REVIEW

Potential of Glucagon-Like Peptide 1 as a Regulator of Impaired Cholesterol Metabolism in the Brain

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ABSTRACT

Cerebral vascular diseases are the most common high-mortality diseases worldwide. Their onset and development are associated with glycemic imbalance, genetic background, alteration of atherosclerotic factors, severe inflammation, and abnormal cholesterol metabolism. Recently, the gut–brain axis has been highlighted as the key to the solution for cerebral vessel dysfunction in view of cholesterol metabolism and systemic lipid circulation. In particular, glucagon-like peptide 1 (GLP-1) is a cardinal hormone that regulates blood vessel function and cholesterol homeostasis and acts as a critical messenger between the brain and gut. GLP-1 plays a systemic regulatory role in cholesterol homeostasis and blood vessel function in various organs through blood vessels. Even though GLP-1 has potential in the treatment and prevention of cerebral vascular diseases, the importance of and relation between GLP-1 and cerebral vascular diseases are not fully understood. Herein, we review recent findings on the functions of GLP-1 in cerebral blood vessels in association with cholesterol metabolism. *Adv Nutr* 2020;11:1686–1695.

Keywords: glucagon-like peptide 1, GLP-1, cerebral vascular disease, cholesterol metabolism, cerebral atherosclerosis

Introduction

Cerebral blood vessel impairment is considered the main cause of vascular dementia and stroke, the incidences of which are rapidly increasing worldwide (1). Vascular dementia and stroke are progressive and irreversible neurodegenerative conditions that are accompanied by memory loss and social and psychiatric disturbance (2). With aging, people experience multiple metabolic impairments and cerebrovascular dysfunction such as diabetes, vascular dysfunction, atherosclerosis, ischemic stroke, vascular dementia, and cerebral small vessel disease (3). Recently, researchers have focused on the relation between cerebrovascular dysfunction, stroke, and dementia and the factors that link them. However, the detailed correlation between memory loss and cerebrovascular damage is unclear (1).

With age, arteries and microcapillaries in both the systemic vascular system and the central nervous system (CNS) transform into more inflammatory-conditioned blood vessels, resulting in severe vascular damage (4). Inflammation in cerebrovascular vessels leads to the infiltration of inflammatory cells into vessel arteriolar walls and triggers endothelial dysfunction, leading to cerebro-atherosclerosis, fibrinoid necrosis, perivascular inflammation, lacunar stroke, secondary thrombosis, arterial thickening, breakdown of the blood–brain barrier (BBB), and vascular dementia (4–6).

Impaired cholesterol metabolism in blood vessels has emerged as an important contributor to cerebrovascular disorders, including stroke and dementia (7, 8). The disturbance of cholesterol metabolism induces decreased plaque clearance in blood vessels, cholinergic dysfunction, abnormal lipid rafts, and increased toxic amyloid B-peptide deposition in dementia (9). Recent studies have also demonstrated that impaired metabolic homeostasis reduces cerebral blood flow and ultimately leads to memory loss (10) and dementia (11). Furthermore, cerebral endothelial dysfunction caused by dyslipidemia (12) is critically associated with the overproduction of chylomicrons by the intestine (13).

Glucagon-like peptide 1 (GLP-1) is an incretin that is mainly produced in L cells located in the intestine and acts by binding to GLP-1 receptors (GLP-1Rs) expressed in the pancreas, blood vessels, gastrointestinal tract, and brain (14). GLP-1 can control B-cell sensitivity and improve glycemic and cholesterol homeostasis (15). Moreover, this hormone maintains stable lipid homeostasis and normal blood flow in atherosclerosis and vascular dementia (16,

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Address correspondence to JS (e-mail: juhyunsong@chonnam.ac.kr).
Abbreviations used: BBB, blood–brain barrier; CNS, central nervous system; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; GLP-1R, GLP-1 receptor.

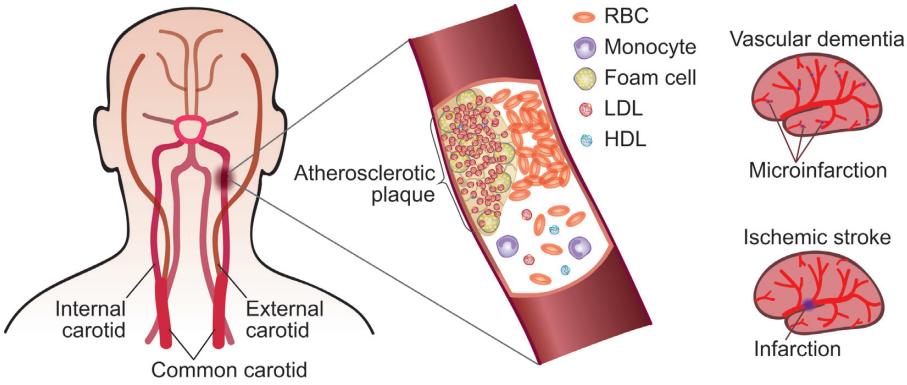

FIGURE 1 Illustration of blood vessels in the brain and the occurrence of neurovascular disorders due to impaired cholesterol metabolism. Ischemic stroke occurs when blood flow to the brain is blocked as a result of atherosclerotic plaque formation, which results in infarction, especially at the common or internal carotid. Vascular dementia occurs when blood flow in the brain is reduced because of microinfarction. Vascular dementia can sometimes develop after a stroke.

17), as well as glucose metabolism (12). Clinically, GLP-1–based therapy has already been tried in the treatment of neurological disorders aside from stroke, including Parkinson disease and Alzheimer disease (18). Thus, GLP-1 may regulate multiple types of metabolic impairments, especially glucose and cholesterol metabolism, in stroke and vascular dementia.

Here, we review recent studies on the roles of GLP-1 in cerebral vascular diseases, focusing on its regulatory effect on cholesterol metabolism. We highlight further studies on the potential application of GLP-1 in the CNS as a promising strategy for understanding the neuropathology and preventing cerebral vascular diseases, including stroke and vascular dementia.

Cerebral Vascular Dysfunction and Cholesterol Homeostasis in the Brain

Cerebral vascular dysfunction in the brain

Based on previous studies, cerebral infarction and cerebro-atherosclerosis caused by cerebral vascular dysfunction occur in ~80% of ischemic strokes and 20% of parenchymal hemorrhagic strokes worldwide (19, 20). Cerebro-atherosclerosis is manifested as large and small intracranial artery thrombosis, artery-to-artery embolism, or lacunar infarction via the formation of atherosclerotic plaques in cerebrovascular blood vessels (20–23). It occurs by the excessive accumulation of lipids and fibrous mediators due to inflammatory response. The excessive accumulation of lipid-laden macrophages, known as foam cells, leads to fatty streaks that induce rupture, erosion, and acute occlusions in blood vessels, resulting in stroke and vascular dementia (24) (**Figure 1**).

Stroke is the main cause of disability and death worldwide (25), and dementia is the second cause of death worldwide among brain diseases (26). Hypercholesterolemia and blood vessel dysfunction such as hypertension are implicated as major risk factors for stroke and vascular dementia (27). Cerebral vascular disorders such as stroke occur from inflammation in blood vessels, ultimately resulting in arterial hypertension and atherosclerosis (28, 29). After stroke, some patients develop a form of dementia known as post-stroke dementia (30), which occurs ≤3 mo after the onset of stroke and induces a gradual cognitive decline (31). Other studies also demonstrated that stroke patients experienced cortical vascular dementia, cognitive impairment, and motor impairment (32–34). Furthermore, elevated blood pressure and increased blood dysfunction were observed in both stroke- and cerebrovascular-related dementia in elderly patients (35).

Vascular dementia is accompanied by cognitive decline, memory loss, and cerebrovascular dysfunction (36). In patients with vascular dementia, the increase in cerebral blood flow, blood vessel thickness, and stiffness leads to endothelial dysfunction. This, in turn, results in a chronic reduction in the supply of oxygen and nutrients to brain tissues (36), which ultimately causes memory loss (37).

As mentioned above, the onset and development of cerebrovascular diseases are strongly linked to blood vessel dysfunction and abnormal cholesterol metabolism. As the main cerebrovascular disorder, stroke contributes to the onset and development of vascular dementia, another cerebrovascular disease, which can aggravate cognitive decline.

Impaired cholesterol homeostasis in the brain

In the CNS, cholesterol is the essential lipid component of neuronal plasma membranes and axon myelin sheaths, contributing to synaptic plasticity and neuronal function in the brain (38). In the human body, almost 23% of cholesterol is present in the brain and is observed in neurons and glia-like astrocytes (39). Cholesterol is a key factor in synapse formation and neuronal connectivity (40) and is essential for electrical synapse transmission (39, 41).

Cerebrovascular diseases such as stroke and dementia are associated with abnormal cholesterol homeostasis (42).

Elevated concentrations of LDL cholesterol and low concentrations of HDL cholesterol in the blood contribute to the development of carotid atherosclerosis (42), which implicates cognitive impairment, cerebral hypoperfusion, and embolism (43). The majority of cerebral cholesterol cannot be directly transported into the brain because of the BBB (38), and cerebral cholesterol concentrations are not influenced by the cholesterol concentration in the plasma. Cholesterol removal from the brain is mediated by 24-hydroxycholesterol (39, 44) as a key step in cerebral cholesterol homeostasis (45).

Cholesterol binds with apoE and is taken up in neurons in the form of endosomes through LDL receptors and LDL receptor–related protein (46). apoE4, the major apolipoprotein in the brain, controls intracellular lipid droplet accumulation in glia (47). Under oxidative stress in the CNS, apoE4 has been reported as the main factor related to the disrupted lipid homeostasis through increasing lipid peroxidation in the brain of patients with dementia (48). Hypercholesterolemia is related to the increase in apoE concentrations and amyloid B accumulation in cortical regions and also induces the onset and development of dementia (45). Diet-induced hypercholesterolemia triggers increased amyloid B peptide aggregation and apoE concentrations in cerebrovascular blood vessels and ultimately aggravates the neuropathology of dementia (49, 50). One study reported that higher concentrations of triglycerides increase the risk of ischemic cerebrovascular diseases (51), while another suggested that treatment of hypercholesterolemia using statin reduced the prevalence of dementia compared with that in control subjects (52).

The excessive accumulation of LDL cholesterol in blood vessels aggravates the development of atherosclerosis and subsequently increases the risk of dementia (53). One study demonstrated that LDL-cholesterol receptor–knockout mice showed memory loss and reduced synaptic plasticity in the hippocampus (54) and excessive toxic amyloid B deposition in the brain (55). In contrast, HDL cholesterol contributes to the suppression of excessive cholesterol in the brain through apoE and heparin sulfate proteoglycans in cerebral microvessels (56). It also inhibits the negative action of oxidized LDL particles on arterial relaxation (57), blocks the expression of cytokines such as endothelial cell adhesion molecules (58), and ultimately reduces vascular dementia onset. Some epidemiological studies have demonstrated that a lower concentration of HDL cholesterol and a higher concentration of total cholesterol promote the onset of dementia, and also aggravate the progression of dementia (59, 60).

The concentration of triglycerides in blood vessels is related to the breakdown of the BBB, which may lead to lacunar stroke (61), and is directly linked to inflammation in the CNS (62). In addition, triglyceride concentrations in blood vessels contribute to the occlusion of small arteries (63) and hypoperfusion in the white matter regions of the brain (64).

Based on previous findings, we assume that the accumulation of LDL cholesterol, the increase in total cholesterol in blood vessels, and the impaired cholesterol homeostasis lead to vascular dysfunction, which is subsequently associated with the onset of dementia and stroke. Hence, the regulation of cholesterol homeostasis in the brain may be critical in alleviating and preventing the various neuropathologies in cerebrovascular diseases.

GLP-1

GLP-1 is an incretin hormone mainly produced by enteroendocrine L cells in response to food intake and controls insulin secretion from pancreatic islets (14, 65) (**Figure 2**). GLP-1 secreted from the nucleus tractus solitarius in the brain stem acts as a neurotransmitter (66) and regulates glucose homeostasis and cholesterol metabolism in the brain (67). GLP-1 derived from the gastrointestinal tract could enter the brain through the BBB and also through circumventricular organs such as the pineal gland (68, 69). GLP-1–expressing neurons in the nucleus tractus solitarius in the brain stem project to broad regions of the brain, including the hypothalamus, arcuate nucleus, paraventricular nucleus, dorsal vagal nucleus, and thalamus (70–72). Although GLP-1 and its specific receptors are important in neuroinflammation, glucose and lipid metabolism, and vascular function, their underlying mechanisms associated with diverse diseases are unclear (67).

GLP-1 and GLP-1R are linked to the inhibition of platelet aggregation and thrombus formation in blood vessels (73). Platelet aggregation is involved in the pathology of vascular disorders, such as atherosclerosis, via blood thrombosis formation and impaired NO action (74). Hypercholesterolemia may promote atherosclerosis through platelet aggregation in blood vessels (75), and some reports have demonstrated that GLP-1 modulated the hyperreactivity of platelets under hypercholesterolemia (76).

Beneficial effect of GLP-1 on cholesterol homeostasis in cerebral vascular diseases

Cholesterol metabolism is important in both systemic metabolic syndromes such as diabetes and CNS diseases such as dementia (**Table 1**). A clinical study showed the preventive and protective effect of GLP-1 analog treatment on cardiovascular mortality and arterial stiffness (77). GLP-1 improved glycemic control and blood glucose metabolism and prevented the development of atherosclerosis (12, 15). Moreover, the beneficial effects of GLP-1 treatment on cardiovascular pathology, including blood pressure regulation and lipid metabolism control, have been reported (78, 79). Other studies have found that GLP-1 concentration is related to the onset of vascular disorders such as atherosclerosis (80, 81). It was also demonstrated that GLP-1 and GLP-1R agonist treatment suppressed vascular inflammation (82) and improved vascular function (83). GLP-1R agonist treatment contributed to lower concentrations of circulating triglycerides and apoB48, a marker of chylomicron particles (84, 85). Some studies have highlighted that GLP-1 regulated intestinal lipoprotein metabolism in response to lipid ingestion and improved dyslipidemia (86, 87).

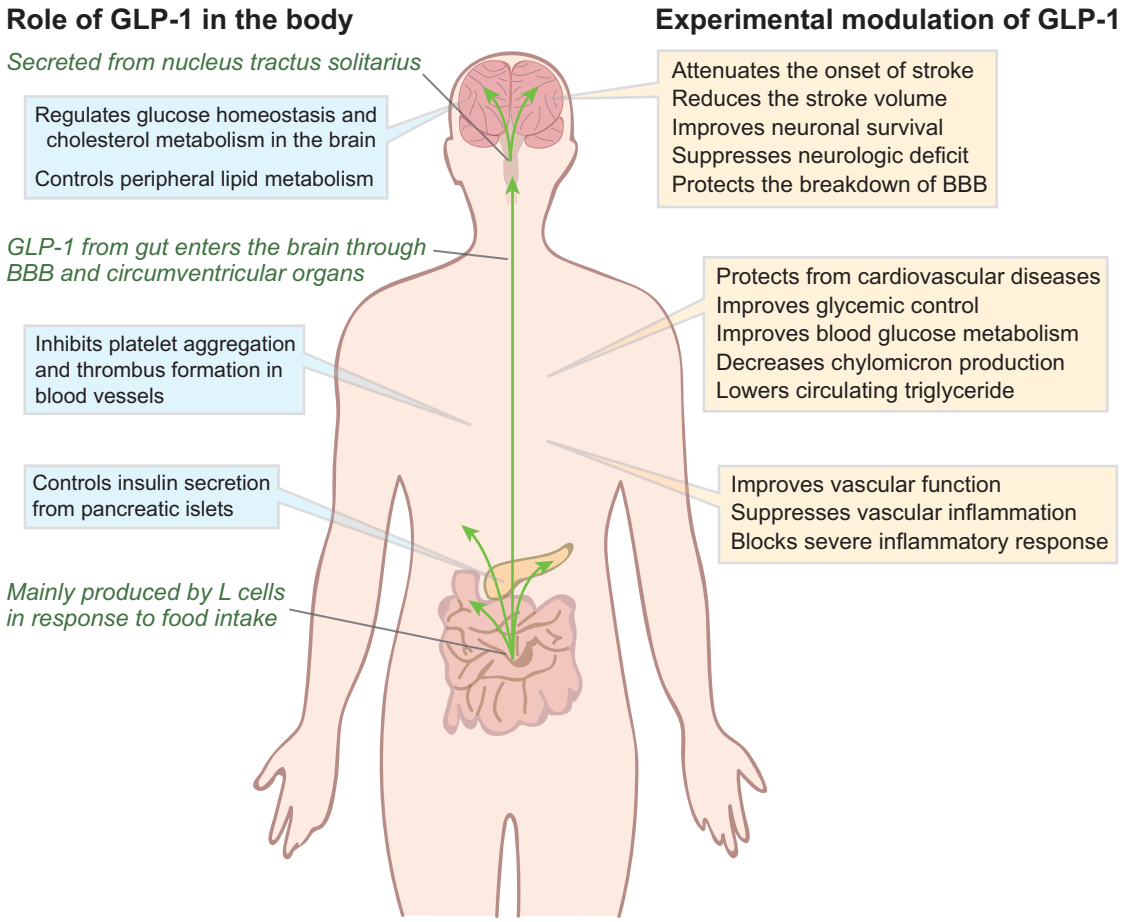

FIGURE 2 Role of GLP-1 in cholesterol metabolism in the body. The secretion of GLP-1 and its movement throughout the body are illustrated by green arrows. The roles of GLP-1 are described in the blue boxes. The effects of the experimental modulation of GLP-1 based on previous studies are shown in yellow boxes. BBB, blood–brain barrier; GLP-1, glucagon-like peptide 1.

A recent study reported that GLP-1 treatment attenuated the onset of stroke (88), whereas another demonstrated that GLP-1 administration reduced stroke volume, improved neuronal survival, and suppressed neurologic deficit (89). Furthermore, the GLP-1 agonist liraglutide downregulated the expression of vascular cell adhesion molecule 1 and E-cadherin in endothelial cells (90), in turn attenuating hypertension and stroke (91). The GLP-1 agonist exendin-4 also reduced blood cell infiltration and adhesion in the atherosclerosis model (92). Recent research has suggested that GLP-1R agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors could act as anti-stroke regulators and clinically decrease the incidence of stroke (93, 94). DPP-4 inhibitors and GLP-1R agonists have been known to block severe inflammatory responses of monocytes and macrophages and subsequently alleviate atherosclerotic lesion progression in apoE-knockout mice (95). In addition, GLP-1R agonists enhanced endothelial cell function and downregulated the expression of cell adhesion markers in blood vessels in a knockout model (96). Furthermore, GLP-1R agonists protected the BBB from breakdown by suppressing the expression of matrix metallopeptidase 9, and GLP-1 analogs lowered vascular permeability by inhibiting intercellular adhesion molecule 1 expression (97, 98).

Some studies have demonstrated that GLP-1R agonists exhibited an antihyperglycemic function and reduced glycated hemoglobin concentrations, blood pressure, and serum lipid concentrations (99, 100). In particular, GLP-1R agonists refined lipid profiles and were associated with a decrease in LDL cholesterol and total cholesterol and triglycerides (101).

Several studies have demonstrated that GLP-1R agonist injection induced low concentrations of cholesterol, such as circulating triglycerides and chylomicron particles (84, 85, 87, 102–104). Others have suggested that GLP-1 administration can enhance lipoprotein metabolism in response to lipid ingestion (86, 105), suppress the expression of lipogenic genes, and contribute to lipid metabolism control (106, 107). Recent studies mentioned that GLP-1 inhibited lipid absorption by decreasing intestinal chylomicron output (108).

Importantly, GLP-1 in the brain was shown to control peripheral lipid metabolism (106) and the stimulation of GLP-1R in the CNS suppressed chylomicron production (109). Thus, GLP-1 may be a therapeutic solution for abnormal

TABLE 1 Previous studies that identified the effect of GLP-1 modulation in human or animal or cell-based models are summarized[1]

	Key findings	Reference
Human studies		
Subjects and methods		
Twenty-four men with T2D were randomly assigned to sitagliptin or voglibose treatment for 6 wk in study 1, and 42 T2D patients were treated with sitagliptin or alogliptin for 6 wk in study 2. Endothelial function was assessed by FMD of the brachial artery.	Sitagliptin significantly reduced flow-mediated vasodilatation of the brachial artery and improved diabetic status, but voglibose did not affect FMD in study 1. Both sitagliptin and alogliptin improved glycemic control and significantly attenuated FMD in study 2.	(16)
For 26 healthy young volunteers, brachial artery diameter and blood flow velocity in the skeletal and cardiac muscle were determined after the infusion of GLP-1.	Acute GLP-1 infusion in healthy humans resulted in skeletal and cardiac muscle microvascular recruitment as well as an increase in brachial artery diameter and blood flow.	(17)
Patients with newly diagnosed and treatment-naive T2D received with liraglutide ($n = 30$) or metformin ($n = 30$). Changes in diverse metabolic parameters and vascular markers were measured 6 mo after treatment.	Liraglutide treatment significantly reduced arterial stiffness, oxidative stress burden, and NT-proBNP level, and improved left ventricular longitudinal myocardial strain and strain rate, left ventricular twisting–untwisting, and endothelial function.	(77)
Patients with T2D were either treated with sitagliptin ($n = 24$) or untreated ($n = 24$). Changes in the parameter related to immune and metabolism were examined using peripheral blood.	Sitagliptin significantly decreased the level of SAA LDL, C-reactive protein, and TNF-α, but increased IL-10 and GLP-1 in serum. Sitagliptin also decreased TNF-α expression but increased IL-10 expression in peripheral blood monocytes.	(78)
Metformin-treated patients with T2D were randomized, and treated with exenatide ($n = 30$) or insulin glargine ($n = 30$). On-drug meal test (postprandial glucose, lipids and lipoproteins, and oxidative stress markers) was performed.	One-year treatment with exenatide significantly reduced prandial glucose, triglycerides, apoB-48, VLDL-C, FFA, and MDA excursions. Insulin glargine predominantly reduced fasting glucose, FFA, and MDA.	(84)
Thirty-five subjects with impaired glucose tolerance ($n = 20$) or recent-onset T2D ($n = 15$) were administered exenatide or normal saline, and metabolic parameters were measured from serum or plasma.	Exenatide reduced postprandial elevation of triglycerides, apoB-48, apoC-III, NEFA, and RLP cholesterol and RLP triglyceride.	(85)
Twenty-eight patients with overweight and obesity with T2D were treated with liraglutide, and body composition and metabolic markers were measured after 24 wk of the treatment.	Liraglutide treatment led to the reduction of fat mass, android fat, trunk fat, and appetite by improving the lipid profile, glucose control, and insulin sensitivity in patients with T2D.	(101)
Thirty patients with T2D were treated with exenatide ($n = 17$) or placebo ($n = 13$), and serum glucose profiles were measured for 2 wk.	Exenatide was associated with reduced glucose concentrations at multiple time points during 24 h, decreased overall hyperglycemic exposure, decreased postprandial triglyceride excursions in the patients with T2D.	(102)
Fifteen healthy male subjects underwent 2 studies each (injection with exenatide vs placebo), 4 to 6 wk apart in random order, and blood samples were measured at multiple time points.	Exenatide suppresses plasma concentration of apoB-48 but not apoB-100, independent of changes in body weight, satiety, glucagon, and FFA concentrations.	(103)
Fourteen healthy male volunteers were administered either GLP-1(7–36) or placebo over 390 min in random order. Blood samples were measured at multiple time points.	GLP-1 administration lowered fasting and postprandial glycemia, abolished the postprandial increase in triglyceride concentrations, delayed gastric emptying, and lowered postprandial plasma concentrations of NEFA.	(104)
Animal and cell-based studies		
Experimental model and methods		
Rats were stereotaxically implanted with a bilateral guide cannula directed at the VTA alone or together with a unilateral cannula directed at either the NAc core or shell and injected with exendin-4 or exendin(9–39).	GLP-1R activation in the VTA and NAc decreased food intake and body weight, but blockage of GLP-1R signaling significantly increased food intake.	(71)
Spontaneously hypertensive rats were treated with sitagliptin for 2 wk.	Sitagliptin treatment improved endothelial function in renal arteries of spontaneously hypertensive rats via the sequential activation of the PKA/LKB1/AMPKα/eNOS axis.	(79)

(*Continued*)

TABLE 1 (*Continued*)

	Key findings	Reference
Male hamsters were administered sitagliptin, exendin-4, or exendin(9–39).	Sitagliptin decreased fasting plasma triacylglycerol, postprandial TRL-triacylglycerol, TRL-cholesterol, and TRL-apoB-48.	(87)
Mice received a transvenous injection of exendin-4, after a 60-min focal cerebral ischemia. Infarct volume, neurologic deficit score, various physiologic parameters, and immunohistochemical analyses were performed at several time points after ischemia.	Exendin-4 treatment reduced infarct volume, improved functional deficit, and suppressed oxidative stress, inflammatory response, and cell death after reperfusion, showing the neuroprotective effect of exendin-4 against ischemic injury.	(89)
For wild-type, global, as well as endothelial and myeloid cell-specific knockout mice of the GLP-1R, arterial hypertension was induced by angiotensin II and liraglutide was administered.	Liraglutide improved blood pressure, cardiac hypertrophy, endothelial dysfunction, vascular fibrosis, and oxidative stress in angiotensin II–induced arterial hypertension.	(91)
High-fat-diet–fed mice were treated with liraglutide for 1 wk.	Liraglutide treatment activated cardioprotective pathways, prevented high-fat-diet–induced insulin resistance and inflammation, reduced monocyte vascular adhesion, and improved cardiac function by activating the AMPK signaling pathway.	(92)
ApoE-deficient male mice were treated with liraglutide or exendin(9–39).	Liraglutide treatment improved endothelial function, increased eNOS expression, and reduced ICAM-1 expression in aortic endothelium.	(96)
Exendin(9–39) or GLP-1(7–36) was delivered through intracerebroventricular or subcutaneous infusion on male mice.	GLP-1 system in the central nervous system loses the capacity to modulate adipocyte metabolism in obese states, suggesting an obesity-induced adipocyte resistance to the central nervous system GLP-1.	(106)
Platelets obtained from 72 healthy volunteers were incubated with GLP-1(7–36), GLP-1(9–36), or liraglutide.	GLP-1(7–36), GLP-1(9–36), and liraglutide exerted platelet inhibitory effects independently of GLP-1R.	(74)
The effects of liraglutide on inflammation were determined in cultured human aortic endothelial cells.	Liraglutide exerted anti-inflammatory effects in endothelial cells through increasing cellular calcium concentration and activating the AMPK-dependent pathway.	(90)
Primary cultured mouse cortical astrocytes were treated with exendin-4 or exendin(9–39).	Exendin-4 treatment reduced ischemia-induced inflammation and blood–brain barrier breakdown.	(97)

[1] AMPKα, AMP-activated protein kinase α subunit; eNOS, endothelial nitric oxide synthase; FFA, free fatty acid; FMD, flow-mediated dilatation; GLP-1, glucagon-like peptide 1; GLP-1R, GLP-1 receptor; ICAM-1; intercellular adhesion molecule 1;LKB1, liver kinase B1; MDA, malondialdehyde; NAc, nucleus accumbens; NEFA, nonesterified fatty acid; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PKA, protein kinase A; RLP, remnant lipoprotein; SAA, serum amyloid A; TRL, triacylglycerol-rich lipoprotein; T2D, type 2 diabetes; VLDL-C, VLDL cholesterol; VTA, ventral tegmental area.

cholesterol homeostasis in dementia, as suggested by reports showing that lowering of LDL cholesterol could improve cognitive dysfunction (110) and dementia neuropathology (111).

As mentioned above, the ability of GLP-1 to regulate cholesterol metabolism and the fact that GLP-1 circulates between the CNS and systemic metabolism suggest that GLP-1 is an important target in the treatment of cerebrovascular diseases in terms of altered cholesterol metabolism and vascular dysfunction. Even though the specific mechanisms underlying the action of GLP-1 in cholesterol homeostasis have been unclear until now, further studies on the role of GLP-1 in vascular dysfunction are essential for the treatment and prevention of cerebral vascular diseases.

Conclusions

Cerebral vascular disorders are strongly related to vascular dysfunction and impaired cholesterol homeostasis. Ischemic stroke and vascular dementia are major cerebral vascular diseases, and cholesterol homeostasis is one of the main causes of the onset of cerebral vascular disorders. Here we reviewed recent data on the promising therapeutic effect of GLP-1 on vascular dysfunction via the modulation of cholesterol homeostasis, both in the CNS and in systemic circulation. We suggest that GLP-1 should be highlighted in developing a solution for cerebral vascular diseases, with a specific focus on its ability to regulate cholesterol homeostasis.

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