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REGIONAL MELATONIN AND SOMATOSTATIN DEPENDENT MECHANISMS IN PANCREATIC INCRETORY ACTIVITY AND IN INTESTINAL BACTERIAL HOMEOSTASIS

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Abstract

For many years, it was generally accepted that melatonin and somatostatin have intracerebral sources of synthesis. Melatonin is produced in the pineal gland and somatostatin in the hypothalamus. However, there are very informative data regarding the extracerebral sources of melatonin and somatostatin synthesis in numerous literary sources published over the past 60 years. At the same time, the biological purpose of extracerebral somatostatin and melatonin has been insufficiently studied. This article presents the readers with an analysis of modern literature and the results of own researches on the biological role of melatonin and somatostatin produced in the pancreas and intestinal tract.

Under experimental conditions on arginine-induced acute pancreatitis model in rats, structural and hormonal changes were studied in the pancreas, mucosa of the small and large intestines in regional pathological process using morphological, morphometric, immunomorphological and enzyme immunoassay methods.

According to the morphological and morphometric analysis results, gross dystrophic changes in the pancreas and intestinal mucosa were observed at relatively early stages of the pathological process – in 2 and 24 hours after the arginine administration. Immunomorphological studies established that the content of melatonin-positive secretory cells noticeably decreased, especially in the areas of mucosal damage in this very period of the pathological process in pancreas, in the mucous membrane of the small and large intestines. At the same time, the content of somatotropin in blood serum and pancreas markedly increased during the indicated period of the experiment.

Severe dystrophic processes on small intestinal mucosa, which are particularly expressed by inhibition of local melatonin-secreting cell function, apparently exclude the inhibitory effect of melatonin on somatostatin synthesis process in pancreas. It is not excluded that there is a directed activation of pancreatic delta cells responsible for the somatostatin synthesis at relatively early stages of "arginine pancreatitis".

Based on our own researches in context with available very informative literature data, we can conclude that extrapineal melatonin and extrahypothalamic somatostatin should be given an important role in the integrative activity of organ-digestive system – the pancreas and small intestine.

Keywords: *melatonin, somatostatin, extracerebral sources of synthesis, autonomous mechanisms, pancreas, intestinal tract, bacterial translocation.*

Biological effects of extrapineal melatonin have not been the subject of special discussion. Most authors tried to confine themselves to stating the facts of melatonin synthesis in a number of organs of digestive, respiratory, cardiovascular systems, as well as in isolated cells of the APUD system scattered throughout the body. Only I. Kvetnoy and co-authors state (1999) in their review article "Extrapineal mela-

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tonin should be considered as a key paracrine molecule for local coordination of cellular functions".

However, at the current stage of "theoretical and clinical endocrinology" development, new, very informative data sporadically appear about the biological purpose of extrapineal melatonin in the integrative activity of mammals and new levels of its structural organization.

The role of extrapineal melatonin is still the subject to extensive discussion. The circumstance deserves special attention. According to it, the optimal concentrations of melatonin continue to be determined in blood serum and urine of laboratory animals during epiphysectomy, which, according to I.M. Kvetnoy and colleagues (1999), testify to the important role of extrapineal melatonin in the integrative activity of mammals.

Apparently, melatonin synthesis in specific peripheral organs and tissues is intended to maintain the function of precisely those organs in which the synthesis of this hormone occurs.

In this aspect, we will try, if possible, to answer some questions.

What is the biological role of melatonin synthesized in tissue basophils:

- acinar apparatus of the pancreas,
- enterochromaffin-argentaffin cells of the gastrointestinal tract

It has long been established that hypothalamic somatostatin has a modulating effect on many processes occurring in all internal organs of mammals. The reciprocal relationship between somatotropin and somatostatin has also been proven. The main biological role of somatostatin is that the latter balances the level of somatotropic hormone in blood with subsequent implementation of its demanded effects in tissues, organs and systems.

The role of extracerebral somatostatin in the integrative activity of mammals has not been finally established to this day.

The main source of somatostatin peripheral synthesis is the secretory cells of the digestive system, located everywhere, both in the central and peripheral parts of the gastrointestinal tract. Such topical features of somatostatin distribution, of course, are far from accidental. In this particular case, the implementation of the biological effects of extrahypothalamic somatostatin should, first of all, be carried out within the organs of digestive system.

Currently, scientific developments devoted to studying the biological effects of somatostatin produced by enterochromaffin cells of the intestine and delta cells of the pancreatic islet apparatus are the subject of a special study. A number of very informative data, both clinical and experimental, provide information according to which somatostatin produced in the islet apparatus of the pancreas has a modulating (inhibiting) effect on the processes of insulin synthesis by the secretory cells of endocrine pancreas. As for somatostatin, produced by the secretory cells of the intestinal mucosa, one of the functions of the hormone is to ensure the constancy of local homeostasis, in particular, to maintain the optimal level of transcapillary metabolism *in situ*.

Naturally, a question arises: what are the mechanisms of (direct and/or indirect) interaction of melatonin and somatostatin within the activity of the digestive system organs, and, in particular, maintaining regional homeostasis? Similar studies concerning the relationship between these extraneuronal hormones are very fragmentary, and sometimes uninformative. A similar situation is also observed regarding both hormones synthesized in the pancreas of mammals.

Very valuable scientific information related to the role of peripheral melatonin and somatostatin (in the pancreas and intestinal tract) in the incretory and excretory parts of the pancreas was obtained by studying the pathogenetic aspects of acute pancreatitis and diabetes mellitus. Thus, there is very informative data regarding the role of somatostatin-dependent processes involved in the induction of diabetes mellitus and acute pancreatitis [*Koerker D. et al., 1974; Bratusch-Marrein P et al., 1979; Kadowaki S et al., 1980; Alba-Roth J et al., 1988*]. In the induction of acute destructive pancreatitis, general endocrine disorders associated with dysfunction of the hypothalamic and pituitary structures are involved in the regional pathological process. So, according to some

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

authors, in the pathogenesis of acute pancreatitis of various origins, an important role is given to somatostatin and somatotropin of neuronal origin, produced, respectively, in the hypothalamus and pituitary gland [*Dollinger H et al., 1976; Botha J et al., 1977; Lankisch P et al., 1977*].

At the same time, in recent years, aspects of the pancreatitis and diabetes pathogenesis have been the subject of special discussion, arising on the background of not only general endocrine-mediator shifts in the corresponding neurosecretory cells in the hypothalamus, pituitary gland and epiphysis, but also due to local hormonal disorders associated with dysfunction of specialized secretory cells located in the pancreas, small and large intestines. We are talking about alpha, beta and delta cells of the islets of Langerhans, acinar cells of the pancreas, endocrinocytes of the proximal and distal parts of intestinal tract. In the pancreas, delta cells of the endocrine system act as a source of somatostatin synthesis, and enterochromaffin cells – in the intestinal mucosa.

In this regard, over the years, employees of the Scientific Research Center, Department of Urology and Andrology, Department of Normal Anatomy and Histology of YSMU have been developing aspects related to the role of extraneuronal melatonin and somatostatin in the modulation mechanisms of pancreatic endocrine function, induction of acute destructive pancreatitis [*Avagyan S, 2008; 2009; 2016; Baroyan K et al., 2014; Avagyan S, 2016; Baroyan K, 2016; Avagyan S et al., 2019; Zilfyan A, 2021*].

Based on the analysis of own studies and literary sources, the authors discuss possible putrescine-dependent general and regional endocrine mediated mechanisms that ensure the function of β-cells of the pancreatic islet apparatus. From general mechanisms, an important role belongs to somatostatin and somatotropin of central origin, which are produced, respectively, in the hypothalamus and pituitary gland. Due to the enzyme immunoassay, it was possible to establish that exogenous putrescine, administered to intact rats at very low concentrations, as close as possible to those determined in the blood serum of a number of mammals, leads to the decreased level of somatostatin in blood serum. Apparently, on the background of a low level of somatostatin, the function of β-cells of the endocrine pancreas is activated, and the effect of somatotropin on β-cells is realized indirectly - through activation of the synthesis of insulin-like growth factor-1 in the liver and ileum. A direct stimulating effect of putrescine on β-cells of the islets of Langerhans is also not excluded.

Based on our own research and analysis of literature data, we hypothesize that under the conditions of normal functioning of mammals, putrescine produced in various organs and tissues plays an important role in the formation of a functional hormone-mediated loop, the action of which is realized both at the level of the central structures of the brain (hypothalamus and pituitary gland) and the organs of the digestive system (pancreas and intestinal tract).

We studied structural and hormonal changes in the pancreas, mucous membranes of the small and large intestines in the regional pathological process course om the arginine-induced acute pancreatitis model in rats, using the methods of morphological, morphometric, immunomorphological and enzyme immunoassay.

As the results of morphological and morphometric analysis showed, gross dystrophic changes in the pancreas and intestinal mucosa were observed at relatively early stages of the pathological process course – 2 and 24 hours after the arginine administration. Immunomorphological studies established that the content of melatonin-positive secretory cells noticeably decreased, especially in the areas of damaged mucous membrane during this period of the pathological process course in the pancreas, in the mucous membrane of small and large intestines. In our opinion, the enzyme immunoassay results to determine the somatostatin level in the blood serum and in the pancreas deserve special attention (Table). ELISA methods for melatonin and somatostatin determination are detailed in our previous studies [*Avagyan S, 2016; Baroyan K, 2016*].

As can be seen from the table, a single arginine administration to experimental animals led to a noticeable increase in the somatostatin level in blood serum at the initial stages of the regional acute inflammatory process of the pancreas. Thus, the somatostatin levels in the blood serum 2 and 24 hours after the arginine administration exceeded the con-

trol level by 2.2 times compared to those observed in the blood serum of control group rats.

At relatively late stages of "arginine pancreatitis", the somatostatin level in all three experimental groups returned to normal, i.e., practically did not differ from that observed in the blood serum of control group animals.

The enzyme immunoassay results for the somatostatin determination in the pancreas are also shown in the table.

As can be seen from the table, relatively high levels of somatostatin were registered in supernatants prepared from pancreas homogenates of experimental animals at a relatively early stage of the regional pathological process. So, 2 and 24 hours after the arginine administration, the somatostatin level in supernatants prepared from pancreatic homogenates was more than 2.5 times higher than the control.

In the subsequent observation period (after 48 hours, 4 and 8 days), the somatostatin level in the pancreas returned to normal, i.e., practically did not differ from that observed in the pancreas of control group animals.

As we noted earlier, extrapineal melatonin, produced in the secretory cells of the small intestine, is given an important role in maintaining regional bacterial homeostasis through its participation in the regulation of the permeability of the microhemocirculatory bed, as well as the balanced synthesis of oxygen-active free radicals by endotheliocytes. The studies carried out at the Scientific Research Center of YSMU, where the features of the bacterial translocation process were studied on the same "arginine pancreatitis" model tested by us, found out that the regional pathological process is accompanied by E. Coli persistence in the pancreas, resulting in in situ activation of IL-1 synthesis by acinar cells [*Bagdasaryan A, 2004*]. That is why in the mechanisms of the emerging bacterial translocation process and subsequent persistence of resident opportunistic and pathogenic gram-negative microorganisms in the pancreas, an important role should be payed to melatonin, which is produced in the endocrinocytes of the small intestinal mucosa.

During our experiment on the "arginine pancreatitis" model the pronounced dystrophic processes of the small intestinal mucosa, also accompanied by the decay of secretory enterocytes largely contributed to the intensification of intestinal bacterial translocation processes, since, such an important factor in maintaining local homeostasis (including bacterial) as melatonin falls out of regional adaptive processes.

In our opinion, it is necessary to pay attention to the following circumstance. It is possible that the reciprocal relationships of somatotropin and somatostatin are also realized within the digestive system functioning both in normal and pathological conditions [*Jaworek J et al., 2009*]. Under conditions of acute pancreatitis modeling, growth hormone - somatotropin penetrates the intestinal barrier, stimulating in situ production of IGF-1, which inhibits the regional pathological process development. That is why, in our opinion, an important role in the induction mechanism of "arginine pancreatitis" should be referred to somatostatin. High concentrations of somatostatin found in the blood serum and pancreas of experimental animals at the early stages of the regional pathological process, should be considered as an unfavorable factor, since high concentrations of somatostatin, on the one hand, can have an inhibitory effect on the growth hormone synthesis in the pituitary gland, and on the other hand, inhibit secretory processes in the incretory and excretory parts of

Table

Changes in the somatostatin content in blood serum and pancreas of experimental animals under conditions of arginine-induced acute pancreatitis model

Groups	In the pancreas			In blood serum		
	M	m	p	M	m	p
Control (n=20)	2.07	±0.32		5.4	±0.7	
Experimental						
2 hours (n=20)	5.76	±0.53	p<0.0005	12.3	±0.9	p<0.0005
24 hours (n=20)	5.37	±0.54	p<0.0005	11.9	±1.9	0.0005<p<0.005
48 hours (n=20)	2.49	±0.44	0.10<p<0.025	5.7	±1.6	0.4 <p
4 days (n=20)	2.19	±0.40	0.4 <p	3.9	±0.8	0.05<p<0.10
8 days (n=20)	2.24	±0.59	0.4 <p	5.5	±0.6	0.4 <p

Note: *p – somatostatin indicators of experimental group rats in relation to the corresponding indicators of control group rats*

pancreas [*Valcavi R et al., 1993; Sliwinska-Mosson M et al., 2014; Zibolka J et al., 2015*].

In our particular case, another autonomous mechanism is involved, which is due to the reciprocal relationship between intestinal melatonin and pancreatic somatostatin. Severe dystrophic processes in the small intestinal mucosa that are expressed by inhibition of the local melatonin-secreting cell function, apparently exclude the inhibitory effect of melatonin on the somatostatin synthesis process in the pancreas. It is also possible that at relatively early stages of "arginine pancreatitis" there is a directed activation of the pancreatic delta cells responsible for the somatostatin synthesis.

Based on our own research with available very informative literature data, we can conclude that extrapineal melatonin and extrahypothalamic somatostatin should play an important role in the integrative activity of the digestive system organs – the pancreas and small intestine.

Within physiological activity of the body, melatonin produced in secretory cells maintains a balanced synthesis of insulin by β-cells of the islet apparatus. Normally melatonin produced in the secretory cells of the small intestinal mucosa prevents the emergence of bacterial translocation, which is fraught with the migration of opportunistic resident microorganisms from the intestinal tract to new econiches of the macroorganism: parenchymal organs, organs of immunogenesis. The implementation of the inhibitory effect of extrapineal melatonin is assessed by its participation in the regulation of transcapillary metabolism of the intestinal mucosa, in particular, the coordination of processes responsible for the synthesis of free radicals (including nitric oxide) by endotheliocytes of microvessels of the small intestinal mucosa.

Under the physiological activity of mammals, somatostatin produced in the delta cells of the islet apparatus of the pancreas maintains a balanced insulin synthesis by β-cells. In this particular case, the realizing effect of somatostatin is carried out indirectly, by preventing the impact on the insular apparatus of "excessive" concentrations of growth hormone – somatotropin. This makes the reader think – what is the "specific weight" of the participation of cerebral and extracerebral melatonin and somatostatin in the mechanisms of incretory and secretory functions of the pancreas and maintaining intestinal bacterial homeostasis aimed at preventing the bacterial translocation process?

In our opinion, in this case, the duplication principle is unlikely to function; implementation of secretory processes in the pancreas and intestinal mucosa through both cerebral and extracerebral melatonin and somatostatin. Most likely, in this situation, horizontal connections are involved, based on the principles of paracrine mutual regulation and interdependence, exclusively due to regionally produced melatonin and somatostatin.

We put forward a hypothesis that under conditions of the organism normal functioning, autonomous paracrine melatonin- and somatostatin-dependent interhormonal functional loops are involved in the digestive system of mammals, coordinating, on the one hand, the exocrine and endocrine functions of the pancreas, and, on the other hand, providing regional endocrine functions in the intestinal tract and bacterial homeostasis, thereby preventing the occurrence of the bacterial translocation process.

The physiological purpose of melatonin produced in the digestive tract is far from being studied enough. In our opinion, studies on the role of extrapineal melatonin in the regulation of bacterial homeostasis in the digestive system are of particular interest. In this particular case, we are talking about the well-known phenomenon of bacterial translocation.

For many years, specialists from various fields of medicine have been studying aspects related to the bacterial translocation of opportunistic microorganisms from the macroorganism econiche, followed by their persistence in a number of internal organs.

It has been established that the bacterial translocation process is involved in extreme situations of various origins – acute and chronic stress, trauma, burns, hemorrhagic shock, intestinal obstruction, obstructive jaundice, acute pancreatitis, toxic hepatitis, multiple organ failure syndrome [*Lemaire L et al., 1977; Deith E, 1994; De Souza L et al., 1996; Adawi D et al., 1998; Demetriades D et al., 1999*].

In experimental studies conducted at the Scientific Research Center of YSMU for a number of years, it was found that the bacterial translocation processes, which occurred in a number of patho-

logical conditions (crush syndrome, acute pancreatitis, obstructive jaundice) as well, are accompanied by a relatively long persistence of E. Coli in new econiches of the macroorganism . Moreover, in addition to the organs of immune system, the lungs, pancreas and liver act as "target organs" [*Bagdasaryan A, 2004; Sahakyan K, 2005*].

The mechanisms underlying the bacterial translocation process are almost unstudied. Apparently, regional disturbances should play a fundamental role in this process, eventually leading to disruption of the barrier mechanisms that prevent the migration of intracorporeal resident microorganisms from their natural econiches into the blood and regional lymph nodes. At present, there are isolated but very informative data that discuss aspects of the "hormonal regulation" of the bacterial translocation process, in particular, the protective role of extrapineal melatonin produced in the intestinal secretory cells [*Akcan A. et al., 2008*].

Thus, there are data that melatonin prevents the development of intoxication caused by endotoxin E. Coli in the blood [*Akopyan A, Mallina R, 1999; Crespo E et al., 1999*].

In our opinion, the "detoxification" effect of melatonin is most likely involved at the level of the gastrointestinal tract and is realized by direct blocking of NOS activity in situ, since it is known that the toxic effects of endotoxin are also due to free radical activation processes. Apparently, melatonin does not affect the process of already established microorganism translocation and toxemia development. In our opinion, the direct effect of the optimal concentrations of melatonin produced in situ, i.e., in EC cells, on the intestinal wall is more possible. As a result, the activity of free radicals and, primarily, NO, which, as is known, has a pronounced effect, has vasodilatory effect on the walls of microvessels, and in high concentrations is a toxic compound. In the latter case, "favorable" conditions are created in the intestinal tract (destruction of the intestinal walls, increased vascular permeability) for the translocation of resident gram-negative microorganisms living in the intestine, and primarily E.Coli, into the blood and new econiches of the macroorganism.

The bacterial translocation processes in a number of neurological diseases are also the subject of special study.

So, particularly our published article [*Avagyan S et al., 2019*] that discusses aspects of bacterial translocation associated with the possible role of E.Coli and Helicobacter pylori in the pathogenesis of Parkinson's disease should be of some interest to the reader. This publication analyzes literary sources and studies by a number of authors [*Gomez-Isla T et al., 2003; Tofaris G, Garsia P, 2006*], according to which, with the development of Helicobacter pylori infection α-synucleins accumulate in the nerve endings of the gastrointestinal tract organs, which, as you know, are given an important role in the pathogenesis of Parkinson's disease. According to the authors, α-synucleins accumulated in neurites migrate perineurally and/or through the blood-brain barrier to the central nervous system, causing a symptom complex of neurodegenerative disorders characteristic of Parkinson's disease.

Our review article also provides our own opinion, according to which both pathways of α-synuclein translocation are unlikely to be involved in Helicobacter pylori infection. Most likely, in our opinion, specific autoantibodies that are produced in the lymphoid tissue of the peripheral organs of immunogenesis and in various parts of the gastrointestinal tract should act as a source of translocation. In this regard, the studies of Sergeeva T.N. and Sergeev V.G. (2011) are of particular interest, where under experimental conditions (in vivo and in vitro) with E.Coli lipopolysaccharide introduction in the same organs, it was possible to detect the synthesis of specific autoantibodies to α-synuclein. That is why, under certain extreme conditions, it is autoantibodies to α-synuclein that penetrate the blood-brain barrier into the central nervous system, thereby triggering autoimmune processes in specific brain structures rich in dopaminergic neurons.

At present, it is generally accepted that the bacterial translocation process has rather a pathological orientation, aggravating the development of systemic and organ disorders, the state of endotoxicosis occurring on the background of systemic multiple organ failure.

Only a few authors believe that the bacterial translocation process is biologically expedient in extreme situations [*Wang X et al., 1996*], since it is due to the migration of resident microorganisms that T-cell mediated immunity reactions are stimu-

lated in the central and peripheral organs of immune system. In this regard, we should pay attention to the studies of V.I. Nikitenko and V.V. Zakharova (2001), according to which "the bacterial translocation from the gastrointestinal tract can be considered as a natural defense mechanism".

The latter, according to the authors, is even older than the cellular immune system, since it is involved not only in warm-blooded animals, but also in insects and plants. Thus, the authors, through experimental and clinical studies using microbiological and radionuclide techniques, showed that "in healthy animals, microorganisms penetrate into the blood and lymph from the gastrointestinal tract mainly through gastric and small intestinal mucous membranes without any stimulation of the translocation process". In our opinion, we should continue researches in this direction to study evolutionarily developed regional mechanisms aimed at maintaining the constancy of bacterial homeostasis in the corresponding econiches of the macroorganism. Moreover, the leading role in this process should be given to regional hormonal mediated mechanisms, which we have shown by the example of melatonin produced in Argentaffin EC cells and its role in preventing the development of regional pathological reactions that provoke the process of intestinal bacterial translocation.

Analyzed literature data allow us to assume that numerous cells, tissues and organs of mammals act as a source of melatonin synthesis. Moreover, the level of synthesized melatonin in a number of internal organs is several times higher than that produced in the epiphysis. In this aspect, it is important to elucidate the mechanisms underlying the formation of at least the circadian rhythmicity of many processes associated with chronological shifts of melatonin itself. In other words, is extrapineal melatonin, which is synthesized in a number of cells and internal organs, interested in the formation of circadian, ultradian, diurnal, and seasonal rhythms in mammals? In addition to its fundamental significance, this problem also needs to be resolved in an applied aspect – what is the specific gravity of intrapineal and extrapineal melatonin, which ensures its specific level in mammalian blood?

All the aspects of our studies concerning the role of extrapineal melatonin in the formation of melatonin-dependent chronological rhythms should, in our opinion, be the subject of a comprehensive study in the near future with the involvement of advanced scientists in various fields of medicine: physiologists, endocrinologists, immunologists, molecular biologists working in applied medicine.

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CONTENTS

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