which it was established that ACTH stimulates the insulin secretion by pancreatic β-cells in a number of animals, including rats, mice and rabbits [*Levobitz H, Pooler K, 1967; Malaisse W et al., 1967; Sussmen K, Vaughan G, 1967; Curry D, Bennet L, 1973; Flores L et al., 1998*]. Subsequent in vitro studies on cultured isolated β-cells of islets of Langerhans isolated from rat pancreas confirmed that exogenously administered ACTH significantly enhances insulin secretion by the aforementioned cells [*Borelli M et al., 1994, 1996; Gagliardino J et al., 1995; 1997*].

In our opinion, of particular interest are the studies of a group of authors [*Al-Majed H et al., 2004*], who attempted to elucidate the regional mechanisms involved in enhancing the insulin production in the pancreas under the influence of ACTH physiological concentrations. Given the important fact that the physiological effects of ACTH in the adrenal cortex are realized through melanocortin-2 (MC2-R) receptors, which adrenocorticocytes of the adrenal bundle are very rich with, the aforementioned researchers on the culture of pancreatic β-cells tried to find out one important fact – whether there are melanocortin-2 receptors on insulinocytes, and how much they are involved in the synthesis and secretion of insulin under conditions of administration of very low, as close as possible to physiological concentrations of ACTH. The authors obtained very informative results, which, in our opinion, are of great importance in the development of modern endocrinology.

So, it was found on in vitro models, that in pancreas as a whole a similar mechanism is involved that functions in the adrenal cortex, and which underlies the mechanism by which ACTH effects on secretory cells. So, the authors, apparently, for the first time discovered that melanocortin-2 through MC2-R is expressed in β-cells of the pancreas, in this case, the activation of ACTH receptors initiates insulin secretion by activating cAMP/protein kinase A. Thus, the authors discovered a mechanism in the pancreas similar to the adrenal glands stimulating ACTH effect, which is realized in both cases by activation of the same melanocortin receptors and by activation of the same cAMP/protein kinase.

It is also long established that the fundamental function of ACTH is to regulate the hormone production of the cortical layer of adrenal glands. It is also known that as an "auxiliary" or "side" function of ACTH is its stimulating effect of lipase activity in adipose tissue [*Hardley M, Haskell-Luevano C, 1999; Solomon S, 1999*].

In the available literature, it was not possible to find specific information about the ACTH effect on lipase excretion by pancreatic acinar cells. In this aspect, it is noteworthy that the structure of a lipase localized in adipose tissue is similar to that localized in acinar cells of the pancreas.

We suggested that ACTH in a mammalian organism has a modulating effect on the processes of lipase excretion localized in the cells of the acinar apparatus of the pancreas.

In our researches [*Zilfyan A, 2019*], the modulating effect of ACTH on lipase excretion by acinar cells of rat pancreas was studied. Before the start of the experiment, a "protocol" of studies was compiled, which reflects all the necessary (mandatory) conditions and steps when studying the effect of endogenously active substances of a hormonal nature on various integrative systems of the mammalian organism. So, in this "protocol" we included a number of necessary conditions, which,

in our opinion, should be observed by experimental researchers while studying various aspects of the endocrine system.

This is about circadian and seasonal rhythms, by which ACTH, corticosterone and transcortin produced specifically in rats are endowed. In the experiment we used a synthetic analog of ACTH – "Synachten" (Germany); lipase activity was determined using the diagnostic kit "Lipas" (Spain).

As shown by in vivo experiments (experiments with intravenous administration of "Synachten" at a dose of 6 + 10-5 *mmol/l*, the first peak of lipase activity in serum was determined at 10-15 minutes, the second at 20-30 minutes. In in vitro experiments (in conditions of the bile duct drainage with the introduction of "Synachten", the peak of lipase activity in the pancreas was determined at 20 minutes. In in vitro experiments (on the cell culture of pancreas (under the conditions of "Synachten" introduction into the culture medium), the release of lipase from acinar cells was observed in a very wide range of concentrations of administered synthetic hormone – 10^{-10}-10^{-15} M.

The studies have established that the synthetic analog of ACTH, in a therapeutic dose, both in vivo and in vitro, has a stimulating effect on the processes of lipase release by acinar cells.

Due to conducted in vitro studies, which excluded the direct effect of glucocorticoids endogenously activated by ACTH on lipase activity processes, it can be concluded that ACTH has a direct dose-dependent effect on pancreatic lipase excretion processes.

Thus, under the experimental conditions, we established a new "side" effect of ACTH in rats, in which the excretory apparatus of the pancreas acted as a target, in which an enhanced release of lipase by acinar cells was observed.

Lecocytic cells and tissue basophils as sources of ACTH synthesis. Physiological purpose of extrahypophysial ACTH in mammals: According to J.E. Blalock and E.M. Smith (1980), preparations of human leukocyte interferon (α-interferon) contain biologically and immunologically active substances - endorphin and corticotropin (ACTH). According to the authors, highly purified α-interferon consists of two molecules, with a molecular weight of 18.500 and 23.000 daltons. The activity of endorphin binds simultaneously with these two molecules. Pepsin treatment of α-interferon with a molecular weight of 23.000 daltons (but not interferon with a molecular weight of 18.500 daltons) generates ACTH activity.

The ACTH structure obtained from α-interferon by pepsin fermentation was confirmed by comparing the studied samples with the known ACTH standard by polyacrylamide gel electrophoresis, in which the detected ACTH and γ-endorphin were subjected to enzyme-linked immunosorbent assay using specific antisera to ACTHα (1-13) and to γ-endorphin. The revealed specific luminescence once again confirmed that ACTH and γ-endorphin were indeed detected in the cytoplasm of the indicated immunocompetent cells. Based on the conducted biochemical, immunomorphological and genetic studies, the authors come to a very important, in our opinion, conclusion that the detection of ACTH and endorphin-like substances in lymphocytes indicates that the immune system can produce substances that are identified as polypeptide hormones that also act on principles of signaling the neuroendocrine system. The second, not less significant conclusion of the authors, is that other lymphocyte products (i.e., other lymphokines) can contain and be closely associated with known polypeptide hormones. The authors put forward a hypothesis according to which the "limphocytic-pituitary-adrenal axis" can be predicated on independent existence.

I suggest to the reader the fundamental scientific achievement of authors [*Smith E et al., 1983*], the authors of previous studies (E.M. Smith and J.E. Blalock) are also among the co-authors.

According to the authors, human lymphocytes, under certain conditions, can serve as a source of thyroid hormone synthesis (along with ACTH and γ-endorphin). In this case, the authors did not use α-interferon as a stimulator-inducer, but staphylococcal enterotoxin A, which is a known T-cell mitogen. The authors found that human lymphocytes stimulated by this mitogen synthesize molecules similar to thyroid-stimulating hormone. According to the authors, the synthesis of immunoreactive

thyroid stimulating hormone by lymphocytes was first detected after 24 hours, and reached its maximum after 48 hours. Polyacrylamide gel electrophoresis revealed radioactively labeled peaks at 80, 50 and 26 kilodaltons. These peaks correspond to trimeric, dimeric, and monomeric thyrotropin-like human proteins.

According to the authors, despite the fact that the exact function of the thyroid-stimulating hormone found in human lymphocytes is unknown, we can make an assumption according to which a similar hormone-producing function of lymphocytes can have both direct and indirect effects on the immune and neuroendocrine systems. Particular attention should be paid to the assumption made by the authors, according to which the direct endocrine effect may include directed stimulation of the thyroid gland with the release of T3 and T4.

As a result of conducted studies, and, first of all, due to the very informative results obtained by the above-mentioned researchers, Blalock J.E. and Smith M.E. (1980) an attempt was made (in our opinion, very successfully) to generalize the obtained data in the discovery of new mechanisms underlying the synchronous activity of the neuroendocrine and immune systems. Thus, immune system cells are able to synthesize neuroendocrine peptide hormones (ACTH), γ-endorphins, thyroid stimulating hormone), which are biologically active and are produced, according to the authors, in physiologically significant quantities. White blood cells (lymphocytes) possess functionally active receptors for the same neuroendocrine hormones. The authors do not exclude the feedback principle involved in the human body. For example, corticosteroids (in a dose-dependent manner) can inhibit the synthesis of ACTH and endorphins in lymphocytes (similar to their long-established inhibitory effect on ACTH synthesis in the pituitary gland). On the other hand, the authors discuss possible "specific" mechanisms of ACTH synthesis in immunocytes mediated by corticotropin releasing factor.

In addition to the enormous theoretical significance of conducted studies it is possible to dwell on their important practical value. Thus, the authors, consider the possibilities of partial restoration of hormonal stimulation due to hypothalamic releasing factor, which in turn can affect the synthesis of specific neurohormones in the immune system cells. The possibility of the suggested concept, the authors themselves, in particular, confirm with facts proving the induction of corticosterone in hypophysectomized mice using a viral antigen.

It should be especially noted that after fundamental studies conducted by mentioned authors in the early 80s of the last century, the number of studies regarding the facts of the detecting extrahypophysial ACTH has noticeably decreased. However, this problem again acquired particular relevance when in recent years (between 2003 - 2017) new information appeared regarding the aspects of ACTH synthesis in tissue basophils, which are known to be considered as an integral component in the general associative cooperation within the framework of functioning APUD system.

So, in 2017, very convincing facts were found according to which synthesis of ACTH and cortitropin releasing factor takes place in tissue basophils (mast cells) [*Teoharides T, 2017*]. Moreover, the same author found receptors on tissue basophils for cortitropin releasing factor. We also consider it necessary to dwell on previously published studies [*Csaba G, 2005; Csaba G et al., 2006; Csaba G, Kovacs P, 2009*]. The authors carried out 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. Apparently, even a not advanced reader with a biological and medical education is able to appreciate the high significance of the research.

As it is known, the functional purpose of peripheral ACTH is not limited to the exclusively stimulating effect on the secretory cells of the adrenal cortical layer and adipocytes. However, due to recently conducted studies, it was found that ACTH (and its synthetic analogues) in dose-dependent way stimulate the insulin synthesis in β-cells and at the

same time activate processes associated with the lipase release from pancreatic acinar cells.

It is noteworthy that both "phenomena" were also obtained under conditions of pancreatic perfusion, that is, the ACTH introduction into the lumen of the bile duct; thereby excluding the effect of other endogenous biologically activate substances on the incretory and excretory apparatus cells. Thus, previously unknown effects of peripheral ACTH were established, i.e., its direct participation in the activity of the incretory and excretory apparatus of the pancreas.

Quite naturally the question is emerging: whether the similar pitotent effect of ACTH is caused by pituitary ACTH? The answer to this question could be positive only in one case - if other (extracerebral) intracorporeal sources of ACTH synthesis in mammals were not found.

In our opinion, the implementation of the ACTH-dependent glucocorticoid function of the adrenal glands and the insulin-producing function of the pancreas does not occur according to the vertical (hierarchical), but the horizontal mechanism, due to the peripheral ACTH (extrahypophysial). In this aspect, attention should be paid to the circumstance according to which the "wide prevalence" of leukocyte-lymphocytic cells and tissue basophils in the mammalian organism should be considered as a priority principle. Both the adrenal glands and the pancreas are very rich with tissue basophils. Namely, tissue basophils localized in the adrenal glands and pancreas can act as a possible source of ACTH synthesis, especially since receptors for corticotropin releasing factor are found on their surface.

There is no doubt that in the near future, in addition to the leukocyte-lymphocytic cells and the APUD system, new extrahypophysial sources of peripheral ACTH synthesis will be detected.

It is possible that in addition to ACTH, other peripheral biological active factors can also act as sources modulating the process of steroidogenesis in the adrenal glands, moreover, we have a specific fact, according to which, in the adrenal glands themselves - in chromafin cells, a factor develops similar by its mechanism of action from the family of opioid peptides - met-enkephalin.

Present publication pursued only one goal - to establish how universal the principle of the hierarchical organization of integrative systems of the mammalian organism is.

Firstly, it is generally accepted to this day that the hierarchical principle underlying neuroendocrine regulation is applied on the periphery only with respect to the adrenal glands - through downward stimulation by the pituitary ACTH, and the thyroid gland through downward stimulation by the pituitary thyroid-stimulating hormone, as well as in relation to organs of genital area (reproductive system).

Secondly, other peripheral organs and tissues (parathyroid, pancreas and prostate glands, adrenal medulla, hormonal and mediator-producing functions of immunogenesis organs, adipose, connective and muscle tissues), according to traditionally established principles, are not subject to direct hierarchical regulation by specific hormones and mediators produced in neurosecretory and glial cells located in specific areas of the brain.

In this regard, I consider it necessary to stipulate one question. In this particular case, we are talking about the fact that the central - hypothalamic-pituitary mechanisms in the hormonal-mediator regulation of the above-mentioned peripheral organs and tissues (in addition to the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid functioning axes) were not detected.

Thirdly, in our opinion, many hormonal-mediator links that function in these organs and tissues are realized not on hierarchical (i.e., on a vertical basis), but on a horizontal basis, by involving peripheral autonomous mechanisms, from which we are interested, mainly, in peripheral endogenously active hormonal and mediator factors. Found on the periphery these factors in their structure and biological activity are similar to those that are produced in neurosecretory cells of the brain.

Fourthly, in our opinion, the right question is why these "privileges" are granted only to the adrenal glands and the thyroid gland (we are talking about the participation of both glands as the final component of the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid systems, respectively).

Fifthly, in our opinion, the corticosteroid function of the adrenal gland and function of the thyroid gland under the conditions of normal functioning of the body is carried out not on the principles of hierarchical organization, but on the principles of more ancient, autonomic intersystem mechanisms of mutual regulation and interdependence evolutionarily fixed on the periphery.

Sixthly, in our opinion, long-established dogmatic provisions on the existence of the aforementioned hierarchical systems should be considered in great doubt, since they are similar to pituitary hormones (in this particular case, ACTH and thyroid-stimulating hormone) both in their structure and functional activity of hormones also produced in a number of peripheral organs, tissues and cells.

In this particular case, we adhere to opposite points of view that are fundamentally different from the well-known dogmatic provisions on the existence of an independent hypothalamic-pituitary-adrenal system.

In our opinion, the corticotropin produced in the central nervous system is intended exclusively for internal use, by ensuring the multifaceted detailing of specific parts of the brain. Apparently, a similar approach should be spread to the intracerebral produced melatonin, GABA, and thyrethropic hormone.

The duplication principle of the synthesis of many biologically active substances, including ACTH, in various body systems undoubtedly reflects the evolutionary process of their rational use in each specific system in which they perform "specific" functions for a given system. At the same time, the principle of intersystem mutual regulation and interdependence using the same biologically active substances can be used only in extreme conditions, when the deficit in the synthesis of biologically active substances in one system is ensured by entering of the same biologically active substances into this system, but from other systems. At the same time, the biologically active substances that entered the concrete system begin to perform those functions that are assigned to this particular system, and not from the systems, from which they came.

REFERENCES

1. *Al-Majed HT, Jones PM, Persaud SJ, Sugden D, Huang GC, Amiel S, Whitehouse BJ.* ACTH stimulates insulin secretion from MIN6 cells and primary mouse human islets of Langerhans. Journal of Endocrinology. 2004; 180: 155-166.
2. *Barsotti AM, de Assis VR, Titon SC, Titon B, Ferreira ZF, Gomes FR.* ACTH modulation on corticosterone, melatonin, testosterone and innate immune response in the tree frog Hypsiboas faber. Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology. 2017; 204: 177-184.
3. *Borelli MI, Estivariz FE, Gagliardino JJ.* Evidence for the paracrine action of islet-derived corticotropine-like peptide on the regulation of insulin release. Metabolism. 1996; 45: 565-570.
4. *Borelli MI, Morano MI, Estivariz FE, Gagliardino JJ.* Glucose-induced secretion of ACTH-like products by rat pancreatic islets. Archives Internationales de Physiologie Biochimie et de Biophysique. 1994; 102: 17-20.
5. *Eutamene H, Theodorou V, Fioramonti L, Bueno L.* Acute stress modulates the histamine content j of mast cells in the gastrointestinal tract through interleukin-1 and corticotropin-releasing factor release in rats. J. Physiol. 2003; 15: 553(Pt3): 959-66.
6. *Flores LE, Francini F, Gagliardino JJ.* Modulator effect of hormones on insulin secretion in vitro in the toad. Comparative Biochemistry and Physiology C-Pharamcology, Technology, Endocrinology. 1998; 120: 77-81.
7. *Gagliardino J, Borelli M, Boschero A, Rojas E, Atwater I.* Modulatory mechanism of ACTH on insulin secretion: effect on cytosolic Ca2+ -membrane potential and Ca2+ -ATPase activity. Archives of Physiology and Biochemistry 1995; 103: 73-78.

8. *Gagliardino JJ, Borelli MI, Estivariz FE, Atwater I, Boschero AC, Rojas E.* Islet release of ACTH-like peptides and their modulator effect on insulin secretion. Advances in Experimental Medicine and Biology. 1997; 426: 121-127.

9. *Hashimoto M, Sato EF, Hiramoto K, Kasahara E, Inoue M, Kitagawa S.* Role of adrenocorticotropic hormone in the modulation of pollinosis induced by pollen antigens. Neuroimmunomodulation. 2015; 22(4): 256-262.

10. *Hauge-Evans AC, Squires PE, Persaud SJ, Jones PM.* Pancreatic beta-cell-to-beta-cell interactions are required for integrated responses to nutrient stimuli: enhanced Ca2+ and insulin secretory responses of MIN6 pseudoislets. Diabetes. 1999; 48: 1402-1408.

11. *Irman-Florjanc T, Erjavec F.* The effect of adrenocorticotropin on histamine and 5-hydroxytryptamine secretion from rat mast cells. Agents Actions. 1984; 14(3-4): 454-457.

12. *Larauche M, Kiank C, Tache Y.* Corticotropin-releasing factor signaling in colon and ileum: regulation by stress and pathophysiological implications. J. Physiol Pharmacol. 2009; 60(7): 33-46.

13. *Lewis J, Tordoff M, Sherman J, Liebeski JC.* Adrenal-medullary enkephalin-like peptides may mediate opioid stress analgesia. Science. 1982; 217(4550): 557-559.

14. *Malaisse WJ, Malaisse-Lagae F, Mayhew D.* A possible role for the adenylcyclase system in insulin secretion. Journal of Clinical Investigation. 1967; 46: 1724-1734.

15. *Smith E, Phan M, Kruger T, Coppenhauer D, Blalock E.* Human lymphocite production of immunoreactive thyrotropin. Proc Natl. Acad. Sci. 1983; 80: 6010-6013.

16. *Solomon S.* POMC-derived peptides and their biological action. Annals of the New York Academy of Sciences. 1999; 8885: 22-40.

17. *Theoharides TC.* Neuroendocrinology of mast cells: Challenges and controversies. Exp Dermatol. 2017; 26(9): 751-759.

18. *Van Loon G, Nousa S, Kvetnanski R.* Adaptive mechanisms in the met-enkephaline and catecholamine responses to repeated stress. Clin. Res. 1985; 33: A537-A537.

19. *Zilfyan A.V., Muradyan A.A., Avagyan S.A., Haruty unyan H. A., Baroyan K.M., Ghazaryan O.V.,* ACTH-dependent process of lipase excretion by rat pancreatic acinar cells The New Armenian medical Journal,Vo l . 1 3 (2019) , N o 4, p .111-116.