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Calcitonin Participant in the Development of Insulin Resistance

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ABSTRACT

The review contains contemporary literature data about calcitonin role in the development of insulin resistance and its potential role in the pathogenesis of carbohydrate metabolism disturbances. Analogues disturbances revealed under diabetes mellitus and under calcitonin treatment are considered. Literature data about hormone diabetogenicity are discussed. The analysis of experimental and literature data testifies that calcitonin under unfavorable conditions (age, obesity, stress) against the background of the decreasing of functional activity of insular apparatus can lead to the development of metabolic syndrome and diabetes mellitus. It is shown that calcium channel blockers inhibit calcitonin effect leads to glucose intolerance and decreases tissue insulin sensitivity. In this connection a question about direct influence on calcium mechanisms of endocrine system as possible method of drug therapy is discussed.

1. INTRODUCTION

Fifty five years, having past after the discovery of thyroid gland hormone—calcitonin (CT), have brought a lot of contradictory facts and interpretations. The main action of CT is the decreasing of calcium serum concentration, mainly due to the calcium sediment in bones and reduction of bone tissue resorption. However, biological significance of CT for mammals, including man, remains to an end unknown. On the one hand, there is no doubt about hypocalcemic, hyperglycemic and analgetic action of CT, on the other hand, CT role in glucose metabolism regulation isn't completely clear. Besides, the disturbances, which arise in organism under the excess or deficiency of mature CT, are not detected till now. Lately some new facts of CT effect on carbohydrate metabolism, enlarging the notions about its physiological role, which significance in organism, apparently, much more than it is suggested yet recently [1].

2. CALCITONIN AND INSULIN RESISTANCE

Insulin resistance (IR) is the reducing of biological effects (glucose assimilation) in tissues and organs to the answer for insulin action on the specific cell receptors. At present there are more than 40 diseases, under which IR develops, are known. Some reasons of IR development can be stresses, Mg deficiency, hypodynamia, alcohol excess and the increasing of contra-insular hormones level. The enhancing level of contra-insular hormones pays the especial attention. As far as we think, that CT for its effect on glucose homeostasis can regard to contra-insular hormones [2, 3], so, hypercalcitoninemia, induced by stress influence [4] or in case of CT treatment, under the unfavorable conditions can lead to the development of IR. We'll consider CT participant in the development of IR in brief.

Three levels of IR. IR can develop on *pre-receptor level*: disorder of pancreas β-cell function; *cell level*: decreasing of tissue insulin sensitivity; *liver level*: increasing of glucose production. As it is known, ß-cell function, secreting insulin, especially clear reveals under the glucose-tolerant test. The sensitivity of ß-cells to glucose is most important quantitative parameter of their functional capacity [5]. CT inhibits insulin secretion against the background of glucose load *per os* and provokes glucose intolerance [3], *i.e. promotes to the development of IR on the pre-receptor level.* The mechanism of CT effects on insulin secretion remains unclear. It can be hypothesized that CT-induced hypocalcemia reduces intracellular Ca^{2+} concentration in β-cell cytosol, decelerates the release of secretory granules localized in microfilament network near the cell membrane [6], thus delaying insulin secretion during GTT. It can be hypothesized that this specific feature of insulin secretion under the effect of CT determines the previously described impairment of alimentary hyperglycemia.

A lot of drugs get worse insulin secretion, and some of them induce a toxic damage of pancreas β-cells. So, it is established, that thyroxin in high doses induces apoptosis of pancreas β-cells in rats and, that thyroxin effect reverse. In this connection, it is thought, that hyperthyroidism can accompany by the strengthening of β-cells apoptosis, leading to the decreasing of basal insulin level and its secretion under glucose effect [7]. It is interesting to note, that CT treatment of rats during 20 days induce the increasing of blood thyroid hormones concentration [8]. So, one may suppose still more mechanism, by which CT can get worse functional state of pancreas β-cells. Apparently, it lies in that, CT by virtue of increasing of thyroid hormones concentration, which is capable to induce apoptosis of β-cells, can indirect reduce β-cells activity.

Glucose level change under the per-oral test to glucose tolerance is the result of peripheral glucose utilization and its production in liver [9]. Peripheral glucose utilization testifies about tissue insulin sensitivity. Insulin induces translocation of glucose transporters GLUT-4 from intracellular depots to the plasma membrane, which leads to increased glucose consumption by the muscle and adipose tissues. The disturbance of insulin capacity to induce translocation of own glucose transporters GLUT-4 from intracellular depot to the plasma membrane leads to IR and the development of diabetes mellitus 2 type [10]. CT reduces the sensitivity of the muscle and adipose tissues to insulin in experiments *in vivo* and *in vitro* [11], *i.e. promotes the development of IR on the cell level.* The following mechanism of this non-specific action of CT can be hypothesized. CT acting on non-specific receptors through Ca^{2+}-dependent processes enhances Ca^{2+} entry through L-type Ca^{2+} channels, thus increasing intracellular Ca^{2+} concentration, and triggers the Ca^{2+} release from depots that inhibits insulin-stimulated mobilization of GLUT-4 from intracellular depots to the plasma membranes.

CT increases glucose level in blood (hyperglycemic effect). The mechanism of hyperglycemic effects of CT preparations is poorly studied; previous findings suggest that they are related to inhibitory effects of CT on insulin secretion and glucose utilization by peripheral tissues and activation of glycogenolysis processes [12]. As a result glucose production stimulates in liver. CT reveals hyperglycemic and glycogenolytic effect due to the intensifying of the processes of glycogenolysis and gluconeogenesis, *i.e.* CT *promotes the development of IR on the liver level.*

Thus, CT participates in the development of IR on the pre-receptor, cell and liver levels.

Insulin antagonists in the development of IR. Besides, one of the reasons of the pre-receptor type IR is the presence in circulation insulin antagonists, which can be hormonal and non-hormonal nature. To

hormonal antagonist attribute to glucagon, corticosteroids, catecholamines, STH and other factors, they are contra-insular ones regarding to mechanism action on some metabolic processes. According to insulin action their antagonism reveals and on the level of insulin-receptor system. In this connection one should note, that CT increases the content of insulin inhibitors, leading to the decreasing of its biological activity. So, STH, catecholamines and cortisol levels in blood increase under the effect of CT [13, 14], *i.e.* CT also indirect can promote to the development of IR. These data testify about the significance of stress and contra-insular hormones in the development of IR.

To *non-hormonal insulin antagonists* attribute to antibodies to insulin and antibodies to insulin receptors, ketone bodies, free fatty acids, sin albumin. It is considered that free fatty acids play an important role on the early stages of IR development [15], and enhanced triglycerides level promotes to the development of IR [16]. A clear positive correlation between the increasing of free fatty acids and triglycerides concentration in blood and the degree of resistance to insulin in muscle and adipose tissue is revealed [15]. Free fatty acids are considered as a new marker of IR [17]. The investigations of the last years were shown that fatty acids inhibit insulin-stimulated glucose transport in muscle cells [18]. It is also established, that chronic increasing of free fatty acids in serum leads to IR development [15] and that fatty acids induce IR of man skeletal muscles due to the defects of insulin-dependent glucose transportation [18]. Enhanced free fatty acids level reveals the direct metotoxical effect on the secretory function of pancreas β-cells and decreases insulin-dependent glucose utilization by muscle cells, resulting peripheral IR develops. CT increases the level of free fatty acids [19] and this way also promotes to IR development.

CT decreases C-peptide level in blood [20], it testifies about the increasing of proinsulin concentration—less active form of insulin.

Ca^{2+} plays the definite role not only in secretion, but and in realization of insulin action. According to the obtained data *in vitro*, Ca^{2+} increases insulin receptor activity in rat's adipose, as a result the dissociation hormone with cell membrane reduces and, so, the effectiveness of hormone action enhances [21]. Indirect one may suppose that CT, decreasing Ca^{2+} level, can reduce insulin receptor activity. This fact is worth of attention as far as it is thought that IR develops due to the decreasing of amount of receptors to insulin and defects of insulin-dependent glucose transportation [22].

IR in the development of diseases. In accordance with the concept of G.M. Reaven [23], IR is a basic component of the metabolic syndrome [24], along with obesity, arterial hypertension, dyslipidemia (elevated triglycerides and low high-density lipoprotein cholesterol), and impared 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. It is known also, that firm IR reveals by glucose intolerance and, finally, leads to the formation of diabetes mellitus 2 type. Some patients with low progressive autoimmune diabetes have the symptoms of metabolic syndrome and peripheral IR at that [25]. In this connection it is interesting to note, that in patients with diabetes mellitus 2 type the risk of the development of micro-vascular complications determines not only chronic hyperglycemia, but and a number of metabolic syndrome components [26].

It is also known, that diabetes mellitus accompanies by the osteoporosis development. At that time it is established, that glucocorticoids treatment during 6 months can lead to the development of osteoporosis—a most often form of osteoporosis, induced by the drugs [27]. It is thought, that CT deficiency can serve as a factor in osteoporosis development [28]. One can suppose that in the pathogenesis of osteoporosis under diabetes mellitus participate both calcium-regulating hormones and glucocorticoids.

Conclusion. Thus, these data allow conclude, that CT participant in IR development reveals on the different levels: pre-receptor—effecting on the functional state of β-cells, direct—inhibits insulin secretion, indirect—increases thyroid hormone level, inducing apoptosis of β-cells, stimulates hormonal secretion (STH, cortisol, catecholamines) and non-hormonal (free fatty acids) antagonists of insulin, reducing the activity of insulin receptors, resulting is the reduction of β-cells action; cell level—decreasing insulin sensitivity of muscle and adipose tissue and preventing glucose assimilation via disturbance of glucose transporters GLUT-4 translocation on cell membrane; liver level—increasing glucose production due to the

intensification of glycogenolysis and gluconeogenesis processes.

The data analysis about antagonistic CT action concerning to insulin allows suppose about diabetogenity of hormone.

3. DIABETOGENIC EFFECT OF CALCITONIN

It is known some cases of disorders, connecting with the excessive secretion or exogenic treatment of hormones-antagonists of insulin, leading to the development of diabetes mellitus. So, steroid diabetes can arise under the hyper-secretion of glucocorticoids or their long-lasting treatment as drug and doesn't arise in case of hyper-secretion of other steroid hormones, such as mineral-corticoids or sex hormones, which occurs non-significant effect on carbohydrate metabolism. As to CT, there is no single opinion about CT diabetogenic effect in literature data, but fact data are rather contradictory [29, 30]. The suggestion about CT diabetogenicity was said as far back as in 1983 [31]. However, clinical observations for the patients with Paget's disease, receiving a long-time CT treatment, are not identical. Some authors [30] 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 [29] 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.

4. CALCITONIN EXCESS CAN PROMOTE TO THE DEVELOPMENT OF METABOLIC SYNDROME AND DIABETES MELLITUS UNDER UNFAVORABLE CONDITIONS

It was interesting to research CT effect on glucose homeostasis under the alteration of pancreas functional state, for example, under obesity and in elderly age, too.

It is admitted to 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 view of that, the results of the examinations *of children-teenagers* 10 - 14 *years old with the* 1-*st degree obesity and negative calcium balance,* receiving one-time injection of CT [32], are worse of attention. The establishment of glucose intolerance under CT effect in glucose tolerance test in children one may consider as an example of negative CT influence on glucose homeostasis under unfavorable conditions, in this case, obesity. Obesity is not only risk factor of the development of mellitus type II diabetes, but and its complications [33]. In children with obesity, metabolic disorders were identified, such as IR and dyslipidemia of an atherogenic nature, which increase with obesity [34]; they have a violated metabolism of glucose, lipids, uric acid [35], elevated levels of insulin, C-peptide [36], and free fatty acids in the blood plasma [37]. According to Kravets E.B. opinion [38], elevated basal insulin level and C-peptide are connected with the strengthening pancreas insular apparatus, what testify about the weakening of efficiency of endogenous insulin effect on peripheral.

In our previous investigations [39] more marked impaired glucose tolerance were revealed *in mature and old rats* during glucose tolerant test against the background of CT. As it is known, the state of the insular apparatus of the pancreas suffers significant changes with age. With the aging of an organism, a relative insulin deficiency develops, caused, despite of high blood insulin content, by decreasing its biological activity. Besides the reduction of insulin-stimulating glucose transport in the elderly persons with normal reaction on oral glucose tolerant test was established [40]. On this background one-time injection of CT in mature and old animals induced more marked glucose intolerance, *i.e.* a negative influence of CT on glucose homeostasis revealed and in animals in mature and old age, when there are the changing of initial state of pancreas β-cells, *i.e.* under its intense activity.

These data indicate that one-time CT injection led to the decreasing of functional state of β-cells under the obesity and in elderly age. In this, it is important to note, that the disturbance of β-cells function, leading to IR, was revealed in mice with the model of mellitus type II diabetes [41]. As it is known, desen-

tization of insulin secretion is an important stage of the manifestation of mellitus type II diabetes [42]. So, under unfavorable conditions, namely, under obesity and also in elderly age, CT can promote to the development of the disturbances of carbohydrate metabolism. It should be noted, that in base of the disturbances of carbohydrate metabolism, such as, metabolic syndrome, diabetes mellitus, and also obesity, there are common metabolic disorders—glucose intolerance, IR and hyperinsulinemia.

Besides, the leading role in the development of metabolic syndrome and diabetes mellitus is given to chronic stress. In this, one should mean, that enhanced CT secretion meets under stress situations, as a result, a hypercalcitoninemia arises [4]. In these situations endogenous CT happen the same effect on the regulation of carbohydrate metabolism as exogenous injections of hormone preparations.

Previously we considered the question about the reduction of tissue insulin sensitivity under CT effect [11]. According to Baranov V.G. [43], 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 homeostasis CT under definite conditions (age, aggravating heredity, obesity, stress,) can promote to the development of metabolic syndrome and diabetes mellitus, *i.e.* CT can consider as a "risk factor" of diabetes mellitus. Besides, as Lasyi V.P. [44] thinks, pathological shifts in carbohydrate metabolism, in one's turn, are caused by the disturbances of insulin secretion. Our investigations was *shown the inhibition of insulin secretion under CT* [3], as it is known, insulin deficiency leads to the development of diabetes mellitus. So long as, insulin effect can be modify by CT action, so also one may think about CT potential role in the pathogenesis of the disturbances of carbohydrate metabolism.

Above-stated allow conclude, that diabetogenic CT effect depends on dose treatment, and also initial state of β-cells. It isn't ruled out, that clinic cases of diabetes mellitus arise only under the combination CT effect and latent defective of β-cells (latent diabetes). In this, it is interesting to note, that in patients with primary manifested diabetes the content of immune CT and parathyrine in blood increase, but in compensation phase of disease under insulin therapy the tendency to normal level of these hormones was observed [45].

We consider, that CT, inhibiting insulin secretion, inducing IR and glucose intolerance, and as a matter of fact, being, in our opinion, contra-insular hormone, can promote to the development of metabolic syndrome and diabetes mellitus, as it happens, for example, in case of hypersecretion of glucocorticoids or its long-lasting therapy.

Preparations of CT effectively use for the treatment of hypercalcemia states (hyperparathyroidism, intoxication of vitamin D), osteoporosis and osteoarthritis, sport trauma, for the acceleration of healing of bone fractures, anaesthetization under metastasis in bone tissue, phantom pain, migraine, in dentistry, psychiatry, under the treatment of back pains, disease of stomach and duodenal ulcer in present time [1]. Contra-indications for CT treatment are hypocalcaemia, pregnancy, lactation. One should have in mind that circumstance that under chronic increasing of CT in blood (both in the result of treatment and in case of CT-produced tumors) target-organs adapted to CT and stop to answer by the disorder of its function for the increasing of serum CT level. But this adaptation is reverse: after the break in CT treatment the initial reaction of target-organ on this hormone restores [31].

These arguments of CT participant under unfavorable conditions in IR development have extremely important significance for the elucidation of origin mechanisms of metabolic syndrome, connected both with hyperinsulinemia and glucose intolerance, and obesity.

The discussed data about CT participant in the regulation of glucose metabolism indicate about contra-insular character its action, enlarge the conception about its physiological role and allow recommend to take into account its effect on glucose metabolism under its treatment in clinic practice.

5. METABOLIC DISORDERS UNDER DIABETES MELLITUS AND UNDER CALCITONIN TREATMENT

Metabolic disorders, induced by CT, are observed and under diabetes mellitus. This fact is worthy of

special attention. So, a significant increasing of LDG activity was found under diabetes [46] and in pre-diabetic state and tendency to diabetes [47], and also in our investigations after CT treatment to rats [12].

The enhancement of free fatty acids level was noted against the background of CT injection [19] and in patients with insulin-dependent diabetes on an empty stomach and after receiving of food [48].

It should be noted and the appearance of anti-bodies to CT in blood in rats under alloxan diabetes, which marks only under high blood glucose level. A correlation between blood glucose level and anti-bodies to CT was found [49]. The authors think that the appearance of auto-anti-bodies to CT serves as a pathogenetic factor of the development of hyperglycemia under alloxan diabetes.

6. CALCIUM CHANNEL BLOCKERS IMPROVE INSULIN RESISTANCE

In present time a many-promised tendency in the investigations of the mechanisms of the functioning of excitable cells is the combination of physiological and bio-physical methods with using of pharmacological drugs.

According to Kosovsky M.I.'s opinion [50], there is a system of insulin sensitivity regulation in organism, which reacting both on the different physiological and pathological changing, and on pharmacological effects. A reverse decreasing of the secrete answer of β-cells arises in the result of long-lasting effect of numbers of stimulus: glucose (the main physiological stimulator), free fatty acids, all pharmacological stimulators, induced depolarization and enters Ca^{2+} into the cells. Many pharmacological drugs, which are capable to interrelate with the structures of ions channels and installed in surface membrane, can influence on the character of their single or multiple rhythmical work, alter the rest potential of cells, synaptic and rhythm-conducting potentials, the parameters of action potential, neuronal and muscle membranes, and, consequently, to regulate their activity in organism.

The interest to the mechanisms of CT effect on glucose homeostasis is explained also by the search of some means of management by this most important bio-regulator. In this point of view the data of studying the interaction of CT and calcium channel blockers (CCB) in plan of the analysis of possible mechanisms of hormone action attract attention. In experiments *in vivo* and *in vitro*, it was shown that isoptin blocked the inhibiting effect of CT and Bay-K 8644 *in vitro*, on the contrary, intensified the inhibiting effect of CT on insulin-stimulated glucose consumption by muscle and adipose tissue [11]. Isoptin, the blocker of slow voltage-dependent L-type Ca^{2+} channels, reduces Ca^{2+} transport and Bay-K 8644, L-type Ca^{2+} channels agonist, increases Ca^{2+} transport across the sarcolemma. Modulation of the inhibitory effect of CT on insulin-stimulated glucose consumption in the muscle and adipose tissue by isoptin and Bay-K-8644 indicates that Ca^{2+} ions and L-type Ca^{2+} channels participate in the process. After binding to the receptor, insulin induces various cell responses, including Ca^{2+} influx into the cytoplasm and amino acid and sugar consumption. It is known, that Ca^{2+} channels were revealed in skeletal muscles, liver, pancreas, neuro-endocrine tissue, brain, and smooth muscles of vertebrates and other tissues [51] and in human adipocytes [52]. Intracellular Ca^{2+} plays a key role in metabolic disorders associated with obesity and insulin resistance [53]. According to some authors, endogenous Ca^{2+} can be involved in the development of diabetes mellitus via decreased insulin sensitivity [54]. Moreover, disorders in Ca-P metabolism were revealed in patients with diabetes mellitus type I [55], and disorders in cell Ca^{2+} homeostasis were revealed in skeletal, cardiac muscles, erythrocytes, liver, adipocytes, and pancreatic β-cells of patients with diabetes mellitus type 2 [56, 57]; negative Ca^{2+} balance was observed in 6-16-year-old children with diabetes mellitus type 1 [55, 58, 59]. It is established that the alterations of [Ca2^{+}]i concentration in early stages of diabetes mellitus can play a causal role in the reduction of hemodynamic, induced by the slowing heard work [60]. Ward D. *et al.* [61] established the increasing of calcium excretion with urine in rats with streptozotocin diabetes mellitus.

In our previous studies we have shown that isoptin, reducing the concentration of intracellular Ca^{2+}, blocks the inhibitory effect of CT on insulin-stimulated glucose uptake by muscle and adipose tissue, probably, due to higher levels of glucose transporters GLUT-4, resulting in increased glucose uptake by

peripheral tissues, thereby preventing the development of insulin resistance [11]. These data are found the verification in literature. Thus, nifedipin (calcium channel blocker) therapy not only promotes to the decreasing of arterial pressure, but and improves IR in the elderly patients with hypertension [62]. This fact is worth of attention and in connection with that the reduction of GLUT-4 content in myocardium sarcoplasm was discovered under diabetes mellitus [63].

There is some information about metabolic neutrality CCB [64-67]. It is established, that CCB—isoptin and nifedipin, reducing total calcium level in blood serum, didn't occur reliable effect on glucose level and at the same time inhibited hyperglycemic effect of CT under their combinative treatment, abolished glucose intolerance, induced by CT injection, during glucose tolerant test [68] and prevented the development of IR [11]. It is supposed that CCB therapy can be correction method of hyperglycemia and tissue IR [69].

The ability of CCB completely to abolish the hyperglycemic effect of CT testifies about that these types of Ca^{2+} channels (slow voltage-dependent L-type and chemo-sensitive) take part in the realization of this hormone action. In this, it is logically to assume that, the blocking of Ca^{2+} channels of membrane of non-specific organs by CCB, decreasing Ca^{2+} transport through sarcoplasm cell membrane, leads to the inactivation of the mechanisms, which are in base of hyperglycemic CT effect. Apparently, CT, revealing its effect on non-specific receptors via calcium-dependent processes, enhances Ca^{2+} entry via L-type Ca^{2+}-channels thus increasing the intracellular Ca^{2+} concentration. As it is known, excessive Ca^{2+} entry or its impaired removal from the cell, are accompanied by impairment of intrinsic cell functions. Thus, intracellular Ca^{2+} plays a key role in the development of a range of pathologies (hypertension, cardiac arrhythmia, diabetes mellitus, encephalopathy, dementia, and others), and also can accelerate aging process. So, the metabolic effect of CCB is concluded in their effect on glucose utilization on cell level due to the reducing of intracellular Ca^{2+} content. Probably, this mechanism can underlie the inhibitory effect of CCB on the hyperglycemic effect of CT.

Thus, these data, that CCB provoke the improvement of IR and glucose tolerance, induced by CT injection, testify about the drawing of Ca^{2+}—mechanisms into these processes and about that CCB can further to the correction of hyperglycemia and tissue IR. It is known also, that CCB effect and on other components of metabolic syndrome, revealing athero-protective [70], hypotension [71], lipolytic [72], antianginal, neuro-protective action.

The understanding of cell mechanisms of IR allows developing new method of aim-tendency therapy of metabolic syndrome and diabetes mellitus II type. Calcium channels (both potassium and sodium) are regulated and modulated by hormones, neurotransmitters and proteins. In recent time there are some conceptions about cyto-, membrane- and channelo-pathies begin to develop [73]. In the connection that it is established the important role of Ca^{2+}-channels L-type in the regulation of glucose-stimulated insulin secretion by β-cells [74, 75] and, that during the development of diabetes mellitus in rats *Zuker* occur the decreasing of expression of mRNA C-and D-isoforms α_1-subunits potential-dependent Ca^{2+}-channels L-type in β-cells their pancreas, what correlates with the lowering of Ca^{2+}-current L-type (I_{Ca}), it is logically to suppose about the role of Ca^{2+}-channels L-type in insulin secrete answer on glucose, in its disturbances under diabetes mellitus and methods of its correction. Ion channels are considered as disease targets. It is the subject of discussions last year [69, 75]. It was shown, that voltage-controllable ion channels are effective target of cyto-pharmacological regulation of the functional state [73]. The idea of direct influence on Ca^{2+}-mechanisms of endocrine system as possible method of drug therapy forms on the base of these data last years.

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