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Role of ghrelin and leptin in the regulation of carbohydrate metabolism. Part I. Ghrelin

Rola greliny i leptyny w regulacji metabolizmu węglowodanów. Część I. Grelina

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Summary

Ghrelin is a polypeptide that is excreted by the secretory cells of the gastric and intestinal mucosa, the arcuate nucleus of the hypothalamus as well as by the epsilon cells (ε) located in the pancreatic islets. It plays an important role in maintaining the energy balance of the organism and influences the endocrine function of the pancreas and glucose metabolism. It takes part in the regulation of glucose homeostasis through the modulation of insulin secretion and insulin sensitivity.

Due to the broad spectrum of ghrelin's biological effects, ways to modify them are presently being investigated. Much attention is focused on the enzyme called ghrelin O-acyl transferase (GOAT), which mediates the physiological functions of ghrelin. Acyl-ghrelin and des-acyl-ghrelin appear to have opposite glucoregulatory effects. The regulation of acylation by GOAT seems therefore to play a role in mediating glucose metabolism. The modulation of GOAT or ghrelin signaling may be a clinically relevant strategy to treat obesity and metabolic diseases such as type 2 diabetes.

Key words: **ghrelin • glucose homeostasis • ghrelin O-acyl transferase • pancreatic islet cells**

Streszczenie

Grelina jest polipeptydem wydzielanym przez komórki wydzielnicze błony śluzowej żołądka i jelit, jądro łukowate podwzgórza, a także przez komórki epsilon (ε), które znajdują się w obrębie wysp trzustkowych. Grelina odgrywa ważną rolę w utrzymywaniu homeostazy energetycznej organizmu oraz wpływa na wewnątrzwydzielniczą funkcję trzustki i metabolizm glukozy. W regulacji homeostazy glukozy grelina bierze udział poprzez modulację wydzielania isuliny, jak i wrażliwości na insulinę.

Wobec różnorodnych biologicznych skutków działania greliny, obecne badania poświęca się potencjalnym możliwościom ich modyfikowania. Dużo uwagi skupiono wokół enzymu zwanego O-acylo transferazą greliny (ghrelin O-acyl transferase – *GOAT*), który jest mediatorem nabywania przez grelinę jej fizjologicznych funkcji. Acylogrelina i dezacylo-grelina wydają się mieć przeciwne właściwości glukoregulujące. Dlatego zmiany w acylacji przez GOAT wydają się pośrednio wpływać na metabolizm glukozy. Modulowanie działania GOAT oraz szlaku sygnałowego greliny może być klinicznie istotne w leczeniu otyłości oraz chorób metabolicznych, takich jak cukrzyca typu 2.

Słowa kluczowe: **grelina • homeostaza glukozy • O-acylo transferaza greliny • komórki wysp trzustkowych**

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Introduction

Glucose homeostasis reflects the balance between the amount of it entering the blood stream and glucose used up by the body. Ghrelin and leptin belong to a numerous group of hormones and other factors which take part in glucose homeostasis regulation.

Ghrelin synthesis

Ghrelin was isolated from rat stomach for the first time in 1999 by Kojima and associates. Its gene is located on the 3rd chromosome (p26-p25). It is a polypeptide built of 28 amino acids and is produced from its precursor, preproghrelin (117 amino acids). Ghrelin is excreted mostly by the secretory cells of the gastric and intestinal mucosa as well as the arcuate nucleus of the hypothalamus. It is also produced by epsilon cells (ε) located in the pancreatic islets [2]. The discovery of these cells opened new perspectives in glucose metabolism control [3]. One of these possibilities is the mutual paracrine influence of ghrelin, insulin and somatostatin within the islets of the pancreas. Moreover, this finding gives hope that ghrelin producing cells or their precursors may be a good source of obtaining β cells in the future – for potential transplantation in patients with diabetes.

It has not been explained yet why the number of these cells increases in the pancreas in cases of β cell deficiency [3]. The α cells develop from the same precursors as the β cells. Their differentiation is related to the proteins Nkx2 and Pax4 [4,23,38]. Molecular mechanisms controlling the differentiation processes have not been fully described until now. The role of the pancreas in ghrelin secretion is supported among others by studies comparing changes in ghrelin, insulin and blood glucose levels as well as ghrelin gene expression in the stomach, pancreas and placenta during fasting and after a meal. These investigations were conducted in adult pregnant and non-pregnant female rats and their fetuses. These results seem to indicate that during the fetal period the pancreas is the main source of ghrelin. The authors suggest that this hormone may play an important role in the development of β cells in the pancreatic islets. Ghrelin slows down apoptosis and takes part in the promotion of β cell proliferation [18].

The role of ghrelin in energy balance regulation

Ghrelin also plays an important role in maintaining the energy balance of the organism, showing central as well as peripheral activity. It strongly stimulates growth hormone secretion. Ghrelin receptors can be found mainly in the hypothalamus and anterior part of the pituitary gland, on growth hormone secreting cells, and are called growth hormone secretagogue receptors (GHS-R) [9,15,24,42]. Furthermore, ghrelin influences the hypothalamic-pituitary-gonadal axis, the endocrine function of the pancreas and glucose metabolism [11,12,27,33,34,42].

Ghrelin, insulin secretion and insulin resistance

Secreted by the pancreas, ghrelin shows local activity in this organ. It is assumed that its influence on the islets of Langerhans cells may have an exo-, para- and autocrine character. Ghrelin takes part in glucose homeostasis by regulating the secretion and affecting the insulin sensitivity of tissues [6,14,26,41,43].

According to Kageyama and coauthors, ghrelin influences β cells and regulates insulin secretion through the GHS-R [25]. Lately Japanese authors presented results of experimental studies concerning its role in the insulin secretion regulatory mechanisms [13]. The association between ghrelin and insulin secretion is the topic of many investigations and of much controversy [6,7,10,21,28,35,44]. Entirely opposing results (confirming either secretion stimulation or inhibition) might be caused by the differences in the research methodology. One of the important conditions is the blood glucose concentration during the study, because it influences both ghrelin and insulin levels. High glycemia inhibits ghrelin secretion and stimulates excretion of insulin. Additionally, ghrelin itself encourages insulin secretion, but only at high blood glucose levels; at lower glucose concentrations it does not present this activity. Such a double role of this hormone was suggested by Takahashi and coauthors, who analyzed the results of many studies, and revealed that there is a relation between the direction in which ghrelin affects insulin secretion and the food intake [39].

The level of ghrelin in the blood stream is associated with changes in the energy balance and hormones. It is assumed that insulin plays an important part in reducing its postprandial concentration. In healthy individuals the ghrelin level in the blood becomes lower after a meal and rises progressively before the next one. It has not been entirely explained yet whether the eating decreases ghrelin concentration directly or through the insulin that is being secreted. Murdolo and coauthors compared the influence of food intake on the ghrelin level between patients with type 1 diabetes and healthy people. In their study they showed that insulin plays a crucial role in meal-related ghrelin suppression [31].

It was determined that in patients with poorly controlled diabetes, the lack of postprandial ghrelin secretion results from a profound insulin deficiency and may explain the polyphagia which can be observed in these individuals. Administration of the basal insulin dose proved to be sufficient to obtain post-meal ghrelin suppression in patients

with type 1 diabetes. Nevertheless, not all authors agree that physiological hyperinsulinemia affects the ghrelin concentration in healthy people. Therefore the significance of postprandial hyperinsulinaemia remains unclear. More unequivocal is the role of distinctive hyperinsulinemia caused by intravenous insulin infusion.

Hagemann and coauthors investigated ghrelin level regulation after administration of GLP-1 [21]. The association between ghrelin and pancreatic polypeptide (PP) concentrations was researched by Takahashi and coauthors [40].

Ghrelin antagonists

Due to the broad spectrum of ghrelin's biological effects, ways to modify them are presently being investigated. Lately much attention has been paid to the role of an enzyme called ghrelin O-acyl transferase (GOAT). Currently GOAT is the only known enzyme that is able to acylate ghrelin. It was proven that GOAT is a critical component of ghrelin activation, and thus mediates the physiological functions of this hormone [37].

GOAT transfers an octanoate group to ghrelin, which is essential for it to acquire its hormonal features. This enzyme plays therefore an important role in the metabolic activity of ghrelin [16,20,22,36,37].

Although ghrelin is mainly secreted from gastric X/A like endocrine cells, it is also released from pancreatic islet cells and regulates insulin secretion. An and coauthors examined the expression and regulation of GOAT in the pancreas [2]. The authors suggest that insulin inhibits the expression of GOAT via the mediation of mTOR signaling. An important anabolic role of mTOR in β cell function was presented by Mori and coauthors [29,30].

Moreover, ghrelin plays a role in the regulation of glucose homeostasis, through the modulation of insulin secretion and insulin sensitivity. Acyl ghrelin and des-acyl ghrelin appear to have opposing glucoregulatory effects and GOAT appears to play a role in maintaining the glucose metabolism [22].

Some authors suggest that inhibitors of this enzyme might have a clinical application in the treatment of obesity and diabetes [1,5,8,17,19,36,45]. This results from the abnormal ghrelin secretion profile observed in patients with diabetes. Studies show that ghrelin antagonists may improve the course of the disease. It has to be remembered, however, that ghrelin not only takes part in metabolism regulation, but also shows many other actions. Therefore using its antagonists in glucose metabolism disorders may have various adverse effects [32]. Further studies on this topic are needed.

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