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Experimental Article

THE ROLE OF MELATONIN AND SOMATOSTATIN PRODUCED IN DIGESTIVE SYSTEM IN THE LESION MECHANISMS OF EXCRETORY APPARATUS OF PANCREAS AND INDUCTION OF BACTERIAL TRANSLOCATION IN ARGININE PANCREATITIS

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Abstract

The role of melatonin and somatostatin produced in digestive system in lesion mechanisms of excretory apparatus of pancreas on arginine pancreatitis model was investigated from immuno-enzymometric and morphological aspects.

The study was held in two directions:

- Investigation of the role of somatostatin produced in the pancreas in induction and process of arginine pancreatitis.
- Investigation of the role of melatonin produced in intestines in the induction of bacterial translocation.

Analyzing the results in the context of available literature data, an assumption is made, according to which the process of intestinal bacterial translocation in acute pancreatitis is melatonin-dependent. This process is mostly associated with disturbance of melatonin synthesis in endocrinocytes located in mucous membrane of lesser intestines, as well as acinar cells of pancreas.

Somatostatin also has an important role in the induction mechanism of arginine pancreatitis. High concentration of somatostatin in blood serum and pancreas of experimental animals in early stages of regional pathological process should be considered as an adverse factor, because, on the one hand, high concentration of somatostatin may inhibit synthesis of somatotropin in hypophysis, on the other hand, it may inhibit secretory processes in endocrine and exocrine apparatus of pancreas.

A hypothesis has been made, according to which autonomous paracrine melatonin- and somatostatin-dependent functional loops providing regional and bacterial homeostasis are involved in digestive system, preventing the migration of opportunistic intestinal microorganisms into new econiches of the host under the conditions of normal functioning of higher mammals' organisms

Keywords: *arginine pancreatitis, melatonin, somatostatin, pancreas, bacterial translocation.*

Introduction

Currently, bacterial translocation of intracorporeal intestinal microorganisms has an important role in pathogenesis of acute destructive pancreatitis [*de Souza L et al., 1996; Samel S et al., 2002; Baghdasaryan A, 2004; Zilfyan A et al., 2005; Baroyan K et al., 2014; Zilfyan A, 2014*]. According to above mentioned authors, as a result of bacterial translocation and further persistence of gram-negative microorganisms in pancreas, an immune-endocrine and metabolic syndrome occur in the latter, predetermining course and flow of regional pathological process.

At the same time mechanisms in the induction of intestinal microorganisms' translocation and their further persistence in new econiches are investigated extremely insufficiently. In the mentioned aspect a subject of discussion is quite infor-

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mative data received by a number of authors, according to which regional hormonal mechanisms are involved in the pathogenesis of intestinal bacterial translocation, first of all, connected with the disturbance of melatonin synthesis by endocrinocytes of lesser intestines [*Akcan A et al., 2008; Sözen S et al., 2012*].

Melatonin, secreted in intestinal tract, provides balanced bacterial homeostasis in normal conditions by regulation of regional trans-capillary exchange and inhibition of in situ processes responsible for synthesis of oxygen containing free radicals, and, first of all, NO [*Sun X et al., 2013*].

At the same time, it is not excluded, that common endocrine disorders, caused by dysfunction of hypothalamic and hypophyseal structures, are also involved in the induction of acute destructive pancreatitis. Present condition is confirmed with an important role of somatostatin and somatotropin in the pathogenesis of pancreatitis of different genesis [*Dollinger H et al., 1976; Botha J et al., 1977; Lankisch P et al., 1977*].

The goal of the study is based on the investigation of regional melatonin- and somatostatin-dependent processes in pathogenesis of experimentally induced "arginine pancreatitis" associated with intestinal bacterial translocation processes.

The following questions were set:

To what extent is the bacterial translocation process of intestinal microorganisms in induced "arginine pancreatitis" melatonin-dependent?

What is the role of somatostatin in induction and process of "arginine pancreatitis" connected, especially, with dysfunction of endocrinocytes of intestinal tract, responsible for melatonin synthesis?

Materials and methods

The experiments were conducted on 86 white female-rats of 150-180 *g*. The model of pancreatitis was reproduced by single injection of relatively high concentration of arginine commercial preparation produced by "Liquor" company (Armenia).

Arginine was injected intra-abdominally (1.5 *ml* arginine, taking into consideration 300 *mg* for 100 *g* weight of animal). According to several authors [*Tani S et al., 1990; de Souza L et al., 1996; Hegyi P et al., 1997; 1999; Al-Mufti R et al., 1998; Tashiro M et al., 2001; Naito Z et al., 2003*] the mentioned dose of arginine is "optimal" to reproduce symptom complex of morphofunctional changes pathognomonic for acute destructive pancreatitis observed by clinicians in their daily practice. Arginine was injected in the daytime (from 1 to 2 pm), i.e. in the period, when the melatonin concentration is the lowest in the blood serum of intact rats. The control group was consisted of intact rats which received intra-abdominal injection of 1.5 *ml* saline liquid, i.e. the amount of liquid in which arginine was solved to be injected in experimental group. The animals of experimental group were displayed from the experiment in 2, 24, 48 hours, 4 and 8 days after arginine injection. Rats of control group were displayed in the same periods. In each group 12 animals were used. During the experiment all necessary conditions were kept assigned by Ethical Committee of YSMU during work with experimental animals. Paraffin and cryostat sections were made from the pancreas pieces. Paraffin sections were colored with hematoxylin-eosin and azure II-eosin after dewaxing. Cryostat sections were exposed to immune-morphological analysis to reveal melatonin in pancreas and lesser intestines. With this purpose the indirect Kuns immunofluorescence reaction was performed. In the first stage of reaction the cryostat sections were processed by rabbit anti-melatonin antigens produced by "ABD-Serotec" (Great Britain). FITC anti-rabbit IgG produced by "Sigma" company (USA) were used in the second stage of Kuns immunofluorescence reaction. According to protocol of immune-morphological studies' conduction recommended by "Sorin" company (USA), necessary controls were set to exclude nonspecific fluorescence and auto-fluorescence in mandatory order. The materials were viewed by luminescent microscope of "Boeco" company (Germany). The content of somatostatin in blood serum and pancreas was revealed by commercial anti-rat kit-set "Cusabio Biotech" Co., LTD (China). The level of somatostatin according to protocol is expressed by *pg/ml*. The immune-enzyme analysis is done by Stat Fax 2012 automatic analyzer (USA).

Statistical analysis was done by SPSS statistical software (11.0 version).

Results

The results of morphological analysis in 2, 24, 48 hours after arginine injection in pancreas

showed domination of catabolic processes, which structurally were expressed by severe dystrophic changes in excretory apparatus. So, ubiquitously structural organization of acinar apparatus was disrupted which was expressed with signs of dyscomplexation of excretory epitheliocytes, vacuolization of cytoplasm, pycnosis of nuclei. In separate adjacent acini lesions of micronecrosis were revealed. Expressed dystrophic changes were also revealed in epithelial cells of intra- and interlobular pancreatic ducts. The stroma of pancreas looked moderately edematous and infiltrated with leucocytes and lymphocytes. Erythrocyte extravasates localized in perivenular spaces were not infrequently seen.

It is worth to mention that the structural organization of endocrine apparatus of pancreas was generally saved in the early stages of regional pathological process. Signs of dyscomplexation and dystrophy were seen only in superficial circular-oriented secretory cells of Langerhans islets, i.e. the places where mostly alpha and delta cells are located.

On the 4th day of "arginine pancreatitis" process initial signs of activation of anabolic reactions were observed in the pancreas, which were expressed by recovery of structural organization of epitheliocytes of acinar apparatus which again acquired the ability of circular orientation on the inner surface of basal membranes. The activation of reparative-proliferative processes in the mentioned period of observation had local character and occurred only in localization of intra- and interlobular pancreatic ducts, where initial signs of activation of reparative processes were also revealed. Exactly in these parts the epithelial cells begun to form soft and oval structures which reminiscent acini.

On the 9th day of regional pathological process of pancreas of experimental rats ubiquitously reparative-proliferative processes dominated, directed exclusively to recover cyto-architectonics of acinar apparatus. As a result of activation of proliferation and remodeling of pancreatic ducts, formation of multiple minor pancreatic acini occurred, which were in different stages of development. This process structurally is expressed by "budding" and "garneting" of acini from adjacent localized intra- and interlobular pancreatic ducts. Overall, the character and time intervals of activation of reparative-proliferative processes were similar in condition of playback on the identical model of acute "arginine pancreatitis" in minor experimental animals [*Bagdasaryan A, 2004*].

One important fact should also be noted, according to which the symptom complex of reparative-proliferative processes in the pancreas established by the study team on the 4th day of regional pathological process is the result of activation of proliferative processes in the epithelial intra-and interlobular pancreatic ducts already after 48 hours of arginine injection which was supported by the previous investigations where in the ducts and acini with immune-morphological analysis method were revealed BrDU-positive epitheliocytes [*Baroyan K et al., 2014*].

Relatively severe dystrophic changes were also observed in lesser intestines of experimental animals in 2, 24, 48 hours after arginine injection. In the mentioned period of regional pathological process cyto-architectonics of mucous membrane was disrupted which was expressed by signs of dyscomplexation of villi, dystrophy of epitheliocytes and separate secretory cells with their sloughing in opening of intestines. The process was local because in the adjacent villi the cyto-architectonics was remained.

Reparative processes directed to recover structures of cellular and non- cellular components of mucous membrane started to dominate in 48 hours, especially in 4 and 8 days after arginine injection into mucous membrane of intestines. Not infrequently "hypertrophic" forms of villi rich in cells of epithelial genesis are met.

Immunomorphological analysis showed that the concentration of melatonin-positive secretory cells (compared to control group) noticeably decreased especially in the damaged parts of mucous membrane in relatively early stages of regional pathological process in pancreas in the mucous membrane of lesser intestines. In these kind of destructive parts only single melatonin-positive cells were revealed, which had non-systematic orientation in the thickness of mucous membrane of lesser intestines.

In the following period of experiment, i.e. starting from 48 hours till 8 days of observation as recovery of cyto-architectonics of mucous membrane occurred, the concentration of melatonin-positive cells, which had acquired characteristic structural orienta-

tion located in separate alternating cells among groups of epitheliocytes, noticeably increased.

The results of immune-enzyme analysis for the determination of somatostatin are shown in table.

As the table shows, single intra-abdominal injection of arginine has led to noticeable increase of somatostatin level in blood serum in initial stages of regional acute inflammatory process in pancreas. So, levels of somatostatin in blood serum in 2 and 24 hours after arginine injection exceeded control level 2.2 times compared to control group.

In relatively late stages of "arginine pancreatitis" process (in 48 hours, 4 and 8 days) the somatostatin level in blood serum of rats in all three case groups was normalized, i.e. practically was not different from that of control group.

The results of immune-enzyme analysis to investigate somatostatin in pancreas are shown in table.

As the table shows relatively high indicators of somatostatin were detected in supernatants, which were made from homogenates of pancreas of experimental animals in relatively early stages of regional pathological process. So, in 2 and 24 hours after arginine injection the somatostatin level in supernatants made from homogenates of pancreas was 2.5 times higher than in control group.

In the following period of observation (in 48 hours, 4 and 8 days) the somatostatin level in the pancreas was normalized, i.e. practically it was not different from the pancreas of the animals in the control group. Comparing the somatostatin levels in blood serum and pancreas same shift dynamics were revealed. Apparently, in the condition of injection of experimental animals relatively high dose of arginine, at the same time both central and peripheral mechanisms responsible for somatostatin synthesis in hypothalamus and pancreas work. At the same time, indicators of somatostatin in pancreas were much lower than those in blood serum of control group.

TABLE.

Content of somatostatin ((*pg/ml*)) in blood serum and pancreas of experimental animals in the induction of "arginine model" of acute pancreatitis

Groups	Serum (n=12)	Pancreas (n=12)
Control (intact rats)	5.4±0.7	2.07±0.32
2 hours	12.3±0.9 $p_1<0.0005$	5.76±0.53 $p_2<0.0005$
24 hours	11.9±1.9 $0.005>p_1>0.0005$	5.37±0.54 $p_2<0.0005$
48 hours	5.7±1.6 $p_1>0.4$	2.49±0.44 $0.25>p_2>0.10$
4 days	3.9±0.8 $0.10>p_1>0.05$	2.19±0.40 $p_2>0.4$
8 days	5.5±0.6 $p_1>0.4$	2.24±0.59 $p_2>0.4$

NOTE: *p_1 and p_2 – ratio of somatostatin indicators in blood serum* and pancreas *of rats of experimental group in comparison with corresponding indicators of control group.*

DISCUSSION

Currently, aspects of pathogenesis of pancreatitis, diabetes are very often discussed connected with involvement of not general endocrine-mediator disorders related to dysfunction of central neuroendocrine structures localized in epiphysis, hypothalamus and hypophysis, and local hormone-mediator disorders arising in special secretory cells located in different parts of digestive system: secretory cells of Langerhans isles (α, β and delta cells), acinar cells of pancreas producing melatonin, endocrinocytes of mucous membrane of lesser intestines (cells producing melatonin and somatostatin). These discussions were based on current information about synthesis in the periphery of such hormones and mediators as somatostatin and melatonin. However, in separate cases only concepts are highlighted which are generally based on assumptions according to which several hormones and peptides produced in periphery, as well as melatonin, ghrelin, leptin, perform double function of pancreas, regulate secretion and metabolic homeostasis [*Chandra R, Liddle R, 2009*].

The assumption is also very competent, according to which during destructive pancreatitis intestinal bacterial translocation processes are melatonin-dependent caused by disturbance of synthesis of extra-pineal melatonin produced in the acinar cells of pancreas, as well as, first of all, in endocrine cells localized in the mucous membrane of

lesser intestines. A concept is pushed forward by the aforementioned authors that the process of bacterial translocation is prone to hormonal "regulation", where the protective role of extra-pineal melatonin produced in the secretory cells of lesser intestines is highlighted [*Akcan A et al., 2008; Sözen S et al., 2012; San X et al., 2013*].

At the same time, as it was mentioned above, the synthesis of such hormones and cytokines of pleiotropic spectrum as somatostatin, melatonin and insulin-like growth factor-1 are disrupted in the digestive organs during acute destructive pancreatitis. In the available literature there were no data which would generalize all information in mentioned aspect in a uniform hypothesis or concept.

That is why, based on the analyzed literature information in context of many studies conducted by investigation team, all available data related to aspects of pathogenesis of pancreatitis in a unified hypothesis were generalized. Certainly, the hypothesis, that is set, cannot be final, because investigators periodically will have a necessity to lighten aspects of pathogenesis of acute destructive pancreatitis from new quality perspectives in accordance with new data about endocrine and mediatory function of secretory cells localized in the organs of digestive system, especially, in pancreas and intestinal tract.

By virtue of morphological, fluorescent-microscopic and immune-enzyme investigations it was found out, that the concentration of melatonin was noticeably decreased in relatively early stages of "arginine pancreatitis" process against the background of expressed destructive processes involving mostly acinar apparatus of the pancreas and multipotent cells of mucous membrane of lesser intestines, in the secretory epithelium.

As it was introduced in the initial fragment of the present chapter, the extra-pineal melatonin produced in the secretory cells of lesser intestines has an important role in the support of regional bacterial homeostasis by participating in regulation of microhemocirculatory flow, as well as balanced synthesis of oxygen-active free radicals by endotheliocytes. The studies were conducted in Scientific Research Center of YSMU where model features of bacterial translocation process were investigated in the same "arginine pancreatitis". It was revealed that the regional pathological process is accompanied with persistence of E. Coli in pancreas which resulted in activation of IL I synthesis process by acinar cells in situ [*Bagdasaryan A, 2004; Zilfyan A et al., 2005; Zilfyan A, 2014*]. That is why, in the mechanisms of bacterial translocation and following persistence of resident opportunistic gram-negative microorganisms in pancreas an important role should be discharged to melatonin produced in the mucous membrane of lesser intestines.

Expressed dystrophic processes in mucous membrane of lesser intestines in "arginine pancreatitis" model were also accompanied with decomposition of secretory enterocytes mostly contributed to intensification of intestinal bacterial translocation processes, because in the condition of the experiment an important factor like melatonin is dropped from the whole chain of regional adaptive processes to support local homeostasis (including bacterial).

It is necessary to pay attention on the following circumstance in the mentioned aspect. It is not excluded that reciprocal relationship of somatotropin and somatostatin is also implemented in the functioning of digestive system both in normal and pathological conditions. Particularly, as many authors claim [*Jaworek J et al., 2009*] in the modeling of acute pancreatitis the growth hormone-somatotropin passes through intestinal barrier stimulating production of IGF-1 in situ which inhibits development of regional pathological process. The studies are very informative to investigate modulator role of somatotropin in the pathogenesis of acute pancreatitis [*Wang X et al., 2001*].

The authors were investigating the influence of exogenous somatotropin on the morphofunctional condition of pancreas and process of bacterial translocation of resident microorganisms in the model of acute necrotic pancreatitis, which was reached by the injection of 5% liquid of taurocholate into bile-pancreatic duct. A bacteriological analysis of mesenterial lymph nodes, liver, spleen and pancreas was done. At the same time level of IGF-1 was checked in the liver and ileum. The findings showed that injection of somatotropin was followed with a decrease of amylase, lipase, endotoxin in blood serum and inhibition of bacterial translocation process of resident intestinal microorganisms. As a probable mechanism of somatotropin action, the authors consider the processes of activation of mRNA IGF-1 in ileum but not in liver.

Somatostatin has an important role in the induction mechanism of "arginine pancreatitis" as well. High concentration of somatostatin in blood serum in the early stages of regional pathological process should be considered as an adverse factor, because on the one hand high somatostatin concentration may inhibit synthesis of growth hormone in hypophysis, on the other hand it may inhibit secretory processes in endocrine and exocrine apparatus of pancreas [*Valcavi R et al., 1993, Sliwińska-Mossoń M et al., 2014, Zibolka J et al., 2015*]. According to several authors [*Córdoba-Chacón J et al., 2013*] it was found, that in natural conditions arginine had stimulating influence on β-cells of pancreas as a result of somatostatin inhibition by delta-cells. Moreover, the authors pushed forward a hypothesis that in natural conditions the main mechanism with the help of which L-arginine stimulated synthesis of growth hormone (somatotropin) in hypophysis was a result of reduced supply of somatostatin from hypothalamus to hypophysis.

At the same time, in conditions of L-arginine injections to experimental animals, the results were diametrically opposite in the respect of shifts of somatostatin concentration in blood serum.

In this connection, interpretation of findings should be implemented taking into account diverse scientific-methodological approaches in the investigation of biological effects of somatostatin in normal and experimental conditions.

All authors cited by the investigation team mentioned, that effects of arginine were investigated in "natural conditions". Wherein, most importantly, piloted doses of injected L-arginine were 3.7 times less that the dose investigated by investigation team which was necessary in modeling of "acute arginine". In contrast to injected dose by authors (nearly 0.8 *g/kg*), dose of arginine used by investigation team (3 *g/kg*) is not physiological, even toxic, as a result of which a syndrome of structural changes occurs in pancreas and mucous membrane of lesser intestines which speaks in favor of activation of catabolic processes *in situ* reminiscent the morphological picture defeat of acinar apparatus in acute destructive pancreatitis.

In the mentioned context, studies, which tried to establish correlation dependence between used high doses of biological active substances leading to development of severe acute dystrophic processes in the organism of mammals and level of somatostatin in blood serum, represent certain interest. It is known that "streptosotocine" model of diabetes is most frequently used to reproduce the syndrome in the experiment characteristic for damage of acinar apparatus of pancreas in patients with diabetes. Many authors [*Kadowaki S et al., 1980*] investigated shifts of somatostatin concentration in blood serum of experimental animals on the "streptosotocine" model of diabetes. The authors found that somatostatin concentration in blood serum of experimental animals proportionally increased to injected dose of streptosotocine.

Comparing the findings with those in literature a conclusion can be made according to which endocrine disorders connected with "hyper-secretion" of somatostatin are also involved in the pathogenesis of diseases of pancreas. Herewith, the same endogenous and exogenous active factors in every specific case can lead to diametrically opposite results. In contrast to the experiment, where relatively high doses of arginine were used resulted in death of experimental animals in 20% cases in early stages of development of regional pathological process, the injection of less concentration into organism resulted in inhibition of synthesis of somatostatin in hypothalamus [*Alba-Roth J. et al 1988*]. The studies were conducted in volunteers (6 adult healthy men). In the condition of arginine injection, somatotropin synthesis were noticeably activated, which, according to authors, was a result of inhibition of somatostatin secretion.

It is known, that the only source of somatostatin synthesis in pancreas of mammals are delta-cells which are mostly localized in the superficial parts of Langerhans isles. It is worth to mention, that in the condition of injection of relatively high doses of arginine into experimental animals, the cyto-architectonics of endocrine apparatus of pancreas, overall, was saved. That is why, an assumption can be made that relatively high concentrations of somatostatin in supernatants, made from homogenates of pancreas, is caused not that much from hormone supply from blood, but as a result of hyper-function of delta-cells of insular apparatus.

Available literature data were very informative in context of interpretation of somatostatin-dependent processes interested in induction of diabetes and acute pancreatitis [*Koerker D et al., 1974; Bra-*

tusch-Marrein P, Waldhäusl W, 1979; Kadowaki S et al., 1980; Alba-Roth J. et al., 1988]. Herewith the authors discuss not only central hypothalamic-pituitary-dependent functional loops, but also intrapancreatic somatostatin-dependent mechanisms in pathogenesis of abovementioned diseases associated with disturbance of endocrine and exocrine function of pancreas. In both cases, according to authors, the same mechanism is involved based on the reciprocal relationship of growth hormone (somatotropin) and somatostatin. Thus, particularly, in pathological conditions high concentration of somatostatin incoming from hypothalamus to hypophysis inhibit somatotropin secretion, which in physiological conditions stimulates synthesis of insulin by β-cells of Langerhans isles.

On the other hand, similar somatostatin-dependent process is involved in the pancreas, where *in situ* produced, i.e. by delta-cells of Langerhans isles; somatostatin simultaneously inhibits influence of endocrine and exocrine processes.

That is why directed activation of somatostatin synthesis processes in delta-cells of Langerhans isles in terms of injection of relatively high concentration of arginine into experimental animals, in relatively early stages of regional pathological process is accompanied with disturbance of cytoarchitectonics of pancreas, temporal activation of catabolic processes in the latter localized mostly in the acinar apparatus. It is not excluded, that high dose of arginine used by investigation team in modeling of acute pancreatitis does not directly inhibit the somatostatin synthesis process *in situ*, i.e. by delta-cells of insular apparatus of pancreas.

In the specific case other autonomous mechanism is involved, which is based on reciprocal relationship between intestinal melatonin and pancreatic somatostatin. Severe dystrophic processes occurred on the mucous membrane of lesser intestines, which, particularly, are expressed by inhibition of function of local melatonin-secretory cells, apparently, exclude inhibiting actions of melatonin on the somatostatin synthesis in pancreas.

It is also not excluded, that directed activation of delta-cells of pancreas, responsible for somatostatin synthesis, occurs in early stages of "arginine pancreatitis" process.

The role of free radicals, particularly oxygen-containing, in pathogenesis of many somatic diseases and extreme conditions is well known. Free radicals are products of aerobic metabolism and are found in almost all parenchymatous and stromal cells of organism of mammals [*Kaul N et al., 1993; Costa A et al., 1996; Dawson T, Dawson V, 1996*]. Particularly, high concentration of free radicals is detected in alimentary tract, especially in jejunum and ileum. At the same time, it is known that melatonin is a strong inhibitor of oxygen-containing radicals, and first of all NO [*Kvetnoĭ I et al., 1999*].

In this connection, on the arginine pancreatitis model it was found that in the mechanisms of induction of regional pathological process bacterial intestinal translocation processes were also involved which led to noticeable increase of activation of NO in endocrine apparatus of pancreas [*Bagdasaryan A, 2004*]. In this connection, in the same model of arginine diabetes, the processes of inhibition of melatonin synthesis in secretory cells of mucous membrane of lesser intestines mostly support the activation *in situ* free radical processes involved in the formation of bacterial translocation.

In this way, two autonomic melatonin-dependent mechanisms are involved in digestive organs in the experimentally induced "arginine pancreatitis".

The first one occurs in conditions of pathological processes in mucous membrane of lesser intestines, which results in disturbance of function of secretory cells producing melatonin. "Deficiency" of melatonin leads to disorders in microcirculatory system of the region, and activation *in situ* processes responsible for synthesis of free radicals, included NO. Especially both these factors, which currently are regarded to regional melatonin-dependent process, mostly cause the phenomenon of bacterial translocation of opportunistic gram-negative microorganisms of intestines.

The second one occurs in pancreas when melatonin synthesis is inhibited in the condition of arginine injection to experimental animals in the acinar apparatus.

The processes of inhibition of melatonin synthesis *in situ* should be considered as a "provoking" factor, which activates somatostatin synthesis by delta-cells of insular apparatus resulted in inhibition of activity of β-cells of Langerhans islets. The mechanisms of paracrine endocrine mutual regulation and mutual dependence in the endocrine apparatus, in specific case, occurred on the background

of expressed dystrophic changes mostly localized in pancreatic acini, where particularly the number of melatonin-positive cells noticeably decreased.

Based on the studies, in the context of available very informative literature data, a hypothesis has been made, according to which an important role should be given to extra-pineal melatonin and extra-hypothalamic somatostatin integrative functioning of digestive organs: pancreas and lesser intestines. It is about produced melatonin and somatostatin in pancreas and mucous membrane of lesser intestines.

Melatonin produced in secretory cells, supports balanced synthesis of insulin by β-cells of insular apparatus of pancreas in physiological functioning of organism. In normal conditions, melatonin produced in secretory cells of mucous membrane of lesser intestines, prevents the threat of development of bacterial translocation process leading to migration of opportunistic resident microorganisms from digestive tract into new econiche of macroorganism: parenchymatous organs, organs of immunogenesis.

Implementation of inhibiting effect of extra-pineal melatonin is assessed by its involvement in regulation of trans-capillary metabolism of mucous membrane of intestines, particularly coordination of processes responsible for free radical (including NO) synthesis by endotheliocytes of micro-vessels of mucous membrane of lesser intestines.

Somatostatin produced in delta-cells of insular apparatus of pancreas, supports balanced synthesis of insulin by β-cells in physiological functioning of mammals' organism. In this specific case the implementing effect of somatostatin is realized in a mediated way, through prevention of exposure on insular apparatus by "excessive" concentration of growth hormone: somatotropin.

It was hypothesised that in physiological functioning of organism, in the digestive system of mammals, autonomous paracrine melatonin- and somatostatin-dependent inter-hormonal functional loops are involved, coordinating, on the one hand, exocrine and endocrine functions of pancreas, on the other hand, providing regional endocrine and bacterial homeostasis in alimentary tract preventing by this bacterial translocation process development.\

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