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FIELD OF VISION

Antidiabetic treatment, stroke severity and outcome

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Abstract

Ischemic stroke is a leading cause of mortality and long-term disability worldwide. Given the detrimental effects of acute stroke, several neuroprotective agents have been evaluated in these patients. However, the benefits of the evaluated agents appear to be limited and none is currently recommended for clinical use. On the other hand, prior treatment with agents that are used for the primary and secondary prevention of stroke, including statins and antiplatelets, has been associated with better outcome in patients who experience an acute stroke. In contrast, there are limited data as to whether prior treatment with antidiabetic agents is beneficial in diabetic patients who suffer a stroke. In this context, the findings of a recent study that showed reduced stroke size following pretreatment with linagliptin, a dipeptidyl peptidase-4 (DDP-4) inhibitor, compared with glimepiride, in both diabetic and non-diabetic mice, appear promising. Despite these preclinical findings suggesting neuroprotective effects of DPP-4 inhibitors in acute stroke, it is still unclear whether these actions will also be observed in humans. Of note, two recent large randomized, placebo-controlled studies did not show any effect of DPP-4 inhibitors on cardiovascular events, including stroke. Several other ongoing trials are evaluating the effects of DPP-4 inhibitors on cardiovascular morbidity and mortality. These studies also provide a major opportunity to assess whether patients treated with this class of antidiabetic agents will suffer from less severe strokes and whether their outcome after stroke will be more favorable.

Key words: Type 2 diabetes mellitus; Stroke; Dipeptidyl peptidase-4 inhibitors; Sulfonylureas; Neuroprotection

Core tip: A recent study showed reduced stroke size following pretreatment with linagliptin, a dipeptidyl peptidase-4 (DDP-4) inhibitor, compared with glimepiride, in both diabetic and non-diabetic mice. It remains to be shown whether these neuroprotective actions of DPP-4 inhibitors will also be observed in humans.

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INVITED COMMENTARY ON HOT ARTICLES

Ischemic stroke is a leading cause of mortality and long-term disability worldwide[1]. This often disabling and frequently fatal event puts a substantial burden on the family members and medical professionals who care for stroke victims[1].

The increasing prevalence of obesity results in an increased incidence of type 2 diabetes mellitus (T2DM) worldwide[2]. T2DM is a major risk factor for cardiovascular events, including stroke[3,4]. In addition, patients with T2DM appear to suffer more severe strokes and have a worse outcome than subjects without T2DM[3,5-7]. The increased incidence of cardiovascular events in patients with T2DM is not only due to hyperglycemia, but insulin resistance, low-grade inflammation and activation of the

Table 1 Major studies that have evaluated the effects of antidiabetic agents on stroke severity and outcome

Ref.	Design	*n*	Agent	Results
Weih *et al*[14]	Retrospective	146	Sulfonylureas	No effect on stroke severity or outcome
Kunte *et al*[15]	Retrospective	61	Sulfonylureas	Better neurological and functional outcome at discharge in patients who were on sulfonylureas prior to stroke
Favilla *et al*[16]	Prospective	1050	Sulfonylureas, metformin, insulin	Less severe stroke on admission in patients who were on sulfonylureas, metformin or insulin prior to stroke than in patients who were not receiving any antidiabetic agent, but no difference in functional outcome and mortality rates at 90 d between the 2 groups Similar stroke severity and outcome between patients treated with different antidiabetic agents prior to stroke (sulfonylureas, metformin and insulin)
Lee *et al*[17]	Case-control	60	Thiazolidinediones	Enhanced functional recovery in patients treated with thiazolidinediones

coagulation cascade are also involved[3,8].

Given the high morbidity and mortality rates associated with acute ischemic stroke, several neuroprotective agents have been evaluated in these patients[9]. However, the benefits of the evaluated agents appear to be limited and none is currently recommended for clinical use[9]. On the other hand, prior treatment with agents that are used for the primary and secondary prevention of stroke, including statins and antiplatelets, has been associated with less severe stroke, better functional outcome and reduced mortality in patients who experience an acute stroke[10-13]. In contrast, there are limited data whether prior treatment with antidiabetic agents is beneficial in diabetic patients who suffer a stroke. In an early study, prior treatment with sulfonylureas had no effect on stroke severity or outcome[14]. In contrast, a more recent study suggested that patients who were on sulfonylureas prior to stroke and continued to receive these agents during hospitalization were more likely to have a better neurological and functional outcome at discharge[15]. In another study, diabetic patients who were on sulfonylureas, metformin or insulin prior to stroke had a less severe stroke on admission than patients who were not receiving any antidiabetic agent. In contrast, functional outcome and mortality rates at 90 d after stroke were similar in patients who were on glucose-lowering treatment and in those who were not[16]. Stroke severity and outcome did not differ between patients who were on sulfonylureas, metformin or insulin prior to stroke[16]. A small retrospective study also suggested that thiazolidinediones enhance functional recovery in patients with stroke[17] (Table 1).

In this context, the findings of a recent study that compared the effects of pretreatment with glimepiride, a sulfonylurea, and linagliptin, a dipeptidyl peptidase-4 (DDP-4) inhibitor, on the outcome of stroke in diabetic and non-diabetic mice, appear promising[18]. It has been previously reported that administration of sulfonylureas after stroke reduces infarct size and mortality, primarily by preventing cerebral edema[19,20]. In this study, 44 male C57BL mice were divided into 2 groups. The first group (n = 21) was exposed to a high-fat diet for 32 wk, which resulted in substantial weight gain and development of insulin resistance and hyperglycemia[18]. At week 25, this group was assigned to oral administration of 10 mg/kg per body weight (bw) linagliptin daily, 2 mg/kg per body weight glimepiride daily or vehicle[18]. The second group (n = 23) was fed a normal diet and was also assigned to linagliptin, glimepiride or vehicle at the same doses with the first group[18]. After 4 wk of treatment, stroke was induced in all mice in both groups by transient occlusion of the middle cerebral artery[18]. Treatment with linagliptin, glimepiride or vehicle was continued for 3 wk following stroke, after which all mice in both groups were sacrificed[18]. The extent of ischemic stroke was assessed with measuring stroke volume and with stereological quantification of surviving neurons in the striatum/cortex[18].

In high-fat diet-fed mice, fed and fasting blood glucose levels decreased in both linagliptin- and glimepiride-treated mice[18]. This reduction was greater in mice treated with glimepiride. In contrast, in normal diet-fed mice, fed and fasting blood glucose levels decreased in glimepiride-treated animals but did not change in linagliptin-treated animals[18]. On the other hand, both high-fat- and normal diet-fed mice that were treated with linagliptin showed an increase in blood glucagon-like peptide-1 (GLP-1) levels due to a significant reduction in DPP-4 activity[18]. In contrast, GLP-1 levels and DPP-4 activity did not change in glimepiride- or vehicle-treated mice regardless of the diet they were fed[18].

Immunohistochemical staining of the cortex/striatum of high-fat diet-fed mice without stroke revealed GLP-1 receptor expression exclusively in the neurons[18]. Cortical pyramidal neurons showed the most pronounced expression of GLP-1 receptors[18].

In high-fat diet-fed mice, treatment with linagliptin resulted in a noticeable, albeit not statistically significant, trend towards reduction of stroke volume[18]. In contrast, glimepiride had no effect on stroke volume[18]. Moreover, stereological counting of surviving neurons revealed significantly more (approximately 30%) surviving neurons in linagliptin-treated mice than in either glimepiride- or vehicle-treated animals[18]. In contrast, in normal diet-fed mice, treatment with both linagliptin and glimepiride resulted in a comparable and non-significant trend for reduced stroke volume and was associated with a comparable and significantly higher number of surviving neurons compared with vehicle treatment[18].

Overall, this study[18] suggests that treatment with linagliptin prior to stroke increases the number of surviving neurons more than glimepiride in diabetic mice. This

neuroprotective effect of linagliptin appears to be glucose-lowering-independent since the reduction in blood glucose levels was smaller during treatment with linagliptin compared with glimepiride. In addition, linagliptin also prevented neuronal death in non-diabetic mice even although it did not affect glucose levels, further supporting a glucose-lowering-independent neuroprotective effect. Similar results have been reported very recently with another DPP-4 inhibitor, alogliptin[21]. Moreover, in humans, even although increased glucose levels at admission are associated with a worse outcome in patients with acute ischemic stroke[22-24], correction of hyperglycemia with administration of insulin does not reduce infarct size or neurological deficit[25-27].

Several alternative mechanisms besides glucose lowering may underpin the beneficial effects of linagliptin in the setting of acute stroke. First, treatment with linagliptin results in increased blood GLP-1 levels and pretreatment with exendin-4, a GLP-1 agonist, was shown to reduce stroke volume and neurological deficit in animal stroke models[28-30]. Antiapoptotic, anti-inflammatory and antioxidant actions, as well as stimulation of the proliferation of neural stem cells and attenuation of microglial activation, appear to contribute to these neuroprotective effects[29-31]. Interestingly, administration of exendin-4 in non-diabetic animals immediately after stroke also reduces stroke volume and improves outcome through similar mechanisms without affecting glucose levels[32]. These effects appear to be GLP-1 receptor-mediated since they are not observed in GLP-1 receptor knockout (-/-) mice[28]. Moreover, GLP-1 readily crosses the blood-brain barrier[33-35] and GLP-1 receptors are expressed in brain neurons in humans[36-39]. In addition, both ischemia and treatment with exendin-4 up-regulate the expression of GLP-1 receptors in pyramidal neurons[29]. Given the putative neuroprotective effects of GLP-1, this increased expression might be a defense mechanism against ischemic damage[29].

A second possible pathway through which linagliptin might exert its neuroprotective effects is the increased bioavailability of other bioactive DPP-4 substrates. Indeed, DPP-4 has many other substrates except GLP-1, some of which appear to exert neurotrophic or neuroprotective effects[40,41]. The latter include glucose-dependent insulinotropic polypeptide[42], pituitary adenylate cyclase-activating polypeptide[43] and stromal cell-derived factor 1a[44], which were reported in preclinical models to promote synaptic plasticity, neurogenesis and neuronal differentiation, to inhibit apoptosis and to reduce stroke size.

Another possible explanation of the different effects of linagliptin and glimepiride on stroke volume is that glimepiride exerts detrimental effects rather than that linagliptin is protective. Indeed, several recent studies suggested that patients treated with sulfonylureas have increased cardiovascular morbidity compared with patients treated with metformin[45-47]. Therefore, it would be of interest to compare the effects of prior treatment of DPP-4 inhibitors with prior treatment with metformin in experimental models of stroke or in patients who suffer a stroke.

Despite these promising preclinical findings suggesting neuroprotective effects of DPP-4 inhibitors in acute stroke, it is still unclear whether these actions will also be observed in humans. Interestingly, a recent randomized double-blind study showed that the addition of linagliptin to metformin reduces the risk of non-fatal stroke more than the addition of glimepiride, despite comparable decreases in HbA_{1c}[48]. Preliminary data also suggest similar reductions in stroke risk with other DPP-4 inhibitors[49]. However, these studies were neither planned nor powered to assess the effects of DPP-4 inhibitors on cardiovascular events[48,49]. On the other hand, two recent large randomized, placebo-controlled studies did not show any benefit of DPP-4 inhibitors on cardiovascular events, including stroke[50,51]. Several other ongoing trials are evaluating the effects of DPP-4 inhibitors on cardiovascular morbidity and mortality. These studies also provide a major opportunity to assess whether patients treated with this class of antidiabetic agents will suffer from less severe strokes and whether their outcome after stroke will be more favorable.

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