Calcitonin and Parathyrin are Glucoregulating Hormones

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Abstract

The comprehensive literature data and our findings about calcium-regulating hormones participant in the glucose metabolism is analyzed. It is showed calcitonin hyperglycemic effect and its mechanisms, established contra-insulin effect of calcitonin to insulin under the pre-receptor, cell level and liver. It is ascertainment the impairment of glucose metabolism under calcitonin - hyperglycemia, insulin resistance and glucose intolerance. It is showed the data of combative effect of calcitonin and calcium antagonists on glucose metabolism. It is discussed calcitonin-diabetogenic effect and the role of calcium antagonists in the correction of hyperglycemia and tissue's insulin resistance. It was revealed the effect of parathyrin on glucose, occurring in decreasing the glucose level and increases glucose tolerance. It is concluded about participant of calcium-regulating hormones in theregulation of glucose metabolism.

Keywords: Calcitonin; Parathyrin; Insulin; Glucose metabolism; Glucose tolerance; Glucoregulating hormone

Introduction

Calcitonin (CT) and parathyrin (PTH) are widely used in medical practice not only for the treatment of bone system diseases but for the treatment of a number of inner organs [1-7]. In case of it their possible effect on endocrine system, in part, carbohydrate metabolism, doesn’t take into account. In this connection on the basis of our data and comprehensive literature data the effect of calcium-regulating hormones on glucose metabolism was considered.

Calcitonin is a Stress Component

Intensification of CT secretion marks not only under the primary alterations of calcium metabolism, but and under some agents, not effecting immediately on calcium depot and the target-cells of hormone, for example, under stress-situations: under immobilizing stress in rats [8-10], childbirth [10], experimental muscle load (running on the treadmill) and in men’s serum, carrying out some muscle load on veloergometer [9,11,12], attacks of bronchial asthma [10], insulin hypoglycemia [13], alcohol influence [14]. Recently it was shown the intensification of pre-CT under the stress (multiple traumas) [15]. It is supposed that CT and low calcium level limit stress activation of hypothalamus-hypophysis-adrenal system and the expression of generaladaptationsyndrome and that, CT is a humoral component of stress [16]. The increasing of CT secretion and hypocalcemia evoked by it promote to limiting the stress-reaction. Besides that, a significant increasing of CT level and decreasing of calcemia arises only under the long stress [16]. In this opinion it should appreciate the increasing level of CT under the primary revealing manifest diabetes in man [17]. Presence of specific and non-specific organs and tissues, which CT occurs the effect causes its effects and allows consider it as a hormone of a wide spectrum action. In the present it is known non-metabolic: analgesic [18], vasodilating, hypotensive [19] and metabolic: anorexic and hyperglycemic effect of CT [20-23].

Calcitonin and Glucose Metabolism

It is well-known now the hyperglycemic effect of the preparations of salmon, pig CT [24,25] and CT-gene-related peptide [19]. Under one-time injection of exogenous CT (the preparation of pigCT-calcitrin) was revealed an expressive hypocalcemic and hyperglycemic effect in rats of all age groups, that testifies about the existence of the correlation between the neuro-endocrine regulation of calcium metabolism and the functional state of pancreas islet’s apparatus, which expression has some aging peculiarities. There are functional (immature, r=0,917, P<0,01), close (adult, r=0,834, P<0,02) and expressive (old rats, r=0,581, P<0,05) negative correlation was established between glucose and calcium level.

It is obviously, that the degree of hyperglycemia after one-time injection of CT in the rats of all age groups depended on the functional state of its islet’s apparatus [21]. The investigation of CT effect on the dynamics of glycaemia evoked glucose load per osn the rats of different age and sex groups also revealed the reliable increasing of initial blood glucose level and glucose intolerance, moreover, the males occurred more sensitive to this hormone action than the females [22]. It is established that CT didn’t effect on the glucose absorption in small intestine, but influenced on the main stages of the intermediate metabolism, intensifying the glycojenolis and insulin resistance of the peripheral tissues [26]. CT decreased insulin-stimulated glucose consumption by muscle and adipose tissue in vivo and in vitro [27].

In our previous investigations in rats [28,29] it was shown, that CT didn’t effect on initial insulin level, but slowed down it secretion under glucose-tolerance test, i.e., it is originated as though delaying of secret reaction of β-cells. Mechanism of CT effect on insulin secretion remains to be unknown. Possibly, hypocalcemia, CT-evoked, leads to the decreasing of intracellular calcium concentration in β-cells cytotol,
what, evidently, inhibit the leaving of secret granules and come to the delaying of insulin secretion. Moreover, it must be taken into account that CT leads to the decreasing of muscle and adipose tissue sensitivity to insulin [27]. In respect of CT effect on the glucagon level were received data about the decreasing of initial level and increasing its level under insulin hypoglycemia in rats [28]. Analogues data were marked and under inspection healthy persons and patients withinsulin-dependent diabetes [30]. Mechanism of inhibitory CT effect on glucagon secretion is unknown yet. Possible, CT effect is depended on the stimulation of Ca$^{2+}$-leaving from α-cells and intercellular translocation of Ga$^{2+}$[31]. The intensifying of glucagon secretion, induced CT, under insulin hypoglycemia, apparently, connected with hypocalcaemia, as far as it is established that the decreasing of Ca$^{2+}$ concentration leads to the increasing of glucagon removal from α-cells [32]. Further investigations will show, whether the increasing glucagon secretion, CT-induced against the background of hypoglycemia, take part in the realization of its diabetogenic action.

Mechanism of hyperglycemic effect of the preparations of CT is studied not enough. The results of our previous investigations allow consider that it is mediated both due to the inhibitory effect of CT on insulin secretion [28,29], the decreasing of glucose consumption by peripheral tissues [27] and due to the intensification of glycogenolysis process [26,33]. The interest to mechanisms of CT effect is explained also by the search of some means of management by this most important bio-regulator. The inhibition by calcium channel blockers (isoptin and nifedipin) hyperglycemic CT effect testifies about the participant of slow potential-depended L-type and chemo-sensitive calcium channels in this effect of hormone [34,35] and gives the basis to consider that calcium channel blockers therapy can be the method of correction of hyperglycemia and insulin-resistance of tissues [36]. Moreover, it is known that calcium channel blockers affect also other components of the metabolic syndrome, revealing athero-protective [37-39], hypotensive [40], lipolitic [41,42], anti-anginal, neuro-protective action. It is shown that potential-managed ion channels are effective target of cyto-pharmacological regulation of functional state [43]. On the basis of this data the concept of directed effect at Ca$^{2+}$-mechanisms of endocrine system as possible way of drug therapy is formed lately.

**Contra-Insulin Effect of Calcitonin**

As gearing data testify CT reveals anti-insulin effect on glucose metabolism [44,45]. It is known, insulin antagonists are the subjects which are capable or direct inhibit insulin action or destroy its molecule or affect the contrary of insulin the metabolic effect. From these conceptions, the antagonism of CT effect to insulin is established concerning to tissues-target for insulin: liver, muscle and adipose tissue. It is known, that the disturbance of glucose homeostasis can arise on the pre-receptor (the alteration of the structure and function of pancreas and/or insulin), cell level (the disturbance of the sensitivity to insulin of adipose and muscle tissue) and on theliver level (the increasing of glucose production) [46]. Therefore, CT provides the opposite action to insulin effect on glucose homeostasis on the pre-receptor level (inhibits secretion and biological insulin effect), on cell level (decreases the sensitivity to insulin of muscle and adipose tissue) and on the liver level (intensifies glycogenolysis and glycconeogenesis) and hyperglycemia, insulin-resistance and glucose intolerance are as the result. As it is known, glucose intolerance under glucose-tolerance test is one of clinical symptoms of insulin-resistance. In accordance with the concept of Reaven [47], insulin resistance is a basic component of the metabolic syndrome [46], along with obesity, arterial hypertension, dyslipidemia (elevated triglycerides and low high-density lipoprotein cholesterol), and impaired glucose metabolism (high fasting glucose, impaired glucose tolerance). The progression of the metabolic syndrome leads to the development of prediabetes, diabetes, cardiovascular disease, nonalcoholic fatty liver disease, gout, syndrome of hyperandrogenism (polycystic ovaries) and cancer. According to some authors [48], decreased tissue sensitivity to insulin is an important link in the pathogenesis of diabetes, and factors, causing a decline in insulin sensitivity, can be considered as risk factors for the incidence of diabetes. So, in our opinion, one can suppose, that concerning to glucose CT under definite conditions can be as a ‘risk factor’ of the development of the metabolic syndrome and diabetes mellitus. The analysis about the antagonistic effect of CT concerning to insulin allow think it is a contra-insulin hormone and suppose about its diabetogenic action.

**Diabetogenic Effect of Calcitonin**

There is no single opinion about CT diabetogenic effect inliteraturedata, but fact data are rather contradictory [49,50]. Clinical observations for the patients with Paget’s disease and a long-time CT treatment are not identical. Gattereau et al. [50] describe the hyperglycemic effect of synthetic salmon CT and the existence of a strong reverse correlation between plasma calcium level and glucose level, and others [49] didn’t reveal the symptoms of diabetes mellitus in patients with Paget’s disease even after 8 years of CT treatment. These data allow suppose that diabetic effect of CT reveals not always, but, apparently, under the changing of the initial state of pancreas β-cells, especially under their intensive activity. It is admitted suppose that CT, long-lasting high concentration in blood, and especially under unfavorable conditions (obesity, age, aggravating heredity et al.) can act on insulin receptors indirect due to the metabolic processes and induce the development of the relative insulin deficiency caused by the decreasing of its biological activity. In our investigations it was shown glucose intolerance in children with the 1st degree obesity [25] and also more expressive glucose intolerance in adult and old rats under glucose tolerance test against the background of CT injection [22].

One should mean and the circumstance that under the chronic increasing of CT content in blood (both as a result of the treatment of this hormone and in case of CT-produced tumors) organs-target adapted to CT and stop to react on it. Concerning to β-cells it means that they stop to answer by disturbance of its function on the increasing CT level in serum. But this adaptation is reverse: after the break of CT treatment the initial reaction of organ-target to this hormone restores [51].

Besides, the increasing secretion of CT occurs in stress situations, in this connection hypercalcitoninemia arises [52]. In these conditions endogenous CT can make the same effect on the regulation of carbohydrate metabolism as exogenous injections of hormone.

**Parathyrinand Glucose Metabolism**

A number of investigations are showed that PTHactivates Ca$^{2+}$-entering in the cells of organs, not being its direct targets. PTHeffect on glucose metabolism practically is unstudied. The single information about the increasing of PTHlevel in blood serum under diabetes mellitus [17] and the metabolic syndrome [53] is available.
Moreover, it is established the increasing of Ca and P excretion with the urine under the metabolic syndrome, what positively correlated with the glycermia and the insulin level in blood [53] and the intensification of bone resorption, that it is connected with the disturbance of Ca-P metabolism and the secretion of calcium-regulating hormones [54]. On the other hand, the disturbances of carbohydrate and lipid metabolism were revealed under the primary hyperparathyriosis [55].

There are some data about the stimulating effect of hypercalcaemia, induced by introducing of Ca-salts, which improved the assimilation of intra-vein glucose injection and increased the concentration of immunoreactive serum insulin [56]. It allowed suppose about the presence of PTH effect on the islet’s apparatus of pancreas.

It was showed the decreasing of the blood glucose level after one-time injection of parathyroiodin (the preparation of bull PTH), which caused by hypercalcaemia, that confirms in tests with the calcium lactat load [57]. Besides, there is a close negative correlation established between glucose and calcium level ($r = -0.813$, $P<0.02$).

It is known that hypercalcaemia induces the increasing of insulin secretion [58,59]. Thereby, a special interest is the data about the decreasing of initial glucose level and the intensification of alimentary secretion [58,59]. Thereby, a special interest is the data about the decreasing of initial glucose level and the intensification of alimentary secretion [58,59].

Correlation of calcium and glucose metabolism

It is rather interesting to note that such glucose-increasing hormones as glucagons, ACTH, STH, gluco-corticoids, thyroxin also occur and hypocalcaemic effect, i.e. as CT they take part in the regulation of calcium and glucose metabolism, that is an additional confirmation of the functional correlation of calcium and carbohydrate metabolism.

The establishment of a functional negative correlation between glucose level and the total calcium content after CT and PTH injection testifies about the close interconnection of calcium and glucose metabolism. With respect to interconnection of calcium-regulating hormones and its effect on glucose and calcium metabolism it can consider that under in vivo the effects of CT and PTH can be, in the known degree, the result of changing of circulating Ca$^{2+}$, in vitro indeed they must consider as the result of direct hormone effect. In other words, in the different cells not having a specialized receptors of CT and PTH occur Ca$^{2+}$-dependent processes subordinated its regulating effects.

Concerning to inter-correlation of the effects of calcium-regulating hormones on glucose metabolism one can suppose that, under hypercalcitoninemia and, correspondently, hypercalcaemia, PTH secretion intensifies, which, in one’s turn, increases calcium level in blood serum, consequence of it there is the increasing of insulin secretion by pancreas β-cells. It is established, that hypercalcaemia [59] and the increasing of intercellular Ca$^{2+}$ concentration take the important role in insulin secretion by pancreas β-cells [58]. CT, however, inhibits insulin secretion [28,29]. In addition, CT increases glucagons secretion, apparently, as it is mentioned above, due to the decreasing of the total calcium content in blood serum. Apparently, by this way a reciprocal interrelations between CT and PTH secretion and their effect on glucose and calcium metabolism occur, which reveals due to their modulating effect on insulin and glucagon secretion. Therefore, PTH acts as insulin agonist and CT— as antagonist.

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References


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