

Research Progress of Perioperative Application of GLP-1 and Its Protective Effects on Organs

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Abstract: Glucagon-like peptide-1 (GLP-1) is a multifunctional hormone with broad pharmacological potential to control inflammation, protect cardiovascular, kidney, and liver functions. Moreover, GLP-1 can also cross the blood-brain barrier and bind with GLP-1R distributed in various parts of the brain, thereby reducing apoptosis caused by neuroinflammation and oxygen stress, and promoting learning, memory, cognitive function, neuroprotection, and nerve cell remodeling. However, the exact molecular pathway by which GLP-1 receptor agonists (GLP-1RAs) exerts protective effects on many organs is not fully understood, so it is a hot topic of research. In this article, the recent research on the multi-organ protection of GLP-1 is reviewed, with emphasis on the research progress in the field of nervous system and perioperative anesthesia.

Keywords: Glucagon-like peptide-1; Glucagon-like peptide-1 receptor agonist; Protection of organs

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1. Introduction

Glucagon-like peptide-1 (GLP-1) is a peptide hormone mainly derived from the gut and partly from brain stem neurons, which regulates insulin secretion, food intake, and intestinal motility^[1]. GLP-1 receptor (GLP-1R) is distributed in the pancreas, the brain, the afferent vagus nerve, the atrial myocytes, the vascular smooth muscle, the lungs, and part of the immune cells, etc., belonging to G protein-coupled receptors^[2-5]. GLP-1 receptor agonists (GLP-1RAs) are effective hypoglycemic agents that promote insulin secretion and inhibit glucagon secretion. They can also slow gastric emptying and suppress appetite to control blood sugar, thus they are currently mainly used in the treatment of type 2 diabetes mellitus (T2DM)^[6] and obesity^[7]. Numerous studies have shown that GLP-1 is a multifaceted hormone with extensive pharmacological potential, which can control inflammation, protect cardiovascular, kidney, and liver functions^[8-10]. In addition, GLP-1 can cross the blood-brain barrier and combine with GLP-1R distributed in various parts of the brain, thus reducing neuroinflammation and apoptosis caused by oxygen stress, and promoting learning, memory, cognitive function, neuroprotection, and nerve cell remodeling^[1,11].

However, the exact molecular pathway of the protective effect of GLP-1RAs on many organs is still not completely clear, which makes it a hot research topic^[12-14]. In this article, the recent research on the

multiorgan protective function of GLP-1 and the treatment of various diseases are reviewed, with emphasis on the research progress in the field of nervous system and perioperative anesthesia.

2. Protective effects of GLP-1 on multiple organs

2.1. Effect on pancreas

GLP-1 secreted by L cells of intestinal mucosa activates GLP-1R on pancreatic beta cells in a glucose-dependent manner (only in the case of hyperglycemia), stimulates insulin secretion, inhibits glucagon secretion by alpha cells of pancreas, and repairs pancreatic beta cells, which promotes proliferation of beta cells and reduces apoptosis of beta cells^[15]. Unlike insulin and other hypoglycemic agents, GLP-1 has no hypoglycemic effect when blood sugar is normal, so there is almost no risk of hypoglycemia^[7]. Recent studies have found that the α cells of the pancreas can also release a small amount of GLP-1, which plays an important role in β cell function through paracrine regulation^[16]. Zummo *et al.* used chemical inhibitors and siRNA knockout to investigate the potential pathway by which GLP-1Rs exenatide (exendin-4) stimulates autophagy. The results of the study indicate that the RAPGEF/EPAC-Ca(2+)-PPP3/calcineurin-TFEB axis is a key pathway regulating autophagy flux, lysosome function, and cell survival in pancreatic β -cells, which is independent of AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) signaling pathways. PPP3/calcineurin and its downstream regulator TFEB are key proteins that mediate autophagy induced by exendin-4^[17]. These studies may provide new therapeutic targets for T2DM.

2.2. Effects on the heart

Many studies have confirmed that GLP-1RAs has a protective effect on the heart. Stimulation of GLP-1 receptors on the sinoatrial node can increase heart rate, prevent coronary artery obstruction, reduce inflammatory factors, reduce myocardial injury, improve left ventricular function, and reduce infarction size^[9]. However, a clinical study found that exenatide did not reduce the size of myocardial infarction in patients with ST-segment elevation myocardial infarction when used as adjunct to percutaneous coronary intervention (PPCI)^[18]. However, the latest view is that heart failure is often accompanied by increased glycolysis and ketone oxidation, mitochondrial function, and creatine kinase response disorders, and GLP-1 can improve myocardial metabolism, energy transduction, and significantly reduce the occurrence of cardiovascular adverse events in T2DM^[19]. GLP-1RAs can play a cardiovascular protective role by anti-oxidative stress, inhibiting inflammatory response, and improving insulin sensitivity^[20-22]. In short, further studies will be needed to fully understand the mechanism and clinical effect of GLP-1RAs in improving cardiac function and preventing heart failure.

2.3. Effect on kidney

GLP-1 is a mediator in the entero-renal axis (a fast-acting feedforward circuit that regulates postprandial fluid and electrolyte homeostasis) and has a direct effect on the kidney^[23]. Tonneijck *et al.* proved for the first time through clinical trials that GLP-1RAs can benefit the heart and kidney by inhibiting Na⁺-H⁺ exchange in proximal renal tubules^[24]. GLP-1RAs activates mononuclear phagocytes, blocks inflammatory cell infiltration, promotes the production of inflammatory cytokines and adhesion molecules, and alleviates oxidative stress, fibrosis, and cell apoptosis in the kidney^[25]. Clinical studies have confirmed that GLP-1RAs can help diabetic nephropathy patients maintain renal sodium homeostasis, reduce albuminuria, and delay the decline of glomerular filtration rate by improving blood glucose, sodium, diuresis, anti-inflammatory, antioxidant stress, inhibiting renal fibrosis, and suppressing immune and inflammatory responses^[26]. However, whether GLP-1RAs can delay the progression of end-stage renal disease remains to be clarified.

2.4. Effects on the gut

GLP-1 release in the intestine activates the enteric-sympathetic -spinal pathway to inhibit stomach movement and appetite. This visceral alarm system can be used to treat obesity and gastrointestinal dysfunction^[27]. In addition to controlling blood sugar, GLP-1 can also inhibit the secretion of gastrin, inhibit gastric emptying, and reduce intestinal motility, and act as GLP-1R for the vagus and central nervous system, delaying the introduction of sensory information into the brain stem to suppress appetite and control food intake to reduce weight. Therefore, the blood GLP-1 in obese patients is significantly higher than that in people with normal weight^[28]. An animal study showed that the increase of endogenous bile acids and cholic 7-sulfate (CA7S) in the gastrointestinal tract can stimulate the expression of TGR5 and induce the secretion of GLP-1 after bariatric surgery. This study revealed a naturally occurring TGR5 agonist that plays a role in systemic glucose regulation but is still confined to the gastrointestinal tract^[29]. The anti-inflammatory properties and intestinal nutrition of GLP-1 play a therapeutic role in inflammatory bowel disease, short bowel syndrome, enterotoxicity, and other celiac diseases^[30]. However, the aforementioned evidence are mostly from animal experiments and small clinical trials of GLP-1RAs. New treatments for intestinal diseases such as GLP-1/GLP-2 dual agonists are still being developed.

2.5. Effect on respiratory system

A retrospective cohort study based on electronic health records showed that compared to other hypoglycemic agents, GLP-1RAs was associated with a lower rate of asthma exacerbation, lower length of hospitalization, lower cost, and lower risk of hospital admission in patients with asthma complicated with diabetes. GLP-1RAs may be a novel approach for the treatment of asthma complicated with diabetes^[31]. A 12-year retrospective cohort study from the US claimed that patients with type 2 diabetes using GLP-1RAs had fewer exacerbations of chronic lower respiratory disease^[32]. GLP-1 down-regulates the expression level of miR-27a by activating AMPK and plays an important regulatory role in diabetic pulmonary fibrosis^[33]. Obesity is a risk factor for asthma. GLP-1RAs can inhibit airway hyperresponsiveness and airway inflammation in obese asthmatic mice and reduce the release of IL-5, IL-13, CCL11, and other inflammatory factors in lung tissue and mucus secretion, which make them a potential drug for the treatment of obese asthmatic patients^[34]. GLP-1RAs are beneficial in the treatment of COVID-19 infected patients with type 2 diabetes by inhibiting inflammatory storm response, regulating right ventricular systolic blood pressure and pulmonary vascular remodeling, thus it is a candidate drug for the treatment of COVID-19 infected patients with pulmonary hypertension^[35]. However, the protective effect of GLP-1 on lung disease and acute lung injury patients without diabetes is yet to be studied.

2.6. GLP-1 in the field of nervous system research

2.6.1. Effects on cognitive and memory functions

T2DM causes adverse effects on brain function and cognitive memory. One of the underlying mechanisms is likely to be insulin desensitization in the brain, where high levels of sugar impair growth factor signaling, reduce energy utilization in the cerebral cortex, and increase inflammation and apoptosis signaling pathways^[36]. A study showed that the expression of Arc, APP, BACE1 and PS1mRNA significantly decreased in T2DM rats treated with GLP-1, by fluorescence quantitative PCR; and Arc protein in hippocampus was significantly decreased by western blotting and immunohistochemistry, and the learning abilities and memory were improved^[37]. Liraglutide increases mTOR expression by activating AMPK and PI3K/Akt signaling pathways, inhibits apoptosis, and protects against cognitive dysfunction through autophagy activation^[38]. Liraglutide can reverse GLP-1R decline in diabetic mice and improve the cellular activity of glycosylation end products, thereby delaying cognitive decline associated with aging^[39]. Liraglutide can also regulate ovarian pathological process and neuroprotective effect through Notch

signaling pathway to prevent cognitive dysfunction in patients with polycystic ovary syndrome^[40]. Bomba *et al.* demonstrated that exenatide can be used to delay age-dependent cognitive decline by reducing p75NTR signaling by promoting activation of the BDNF-TrkB neurotrophic axis and inhibiting apoptosis^[41]. In an observational study of 3001 older adults in Sweden, multiple regression analysis found that higher insulin sensitivity and GLP-1 levels were associated with better cognitive outcomes^[42]. A clinical study of 50 patients with T2DM, all of whom underwent cognitive assessment and near-infrared spectroscopy monitoring of brain function, found that liraglutide significantly increased activation in the dorsolateral prefrontal cortex and orbitofrontal prefrontal cortex, with significant improvements in memory and attention. This beneficial effect is independent of its hypoglycemic effect and weight loss, and it is more effective in the early stages of Alzheimer's disease intervention^[43]. The early symptoms of cognitive decline in diabetic patients may be abnormal sense of smell. After 3 months of GLP-1RAs treatment, the Montreal Cognitive Assessment (MoCA) score and the total score of the smell test improved in obese diabetic patients, and the right parahippocampal activation was enhanced by odor^[44].

2.6.2. The influence of postoperative cognitive function

Gong *et al.* observed that the expression of caspase-3, Bax, HMGB1, IL-1 β , and TNF- α activated by hippocampal activation were down-regulated in aged rats after 24h and 48h after exploratory abdominal section by intraperitoneal injection of DA-JC4 (GLP-1 and GLP double agonist). The expressions of Bcl-2, LC3-II and Beclin-1 were up-regulated, and their neuroprotective effects were related to the inhibition of postoperative neuroinflammatory response^[45]. The animal studies of Ruze *et al.* found that the possible mechanism for the improvement of cognitive function after bariatric surgery was that after duodenal jejunal bypass surgery, the increase of GLP-1 in rat brain was conducive to cognitive function, cerebral glucose uptake and transport, enhancement of glucose sensing and homeostasis, and significant improvement of neuronal activation^[46]. Qin *et al.* reported for the first time the effect of liraglutide on aging rats with postoperative cognitive dysfunction that were anesthetized with 3% sevoflurane and proved that it can improve the cognitive function of aging rats after anesthesia, and its mechanism is anti-apoptosis and anti-inflammation^[47]. Sedky found that the beneficial effects of liraglutide on ketamine induced hyperactivity and cognitive dysfunction were related to the reduction of TNF- α and oxidative stress^[48].

2.6.3. Influence on cerebral ischemia

Stroke is one of the most common causes of death and disability worldwide. GLP-1RAs like exenatide can effectively reverse the constriction of cortical arterioles induced by metabolites lactate or hypoxia and glucose deficiency, promote the continuous increase of PO₂ in brain tissue, regulate cerebral blood flow and improve cerebral perfusion, and protect the nerves of ischemic stroke^[49]. Traumatic brain injury (TBI) can cause neurodegeneration and nerve damage for months or even years through chronic inflammatory processes. Studies on rat models of cortical contusion (CCI) have shown that exenatide promotes neurological, cognitive, and cerebral blood flow recovery after TBI, attenuates neurodegenerative and inflammatory responses, such as significantly reducing the overexpression of TNF- α and IL-1 β and inhibiting the phosphorylation of p38 and ERK1/2. Therefore, it can potentially improve neurological prognosis^[50]. A meta-analysis of a Mendelian randomized design study summarized the effects of eight hypoglycemic drugs on stroke risk, and the results showed that hyperglycemia was cause-and-effect with increased risk of ischemic stroke, and GLP-1RAs could reduce the risk of ischemic stroke^[51]. These results can guide clinicians in the treatment of patients at high risk of ischemic stroke.

2.6.4. Influence on neurological diseases

GLP-1RAs may be an effective adjunct in the treatment of depression and/or diseases related to multiple

neurological disorders ^[52]. GLP-1RAs is also neuroprotective in humans and animals with neurodegenerative diseases, and its neuroprotective effect is independent of blood sugar levels. It is beneficial for the treatment of single-gene progressive neurodegenerative diseases such as Wolfram syndrome ^[53], chorea ^[54], epilepsy ^[55], mood disorders ^[56], schizophrenia ^[57], overeating, alcohol and cocaine abuse ^[58-60], and Alzheimer's disease ^[61]. *In vitro* cell experiments confirmed that GLP-1 could not only reduce carboxymethyl lysine (CML)-induced apoptosis of PC12 neurons, but also increase the level of peroxisome proliferator-activated receptor- γ (PPAR- γ), and this protective effect could be eliminated by GW9662. Moreover, the GLP-1R promoter sequence was detected in the PPAR- γ antibody extraction mixture, suggesting that GLP-1RAs could be used to treat cognitive deficits associated with neurological disorders ^[62]. Studies have shown that exenatide can improve mitochondrial morphology and brain energy metabolism and reduce oxidative damage and synaptic damage, which results in cognitive decline and behavior change in Alzheimer's model mice ^[63]. Although GLP-1RAs has been shown to have protective effects on the function of blood vessels, microglia and neurons, its neuroprotective effect is not related to its hypoglycemic effect. In the future, biomarkers guiding the changes of brain energy homeostasis region still need to be studied.

3. The relationship with perioperative anesthesia

Currently, there are not many large-sample clinical trials of long-acting GLP-1RAs. Biological distribution and dose of radiolabelled ⁶⁸Ga-Tuna-2, a noninvasive imaging marker, have been assessed by PET/CT to indirectly evaluate pharmacological properties and drug targets of GLP-1RAs in humans ^[64]. Anesthesiologist Zhou found that exenatide can partially reverse postoperative cognitive and behavioral disorders caused by surgery by down-regulating levels of NF- κ B and IL-1 β , improving tau hyperphosphorylation, and enhancing p-GSK-3 β (Ser9) activity ^[65]. With GLP-1RAs in the clinic, anesthesiologists have questioned whether patients should stop using non-insulin hypoglycemic drugs on the day of surgery because GLP-1RAs does not cause hypoglycemia and has many benefits. Hulst, an anesthesiologist, found that GLP-1RAs had better blood glucose control effect in the perioperative period without the risk of hypoglycemia, and its gastrointestinal side effects of nausea and vomiting were mild. If GLP-1RAs was stopped before surgery, it would lead to long-term inadequate blood glucose control ^[66]. Therefore, it is recommended that GLP-1RAs should be used during the perioperative period.

As the use of GLP-1RAs increases in patients with diabetes and weight loss, its common gastrointestinal side effects, such as nausea, vomiting, and diarrhea, may concern anesthesiologists, but these symptoms are mostly mild. However, GLP-1RAs should be used with caution in patients with gastroparesis, intestinal obstruction, pancreatitis, acute kidney injury requiring renal replacement therapy and other symptoms. There have been no large sample clinical studies on the perioperative application of GLP-1RAs. Besides, the protective mechanism of GLP-1RAs on the heart, kidney and cerebral nerves needs to be confirmed by more powerful clinical trials.

4. Outlook

GLP-1RA is used in the treatment of T2DM, which not only has a definite effect of improving blood sugar, but also has a multi-organ protective effect. There has been a growing interest towards the research of this kind of drugs. However, most of the current studies are animal studies and only few are clinical trials, which is partly due to the lack of specific and sensitive biomarkers to detect GLP-1R activation in humans. We look forward to more studies and clinical trials on the mechanism of GLP-1 and its receptor agonists in the future.

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Disclosure statement

The authors declare no conflict of interest.

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