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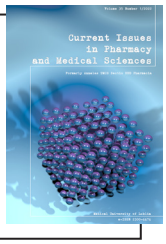

New perspectives on the use of glucagon-like peptide 1 in diseases of the central nervous system

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ABSTRACT

Glucagon-like peptide 1 is a neuromodulatory peptide that regulates the carbohydrate metabolism. It can cross the blood-brain barrier, and, indeed, while mostly produced in the distal small intestine and colon, it is also synthesized in the nucleus of the solitary tract of the brain stem. The wide distribution of glucagon-like peptide 1 receptors in the different areas of the brain is responsible for the pleiotropic effects of glucagon-like peptide 1 in the central nervous system. Notably, the peptide plays important roles in regulating food intake, in memory functioning, as well as in neuroprotective processes and emotions. This makes it an important tool in the treatment of many central nervous system related abnormalities, such as neurodegenerative diseases, addictions and neuropsychiatric disorders.

INTRODUCTION

Incretin hormones, commonly called "incretins", are widely known to regulate the functioning of the digestive system. They include glucose-dependent insulinotropic peptide (GIP) and the glucagon-like peptide 1 (GLP-1).

GLP-1 peptide is produced from preproglucagon in L-type enteroendocrine cells in the distal small intestine and colon as a response to food intake. It minimizes postprandial glycemia by increasing the secretion of endogenous insulin, reducing glucagon synthesis and slowing down gastric emptying. These GLP-1 peptide-induced effects are a result of the stimulation of receptors that are located in the pancreatic islets β cells. Under physiological conditions, the GLP-1 peptide is rapidly degraded by the dipeptidyl peptidase-IV (DPP-IV) enzyme and its half-life is only 2–3 min in plasma [1]. In order to prolong its action, GLP-1 peptide analogs and DPP-IV inhibitors have been introduced. GLP-1 peptide analogues, such as exenatide, lixisenatide, liraglutide or dulaglutide, act directly on GLP-1 peptide receptors, while DPP-IV inhibitors, such as saxagliptin or linagliptin, inhibit the activity of the DPP-IV enzyme responsible for the degradation of endogenous GLP-1 peptide. The safety of these substances is confirmed. The most important advantage of these drugs is their antihyperglycemic effect. This comes without risk of hypoglycemia. Currently, drugs increasing the activity of the GLP-1 peptide are used in the treatment of type II diabetes [2].

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Nowadays, the GLP-1 peptide receptors are well known to be present not only in the gastrointestinal tract, but also in the heart and kidneys, through which the GLP-1 peptide regulates blood pressure, heart rate, and has a cardioprotective effect. Moreover GLP-1 peptide affects calcitonin secretion, regulates Ca2+ level and bone metabolism. GLP-1 peptide receptors are also located in the lung, but their role is currently unclear [3].

Existing literature data concerning the GLP-1 peptide have focused primarily on the role of the GLP-1 peptide in the peripheral tissues. The importance of the GLP-1 peptide in diabetes and co-occurring diseases of the cardiovascular system [4] and kidney disease [5] has been confirmed. However, over time, as the relationship between the administration of drugs increasing the activity of the GLP-1 peptide and body weight loss was observed, research on the GLP-1 peptide was extended to examine its effect on the central nervous system (CNS). As of the time of writing, there are reviews describing the role of the GLP-1 peptide in neurological disorders [6,7] and in addictive disorders [8], however, they do not describe the potential importance of the GLP-1 peptide in many clinical disorders, hence, this review.

Neuromodulatory function of GLP-1 peptide in the CNS

Receptors for the GLP-1 peptide are also located in the brain [9], and particularly high expression of these receptors occurs in the brain stem, in the nucleus of the solitary tract. Here, the peptide is synthesized in preproglucagon neurons

[10] and acts as a regulatory neuropeptide throughout the entire brain. The nucleus solitarius receives signals from the digestive tract and circulatory system about the content of glucose, insulin, ghrelin and other peptides in the blood. These signals are then transmitted to other brain structures containing receptors for the GLP-1 peptide, such as: the hypothalamic nuclei (the arcuate nucleus, the paraventricular nucleus, the ventromedial nucleus), which participate in the regulation of food intake; and the mesolimbic system components, i.e. the VTA and the nucleus accumbens [11], that evoke the feeling of pleasure and satisfaction after eating a meal. Therefore, the GLP-1 peptide in the brain plays important roles in the regulation of food intake and its rewarding effects.

The presence of receptors for the GLP-1 peptide has also been demonstrated in other brain structures, such as the hippocampus, amygdala, olfactory bulb, thalamic nuclei, periaqueductal gray matter, substantia nigra and rostral ventrolateral medulla [12]. Therefore, the GLP-1 peptide, in addition to regulating food intake, has influence upon memory functions, neuroprotection and the emotions. This comes about due to the existence of interactions in the brain between the GLP-1 peptide and other neurotransmitters, including dopamine, glutamate and γ-aminobutyric acid (GABA) [13]. Still, despite the fact that GLP-1 peptide is known to have a role in neurotransmission, neuroinflammation, neuroprotective processes and cognitive function [14], detailed mechanisms are not fully recognized.

As chronic brain inflammatory processes are closely associated with numerous neurodegenerative diseases, neuropsychiatric disorders, epilepsy, addiction and other CNS disorders, GLP-1 peptide seems to be a suitable target for treating various diseases in the brain.

The effects of GLP-1 peptide on learning, memory and neuroprotection

The presence of receptors for GLP-1 peptide in the hippocampus indicate their role in the processes of learning and memory. In the research of [15], rats which received intracerebroventricularly a GLP-1 analog displayed improved spatial memory in the Morris water maze test and this effect was reduced after administration of a GLP-1 antagonist. Similarly, chronic administration of the same GLP-1 analog in GLP-1 *knock-out* mice provided protection against kainate-induced hippocampal apoptosis [15]. In other research, administration of Exendin-4, a GLP-1 analog, was found to enhance differentiation and neurite outgrowth in rat pheochromocytoma (PC12) cells and in human neuroblastoma SK-N-SH cells and also protected hippocampal neurons against glutamate-induced apoptosis [16]. The molecular mechanisms underlying the neuroprotective effects of central GLP-1R agonism are, according to [16], at least in part, mediated through the ability to increase cAMP formation and subsequently to enhance activation of PI3-kinase and ERK [16].

The effects of GLP-1 peptide on neurodegeneration

Much research has been conducted on the importance of the GLP-1 peptide in neurodegenerative diseases, such as Alzheimer disease (AD), Parkinson disease (PD) and multiple sclerosis (MS). These studies have determined the influence of the GLP-1 peptide on the pathomechanisms underlying the above-mentioned diseases, as well as on the symptoms accompanying these disorders.

AD is an incurable and progressive disease that manifests itself with multiple cognitive deficits involving memory, language, motor skill and perception. AD pathology is characterized by the deposition of amyloid-β (Aβ) plaques and tau neurofibrillary tangles in the brain. It leads to the death of nerve cells and, consequently, to reduced production of neurotransmitters essential for proper brain function. As receptors for the GLP-1 peptide are also found in the hippocampus and amygdala [13], i.e. in the structures responsible for memory, the importance of the GLP-1 peptide has also been investigated in research conducted regarding the memory disorders that are typical for AD manifestation. In the course of such work, it was found that the administration of an analog of GLP-1, liraglutide, prevents memory impairments and synapse loss and deterioration of synaptic plasticity in the hippocampus in animals. Moreover, overall β-amyloid plaque count in the cortex is also reduced [17]. The first results from clinical trials demonstrate that the preclinical results translate to the clinic [18].

PD is a degeneration of brain structures associated with the loss of nerve cells in the substantia nigra, responsible for the synthesis of the neurotransmitter dopamine. This causes a weakening of dopaminergic transmission, manifested by slow movement, muscle stiffness, resting tremor, and gait and posture disorders. The known neuroprotective properties of the GLP-1 peptide and the coexistence of receptors for the GLP-1 peptide on CNS neurons in key areas of the brain for the pathogenesis of PD, has prompted numerous experiments on the influence of the GLP-1 peptide on the functioning of dopaminergic neurons in an animal model of PD. In some preclinical experiments, exendin-4 has been shown to have a positive effect on the cellular and functional properties of dopaminergic neurons [19, 20], possibly by reducing neuroinflammation [21]. Moreover, recent clinical studies have confirmed the positive effect of GLP-1 mimetics on the cognitive behavior of patients with PD [18].

MS is a disease of the CNS classified as a neurodegenerative disease. It is characterized by chronic, progressive, immune-mediated neuroinflammatory events leading to neuronal demyelination, loss of myelin-producing oligodendrocytes, and ultimately destruction of nerve fibers [22]. Current knowledge on the role of the GLP-1 peptide in MS is very limited, but there are few reports confirming this correlation. Ammar *et al.* [23] have demonstrated that liraglutide, an analog of GLP-1, reduces the demyelination and restores impaired behavioral and motor functions in an animal model of MS. Furthermore, it has been revealed that liraglutide can inhibit apoptosis. In turn, the researchers of [24] noted that administration of dulaglutide, a GLP-1 analog, alleviates clinical symptoms and experimental autoimmune encephalomyelitis in mice. These reports warrant that further investigations on the correlation between the GLP-1 peptide and MS are necessary and may be fruitful in countering it.

The role of the GLP-1 peptide in anxiety and depressive behaviors

Today, anxiety and depressive disorders are a significant problem. Despite many studies conducted around the world, the mechanisms underlying the above-mentioned behaviors are still not fully understood. Relatively recently, the GLP-1 peptide was confirmed to play a role in these behaviors. Research indicates that GLP1 neurons are anatomically located to receive and modulate responses to stress. Moreover, according to recent investigations, stress stimuli activate GLP-1 neurons in the nucleus of the solitary tract, stimulating avoidance behavior and initiating sympathetic nervous system and hypothalamic–pituitary–adrenal axis response [25]. The results of experiments using animals are, however, ambiguous. Anderberg et al. [26] showed that short-term administration of the GLP-1 peptide and its analogue, exenatide, increased anxiety behaviors in rats, while chronic administration of exenadine-4 did not affect anxiety behaviors, but weakened depressive behaviors in these animals. In turn, Komsuoglu Celikyurt *et al.* [27] demonstrated that chronic exenatide administration induced anxiolytic and antidepressant-like effects in mice. Taking into account the existing divergent literature data, the role of the GLP-1 peptide in anxiety and depressive disorders should be further investigated.

The effects of GLP-1 peptide on reward system

The reward system is a collection of brain structures in the CNS regulating food intake, motivational and sexual behavior. Stimulation of the reward system induces increased release of dopamine, which determines the feeling of pleasure. Taking into account the distribution of receptors for the GLP-1 peptide in structures closely associated with food intake, rewarding and motivational behaviors, such as the hypothalamus, nucleus accumbens, ventral tegmental area (VTA), amygdala and others [13,28], he GLP-1 peptide is believed to affect the reward system.

Alhadeff *et al.* [11], in assessing the activity of the GLP-1 peptide in the VTA and nucleus accumbens in rats, showed that activation of its receptors reduces food intake, while blocking these receptors brings about the opposite effect, i.e. increased appetite. This outcome suggests that the relationship between food intake and the activation of GLP-1 receptors occurs through direct activation of the mesolimbic reward system. Clinical studies have confirmed that semaglutide (a GLP-1 analog) induces reduced appetite in humans [29], and indeed, semaglutide has been recently approved into the therapy of obesity.

However, research has also been conducted on the influence of the GLP-1 peptide on the rewarding effect of not only food, but also of various addictive substances. In such work, it was evidenced that the administration of a GLP-1 analogue inhibited the rewarding effect of various addictive substances, i.e. morphine [30], cocaine [31,32], amphetamine [31], ethanol [33,34] and nicotine [35] in experimental animals. At the same time, EX-9-39, an antagonist of GLP-1 peptide receptors, increased the rewarding effects of alcohol in rats [36]. All these findings clearly demonstrate that stimulation of GLP-1 receptors modulates the rewarding effects of addictive substances and that GLP-1 drugs may be an important pharmacological tool in the pharmacotherapy of addiction [37] in the future.

GLP-1 peptide as a potential tool in other diseases of the CNS

There are preliminary reports that the GLP-1 peptide may be a potential tool in the treatment of other CNS disorders, such as stroke and epilepsy. Stroke is a medical condition in which the blood vessels carrying oxygen and nutrients to the brain, burst or are blocked by a clot. Since neuroinflammation is the basis of stroke, the GLP-1 peptide was investigated to ascertain whether administration of its analogues will have a beneficial effects on stroke. Accordingly, the GLP-1 analogue exenatide has been shown (in rodents) to decrease the area of the brain that has degenerated after stroke, by reducing microglial inflammation, reversing hyperexcitability, and minmizing neuronal loss [14].

Epilepsy is a brain disorder that induces recurring seizures. As epilepsy is also associated with neuroinflammation, it is not surprising that literature data have clearly confirmed the beneficial neuroprotective effects of the GLP-1 peptide in this condition. In these studies, increased hippocampal brain-derived neurotrophic factor (BDNF) levels was increased and the number of necrotic neurons in the hippocampus was reduced through administration of GLP-1 peptide analogues. As a result, a reduction or delay in epileptic seizures was observed [14].

CONCLUSIONS

The possibilities and achievements of modern experimental pharmacology and molecular biology allow for a more complete understanding of the effects and interactions different neuromodulatory substances. There is a lot of preclinical and clinical solid evidence that GLP-1 peptide has beneficial effect on the CNS. Nowadays, GLP-1 peptide analogues seem to be potential tools for use in the treatment of many CNS diseases. An understanding of the GLP-1 peptide effects on the CNS in more detail gives hope that the GLP-1 peptide may constitute a new direction in the pharmacotherapy of various CNS diseases.

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