The role of glucagon-like peptide 1 in glucose homeostasis and in other aspects of human physiology

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The incretin axis  Insulin, a hormone secreted by the pancreatic β cells, is a key regulator of carbohydrate and lipid metabolism. One of the numerous biological functions of insulin is the reduction of the blood glucose concentration. Under physiological conditions, insulin secretion is potentiated in response to a rise in blood glucose levels. However, not every hyperglycemic stimulus up-regulates insulin secretion to an identical extent. It appears that oral administration of glucose is a more potent secretory stimulus than its intravenous infusion.¹ This phenomenon indicates the existence of an additional β-cell stimulating mechanism, which is linked to the gastrointestinal tract and is independent of blood glucose levels.

This observation gave rise to the "incretin effect" concept, i.e., stimulation of insulin secretion as a response to food consumption before blood glucose levels rise. The first substance which fit the description of incretin was glucose-dependent insulinotropic polypeptide (GIP), formerly known as gastric inhibitory polypeptide.² Another intestinal hormone with the incretin effect is the glucagon-like peptide 1 (GLP-1). Its effect on carbohydrate metabolism results from direct stimulation of insulin secretion, increase in insulin gene expression, trophic effect on β cells, prevention of their apoptosis, and inhibition of glucagon secretion. Furthermore, this hormone increases the feeling of satiety and inhibits emptying of the stomach.³,⁴

GLP-1 structure  GLP-1 is a product of the same gene which encodes glucagon, a fact that was proven after cloning it.⁵ It is secreted primarily by L cells located in the duodenum, jejunum, ileum, and the colon. It is produced in significantly smaller amounts by the pancreas and hypothalamus.⁶ Its main biologically active form is GLP-1(7-36). Other forms are GLP-1(7-37), as well as GLP-1(1-36) and GLP-1(1-37), which are secreted mainly by the pancreas. The active form is a result of enzymatic processing of proglucagon into proglucagon, from which major proglucagon fragment is then detached. This transformation is

KEY WORDS
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ABSTRACT
This paper reviews the structure, function, and pathophysiology of glucagon-like peptide 1 (GLP-1). It describes the physiology and pathophysiology of the incretin axis, of which GLP-1 is a component, as well as the biosynthesis, secretion, activity, and degradation of this intestinal hormone. Effects of GLP-1 on the endocrine function of the pancreas, cardiovascular system, central nervous system, and on water-electrolyte balance have been also presented.
catalyzed by protein convertase PC 1/3. The next precursor is tGLP-1, which is subsequently transformed into GLP-1. This peptide turn undergoes amidation, catalyzed by peptidylglycine α-monooxygenase as well as peptidylamide glucan liase. Eventually, the mature form of GLP-1 consists of 31 amino acid residues.

**GLP-1 metabolism**  GLP-1 is secreted in response to food intake and reaches its peak concentration in blood plasma within 10 min of consumption. Apart from food components, glucose, and fatty acids, other stimulants of GLP-1 secretion include GIP, gastrin-releasing polypeptide (GRP), and impulses transmitted by the vagus nerve through acetylcholine. Once secreted into the circulatory system, GLP-1 is broken down within minutes, mainly by the enzyme dipeptidyl peptidase-4 (DPP-4). Another, less important mechanism of elimination is renal clearance. As a result of very efficient elimination mechanisms, especially DPP-4 activity, the concentration of the active GLP-1 form constitutes only 20% of its overall concentration. DPP-4, also known as CD-26, is a transmembrane glycoprotein, which forms a homodimer with a molecular mass of about 250 kDa. Each subunit consists of a large extracellular domain with proteolytic qualities, a single transmembrane chain, and a small intracellular fragment. This enzyme is expressed on the surface of numerous cells, such as lymphocytes, endothelial cells, enterocytes, in the liver, lungs, kidneys, and others. Under the influence of DPP-4, GLP-1 is transformed into GLP-1(9-36), GLP-1(7-35), and GLP-1(7-34). They do not display incretin activity, and they may have an antagonistic effect on GLP-1(7-36). DPP-4 breaks down not only GLP-1, but also neuropeptide Y, peptide YY, GIP, growth hormone-releasing hormone, tissue hormones, and chemokines.

**The GLP-1 receptor**  GLP-1 binds with a specific receptor, GLP-1 receptor (GLP-1R), which shows a structural similarity to the glucagon receptor. GLP-1R has the classic structure of G-protein-coupled and adenylyl-cyclase-coupled receptors, which penetrate the cell membrane 7 times. The receptor’s molecular mass is about 65 kDa. Stimulation of the receptor results in a rise in intracellular cyclic adenosine monophosphate (cAMP) and calcium concentration, which in β cells is a signal for exocytosis of previously synthesized insulin. In addition, activation of protein kinase A potentiates insulin biosynthesis, modifies gene expression, and has a trophic as well as promitotic effect on β cells. Besides insulin-producing cells, GLP-1R is also expressed in α cells, in the brain, central nervous system, gastrointestinal tract, kidneys, liver, and lungs. Such prevalence of GLP-1R in peripheral tissues suggests pleiotropic activity of this intestinal hormone.

**The effect of GLP-1 and incretin mimetics on β cells**  Numerous experiments indicate that native GLP-1 increases β-cell mass in animals with experimental diabetes (chemically or surgically induced) by stimulating their proliferation, neogenesis of pancreatic islets from precursor cells, and by inhibiting β-cell apoptosis. A similar effect is observed in animal models, as well as in in-vitro studies on long-acting incretin mimetics: exendin-4 and liraglutide. The mechanism of antipoptotic effect produced by GLP-1 on β cells is dependent on both the cAMP and phosphatidylinositol kinase pathways. It has been shown that activation as well as stimulation of inhibitor of apoptosis 2 and Bcl-2 antipoptotic gene expression occurs during this process.

In recent research, however, no significant effect of GLP-1 (10 μg/kg or 100 μg/kg was administered intraperitoneally [IP] from the third to sixth day of the disease) on the mass of β cells in most of nonobese diabetic (NOD) mice with autoimmune diabetes, when GLP-1 was administered as the only therapeutic agent. In this experiment, normoglycemia combined with a decrease in anti-insulin antibody titer in the fifth week after GLP-1 therapy was obtained in 4 out of 14 animals, while only 7 out 7 which received placebo injections (PBS solution) were characterized by elevated glycemia values and significantly reduced β-cell mass. However, when GLP-1 (100 μg/kg 2×/day IP) was administered together with gastrin (1.5 μg/kg 2×/day IP), a return to normoglycemia was observed in all NOD mice. At the same time, an increase in mass and a decrease in the extent of β-cell apoptosis were observed, alongside an increase in the number of precursor cells staining for insulin presence within the pancreatic ducts. Of note, combined therapy of GLP-1 and gastrin had an inhibitory effect on autoimmune process directed against the antigens of pancreatic islet β cells. In those animals, a decline in anti-insulin antibodies was observed, and the transfer of “immunologically modified” monocytes harvested from their spleens prevented disease development in the recipients, i.e. mice predisposed to autoimmune diabetes.

Current observations concerning the effect of high (supraphysiological) GLP-1 concentrations, as well as chronic stimulation by GLP-1 (and its analogues) on pancreatic duct β cells in humans are not unequivocal. On one hand, researchers have reported cases of nesidioblastosis (hyperplasia of pancreatic islet β cells with accompanying postprandial simultaneous hypoglycemia) in patients who had undergone bariatric surgery (especially the Roux-en Y operation), which is linked to GLP-1 hypersecretion. It was proven that in healthy people GLP-1 concentration does not exceed 20 pmol/l, while in patients who had undergone bariatric surgery, GLP-1 values exceed 100 pmol/l, accompanied by a doubling of an insulin concentration 30 min after a standard meal.
| Mechanisms of GLP-1 activity |  |
|-----------------------------|-----------------------------|
| **pancreas**                 | stimulates glucose-dependent insulin secretion  |
|                             | potentiates β-cell response to glucose  |
|                             | potentiates transcription of insulin-encoding gene, increases mRNA stability and biosynthesis  |
|                             | stimulates β-cell neogenesis and proliferation  |
|                             | inhibits β-cell apoptosis  |
|                             | inhibits glucagon secretion  |
|                             | stimulates somatostatin secretion  |
| **gastrointestinal tract**  | inhibits gastric emptying  |
|                             | inhibits secretion of gastric juices  |
| **central nervous system**   | inhibits food and water intake  |
|                             | stimulates satiety, affects loss of body weight  |
|                             | has neurotrophic and neuroprotective activity  |
| **cardiovascular system**    | vasodilatory activity via an endothelium-dependent mechanism  |
|                             | cardioprotective activity during ischemic-reperfusible injury  |
|                             | inhibits cardiomyocyte apoptosis after experimental ischemia  |

GLP-1 has neurotrophic and neuroprotective properties. As human life span becomes longer, there is an increase in the number of people with such diseases as Alzheimer’s or Parkinson’s characterized by neurodegenerative lesions dependent on age. In Alzheimer’s disease, lesions are caused by a toxic protein, amyloid β (Aβ), excess glutamine, and disruption of calcium homeostasis. While binding with the GLP-1R, GLP-1 displays neurotrophic properties, protects against excess glutamine, and reduces the amount of Aβ. This creates a possibility for the use of GLP-1 in the treatment of Alzheimer’s disease. During research on GLP-1’s effect on calcium canal regulation in the hippocampus neurons, a decrease in glutamine’s toxic activity, reduced depolarization, and a higher cell survival rate were observed. In animals, GLP-1 constitutes a neuroprotective factor for pyridoxine-induced peripheral neuropathy. Hence, GLP-1 may prove useful in the treatment of diabetic neuropathy.

A study on rats with the use of a floating platform showed a beneficial effect of GLP-1 on learning and spatial memory. Animals which had been treated with GLP-1 intracerebroventricularly, or which had genetically enhanced GLP-1R expression, more easily, and via a shorter route, found their way to the floating platform. By affecting the central nervous system, GLP-1 causes a rise in temperature along with secretion of pituitary hormones including thyroid stimulating hormone, luteinizing hormone, and vasopressin. In mice with mutation of the receptor (knockout GLP-1R—/—), the main function of the hypothalamic-pituitary-adrenal axis is preserved, while there is an increase in corticosteroid concentrations in response to stress. GLP-1 regulates appetite. Administered intracerebroventricularly to rats, it reduced food intake by acting on the GLP-1Rs in the hypothalamus. GLP-1 also reduces food intake through its central effect on the hypothalamus, which increases satiety and delays emptying of the stomach. Peripheral GLP-1Rs delay stomach emptying, trigger the end of feeding, and cause satiety through the vagus nerve. Vagotomy reduced the anorectic effect of GLP-1, thus indicating the significance of this anorectic signal transmitted to the hypothalamus.

The effect of GLP-1 on food intake was studied in rats under various laboratory conditions. The stress that accompanied the animals when transferred to clean cages reduced the anorectic effect of GLP-1. GLP-1 administered intracerebroventricularly to chicks caused a decrease in food intake, although it did not affect energy expenditure, calculated on the basis of oxygen intake and carbon dioxide production, this decrease in the RQ ratio indicated a change in the proportion of energy substrates used from carbohydrates to fats. The effect of the lower parts of the brain stem and the adrenergic system on an increase in energy expenditure was observed after intravenous...
in the blood rises after meals, and if administered peripherally, they inhibit food intake. Simultaneous administration of GLP-1 and peptide YY, both in mice and in humans, synergistically potentiated the inhibitory effect on food intake.

Oral administration of glutamine effectively increased GLP-1 concentrations in lean subjects and in obese subjects without diabetes. The rise in GLP-1 concentration was least pronounced in obese diabetic individuals. At the same time, there was a rise in both insulin and glucagon concentrations.

Stimulation of GLP-1 production depends on the type of food product. Quickly absorbed protein products, such as whey protein, result in a stronger GLP-1 response than casein, which is slowly absorbed.

Intravenous administration of GLP-1 in humans enhances the feeling of satiety and fullness, and mitigates hunger and the desire to eat, as well as significantly reduces food intake. Oral administration of glutamine effectively increased GLP-1 concentrations in lean subjects and in obese subjects without diabetes. The rise in GLP-1 concentration was least pronounced in obese diabetic individuals. At the same time, there was a rise in both insulin and glucagon concentrations.

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Administration of GLP-1 for 6 weeks in form of continuous subcutaneous infusion or subcutaneous injections 4 times a day before meals led to a 15% reduction in food intake and loss of body mass.69

A role of GLP-1 in the pathogenesis of obesity has not been established to date.70 In most studies, reduced GLP-1 concentration was noted in obese subjects.71,72

Leptin is a long-acting signal in energy homeostasis, which gives information on the body’s fat reserves; however, most hormones of the gastrointestinal tract are secreted shortly after food intake.73 Most hormones produced in the gastrointestinal tract, apart from ghrelin, have an anorectic effect which increases satiety. This stops feeding and promotes satiety, thus delaying the next meal.74 The role of gastrointestinal tract hormones in obesity and their role in reduction of body mass was better understood thanks to the effects obtained after bariatric surgery.

Currently, the most commonly applied surgical techniques in bariatry are:

1. restrictive operations which reduce food consumption, such as gastric banding
2. absorption-restricting operations, such as bilo-pancreatic bypass
3. operations combining restriction and reduction of absorption, such as bilio-pancreatic bypass with a duodenal switch, or distal gastric bypass.

The loss of body mass observed after these operations was initially solely attributed to food restriction due to reduced stomach volume or reduced absorption. It turned out, however, that reduced appetite was yet another factor which facilitated body mass reduction in patients who had undergone these operations.75 This mechanism may be caused by changes in the passage of food through the gastrointestinal tract and its effect on hormone secretion – an earlier increase in concentrations of glycemia-counteracting hormones, such as GLP-1, was found.76

Reduced fasting GLP-1 concentrations in the blood, observed after weight loss, may have an effect on increase in appetite and on a tendency to a commonly observed reiterated increase in body mass.77 The incretin axis constitutes a potentially important therapeutic target in the treatment of obesity.78,79

The effect of GLP-1 on ion equilibrium and the kidneys Towards the end of the 20th century, it was proven that glucagon administration in experimental animal model induced changes in glomerular filtration, diuresis, as well as electrolyte and urea excretion.80

GLP-1 also possesses at least part of these properties. It shows diuretic and natriuretic activity in both lean and obese subjects. Glomerular filtration in obese people decreases under the influence of GLP-1, while in lean people it does not change significantly.81,82 Of note is the fact that in experimental animals, GLP-1 increases glomerular filtration83 and potassium excretion. The latter phenomenon is not observed in humans.83

It is controversial what causes these different effects. We cannot rule out that results of the studies in humans are erroneous due to flawed methodology. Another possible explanation is that in obese people in whom hyperfiltration occurs (or in whom one can expect hyperfiltration), GLP-1 acts differently, protecting the kidneys from additional increase in filtration after meals.

Regardless of the above-mentioned controversy, all available data indicate that GLP-1 (both in animals and in humans), has a natriuretic and diuretic effect. This may be of potentially great clinical significance because an increase of both sodium and urine excretion may have an antihypertensive effect. Both these effects may explain the drop in blood pressure observed after administration of GLP-1 in sodium-sensitive rats with hypertension,84 as well as after administration of GLP-1 analogues in humans.85 At the same time, in humans at least, GLP-1 seems not to have a negative effect on potassium equilibrium.

The effect of GLP-1 on the cardiovascular system Apart from the well-documented cardiovascular effect of GLP-1, its role in the cardiovascular system also arouses interest. This is caused not only by numerous observations in experimental research with the use of incretin, but also by greater interest in the effect of potential antidiabetic drugs on the cardiovascular system. In the case of GLP-1, its effect on the cardiovascular system may include a direct effect on the cardiac muscle and the vascular system. This concerns both patients with type 2 diabetes and those without diabetes.

The first observations concerning GLP-1’s vasodilatory effect via an endothelium-dependent mechanism were made in the pulmonary artery’s vascular bed.86 The possibility of improvement of endothelial function was confirmed in patients with diabetes and stable coronary disease.87 Recently it has been observed that a product of GLP-1 (7-36) degradation by DPP-4, namely GLP-1 (9-36), also has a vasodilatory effect, and that this activity does not require the GLP-1R.88 In reference to its effect on the heart, GLP-1’s cardioprotective properties under conditions of ischemia and reperfusion may depend on activation of intracellular defense mechanisms and modulation of cardiomyocyte metabolism. Experimental research on animals revealed that GLP-1 administration may reduce myocardial infarct size.89 In clinical research on patients with acute myocardial infarction, it was observed that administration of GLP-1 after reperfusion through direct coronaryoplasty improves systolic function of the left ventricle.90 The mechanisms of this beneficial effect are currently investigated. It was shown that GLP-1 leads to kinase activation, on which the extent of reperfusion injury depends.89,91 This includes phosphatidyl inositol 3-kinase (PI3K) cascade, as well as extracellular...
regulated kinase. Under conditions of myocardial reperfusion damage, they are also among reperfusion injury salvage kinases (RISK). Activation of the RISK pathway leads to translation of protective proteins, activation of antiapoptotic mechanisms, and prevents opening of megacannels. Under experimental conditions, Bose et al. proved that the mechanism of GLP-1’s cardioprotective activity entails PI3K activation, followed by p70S6K activation. The p70S6K pathway regulates the translation and synthesis of proteins which are key to the growth and survival of cells in mammals.

The human heart consumes a few kilograms of adenosine-5’-triphosphate daily, which is essential to sustain basic functions of the myocardium. Cardiac muscle in mammals has the capacity for aerobic metabolism of fats and carbohydrates. Under normal conditions, energy is obtained mainly from metabolism of free fatty acids. Under ischemic conditions, metabolism is shifted towards glucose consumption, which is more effective in terms of energy. Chronic hemodynamic load on the heart leads to reactivation of fetal genes and change of the dominant oxidation supplement in the cardiomyocytes to glucose. At the beginning, this adaptive activity is beneficial, but with time it leads to the development of insulin resistance in the myocardium. This leads to a loss of metabolic elasticity which is essential for the proper cardiac function, and leads to the development of cardiomyopathy. An example of a possible beneficial effect on cardiac metabolism is the use of free fatty acid oxidation inhibitors (partial fatty-acid oxidation), trimetazidine and ranolazine, in the treatment of coronary artery disease and chronic heart failure. For this reason, potential positive effects of GLP-1 in ischemia and coronary insufficiency are a subject of considerable interest.

In experimental animal models, it has been shown that GLP-1 administration during ischemia and reperfusion reduces accumulation of lactates and pyruvates in ischemic tissues. Studies on cultures of human myocytes demonstrated an improvement in glucose metabolism. The question remains whether metabolic effect observed after administration of GLP-1 could be linked to insulin’s effect on the myocardium, or to the direct activity of GLP-1. Zhao et al. illustrated, in a model of isolated rat hearts, that GLP-1 increases glucose consumption almost 3-fold, and accelerates the restoration of myocardial function after episodes of ischemia in an alternate mechanism to insulin activity, which is independent of activation of protein kinase Akt-1, and translocation of insulin-regulated glucose transporter (GLUT)-4. This mechanism probably includes an increase of nitrous oxide production in the myocardium, increase in mitogen-activated protein p38 kinase activity, and translocation of GLUT-1. In vivo studies in dogs with pacing-induced dilated cardiomyopathy have shown that GLP-1 infusion induces a substantial improvement of left ventricular function and increases glucose myocardial intake. In other studies, also on dogs with pacing-induced dilated cardiomyopathy, during euglycemic metabolic clamp, it was shown that not only GLP-1(7-36), but also GLP-1(9-36), a product of its degradation, have a similar beneficial effect on the heart. Furthermore, it has been demonstrated that some beneficial effects of GLP-1(7-36) administration also occur in mice which do not possess a receptor for this form of GLP-1. This may indicate that also GLP-1(9-36) is biologically active in the myocardium and in the blood vessels, and may have its receptor. It is important to explain these observations because administration of DPP-4-resistant GLP-1 analogues and DPP-4 inhibitors would be devoid of part of the beneficial effects on the myocardium and the blood vessels.

Recently, it has been proven for the first time that long-term infusion of GLP-1 extends survival time in obese, spontaneously hypertensive, heart failure-prone rats. GLP-1’s activity in this experimental model of heart failure was linked to an improvement in contractility and in left ventricle output both in vitro and in vivo. It was also associated with higher glucose consumption and reduced cardiomyocyte apoptosis. Research on the effect of GLP-1 on apoptosis and glucose intake was conducted on models of isolated rat hearts. Reduction of apoptosis in the group treated with GLP-1 was linked to a decrease in caspase-3 activity in the myocardium. Similar, positive observations regarding myocardial function were made earlier in small groups of patients with chronic heart failure, and those who had undergone aorto-coronary bypass. These studies showed that patients without diabetes had similar benefits to those with diabetes. This again indicates that GLP-1 can directly act on the cardiovascular system, independently of glycemia control. The figure summarizes the most important effects of GLP-1 activity on the cardiovascular system.

In summary, the incretin axis constitutes a promising target for therapeutic action in type 2 diabetes. GLP-1, the most important hormone of the incretin axis, demonstrates multidirectional activities, the most important of which have been summarized in the table. Drugs associated with the incretin axis may potentially regenerate its impaired function, upregulate insulin secretion, positively affect body mass, appetite, blood pressure, and cardiovascular function. Our knowledge on how to fully exploit therapeutic possibilities of the incretin axis still incomplete, and the issue certainly requires further research.

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The role of glucagon-like peptide 1 in glucose homeostasis...
ARTYKUŁ POGŁĄDOWY

Rola glukagonopodobnego peptydu 1 w homeostazie glukozy oraz innych aspektach fizjologii człowieka

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SŁOWA KLUCZOWE
GLP-1, hormony jelitowe, oś inkretynowa, wydzielanie insuliny

STRESZCZENIE

W niniejszej pracy przedstawiono strukturę, funkcję i patofizjologię glukagonopodobnego peptydu 1 (glucagon-like peptide 1 – GLP-1). Opisano fizjologię i patofizjologię osi inkretynowej, w której skład wchodzi GLP-1, a także omówiono biosyntezę, wydzielanie, działanie i degradację tego hormonu jelitowego. Przedstawiono także działanie GLP-1 na część wewnętrzno-wydzielniczą trzustki, układ sercowo-naczyniowy, ośrodkowy układ nerwowy oraz gospodarkę wodno-elektrolitową.