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Insulin-like growth factor I (IGF-I) and its present significance in digestive system diseases*

Insulinopodobny czynnik wzrostu I (IGF-I) i jego aktualne znaczenie w chorobach układu pokarmowego

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Summary

Insulin-like growth factor I (IGF-I) is a main mediator of growth hormone's (GH) action. Under physiological conditions, IGF-I is responsible for growth and development of organism through influence on proliferation and differentiation of cells. IGF-I is produced in almost all tissues of organism and its activity is determined by interaction with specific receptors (IGF-IR, IGF-IIR) and IGF-binding proteins (IGFBP-1 - IGFBP-6), and by proteases hydrolyzing IGFBPs as well.

Currently, a surge of interest on insulin-like growth factor I as a potential factor contributing to the development of neoplasms, including neoplasms of digestive system, is observed. IGFBPs and IGF-IR may also be of importance in etiology and pathogenesis of cancer. It is assumed that high serum concentration of IGF-I may increase the risk of cancer development whereas high serum concentration of IGFBP-3 may inhibit the progression of the disease.

Until recently, attempts of modulating the concentration of IGF-I with the use of pharmacological agents of diverse mechanisms of action under innovative anti-cancer therapies, have been made. Lately, it is pointed to the possibility of application of IGF-I in the management of certain diseases of digestive system. It was observed that IGF-I not only contributes to the maintenance of normal structure and function of epithelium in the gastrointestinal tract but also stimulates repair processes in damaged mucosa. Results of preliminary studies on the treatment of short bowel syndrome, gastric ulcer disease, enteritis induced by chemo- and radiotherapy, and inflammatory bowel disease with the use of exogenous IGF-I are encouraging.

Keywords: **insulin-like growth factor I • digestive system diseases • digestive system neoplasms**

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THE STRUCTURE OF IGF-I AND EFFECTS OF ITS ACTION

Insulin-like growth factor I (IGF-I; somatomedin C) is a polypeptide hormone that belongs to a family of insulin-like growth factors (IGFs). The family of IGFs plays an important role in the proliferation, differentiation and apoptosis of cells [39].

It was stated that two insulin-like factors (IGF-I and IGF-II) are present in human [39]. Their action develops as a result of binding to two types of membrane receptors, which were denoted as IGF-IR and IGF-IIR, respectively. However, the interaction of IGFs with their receptors may be modulated by six types of IGF-binding proteins (IGFBP-1 – IGFBP-6) and activity of numerous proteases that catalyze the hydrolysis of IGFBP [1, 37, 39].

IGF-I is made of 70 amino acids forming a single polypeptide chain, within of which there are three disulfide bonds. The appellation "insulin-like" results from a large similarity to insulin, both in terms of the structure (ca. 50% of homology) and effects of action [27, 35].

Somatomedin C is considered to be one of the key factors affecting body's growth and development [39]. Its action is multi-directional. IGF-I not only stimulates the proliferation of cells (being a strong mitogen) but also inhibits apoptosis. IGF-I enhances the transport of amino acids and glucose into cells and boosts the synthesis of proteins and glycogen (anabolic action). Somatomedin C also triggers an increase in content of mineral compounds (sulphates, phosphates) and in the synthesis of collagen in cartilaginous and bone tissue [5, 6].

REGULATION OF IGF-I SECRETION

Growth hormone (GH), which is produced by anterior lobe of hypophysis, constitutes a major factor initiating the synthesis and secretion of somatomedin C by hepatocytes. The whole process is controlled through a mechanism of negative feedback, according to which GH stimulates the hepatic production of IGF-I and achieving of high IGF-I concentration in the blood flowing into the pituitary gland inhibits further secretion of growth hormone [1, 25].

The synthesis of insulin-like growth factor I takes place in hepatocytes as a response to GH. Subsequently, the factor is released to the blood and transported to target tissues and organs. In this spin, IGF-I has the function of a hormone. It is currently known that IGF-I may also be produced locally, i.a., in the gastrointestinal tract (GIT), adipose tissue, encephalon, kidneys, cartilaginous tissue, and bone tissue, where it may exert paracrine or autocrine action [19, 35, 37].

SIGNIFICANCE OF IGF-BINDING PROTEINS AND THEIR PROTEASES IN THE CULTIVATION OF EFFECTS OF IGF-I ACTION

As mentioned, insulin-like growth factor I occurs in the blood serum primarily in the form bound with proteins denoted as IGFBP. Binding with proteins is one of the main factors which determine biologic activity of IGF-I. So far, six types of proteins binding insulin-like factors have been described. However, it is assumed there are more than these [1, 27, 39].

Basically, IGFBP have three functions. They are responsible for the transport of insulin-like growth factors in the blood, protect IGF-I and IGF-II against proteolysis and modulate the interaction between growth factors and their receptors (IGF-IR, IGF-IIR) [27, 39].

Proteases of IGFBP constitute a major factor regulating an influence of IGFBP on the action of insulin-like growth factor I. Three groups of proteases can be distinguished; these are: serine proteases, matrix metalloproteinases, and catepsines. As a result of peptide bonds hydrolysis, catalyzed by these enzymes, a decrease of affinity of IGFBP to IGF-I occurs and IGF-I is liberated out of protein complex [10, 27, 39].

RECEPTOR IGF-IR

The action of insulin-like growth factor I is determined by binding to type 1 receptor (IGF-IR), which is found on the surface of target cells. IGF-IR is a tetrameric glycoprotein, made of two α and two β subunits. Subunits α are responsible for binding of IGF-I on the external side of cell membrane and subunits β participate in induction and transmission of a signal to the inside of a cell [5, 16, 39].

Structurally, receptor IGF-IR is similar to insulin receptor (IR) in 60%. Due to the resemblance, IGF-I may also bind to IR, however with lower affinity than insulin itself [5, 39].

Interaction of IGF-I with IGF-IR leads to stimulation of tyrosine kinase activity within subunit β of the receptor with subsequent activation of Ras/Raf proteins and mitogen-activated protein kinases (MAPK). An alternative pathway of signal transduction involves metabolism of phosphatidylinositol [39]. Stimulation of IGF-IR by IGF-I results in mitogenic and anti-apoptotic action [39].

THE SIGNIFICANCE OF IGF-I IN ETIOLOGY AND PATHOGENESIS OF DIGESTIVE SYSTEM NEOPLASMS

Recently, more and more research teams have been focusing their attention on the family of IGFs. Based on results from studies in both animals and humans, one can assume

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that IGF-I may participate in initiation and development of neoplasms. There is some evidence pointing to an association between IGF-I and breast, prostate, and lung cancer [14, 27]. Particularly, an impact of IGF-I on proliferation, differentiation and apoptosis of cells matters. Moreover, its potent mitogenic action was observed not only within normal tissues but also within tissues undergoing transformation to a neoplasm [25, 39].

It is currently believed that a high concentration of circulating IGF-I may increase the risk of cancer, whereas a high serum concentration of IGFBP-3 may inhibit the progression of a neoplasm [14, 27, 39]. However, after having taken into account some data from literature one can state it not always happens. Additionally, it has also been paid attention to over-expression of IGF-IR in numerous types of malignancies [27, 31, 39].

ESOPHAGEAL CANCER

There are some papers where a contribution of IGFs' family to the development of esophagus cancer is pointed out. In a study by Chen et al., an association between the cancer and over-expression of IGF-IR was demonstrated. During further studies it has been observed that IGF-I, through its autocrine action, affects the growth of transformed cells and protects them against apoptosis induced by such agents as cisplatin, 5-fluorouracil and camptothecin compounds [3, 21]. Sohda et al. stated that average serum concentration of IGF-I in patients with esophageal cancer was positively correlated with pathological stage and depth of invasion. Moreover, the authors observed that survival rates among individuals with high IGF-I expression had been poorer than those in patients with low somatomedin C expression [33].

Some research concerned Barrett's esophagus, a premalignant lesion which is capable of progressing to adenocarcinoma. Iravani et al. had analyzed IGF-IR protein expression in taken specimens at different stages of Barrett's-associated neoplasia development and noted a gradual increase in IGF-IR expression level during the progression to adenocarcinoma [12].

COLORECTAL NEOPLASMS

In a study by Ituarte et al., a group of patients with acromegaly was subjected to an analysis. The condition occurs in adults and its symptoms are caused by excessive exposure to GH. It was observed that those patients had a dozen-fold greater risk of developing colon cancer [13].

In a study performed among males, on the other hand, it was demonstrated that the risk for colorectal cancer was 1.5-fold higher in individuals with a large IGF-I concentration than in those who had lower levels of the factor [22].

Research was also conducted where expression of IGF--IR was assessed in adenomatous polyps, being one of the preneoplastic conditions within the large intestine. It was shown that expression of IGF-IR at mRNA level was stronger in patients with colorectal polyps than in the control group [32, 41]. Moreover, results of the research point towards a correlation between IGF-IR expression level and the risk of neoplastic transformation in mucous membrane of the colon and rectum [32, 41].

So far, realized studies on the role of IGF-I binding proteins in the development of colorectal neoplasms have yielded inconsistent data. Results obtained by Kaaks et al. suggest that females with a higher level of IGFBP-3 present greater risk for colorectal cancer in comparison to females with a lower IGFBP-3 level [16]. A positive correlation between a serum IGFBP-3 concentration and the colorectal cancer risk was observed in a study that was conducted among males in a Chinese population [28]. Giovannucci et al. showed that there was a reverse correlation, though, i.e. a low IGFBP-3 concentration might contribute to neoplasia [8].

A study by Krasnodębski et al. pointed towards type 2 diabetes as an additional factor predisposing to adenocarcinoma of colon and rectum [18]. Increased risk for colorectal neoplasms among patients with type 2 diabetes is well explained by a hypothesis, according to which hyperinsulinemia leads to a rise in a concentration of unbound IGF-I through inhibition of IGFBPs' production. Moreover, supraphysiological concentrations of insulin may result in activation of receptors IGF-IR. Greater somatomedin C availability along with enhanced activation of IGF-IR due to hiperinsulinemia may be responsible for shifting the pathway of cells' differentiation in the large intestine's musoca towards neoplasia [8, 18].

LIVER NEOPLASMS

In current available literature, one can find works presenting that there is also a relationship between the family of IGFs and neoplasms of the liver. In one of the studies, it was observed that the development of hepatocellular carcinoma (HCC) was accompanied by a significant reduction of a serum IGF-I concentration within a period of 6-12 months before diagnosis [24].

Results given by Masoodi et al. indicate that a serum level of IGF-I may be useful at determining the severity of metastases. The authors found that a mean serum IGF-I concentration in patients with less severe liver metastases was greater by 43% than in those with more severe liver metastases. Noteworthy, they stated that a lower serum somatomedin C level observed in the latter group of patients was independent of functional liver damage [23].

In HCC, Liu et al. found increased expression of IGF--IR at the protein level [20]. Gong et al. demonstrated that mRNA levels for genes encoding IGFBP-1, IGFBP-3,

IGFBP-4 were significantly lower in patients with HCC than in healthy individuals [9]. According to the authors, a decrease in expression of IGF-I binding proteins may have resulted in enhancement of mitogenic action of IGF-I, and consequently - the development of HCC.

PRESENT SIGNIFICANCE OF THE IGFS' FAMILY IN TREATING DISEASES

Cancer

Based on findings from aforementioned works, one can consider there are many premises pointing towards the possibility of therapeutic usage of agents that are able to affect the concentration of IGF-I in the treatment of diseases, and especially malignancies.

One of the primary therapeutic concepts is to diminish the concentration of circulating IGF-I as a result of administration of growth hormone receptor antagonist. Pegvisomant is an analog of GH which blocks binding of endogenous GH to its receptors on the cell surface and inhibits action of GH [11, 31]. The effectiveness of pegvisomant (s.c.) was confirmed in the treatment of patients with acromegaly [11, 29, 31].

An another strategy in anti-cancer pharmacotherapy may be the neutralization of circulating IGF-I with monoclonal antibodies. So far, there have been developed antibodies which are distinguished by high affinity to IGF-I. However due to poor penetration of a tumor and high production costs, anti-IGF-I antibodies do not currently command the interest of researchers [1, 31].

Some alternative to GH receptor antagonists and to antibodies against IGF-I might be IGF-I binding proteins (IGFBP), which may reduce the risk for neoplasms by diminishing the amount of somatomedin C in surroundings of cell receptors [31]. In a in vivo study by Van den Berg et al., it was shown that IGFBP-1 was able to inhibit the growth of breast cancer [36].

For past several years, clinical trials on monoclonal antibodies against IGF-IR (e.g.: AVE1642, cixutumumab, figitumumab, ganitumab) have been conducted. Their effectiveness and safety has been evaluated, i.a., in the treatment of breast cancer, esophageal cancer, HCC, lung carcinomas, multiple myeloma, prostate cancer, and some sarcomas [4, 29, 31]. It has been observed that next to the main mechanism of action of anti-IGF-IR antibodies, which consists in blocking the binding of the ligand to its receptor, some of them are capable of inducing the down-regulation of IGF-IR [29, 31].

Digestive system diseases

Somatomedin C is produced in numerous body tissues, including digestive system as well. The presence of IGF-I was confirmed, i.a., in the small and large intestine [11, 42]. In addition, it has been demonstrated that IGF-I plays an important role in maintaining of the right structure and function of intestinal epithelium [2, 38]. The factor is secreted by salivary glands and other glands in the GIT [7]. Receptor IGF-IR is found in mucosa and smooth muscles of GIT, and in the largest amount in intestinal crypts [2, 11].

• Short bowel syndrome

Past observations have pointed to the possibility of IGF-I utilization in the treatment of some GIT conditions. Relatively many papers are on the short bowel syndrome (SBS), being the clinical consequence of the small intestine resection. SBS is characterized by impaired absorption of nutrients, which may require applying of parenteral nutrition. Early animal studies showed that administration of IGF-I greatly improved the functioning of spared parts of the intestine [11]. In further studies in animals, accelerated joining of intestinal parts, good adaptation of the intestine to new conditions, restoration of mucous membrane, and increased absorption of water and nutrients following the IGF-I administration was observed [38]. The team of Gillingham et al. also observed that applying of IGF-I enabled the restriction of total parenteral nutrition in favor of enteral nutrition. Moreover, the authors demonstrated that IGF-I helped increase the body weight of rats with SBS [7].

Based on cited results, on can believe that in the future IGF-I may account for valuable addition to SBS therapy.

• Gastric ulcer disease

In a rat model of gastric ulcers, significantly increased IGF-I expression was shown in areas adjacent to the lesions in mucous membrane. There were also observed intense epithelization and healing by second intention [26]. Results by Karolkiewicz et al. point to potential benefit from IGF-I administration in the treatment of gastric ulcers. The authors demonstrated that lower expression of IGF-I at mRNA level in stomachs of rats with diabetes induced with streptozotocin injection was one of the factors responsible for the impairment of the healing process of ulcers in the course of diabetes, whereas systemic administration (s c.) of exogenous (recombinant human) IGF-I led to normalization of the process [17].

There are still ongoing studies which aim at determining the mechanism of aforementioned action. Nguyen et al. showed that a rise in IGF-I expression at mRNA and protein levels accelerated the healing process mainly as a result of activation of phosphatidylinositol 3-kinase pathway. Moreover, the expression of IGF-I was found to be associated with expression of cyclooxygenase 2 (COX-2), which in turn triggered production of a large amount of prostaglandin E_2, having a trophic action on mucosa of GIT [26].

• Enteritis induced by chemo- and radiotherapy

Radiation therapy and chemotherapy are commonly used in the treatment of neoplasms. Next to destructing transformed cells, other effects of such treatment involve damage to normal tissues, including secondary enteritis. It was shown that IGF-I protected intestinal cells against negative consequences (i.a. apoptosis) of radiation of organs within the abdominal cavity and true pelvis, and receiving antineoplastic agents [11]. However, there are also data on increased cytotoxicity within GIT during combined administration of IGF-I and methotrexate [11].

Taking into account results of the studies, where the accelerated recovery of intestinal epithelium was demonstrated after using IGF-I, further research on the potential of the treatment of a complication of chemo- and radiation therapy within GIT seem to be justified [11].

• Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a group of chronic conditions of GIT, which mainly covers ulcerative colitis (UC) and Crohn's disease (CD). Based on performed studies, one can believe that IGF-I positively affects the function of intestines via stimulating a repairing process within mucosal membrane [2, 26, 38]. For the meantime, results of some authors have shown that a locally raised concentration of somatomedin C may induce a fibrotic process within the intestinal wall during ongoing inflammation [11, 42]. It was namely found that insulin-like growth factor I could induce the proliferation of fibroblasts, myofibroblasts, and smooth myocytes, and enhance the collagen production by these cells as well [11, 42].

The fibrotic process may also be affected by proteins that bind IGF-I. It has been observed that IGF-I stimulates the synthesis and secretion of IGFBP-5 by smooth muscle cells, which in turn potentiates the auto- and paracrine action of IGF-I in the mechanism of positive feedback. As a result, a rise in the thickness of a muscular layer, collagen deposition, and progressive strictures of intestines occur [11, 40, 42].

Nevertheless, one should not neglect the therapeutic potential of IGF-I use in UC and CD. A frequent complication of IBD in children (40-50%) is growth retardation. Presently, it is believed that this complication results not only from impaired absorption of nutrients in intestines, but also from chronic inflammation that causes resistance to GH and a decrease in serum IGF-I [34]. Therefore, one can assume that administration of IGF-I would be as much as twofold beneficial in children with growth retardation associated with IBD (improvement in height and intestines' function) [11].

In currently available literature, there are numerous articles on significance of IGF-I and receptor IGF-IR in digestive system neoplasms. It was found that an increased concentration of somatomedin C or overexpression of IGF-IR might be associated with a higher risk for cancer development. For several years, clinical trials have been conducted on effectiveness and safety of monoclonal antibodies against receptor IGF-IR, mainly in the treatment of solid tumors.

One should also consider that in the course of some types of neoplasms (e.g. liver), the serum concentration of insulin-like growth factor I may gradually decrease.

Both in vitro studies and research in animals showed a beneficial influence of exogenous IGF-I on the healing process in damaged mucosa of GIT in models of short bowel syndrome and gastric ulcer disease. Attempts of therapeutic usage of IGF-I in enteritis induced by chemo- and radiotherapy, and in inflammatory bowel disease have also been made. The next step will be starting research in humans, which certainly allow us to assess therapeutic potential of insulin-like growth factor I in digestive system diseases.

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