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REVIEW

Incretin-Based Antihyperglycemic Agents for the Management of Acute Ischemic Stroke in Patients with Diabetes Mellitus: A Review

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ABSTRACT

Diabetes mellitus (DM) is a major risk factor for ischemic stroke. Moreover, patients with DM suffer more severe strokes and have worse functional outcome following an acute stroke than patients without DM. In this context, data from animal studies and emerging evidence from clinical studies suggest that incretin-based antihyperglycemic agents might exert beneficial effects in patients with DM who suffer ischemic stroke. It appears that these agents exert neuroprotective actions that might both reduce infarct size and promote recovery. The present review summarizes the evidence on the potential role of incretin-based antihyperglycemic agents in the management of acute ischemic stroke.

Keywords: Diabetes mellitus; Incretin-based antihyperglycemic agents; Ischemic stroke; Outcome; Neuroprotection

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INTRODUCTION

Ischemic stroke is a leading cause of death and long-term disability worldwide [1]. Type 2 diabetes mellitus (T2DM) is a major modifiable risk factor for ischemic stroke [2]. Indeed, patients with T2DM have a 2- to 6-fold higher risk of ischemic stroke and are also at higher risk of stroke recurrence [3–5]. Moreover, T2DM is associated with more severe stroke, resulting in higher rates of mortality and long-term dependency [4, 5].

During the acute phase of ischemic stroke, hyperglycemia is frequently observed and is associated with larger infarct and worse outcome [6]. Serum glucose levels persistently greater than 200 mg/dl, especially during the first 24 h after stroke, independently predict expansion of the ischemic area and poor neurological outcomes, suggesting that management of hyperglycemia is an essential part of the acute management of patients with ischemic stroke [7]. Regarding in-patient glycemic control, the American Diabetes Association recommends a glucose target between 140 and 180 mg/dl for most patients in non-critical care units and subcutaneously administered insulin is considered the agent of choice [8]. Recent guidelines for the early management of acute stroke issued by the American Heart Association and the American Stroke Association make similar recommendations [9]. However, insulin therapy is associated with

increased incidence of hypoglycemia and does not appear to reduce mortality in hospitalized patients [10–12]. Moreover, treatment with insulin does not appear to have any effect on the neurological deficit after an acute ischemic stroke [13, 14].

In this context, emerging evidence suggests that incretin-based antihyperglycemic agents, i.e., dipeptidyl peptidase (DPP)-4 and glucagon-like peptide 1 (GLP-1) receptor agonists, might exert beneficial effects in patients with T2DM who suffer ischemic stroke. It appears that these agents exert neuroprotective actions that might both reduce infarct size and promote recovery. The present review summarizes the evidence on the potential role of incretin-based antihyperglycemic agents in the management of acute ischemic stroke. We also briefly discuss the effects of these agents on the incidence of ischemic stroke in patients with T2DM. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

EFFECTS OF GLP-1 RECEPTOR AGONISTS ON ISCHEMIC STROKE RISK

Several large, randomized, placebo-controlled trials evaluated the effects of GLP-1 receptor agonists on the incidence of ischemic stroke in patients with T2DM. In the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial (n = 6068 patients with an acute coronary event within 180 days before screening), lixisenatide had no effect on the risk of nonfatal stroke during a median follow-up of 25 months [15]. In the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) (n = 14,752 patients with or without established cardiovascular disease), extended-release exenatide also had no effect on the incidence of fatal or nonfatal stroke [16]. In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial (n = 9340 patients $\geq$ 50 years old with coronary heart disease, cerebrovascular disease, peripheral vascular disease, chronic kidney disease of stage 3 or greater, or chronic heart failure of New York Heart Association class II or III or $\geq$ 60 years old with microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or ankle–brachial index $<$ 0.9), liraglutide had no effect on the incidence of fatal or nonfatal stroke or transient ischemic attack during a median follow-up of 3.8 years [17]. In the Harmony Outcomes (n = 9463 patients with established coronary heart disease, cerebrovascular disease, or peripheral vascular disease), albiglutide had no effect on the risk of fatal or nonfatal stroke during a median follow-up of 1.6 years [18]. In contrast, in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) (n = 3297 patients $\geq$ 50 years old with coronary heart disease, cerebrovascular disease, peripheral vascular disease, chronic kidney disease of stage 3 or greater, or chronic heart failure of New York Heart Association class II or III or $\geq$ 60 years old with microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or ankle–brachial index $<$ 0.9), treatment with semaglutide reduced the risk of nonfatal stroke by 39% during a median observation time of 2.1 years [19]. In a meta-analysis of ELIXA, LEADER, and SUSTAIN-6, GLP-1 receptor agonists had no effect on the risk of stroke [20].

GLP-1 RECEPTOR AGONISTS AND ACUTE ISCHEMIC STROKE

Activation of GLP-1 receptor by GLP-1 has been shown to be neurotrophic and to protect neurons against various insults [21]. Moreover, GLP-1 has been shown to cross the blood–brain barrier [22]. Liraglutide can also pass the blood–brain barrier but it is unclear whether other GLP-1 receptor agonists have the same property [23]. Accordingly, several preclinical studies evaluated the effects of GLP-1 receptor agonists in models of acute ischemic stroke. In these studies, a consistent reduction in infarct size was noted, along with an improvement in

the functional outcome and a decrease in the neurological deficit [24–33]. These benefits have been observed with the use of both exenatide and liraglutide [24–33]. In the only study that compared these agents, they were similarly effective in improving brain perfusion and motor and cognitive deficits and in reducing brain edema, oxidative stress, inflammation, and apoptosis in diabetic mice with middle cerebral artery-induced stroke [34].

Notably, a neuroprotective effect was observed when GLP-1 receptor agonists were administered either prior to or after the ischemic insult [24–33]. However, in one study, exenatide was not beneficial when administered more than 3 h after ischemic stroke, suggesting that there is a limited time frame for this treatment [35]. In contrast, liraglutide improved the functional outcome even when administered 1 day after stroke [32]. In studies that compared different times of administration after stroke, GLP-1 receptor agonists appeared to be more beneficial when administered immediately after the ischemic insult [33, 35].

Very few studies compared the effects of GLP-1 receptor agonists with other antihyperglycemic agents in animal models of ischemic stroke. In an early study in diabetic and non-diabetic rats, treatment with liraglutide for 14 days prior to middle cerebral artery occlusion-induced stroke reduced the infarct volume and the neurological deficit more than vehicle and also attenuated oxidative stress, increased the expression of the anti-apoptotic protein B cell lymphoma-2 (Bcl-2), and reduced the expression of the pro-apoptotic protein Bax, resulting in decreased apoptosis of neuronal cells in the ischemic hemisphere [31]. These benefits were similar in diabetic and non-diabetic rats [31]. In contrast, stroke volume, neurological deficit, and severity of oxidative stress were similar in diabetic rats receiving either insulin or vehicle [31]. In a more recent study in diabetic rats, treatment with liraglutide for 7 days prior to middle cerebral artery occlusion-induced stroke reduced brain infarct volume whereas metformin had no effect despite similar reductions in blood glucose levels [30].

The beneficial effects of GLP-1 receptor agonists in animal models of ischemic stroke appear to be GLP-1 receptor-dependent, since knockout mice not expressing GLP-1 receptors show no benefit from GLP-1 receptor agonist treatment [24]. Moreover, GLP-1 receptor expression is reduced in ischemic brain regions and this decrease is reversed by GLP-1 receptor agonists [25]. Several mechanisms appear to be implicated in the neuroprotective effects of GLP-1 receptor agonists. These agents attenuate microglial activation in the infracted area, which also appears to play a role in neuronal death [25]. GLP-1 receptor activation also inhibits cyclooxygenase-2 through the modulation of the c-Jun NH2-terminal kinase (JNK) signaling pathway [26]. The latter induces an inflammatory response, which also contributes to neuronal death [26]. Exenatide was also shown to reduce the production of the proinflammatory cytokine tumor necrosis factor alpha [36]. Inhibition of neuronal apoptosis has also been shown to be associated with a decrease in infarct size during treatment with GLP-1 receptor agonists [28, 31]. Activation of GLP-1 receptor also reduces oxidative stress following ischemic stroke and this appears to contribute to the reduction in infarct size [27, 34]. On the other hand, the neuroprotective effects of GLP-1 receptor agonists appear to be glucose-lowering independent, since they are observed in non-diabetic animals and despite the absence of change in glucose levels [29, 30]. It also appears that GLP-1 receptor agonists do not affect cerebral blood flow [24].

EFFECTS OF DPP-4 INHIBITORS ON ISCHEMIC STROKE RISK

In several randomized, placebo-controlled trials, DPP-4 inhibitors had no effect on the risk of ischemic stroke in patients with T2DM [37–39]. In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 trial [n = 16,492 patients $\geq$ 40 years old with coronary heart disease, cerebrovascular disease, or peripheral vascular disease, or $\geq$ 55 years old (men) or $\geq$ 60 years old (women) with dyslipidemia, hypertension, or active smoking], saxagliptin

did not reduce the incidence of ischemic stroke during a median follow-up of 2.1 years [37]. In the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial (n = 5380 patients with an acute coronary syndrome within 15–90 days before randomization), alogliptin had no effect on the risk of nonfatal stroke during a median follow-up of 18 months [38]. In the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) (n = 14,671 patients $\geq$ 50 years old with coronary heart disease, cerebrovascular disease, or peripheral vascular disease), sitagliptin did not reduce the risk of fatal or nonfatal stroke during a median follow-up of 3 years [39]. In a meta-analysis of these three trials, DPP-4 inhibitors had no effect on the risk of stroke [20].

DPP-4 INHIBITORS AND ACUTE ISCHEMIC STROKE

Accumulating preclinical data suggest that DPP-4 inhibitors might exert neuroprotective actions in animal models of ischemic stroke. In diabetic mice, administration of linagliptin for 4 weeks prior to transient middle cerebral artery occlusion-induced stroke resulted in a noticeable, albeit not statistically significant, trend towards reduction of stroke volume [40]. In contrast, glimepiride had no effect on stroke volume [40]. Moreover, stereological counting of surviving neurons revealed significantly more (approximately 30%) surviving neurons in linagliptin-treated mice than in glimepiride-treated animals [40]. Therefore, treatment with linagliptin prior to ischemic stroke appears to exert neuroprotective effects [40]. These effects appear to be unrelated to the glucose-lowering effect of linagliptin. Indeed, glucose levels decreased to a similar degree in linagliptin- and glimepiride-treated mice [40]. Moreover, in non-diabetic mice, both linagliptin and glimepiride induced a comparable and non-significant reduction in stroke volume and an increase in the number of surviving neurons [40]. In another study in non-diabetic mice, treatment with alogliptin for 3 weeks prior to ischemic stroke also reduced the volume of the infracted lesion and alleviated the severity of neurological deficit [41]. In contrast with GLP-1 receptor agonists, DPP-4 inhibitors do not appear to cross the blood–brain barrier [42]. It is possible that the neuroprotective effects of DPP-4 inhibitors are due to an increase in GLP-1 levels in the brain [40]. However, other investigators showed that the beneficial effects of DPP-4 inhibitors in animal models of ischemic stroke are independent of GLP-1 [43, 44]. Another possible explanation is that DPP-4 has many other substrates except GLP-1, including peptides with potential neurotrophic or neuroprotective effects [45, 46]. These include glucose-dependent insulinotropic polypeptide, pituitary adenylate cyclase-activating polypeptide, and stromal cell-derived factor 1a (SDF-1a) [47–49]. In preclinical models, these peptides were shown to promote synaptic plasticity, neurogenesis and neuronal differentiation, to inhibit apoptosis, and to reduce stroke size [47–49]. Indeed, linagliptin increased brain SDF-1a levels in mice subjected to stroke whereas inhibition of SDF-1a abolished the beneficial effects of linagliptin on stroke volume and motor function [44]. In addition, alogliptin was shown to increase the levels of brain-derived neurotrophic factor (BDNF), a potent brain neuroprotective cytokine, both in the cortex and in the whole forebrain [41]. Notably, acute administration of linagliptin at the time of stroke does not affect the outcome; therefore, it is questionable whether DPP-4 inhibitors have a role in the acute management of patients with ischemic stroke [43]. Despite these promising results of preclinical studies, there are very few data regarding the role of DPP-4 inhibitors in improving the outcome of patients with acute ischemic stroke. In a small study (n = 123), we reported that patients who were hospitalized with acute ischemic stroke and were treated with DPP-4 inhibitors prior to stroke had a trend for less severe stroke at admission and also had better functional outcome and lower in-hospital mortality than patients treated with other antihyperglycemic agents [50].

CONCLUSIONS

Several preclinical studies consistently showed that GLP-1 receptor agonists reduce infarct volume and improve the functional outcome after ischemic stroke. These beneficial effects appear to be mediated by anti-inflammatory, antioxidant, and anti-apoptotic actions of these agents. On the other hand, glucose lowering does not appear to be implicated in the neuroprotective effect of GLP-1 receptor agonists, suggesting that they could have a role in the management of both diabetic and non-diabetic patients who suffer an ischemic stroke. More limited data suggest that DPP-4 inhibitors might also ameliorate neuronal damage following an ischemic stroke. However, it is unknown whether these results will translate into a clinical benefit in humans. Well-designed studies are needed to clarify the role of incretin-based antihyperglycemic agents in the management of acute ischemic stroke and to define the optimal dose and time of administration.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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