

## Diabetes & its Complications

# A Modern Understanding of The Role and Place of Gastrointestinal Peptides in The Pathogenesis of Type 2 Diabetes

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In the pathogenesis of type 2 diabetes in recent years, more and more attention is paid to gastrointestinal peptides (GIP) - substances produced in the cells of the stomach and intestines and having a pleiotropic effect due to their extensive receptor field. It has been proven that GIP have a pronounced effect on eating behavior, digestion, carbohydrate and lipid exchanges, and their concentrations depend on food intake, the presence of type 2 diabetes in a patient.

The influence of GIP on the course of cardiovascular diseases is also being actively studied, since the latter are the main cause of death among patients with type 2 diabetes.

Among all the GIP that play a role in the development of type 2 diabetes, in recent years, ghrelin and its partial antagonist obestatin, as well as incretins are the most actively studied: the family of glucagon-like peptides and glucose-dependent insulinotropic polypeptide.

Research results M.Nakazato revealed that the level of ghrelin in humans increases immediately before a meal and quickly decreases after a meal. Thus, ghrelin can be considered an indicator of short-term energy balance and a signal to initiate a meal, a kind of "hunger hormone" [1].

When conducting experimental studies, accompanied by various types of negative energy balance (fasting, insulin-induced hypoglycemia, chronic leptin, low protein content in the diet), the expression of the ghrelin gene increases. On the contrary, when eating, a decrease in the expression of ghrelin mRNA is detected, which is most pronounced on a diet high in fat. The concentration

of ghrelin decreases with obesity and, on the contrary, increases with cachexia [2,3]. It should be noted that in obese patients, postprandial decrease in the level of ghrelin is somewhat delayed in time, which may contribute to the development of obesity.

Daily subcutaneous administration of ghrelin leads to an increase in body weight, and there is a significant increase in adipose tissue in the absence of effects on muscle mass. It was also found that the introduction of ghrelin not only stimulates the ingestion of food, but also increases its duration [4].

In the works of Treander-Carrillo et al. It was revealed that prolonged administration of ghrelin directly into the ventricles of the brain leads to an increase in the amount of food taken, a significant increase in body weight due to adipose tissue. It should be noted that this method of administration was not accompanied by an increase in glycemia, plasma insulin levels, glucocorticoids, leptin and free fatty acids [5].

With the introduction of ghrelin into the ventricles of the brain, insulin-dependent glucose uptake (an effect unrelated to hyperphagia) increases. These effects of ghrelin are dose-dependent and are likely to be controlled by the sympathetic nervous system [5].

Proved is the significant effect of ghrelin on carbohydrate metabolism, in particular the ability to inhibit insulin secretion. The introduction of ghrelin to healthy volunteers leads to a decrease in insulin concentration and the development of hyperglycemia. Hyperglycemia may be associated with both the stimulation of ghrelin glycogenolysis and the suppression of the inhibitory effect

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of insulin on gluconeogenesis.

In addition to the above effects, ghrelin has the ability to influence the digestive process, in particular, to suppress the endocrine function of the pancreas, induced by cholecystokinin [6]. Under the action of ghrelin, the production of hydrochloric acid is activated, the evacuation function of the stomach increases, which may be due to the effect of ghrelin on the autonomic nervous system, including the activity of n.vagus.

In addition to direct effects on the gastrointestinal tract and the centers of saturation in the hypothalamus, ghrelin regulates the intake and use of nutrients indirectly through the effect on growth hormone secretion. At least two mechanisms are involved in this process:

- Ghrelin stimulates the production of somatoliberin in the hypothalamus (somatoliberin-producing neurons have GHSR on their surface).
- Ghrelin directly affects the anterior pituitary, stimulating the production of growth hormone (the transmission of ghrelin signal in pituitary cells is realized by increasing the concentration of calcium ions).

In turn, growth hormone stimulates the synthesis of insulin-like growth factor in the liver, which is the most important mediator of regulation of the metabolism of proteins, carbohydrates and fats and, accordingly, the differentiation of muscle, bone and adipose tissues [7].

In recent years, the role of ghrelin in the regulation of the cardiovascular system has been actively studied. To date, its effect on the synthesis of nitrous oxide (NO) and blood pressure has been proven. In patients with insulin resistance, in whom their own circulating ghrelin level is reduced, the administration of a non-acylated form of ghrelin improves endothelial function by increasing the bioavailability of NO. At the same time, ghrelin has a vasodilating effect regardless of the route of administration: both after intravenous and after intraarterial administration, patients with type 2 diabetes showed a decrease in blood pressure [8]. They also report on the possible cytoprotective effect of ghrelin: in an experiment, it showed the ability to inhibit apoptosis in endotheliocytes and cardiomyocytes [9].

Among all the families of incretins, glucagon-like peptide-1 (GLP-1) and gastrointestinal peptide (GIP) are the most studied. An important unifying feature of their action is stimulation of glucose-dependent insulin secretion by  $\beta$ -cells in response to carbohydrate intake and suppression of glucagon secretion. When glucose levels are higher than basal GLP-1 and GIP, they normally increase insulin production and inhibit glucagon production, and when glucose levels fall below normal, stimulation of insulin secretion stops, and glucagon secretion increases. Thus, under the influence of GLP-1 and GIP, the amplitude of fluctuations in the level of glycemia decreases, thereby reducing the risk of hypoglycemia and the risk of developing complications of type 2 diabetes.

GLP-1 - incretin hormone, first isolated by G. Bell in 1983. GLP-1 is secreted by ileal L-cells from proglucagon molecule (which is converted to glucagon in the  $\alpha$ -cells of the pancreas as a result of post-translational processing). GLP-1 consists of 30 amino acid residues; in the blood, it is represented as two biological active forms: GLP-1 - (7-37) and GLP-1 - (7-36) NH<sub>2</sub>, which makes up 80% of the total GLP-1 pool [10]. The stimulus for secretion of GLP-1 is food intake, carbohydrates have the maximum stimulating effect. In addition to the composition of food, the secretion of GLP-1 is influenced by the rate of food intake in the intestine and its rate of adsorption, as well as neurogenic and hormonal stimuli. The secretion of incretins begins on average 10-15 minutes after meals, reaches a maximum in 30-45 minutes and returns to the basal level in 2-3 hours. The half-life of GLP-1 is less than 2 minutes. Inactivation of GLP-1 occurs under the action of endopeptidases, mainly dipeptidyl peptidase-4 (DPP-4) [11]. GLP-1 receptors are ubiquitous: they are found in the pancreas, gastrointestinal tract, liver, cardiovascular system, ventricles of the brain, and lungs.

Stimulation of GLP-1 receptors in the pyloric sphincter leads to a slowdown in the evacuation of food from the stomach, prolongation of stretching of the stomach with food and accelerating the onset of saturation. In addition, GLP-1 contributes to the so-called "intestinal brake", which is characterized by slowing the movement of nutrients through the intestines. GLP-1 induced effects (slowing gastric emptying, reducing contractile activity and slowing intestinal motility, suppressing glucose absorption) ultimately lead to a decrease in postprandial glycemia.

The most significant metabolic effect of GLP-1 is its pronounced insulinotropic effect: GLP-1 potentiates insulin biosynthesis, stimulating the transcription of its gene. It should be noted that the effect of GLP-1 is antihyperglycemic, not hypoglycemic: GLP-1-induced insulin secretion occurs only at high glycemia. GLP-1 does not affect insulin secretion at normal or low blood glucose levels, that is, it does not cause hypoglycemia [10].

Thus, the main effect of GLP-1 is the stimulation of glucose-dependent insulin secretion, the so-called "incretin effect", which provides greater (by 25-50%) stimulation of insulin secretion in response to oral glucose compared with its intravenous administration [12]. Up to 70% of postprandial insulin secretion in healthy people, as studies have shown, is due precisely to the effect of incretins, contributing to a decrease in patients with type 2 diabetes.

It has been proven that GLP-1 has a cytoprotective effect, including against  $\beta$ -cells of the pancreas: the introduction of GLP-1 in the experiment prevented their apoptosis. GLP-1 stimulates hypertrophy and proliferation of  $\beta$ -cells, accelerates their differentiation and neogenesis from epithelial progenitor cells, which is accompanied by an increase in the mass of  $\beta$ -cells [13]. In addition to affecting  $\beta$ -cells, GLP-1 has the ability to directly affect  $\alpha$ -cells of the pancreas, reducing the secretion of glucagon. The level of glucagon under the influence of GLP-1 is also reduced

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due to an increase in the synthesis of insulin and somatostatin [11].

Currently, GLP-1 in the liver decreases gluconeogenesis and glycogenolysis, in muscle tissue it increases glucose uptake and increases glycogen synthesis, thereby reducing insulin resistance and increasing sensitivity to endogenous insulin [11].

Data on the role of GLP-1 in lipogenesis today are contradictory: some authors indicate that it has a stimulating effect on lipogenesis, while in other studies no similar effect was found. In studies Goralska J. et al. It was found that pharmacological agonists of GLP-1 have the ability to enhance the processes of mitochondrial oxidation in adipocytes, which may contribute to the reduction of body weight [14].

Currently, the relationship of visceral obesity with the development of type 2 diabetes mellitus has been proven. There are several types of adipose tissue: white, brown and beige. It is well known that the main functional purpose of white adipose tissue is the accumulation of energy in the form of fat (triglycerides). As energy demands increase, triglycerides are oxidized to free fatty acids. Free fatty acids go to the synthesis of glucose, as the main energy substrate, or very low density lipoproteins are synthesized in the liver. In patients with trunk obesity in adipocytes of visceral adipose tissue, lipolysis is enhanced, the splitting of triglycerides is accompanied by the influx of large amounts of free fatty acids into the portal bloodstream and into the liver. In such patients, in most cases, fatty hepatitis develops and an examination reveals an enlarged liver overloaded with fats.

Brown adipose tissue is formed during ontogenesis between the 14th and 24th weeks of gestation, is located paravertebral and suprascapular regions and is more pronounced in newborns and young children. The main purpose of this tissue is the implementation of thermogenesis and the protection of the body from hypothermia. It was well shown in the experiments that activation of brown adipose tissue, as well as improvement of carbohydrate metabolism (decrease in peripheral insulin resistance, improvement in peripheral glucose utilization). A large number of experimental works suggests that regular physical activity contributes to the transition of white adipose tissue into a transitional form — beige and brown — accompanied by clear improvements in metabolic parameters. Therefore, regular aerobic exercise and phased weight loss play a key role in the treatment of obesity and type 2 diabetes mellitus [15-20].

Adipose tissue is an important endocrine organ secreting a number of signaling molecules, such as resistin, leptin, adiponectin [21]. Leptin is a peptide consisting of 167 amino acid residues. It was opened in 1994 [21]. Leptin is synthesized by white adipose tissue, its receptors are found in the nuclei of the hypothalamus, pancreas, liver, T-lymphocytes. Activation of these receptors regulates the eating behavior and body mass.

It is known that GLP-1 is involved in the regulation of the cardiovascular system. Both native GLP-1 and its pharmacological

analogs affect endothelium-dependent vasodilation both in the experiment and in clinical studies [22]. The antiatherogenic effect of GLP-1 has been proven in a number of animal studies, and in patients with type 2 diabetes, the administration of GLP-1 agonists and analogues reduced the thickness of the intima-media complex [23]. However, similar results were not obtained from all researchers [24]. The anti-apoptotic effect has been proven for both native GLP-1 and its derivatives. GLP-1 analogs and agonists also showed the ability to increase resistance to oxidative stress, in particular, reducing the concentration of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and the level of apoptosis caused by it, as well as hyperglycemia-induced fibrinolysis inhibitors, vascular adhesion molecules VCAM-1 and ICAM-1 [25].

Some bariatric surgeries used to treat type 2 diabetes lead to an increase in GLP-1 concentration. However, the number of long-term studies today is small due to the relatively recent introduction in practice of these methods of treatment of type 2 diabetes. Experimental data also indicate improved hemodynamic parameters and the development of cardioprotective effects after performing various bariatric operations on experimental animals suffering from type 2 diabetes [26-28]. Thus, in studies by Zhang X. et al. [26] rats (Wistar strain) with streptozotacin-induced type 2 diabetes as a result of a high-fat diet were performed duodeno-jejunal bypass surgery (n = 7) and longitudinal gastrectomy (n = 7). Laparotomy was performed in the control group (n = 7). 8 weeks after bariatric operations, echocardiographic parameters were studied (end diastolic diameter of the left ventricle, thickness of the posterior wall of the left ventricle, left ventricular ejection fraction). In the histological preparations of the left ventricular myocardium, the degree of fibrosis, the content of triglycerides in cardiomyocytes, the number of cells subjected to apoptosis were evaluated. According to the study, the left ventricular ejection fraction in the duodenojejunal bypass and longitudinal resection groups was significantly higher than in the control group (p<0.001), while the final diastolic diameter of the left ventricle and thickness of the posterior wall of the left ventricle were significantly less than in the control group (p<0.05). The number of cells undergoing apoptosis was significantly lower in the duodenojejunal bypass and longitudinal resection of the stomach than in the control group (p<0.001), with no significant differences between the duodenojejunal bypass and longitudinal resection of the stomach. Also, there were no significant differences between the three groups in the content of triglycerides in cardiomyocytes.

GIP helps to stimulate the synthesis of fatty acids from glucose, and also enhances the formation of adipose tissue. GIP is significantly more involved in lipid metabolism than GLP-1: it stimulates their deposition in adipose, muscle and liver tissues, which contributes to the development of obesity. The introduction of GIP receptor antagonists in the experiment reduced the deposition of lipids in the liver and muscles. In clinical studies, the introduction of GIP led to increased blood flow to the subcutaneous adipose tissue.

It is also known that GIP has the ability to stimulate insulin secretion in response to glucose consumption. It is believed

that the interaction between GIP and GLP-1 causes up to 50% of all postprandial insulin secretion [10]. It is assumed that GIP has a double effect on carbohydrate metabolism, having both insulinotropic and glucagonotropic effects, while in patients with type 2 diabetes, the insulinotropic effect of GIP is less pronounced than glucagonotropic. In diabetes mellitus type 2, it has been proven that GIP stimulates the synthesis of glucagon in  $\alpha$ -cells of the pancreas, and also slightly enhances the growth of  $\beta$ -cells. Probably, the disturbed ratio of these effects leads to a predominantly glucagonotropic effect of GIP in type 2 diabetes mellitus [30].

Despite the decrease in insulinotropic effect, the postprandial level of GIP in patients with type 2 diabetes does not differ from the norm (unlike GLP-1, the postprandial concentration of which is significantly reduced in type 2 diabetes) [30]. The influence of GIP on the activity of the cardiovascular system continues to be studied. The experiment proved its ability to somewhat enhance hypertrophy and myocardial fibrosis in the experiment. It is also likely that the GIP has some anti-inflammatory effects [31]. However, these studies require more thorough analysis.

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