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Insulin-Like Growth Factors - Modern Concepts of Their Role in Normal and in Metabolic Syndrome

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Abstract
The occurrence of proliferative disorders is associated to a large extent with growth-stimulating hormones. In this regard, insulin-like growth factors are of particular interest. They belong to the family of insulin-like substances that exhibit significant growth-stimulating activity [5,10,19].

Keywords: insulin, human blood, antibodie.

Back in the 1970s, insulin-like activity was found in human blood serum, which was not suppressed by antibodies to insulin (Nonsuppressible insulin-like activity-NSILA), mimicked the action of insulin on adipose tissue in vitro and in vivo, and had growth-stimulating properties [2, 10.44]. NSILA consists of 2 components: NSILA-P - 90% and NSILA-S - 5-10%. At physiological concentrations, NSILA-P stimulates cell proliferation and DNA synthesis, but does not regulate glucose levels. Of greatest interest is NSILA-S, which is divided into 2 components with strong growth activity: insulin-like growth factors (IGF) I and II [10,19,20].

Somatomedins also belong to the group of growth peptides. Back in 1957, it was found that the addition of growth hormone to hypophysectomized animals promotes the appearance in the blood serum of a factor that stimulates the incorporation of 35SO4 into cartilage. It received the name "sulfonating" and was later called somatomedin [2,19,23].

According to modern concepts, somatomedins (SM) are a polypeptide chain with a molecular weight of 5-10 kDa, have insulin-like activity. The biological effects of SM in cartilage tissue include: stimulation of 35SO4 incorporation into cartilage proteoglycans, stimulation of labeled thymidine in fibroblast DNA, and stimulation of protein synthesis [2,19,44].

Somatomedins A, B, C are isolated as independent substances. Thus, SM-A is a neutral polypeptide whose activity is determined by the incorporation of labeled sulfate into the cartilage of the chick embryo. SM-B- stimulates the incorporation of thymidine into the DNA of fibroblasts and the replication of glial cells. SM-S is determined by the incorporation of sulfate into cartilage; it stimulates DNA synthesis and the rate of mitosis in fibroblast culture [27]. In this it resembles

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peptide growth factors: fibroblast growth factor, platelet growth factor, epidermal growth factor, nerve growth factor (NGF), erythropoietin and thymosin. Most of them have insulin-like activity, and NGF has common amino acid sequences with insulin [2,12,35,40,44].

Currently, it is believed that SM can be identical to IGF I and II, as well as MSA. This is especially true for CM-S, which is considered identical to IGF-I. There is an assumption that SM-A is possibly a deaminated form of IGF-I, and MSA is close to IGF-II- [2,10,44].

However, the identity of IGF-I and SM-C remains controversial. Both polypeptides were isolated by different methods, but when they were determined by the radioligand method, it was suggested that IGF-I and SM-C might be identical [1,2,29].

The site of IGF synthesis has not been precisely established. It is suggested that the liver may be the main organ producing IGF [1,2,10]. However, stimulation of SM production by an isolated perfused liver requires excessively high concentrations of growth hormone [10]. Partial hepatectomy results in a 75% drop in plasma SM levels. In recent years, reports have appeared on the detection of IGF in skeletal muscle and brain extracts [16, 18]. W.S. Salman et al. (1983) isolated sulphurizing activity from the kidneys, heart, lungs, pituitary gland, but did not find it in the liver. Similarly, M. Schmidt et al. liver extracts did not stimulate rat cartilage growth [46,47].

Of great interest are data on the possibility of IGF synthesis in the pancreas, since many authors discuss the issue of a common origin in the evolution of insulin and other hormones with insulin-like activity, especially since the proinsulin and IGF-II genes are linked on the same chromosome [3,10,11].

IGFs are transported in the blood by specific binding proteins. The proteins isolated from blood plasma and amniotic fluid are the most studied [26,48].

Two types of IGF receptors have been identified in the liver, brain, placenta, erythrocytes, lymphocytes, chondrocytes, vascular cells, and thyroid cells [26,28].

The biological effects of IGFs include their insulin-like and mitogenic effects [22,24,26]. Insulin-like action of IGF is observed in adipose and muscle tissue. In fat cells, IGF-I and IGF II stimulate the transport and, as a rule, further metabolism of glucose and the synthesis of lipids from it through insulin receptors [22,24,28]. In muscle tissue, IGFs stimulate glucose incorporation, glycolysis, and glycogen synthesis both through their own receptors and through insulin receptors [36,49]. In the experiment, intravenous administration of IGF to rats caused a decrease in blood sugar and an increase in the incorporation of 14C-glucose into diaphragmatic glycogen and total lipids of adipose tissue, and, like insulin, IGF I and II caused a significant drop in blood glucose at 30 minutes [10,40,42].

IGF, along with pituitary hormones, play a significant role in the regulation of cell growth and

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differentiation [10]. Both factors stimulate the incorporation of thymidine into fibroblast DNA and sulfate incorporation into cartilage, enhance protein synthesis, increase the amount of RNA, and are mitogens [46,47]. Their growth-stimulating effect is expressed 50-100 times stronger than that of insulin, however, their specific metabolic activity is as much less than that of insulin, due to the low affinity of insulin receptors for these factors [30,34].

IGF-1 plays an important role in the GH regulation system (long feedback). IGF-1 also acts at the hypothalamic level, suppressing the secretion of somatoliberin and stimulating the secretion of somatostatin, and at the pituitary level, inhibiting the transcription of the STH gene. In addition, IGF-1 suppresses the expression of the ghrelin receptor and the somatoliberin receptor in the pituitary gland. When the IGF-1 gene is knocked out in the liver, the main function of IGF-1 is not the stimulation of growth processes, as previously assumed, but inhibition of GH secretion is possible [1,10,13].

CM-C concentration changes with age and gender [12,19]. SM-C levels are lowest at birth and increase during infancy and childhood, reaching the highest levels during puberty and slowly decreasing in adulthood [24]. Women have a slightly higher level of SM-C than men.

IGFs play an important role in the development of pathological processes associated with mitosis and cell mutation. In particular, sufficient clinical material has shown an increase in the concentration of IGF in neoplastic processes [32,33]: osteogenic sarcoma [7,31], colonorectal cancer [8,31], endometrial cancer [23,30], thyroid-associated ophthalmopathy [49]. The role of IGF in the genesis of various atropathies has been shown [37,38,39,43].

The main number of experimental and clinical studies of IGF/SM was carried out in patients with diabetes [3,9,12] . In recent years, there have been few studies of growth factors in MS [32], arterial hypertension, and obesity.

Some researchers have found a close relationship between growth, IGF and growth hormone in insulin deficiency and starvation [9,11,23]. So, children with proteinaceous dystrophy and diabetes mellitus grow poorly, despite the often elevated levels of growth hormone, but low levels of IGF. These data may indicate the possible involvement of food in the regulation of IGF activity [23, 24].

A number of researchers have determined IGF in patients with diabetes mellitus and metabolic syndrome. At the same time, some authors found normal levels of IGF I and II in DM with a slight dependence on the degree of compensation of the disease. Others showed reduced levels of IGF [14]. So S.A. Amiel et al. [15] found that adolescents with DM had a low level of IGF-I, but a normal level of IGF-II, observing a negative correlation between the amount of IGF-I and II in the blood and the degree of disease compensation. M. Maes et al. (1999) also found reduced IGF levels in adult diabetics, suggesting that the factors that reduce IGF-I and II levels in diabetes are the same for both

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types of disease. Third researchers have noted elevated levels of IGF in diabetes [12,13] and metabolic syndrome associated with diabetes, hypertension and obesity [14,32]. However, there remains a controversial question about the relationship between elevated levels of CM-C and HBAIc; SM-S, age and gender of the examined patients; SM-S and disease duration. The inconsistency of the obtained data can be explained by the fact that IGF I and II were determined by different methods and the protein carrier of these factors was not taken into account. At the same time, there are no data on the content of IGF-I/SM-C at different stages of the development of MS and diabetes mellitus.

Data on different sensitivity to insulin and IGF may explain to some extent the histopathological feature of diabetic retinopathy (DR) and diabetic macroangiopathy (DMA), as these complications are the result of cell proliferation [12,41]. Various cells are involved in this process: in DR, endothelial cells, and in DMA, vascular muscle cells. It has been suggested that intensive insulin therapy may enhance the production of IGF, which in turn stimulate the proliferation of retinal capillary cells. Froesch E.R. et al. [26] found the development of retinopathy in patients with Mauriac's syndrome after intensive insulin treatment. Arterial endothelial cells were noted not to proliferate in DMA, although insulin and IGF levels were also high. Perhaps the proliferation of arterial endothelial cells is regulated differently. At the same time, aortic muscle cells responded to both insulin and IGF. Thus, hyperinsulinemia and insulin resistance in combination with a high level of IGF can cause the proliferation of vascular muscle cells [12,26,44].

Our previous studies have shown that patients with newly diagnosed insulin-dependent diabetes mellitus (IDDM) in late puberty and post-puberty against the background of basal hyperinsulinemia are characterized by an increase in the level of IGF-1. In patients with IDDM, an increase in the level of IGF-1 correlates with the degree of development of diabetic retinopathy. Diabetic nephropathy is also accompanied by an increase in IGF-1, but improvement in kidney function does not lead to a decrease in IGF-1. A high correlation of IGF-1 with vascular proliferative changes was noted, causing vascular remodeling, the development of inflammation and atherosclerosis of the arteries, which leads to the development of cardiovascular complications [12,48].

The issue of the local effect of IGF is discussed in the literature. This is based on data on IGF synthesis in various tissues [21]. And although the amount of IGF formed in tissues is not comparable with a high level in serum, one can agree with the opinion of the authors that target tissues of growth hormone are capable of synthesizing growth factors. IGF locally can stimulate proliferation and, thus, play a role in the occurrence of vascular complications in DM and MS [4,21,23,24].

Thus, proliferative processes take place at all stages of the development of the organism. The possibility of IGF/SM as growth stimulants is emphasized. An interesting fact about the role of

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IGF/SM in the development of vascular remodeling and as a predictor of cardiovascular diseases. However, the available data are still insufficient for final conclusions about the specifics of the IGF/SM regulation of proliferation processes in diabetes, MS, and their cardiovascular complications.

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