I t has long been recognized that type 2 diabetes is a cardiovascular (CV) disease equivalent (1). The recognition has led to the aggressive pursuit of glycemic control as a mechanism to reduced CV mortality. As such, reducing macrovascular complications related to type 2 diabetes has been a major target of antiglycemic therapies. To date, this clinical objective has remained elusive in contrast to the improvements in microvascular complications. Recent insights from large-scale clinical trials (2–5) have suggested that glucocentric approaches to mitigating CV risk in type 2 diabetes are insufficient and that attention to other CV risk factors such as lipids and blood pressure are equally important in these patients. More recently, investigators have sought strategies that are not merely antiglycemic but also cardioprotective. In this regard, incretin-based therapies have emerged as an exciting approach that seems to address both objectives. Nearly 120,000 type 2 diabetic subjects are currently being studied with respect to whether incretin-based therapies will reduce adverse CV events.

It is also well recognized that type 2 diabetes is a major risk factor for the development of ischemic stroke. Patients with diabetes are 2.9 times more likely to develop ischemic stroke than are age-matched control subjects (6,7). Moreover, the therapeutic options for reducing ischemic brain injury secondary to stroke have lagged behind comparable interventions designed to reduce myocardial infarct size and subsequent mortality, despite the fact that stroke is the third leading cause of death in the U.S. The pathophysiology of stroke involves the loss of striatal and progressively cortical neurons through ischemic injury and apoptosis (6,7). Therapeutic efforts to reduce stroke size involve efforts to preserve the cortical penumbra surrounding the area of striatal neuronal cell death. The latest study from Darsalia et al. (8) from the Karolinska Institutet published in the current issue of Diabetes demonstrates that 1 month of pretreatment with the dipeptidyl peptidase-4 (DPP-4) inhibitor linagliptin (10 mg/kg body weight per day) followed by 3 weeks of posttreatment significantly reduced neuronal loss but not overall infarct size in a high-fat diet–fed diabetic (prandial glucose = 11–12 mmol/L) mouse model of middle cerebral artery (MCA) occlusion. The benefit was independent of glycemic control and was associated with marked increases in plasma levels of glucagon-like peptide 1 (GLP-1) (7–36). In high-fat diet–fed mice, the neuronal salvage was greater in the linagliptin-treated group compared with glimeperide-treated mice, despite less effective glucose control suggesting mechanisms distinct from glycemic control alone. However, in normal mice, both linagliptin and glimeperide had similar beneficial effects in reducing both stroke volume and neuronal loss. The findings follow results reported from this same group using the GLP-1 receptor analog exenatide (9) in GK rats with severe hyperglycemia (glucose = 20 mmol/L) where both infarct size and neuronal salvage were favorably influenced in a dose-dependent fashion but independent of glycemic control. Together, these studies provide provocative descriptive evidence of putative benefits of incretin-based therapies in an experimental model of type 2 diabetes and ischemic stroke.

The role of GLP-1 in the central nervous system has been studied increasingly (6,7), and there is an emerging body of evidence in cell cultures and rodent models that suggests that GLP-1 protects against neuronal degeneration in experimental models of Parkinsonism, Huntington’s disease, and Alzheimer’s disease (6,10). GLP-1 receptors have been identified on neurons and are increased in expression in the penumbra following ischemia (11). Activating the incretin pathway in neurons can produce cellular protection and proliferation and the differentiation of precursor cells into neurons, similar to what has been reported in pancreatic β-cells. Additionally, functional benefits of GLP-1 receptor stimulation in rodent models of stroke have been described. The use of transient MCA occlusion models has shown that both pretreatment and posttreatment with the GLP-1 receptor agonist exendin-4 provides beneficial effects on infarct size, and these benefits are abolished in GLP-1 receptor knockout mice (12,13). However, the precise cellular mechanism by which GLP-1 exerts its neuroprotective effects is as yet unknown.

Similarly, in the current study it is not possible to identify the putative mechanism of neuroprotection of DPP-4 inhibition, which has many “off-target” effects. Surely, GLP-1 potentiation is a principal target of DPP-4 inhibition and accounts for the antiglycemic effects. However, in humans with type 2 diabetes, DPP-4 inhibition leads to a two- to threefold increase of basal GLP-1 levels (10–30 pmol/L). The dose of linagliptin used in high-fat diet–fed mice was ~200 times higher than those used in humans with type 2 diabetes (5 mg per day). Moreover, the authors report that plasma levels of active GLP-1 rose by ~3,000% (30-fold or ~300 pmol/L). As such, these findings may be difficult to extrapolate to humans, in which DPP-4 inhibition is unlikely to achieve such high plasma levels of GLP-1. The actual levels of plasma GLP-1 achieved are critical for at least two reasons. First, linagliptin does not cross the blood brain barrier, and therefore its effects are
On-target effects of DPP-4 inhibitors

| Potential mechanisms of benefit | Neuroprotective |
|--------------------------------|----------------|
| 1. Increase circulating half-life of physiological concentrations of GLP-1 (7–36) amide | Neuroprotective |
| a. Increase circulating insulin concentrations | Neuroprotective |
| b. Decrease hyperglycemia and glutamate levels | Neuroprotective |

Off-target effects of DPP-4 inhibitors

| Potential mechanisms of benefit | Neuroprotective |
|--------------------------------|----------------|
| 1. Increase of brain natriuretic peptide | Neuroprotective |
| a. Decrease blood pressure reduces | Neuroprotective |
| b. Natriuretic effects decrease brain swelling | Neuroprotective |
| 2. Increase circulating half-life of stromal derived factor-1 | Neuroprotective |
| a. Increase honing of neuronal progenitor cells | Neuroprotective |
| 3. Reduce lymphocyte activation through inhibition of CD26 | Neuroprotective |
| a. Anti-inflammatory | Neuroprotective |

Potential deleterious effects

| Neuronal tolerance to hypoxia | angiotensin-II |
|-------------------------------|----------------|
| 1. Decrease glucagon levels, which suppresses ketosis and reduces | vasoconstrictor |
| 2. Increase circulating half-life of neuropeptide Y, which potentiates | response to angiotensin-II |

Given the preponderance of preclinical studies showing that incretin-based therapies are both cardio- and neuroprotective, does the mechanism of action really matter? Can we conclude that this is a class effect whether one chooses to pharmacologically activate the GLP-1 receptor with GLP-1 analogs or through DPP-4 inhibition? Is the growing enthusiasm regarding incretins and CV disease unfounded? The jury is still out. However, one thing is clear. The benefits of incretin-based therapies extend beyond their antihyperglycemic effects and, as such, hold greater promise for reducing CV and neurological complications of type 2 diabetes than strategies that simply focus on tight glycemic control. On a cautionary note, the same was true for peroxisome proliferator-activated receptor-γ agonists in preclinical studies. 

But, the jury is deliberating. As a result of new post-approval regulatory requirements of the Food and Drug Administration, there are nearly 120,000 patients with type 2 diabetes currently enrolled in CV safety and outcomes trials of incretin-based therapies including both GLP-1 analogs and DPP-4 inhibitors. Notably, nonfatal stroke is part of a composite end point being examined in all of these trials and specifically the CAROLINA trial in which 6,000 type 2 diabetic patients will be randomized to receive linagliptin compared with glimepiride, which recapitulates the circumstances investigated in the current study. If these clinical trials are positive, then these investigators should be heralded as prescient. However, if they are neutral, we will ask why we rushed to judgment without understanding more fully the mechanism of action.

ACKNOWLEDGMENTS

No potential conflicts of interest relevant to this article were reported.

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