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*Experimental Article*

# PUTRESCINE-DEPENDENT HORMONAL-TRANSMITTER MECHANISMS PROVIDING INCRETORY FUNCTION OF PANCREAS

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*Abstract*

*Determination of the role of polyamines (putrescine, spermidine and spermine) in the integrative activity of mammal organism is a subject for a broad discussion at present. At the same time, the putrescine-mediated mechanisms, interested in the implementation of incretory and excretory functions of pancreatic gland, are studied insufficiently.*

*The shifts in somatostatin content in blood serum and pancreatic gland were studied in the conditions of putrescine administration to intact animals similar to those in blood serum of higher mammals in various time intervals.*

*Authors discuss possible putrescine-dependent total and regional endocrine-mediated mechanisms providing the function of β-cells of pancreatic insular apparatus based on the analysis of conducted own researches and literary sources. From total mechanisms somatostatin and somatotropin of central genesis, which are relatively produced in hypothalamus and pituitary, play an important role. Due to the conducted enzyme immunoassay it was established, that exogenous putrescine, inserting to intact rats in extremely low concentrations maximally close to those revealed in blood serum or a series of mammals, leads to the decrease of somatostatin level in blood serum. Apparently, the function of β-cells of pancreas insular apparatus is activated on the background of somatostatin low level, and the effect of somatotropin on β-cells is indirectly implemented – by the activation of insulin-like growth factor-1 synthesis in the liver and twisted intestine.*

*Direct stimulating effect of putrescine on β-cells of Langerhans islets is not excluded, which is confirmed in analyzed literary sources of present article.*

*On the basis of conducted studies and literary data analysis it is hypothesized that putrescine plays a significant role in the formation of functional hormonal-mediator loop, the effect of which is implemented both on the level of brain central structures (hypothalamus and pituitary), and digestive system organs (pancreatic gland and intestinal tract) under the conditions of normal functioning of higher mammalians organism, produced in various organs and tissues.*

***Keywords:*** *putrescine, somatostatin, somatotropin, insulin-like growth factor, β-cells of pancreatic gland, hormonal-transmitter mechanisms.*

## Introduction

Biological effects of polyamines (putrescine, spermine, spermidine) are subjects for comprehensive study over the last fifty years. The role of putrescine, produced in various organs and tissues, is reviewed from qualitatively new positions in the activity of many integrative systems of organism, both in the norm and in case of multiple somatic diseases [*Flamigini F et al., 1986; 2007; Harris S et al., 2000; Mackintosh C et al., 2000; Tantini B et al., 2001; 2006; Zhao Y et al., 2007; Bordallo C et al., 2008; Zilfyan A et al., 2008; Avagyan S, 2009*].

Thus, particularly, the mechanisms of polyamines' modulating effect on β-cells of Langerhans islets of pancreatic gland, glycogen metabolism in liver, energy supply of parenchymal organs with glucose are the subject of a broad discussion

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[*Welsh N, Sjöholm A, 1988; Welsh N, 1990; Sjöholm A, 1993; 1996; Sjöholm A et al., 2001*].

Meanwhile, according to modern beliefs, a series of endogenously active compounds of hormonal and cytokine nature play an important role in the pathogenesis of digestive system diseases. First of all, these are somatostatin, somatotropin and insulin-like growth factor [*Lankisch P et al., 1977; Jaworek J et al., 2009; Li J et al., 2011; Sliwińska-Mossoń M et al., 2014*].

The obtained results of immunoenzymometric and immunomorphological studies, referring to the role of endogenous putrescine in the mechanisms of insulin-like growth factor-1 stimulation, synthesis of insulin in β-cells of pancreatic gland, metabolism of glucose in the parenchymal organs, were the subjects of a special debate in previous researches [*Avagyan S, 2009*].

However, the effect of putrescine on the processes of somatostatin synthesis in hypothalamus and digestive system organs wasn't studied.

Meanwhile, intrahypothalamic and extrahypothalamic somatostatin plays an extremely important role in the processes of insulin formation in pancreatic gland, both in normal conditions and in case of digestive system diseases: diabetes mellitus and diabetes insipidus, acute and chronic pancreatitis.

The aim of present study was the determination of putrescine-dependent mechanisms of pancreas' incretory apparatus modulation indirectly associated with its modulating effect on the processes of somatostatin and somatotropin synthesis.

## Material and methods

The objects of study were 75 white male rats with 130-150 *g* mass. The animals were divided into two groups: control and experimental. The control group was consisted of intact animals. Putrescine was intraperitoneally inserted to the animals of experimental group daily, for 3 days. Single dose of putrescine was $10^{-6}$ *mcg/ml*. Control group animals were intraperitoneally inserted only physiological saline of 1*mm* for 3 days, i.e. to the extent in which putrescine was dissolved for the administration to experimental animals. The animals were deducted from the experiment by decapitation in 24 hours and 4 days after the administration of the last dose of putrescine. Whereby, all necessary conditions presented by the Ethics Committee of Yerevan State Medical University during the work with laboratory animals, were taken into account. A serum was obtained in the process of decapitation, which was kept in the freezer at a temperature of 40°C in the first three days before the study.

Simultaneously, supernatants from homogenates of pancreatic gland were made according to a well-known scheme, presented in the previous study [*Avagyan S, 2009*]. The supernatants also were kept in the freezer. The serum and supernatants of animals from control and experimental groups were exposed to enzyme immunoassay on the subject of somatostatin determination. A kit "Rat-Somatostatin" of DRG International Inc. (USA) production was used. Somatostatin content was determined with the use of autoanalyzer Stat-Fax-2002 (USA). The hormone level was expressed in *pg/ml*.

Statistical analysis was conducted with the use of statistical software package SPSS (version 11.0), envisaged for Microsoft Windows (SPSS, Inc., Chicago, IL). The data are presented as mean values with average error (mean ± SEM). The correlation between the values was analyzed with the use of Student t-test. The comparison between the groups was carried out on the basis of t-test.

## Results

The results of conducted enzyme immunoassay are shown in the Table.

As the Table shows, significant changes of somatostatin level in blood serum occurred in 24 hours after the administration of the last, third injection of putrescine to experimental animals. Thus, the somatotropin content was lower than control level by 2.2 times during the mentioned period.

The level of somatostatin in blood serum was normalized in 4 days after the administration of the last dose of putrescine, i.e. practically it didn't differ from that of registered in blood serum of rats of control group. The enzyme immunoassay of supernatants prepared from homogenates of pancreatic gland on the subject of somatostatin determination was the subsequent stage of studies.

As seen from table, there weren't any significant changes in somatostatin content in pancreatic

TABLE.

Shifts in the content of somatostatin in blood serum and pancreatic gland under the conditions of putrescine administration to experimental rats

| Administration time | Somatostatin content in *pg/ml* (n=75) | |
|---|---|---|
| | Serum | Pancreas |
| Control group | 6.0±0.90 | 2.1±0.11 |
| In 24 hours | 2.7±0.27<br>0.005>p>0.0005 | 1.8±0.23<br>0.25>p>0.1 |
| In 4 days | 4.8±0.62<br>0.1>p>0.05 | 1.7±0.2<br>0.1>p>0.05 |

*NOTE: p – indices of experimental group in comparison with similar indices of control group.*

gland throughout the experiment, i.e. starting from first hours and to the end of 4 hours after the administration of the last – third dose of putrescine. Hormone indicators in both experimental groups practically didn't differ from those observed in blood serum of rats of the control group.

**Discussion**

It is necessary to specify one important question before the discussion of obtained results. The presented results of the study are not enough for the advancement of certain opinions about the role of putrescine mediated, somatostatin-dependent processes of insulin synthesis in β-cells of pancreatic insular apparatus. Meanwhile, the aspect of obtained results' discussion is considered to be quite expedient, because our previous scientific research results will be interpreted as a whole, where the biological effects of putrescine will be studied under the same conditions as those presented in the study [*Zilfyan A et al., 2008; Avagyan S, 2009*].

Thus, in particular, a series of factors were studied under the condition of putrescine administration: insulin content, glucoses, insulin-like growth factor-1 that are directly and/or indirectly presented as modulators of insulin synthesis in pancreatic insular apparatus according to multiple quite informative findings. Certainly, Obtained own data will be analyzed in the context with available quite informative findings in literature, affecting endocrine-transmitter mechanisms, participating in the secretory activity of pancreatic insular apparatus.

As the results of enzyme immunoassay showed, the content of somatostatin notably decreased in 24 hours after putrescine administration in blood serum of experimental animals. However, somatostatin content was defined in pancreatic gland within certain values. That's why it's not excluded, that three-stage administration of putrescine to intact animals was accompanied with the decrease of somatostatin synthesis in hypothalamus. It is established, that there is a reciprocal relationship between somatostatin and somatotropin, producing in certain brain structures. Apparently, the level of somatotropic hormone balanced by somatostatin, which, as you know, activates the processes of insulin synthesis by β-cells of pancreatic insular apparatus, is interfered under the conditions of putrescine administration.

Probably, putrescine plays a significant role in the formation of functional hormonal loop-somatostatin-somatotropin under the conditions of mammal organism's normal functioning, endogenously producing in various organs and tissues, the effect of which is realized on the level of brain central structures – hypothalamus and pituitary. Thereby, the mediated putrescine-dependent mechanism interested particularly in the activation of insulin synthesis by cells of insular apparatus of pancreatic, is not excluded.

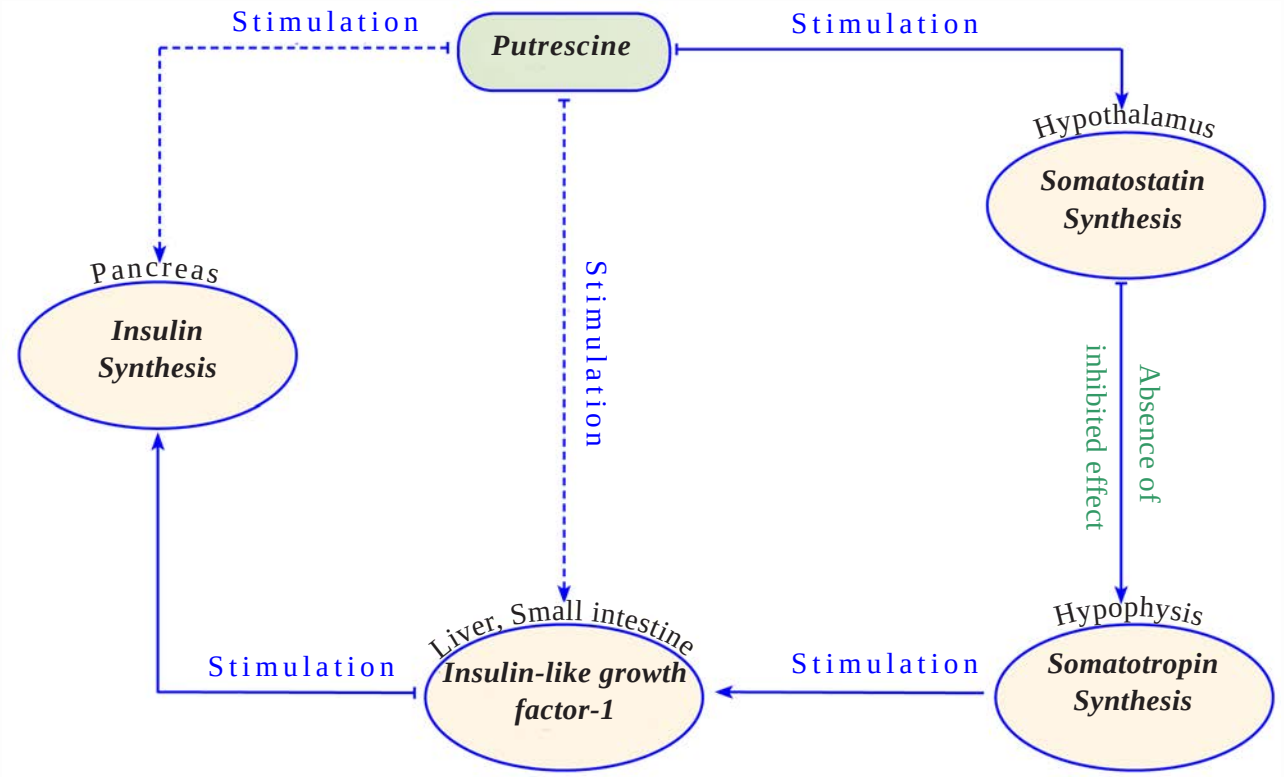
Direct effect of putrescine on incretory function of pancreatic gland is also allowed, because it is established, that putrescine has expressed stimulating influence on the processes of insulin synthesis in cultivated β-cells of insular apparatus according to a series of studies [*Welsh N, Sjöholm A, 1988; Welsh N, 1990; Sjöholm A, 1993; 1996; Sjöholm A et al., 2001*].

It is not excluded, that both mechanisms are involved in this certain case, as a result of which the processes of insulin synthesis in pancreatic gland are activated.

One more significant circumstance should also be mentioned. Thus, it is established, that biological effects of somatotropin on the background of somatostatin synthesis inhibition on incretory apparatus of pancreatic gland are implemented not by its direct impact on β-cells of Langerhans islets, but indirectly – in a way of insulin-like growth factor-1 activation, which resulted an increased syn-

***Scheme.***

Possible putrescine-dependent endocrine-transmitter mechanisms underlying on the basis of insulin synthesis in pancreatic gland




thesis of insulin in pancreatic gland [*Jaworek J et al., 2009; Li J et al., 2011*]. There is an opinion, according to which somatostatin also has direct inhibitory effect on β-cells of pancreatic gland [*Li J et al., 2011; Sliwińska-Mosson M et al., 2014*].

At the same time, according to previous studies [*Avagyan S, 2009*], it was established, that the administration of putrescine to intact animals is accompanied by transient increase of insulin-like growth factor-1 level in blood serum. That's why it is not excluded, that putrescine-dependent functional loop is also involved under the condition of the experiment – somatostatin-somatotropin-insulin-like growth factor-1, due to which the processes of insulin synthesis in pancreatic gland are activated. The direct impact of putrescine on the processes of insulin-like growth factor-1 synthesis in liver and twisted intestine is also allowed.

It is appropriate to present the whole cycle of conducted studies in terms of summarizing scheme.

Putrescine has a direct and indirect impact on the processes of insulin synthesis in pancreatic gland. The indirect impact is implemented by the cascade of hormonal changes in relevant neurohormonal brain structures: putrescine reduces somatostatin level in hypothalamus, which leads to the activation of functional loop of somatotropin-insulin-like growth factor-1 with further insulin-like growth factor-1 dependent activation of insulin producing function of pancreatic insular apparatus. The direct impact of putrescine on the processes of insulin-like growth factor-1 synthesis in parenchymal organs also isn't excluded. Certainly, the processes modulating incretory functions of pancreatic gland are not only putrescine-dependent. Endogenously active substances of metabolic, immune and endocrine genesis, wherein putrescine-dependent functional hormonal and cytokine factors are also of great importance, are interested in the realization of synthesis processes and inhibition of insulin by β-cells of pancreatic gland.

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