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Mini Review

Hyperglycemia: Calcitonin Significance

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Abstract

The article represents the generalizing data for the studying of calcitonin effect on glucose metabolism. It was revealed its hyperglycemic, contra-insular effect, reducing tissue insulin sensitivity, glucose intolerance, participant in the development of insulin resistance. It was established that calcium channel blockers completely to abolish the hyperglycemic and inhibiting effect of CT on insulin-stimulated glucose consumption by the muscle and adipose tissues, preventing the development of insulin resistance. These data allow recommend to take into account CT effect on glucose metabolism under its treatment in clinic practice.

Keywords: Calcitonin; Glucose Metabolism; Hyperglycemia; Contra-Insular Effect; Insulin Resistance; Glucose Intolerance; Calcium Channel Blocker

Introduction

In man and mammals Calcitonin (CT) produces by parafollicular cells of thyroid gland, in birds and lower Vertebrata – in ultimobranhial glands. Parafollicular, or light, cells (C-cells are still called them), which differed hystologicaly and citochemistry from follicular ones, secreting thyroxin, were described by E.C. Baber yet in 1876. However CT was discovered only in 1962 by D.H. Copp and B. Cheney. Fifty eight years, having past after the discovery of 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, bhyperglycemic 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]. We'll consider and generalize some our data for the studying of CT effect on glucose metabolism in brief.

Calcitonin Effect on Glucose Metabolism

It is established that CT is a gluco-regulating [2] and contra-insular hormone [3], reducing tissue sensitivity to insulin [4]. As a result of its effect on glucose metabolism is hyperglycemia, insulin resistance and glucose intolerance. It was interesting to research the mechanism of these effects of CT.

Hyperglycemia

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 [5]. 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.

Insulin Resistance

CT reduces the sensitivity of the muscle and adipose tissues to insulin in experiments *in vivo* and *in vitro* [4]. 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.

Glucose Intolerance

CT increases initial glucose concentration and evokes glucose tolerance impairment in rats of all age groups [6]. CT inhibits insulin secretion against the background of glucose load per os [3]. The mechanism of CT effects on insulin secretion remains unclear. It can be hypothesized that CT-induced hypocalcemia reduces intracellular Ca2+ concentration in β -cell cytosol, decelerates the release of secretory granules localized in microfilament network near the cell membrane [7], thus delaying insulin secretion during GTT. It can be hypothesized that this specific feature of insulin secretion under the effect of CT determines the impairment of alimentary hyperglycemia.

Participation in the Development of Insulin Resistance

It is shown that CT participates in the development of insulin resistance on the pre-receptor 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 [8]. These data allow suppose about diabetogenic effect of CT. However to analyze a lot of literature data we can consider 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, for

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example, under obesity and in elderly age.

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 our examinations of children-teenagers 10-14 years old with the 1-st degree obesity and negative calcium balance, receiving one-time injection of CT [9] it was established glucose intolerance in glucose tolerance test. So, one may consider as an example of negative CT influence on glucose homeostasis under unfavorable conditions, in this case, obesity. In our previous investigations [6] 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 [10]. On this background one-time injection of CT in mature and old animals induced more marked glucose intolerance. 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.

Calcium Channel Blockers Abolish Effects of Calcitonin

It is shown in experiments that calcium channel blockers isoptin and nifedipin reduced plasma calcium level and did not affect significantly the blood glucose levels, did not change the pattern of alimentary hyperglycemia in response to glucose load, but completely abolished the hyperglycemic effect of CT, and prevented CT-induced impairment of glucose tolerance. Besides that isoptin, decreasing intracellular Ca^{2+} concentration blocks the inhibiting effect of CT on insulin-stimulated glucose consumption by the muscle and adipose tissues *in vivo* and *in vitro*, probably, due to higher levels of glucose transporters GLUT-4, resulting in increased glucose uptake by peripheral tissues, thus preventing the development of insulin resistance [11]. These data are found the verification in literature. Thus, nifedipin therapy not only promotes to the decreasing of arterial pressure, but and improves IR in the elderly patients with hypertension [12]. 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 [13]. The ability of calcium channel blockers completely to abolish the hyperglycemic and inhibiting effect of CT on insulin-stimulated glucose consumption by the muscle and adipose tissues 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 theses hormone actions. In this connection ion channels are considered as disease targets and direct influence on calcium mechanisms of endocrine system as possible method of drug therapy is discussed.

The discussed data about CT significance in glucose metabolism enlarge the conception of its physiological role and allow recommend to take into account its effect on glucose metabolism under its treatment in clinic practice.

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