ABSTRACT

Patients with type 2 diabetes mellitus are at risk for accelerated cognitive decline and dementia. Furthermore, their risk of stroke is increased and their outcome after stroke is worse than in those without diabetes. Incretin-based therapies are a class of antidiabetic agents that are of interest in relation to these cerebral complications of diabetes. Two classes of incretin-based therapies are currently available: the glucagon-like-peptide-1 agonists and the dipeptidyl peptidase-4 -inhibitors. Independent of their glucose-lowering effects, incretin-based therapies might also have direct or indirect beneficial effects on the brain. In the present review, we discuss the potential of incretin-based therapies in relation to dementia, in particular Alzheimer’s disease, and stroke in patients with type 2 diabetes. Experimental studies on Alzheimer’s disease have found beneficial effects of incretin-based therapies on cognition, synaptic plasticity and metabolism of amyloid-β and microtubule-associated protein tau. Preclinical studies on incretin-based therapies in stroke have shown an improved functional outcome, a reduction of infarct volume as well as neuroprotective and neurotrophic properties. Both with regard to the treatment of Alzheimer’s disease, and with regard to prevention and treatment of stroke, randomized controlled trials in patients with or without diabetes are underway. In conclusion, experimental studies show promising results of incretin-based therapies at improving the outcome of Alzheimer’s disease and stroke through glucose-independent pleiotropic effects on the brain. If these findings would indeed be confirmed in large clinical randomized controlled trials, this would have substantial impact.

INTRODUCTION

The prevalence of diabetes mellitus is increasing, with more than 380 million people being affected throughout the world1. Type 2 diabetes mellitus accounts for 90% of these cases2. End-organ complications, in particular vascular disease, are a major concern in diabetes care and treatment. Well-known vascular complications of type 2 diabetes mellitus include coronary heart disease, nephropathy, retinopathy and lower-limb amputations3. Accelerated cognitive decline is another complication in type 2 diabetes mellitus, potentially resulting in mild cognitive impairment (MCI) or dementia2. Also, patients with type 2 diabetes mellitus have an increased risk of stroke, and have a worse stroke outcome compared with patients without type 2 diabetes mellitus3.

The pathophysiology of type 2 diabetes mellitus is characterized by insulin resistance, relative insulin deficiency and pancreatic β-cell dysfunction4. Reduction of insulin resistance and raising of endogenous insulin secretion are important targets of antidiabetic drugs. Many classes of such antidiabetic drugs have been available for decades; for example biguanides, sulfonylurea, thiazolidinediones (TZD), insulin and α-glucosidase inhibitors. Incretin-based therapies are another class of antidiabetic agents that have recently become available for treatment of type 2 diabetes mellitus. These compounds are of possible interest also in relation to dementia and stroke, because besides improving glucose homeostasis, they might have additional direct or indirect beneficial effects on the brain. In the present review, we will discuss the potential of incretin-based therapies in relation to cognitive decline and dementia, in particular Alzheimer’s disease (AD), in patients with type 2 diabetes mellitus. We will also discuss incretin-based therapies in relation to stroke risk in patients with type 2 diabetes mellitus, and their potential to improve stroke outcome.
**Incretin-based therapies in type 2 diabetes mellitus are divided into two categories, the glucagon-like-peptide-1 (GLP-1) agonists and the dipeptidyl peptidase-4 (DPP4)-inhibitors. Currently registered GLP-1 agonists for type 2 diabetes mellitus treatment are exenatide (the synthetic form of exendin-4, a naturally occurring GLP-1 agonist), liraglutide, lixisenatide and dulaglutide. GLP-1 agonists require subcutaneous administration. Examples of currently registered DPP-4 inhibitors are sitagliptin, linagliptin, saxagliptin, vildagliptin and alogliptin. DPP-4 inhibitors are administered orally. Whereas endogenous GLP-1 has a half-life in the order of a few minutes, the half-life of incretin-based compounds is several hours, thus enabling their application for diabetes treatment. GLP-1 agonists and DPP-4 inhibitors are currently used as second-line therapies in type 2 diabetes mellitus, or in triple therapy regimens, and are also applied for first-line use in the case of intolerance or contraindications to metformin. Incretin-based therapies have a favorable safety profile and a low risk of hypoglycemia.**

**Biology of Incretin Hormones in Peripheral Organs and the Brain**

**Biology of Incretins**

Incretins are gastrointestinal hormones secreted from the gut into the bloodstream, minutes after oral nutrient intake, that promote insulin secretion from the pancreatic β-cells. The most important incretins in humans are GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). Both GLP-1 and GIP have an insulinotropic effect, and together contribute approximately 50–70% of the total insulin secretion after oral glucose ingestion, denoted as “the incretin effect.” Oral food ingestion is the primary physiological stimulus for GLP-1 and GIP secretion, from the intestinal endocrine L-cells and K-cells, respectively. After secretion, levels of intact circulating GLP-1 and GIP drop rapidly as a result of enzymatic inactivation by DPP-4 and renal clearance. For that reason, in the circulation the GIP drop rapidly as a result of enzymatic inactivation by DPP-4 inhibitors are administered orally. Whereas endogenous GLP-1 has a half-life in the order of a few minutes, the half-life of incretin-based compounds is several hours, thus enabling their application for diabetes treatment. GLP-1 agonists and DPP-4 inhibitors are currently used as second-line therapies in type 2 diabetes mellitus, or in triple therapy regimens, and are also applied for first-line use in the case of intolerance or contraindications to metformin. Incretin-based therapies have a favorable safety profile and a low risk of hypoglycemia.

**Table 1**

| GLP-1 receptor | GIP receptor |
|----------------|-------------|
| Pancreatic β-cells | Pancreatic β-cells |
| Heart | Heart |
| Lung | Lung |
| Stomach, intestine (ileum and colon) | Stomach, duodenum |
| Kidney | Kidney |
| Brain | Brain |
| Autonomic nervous system: | Thyroid |
| nodose ganglion of the vagal nerve | |
| Skin | |
| Trachea | |
| Thyroid | |
| Spleen | |
| Adrenals | |
| Bone | |
| Adipose tissue | |
| Testis | |

GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like-peptide-1.

**Table 2**

| Action | GLP-1 | GIP |
|--------|-------|-----|
| Endocrine pancreas | Glucose-independent insulin release ↑ | Glucose-independent insulin release ↑ |
| | β-Cell proliferation ↑ | β-Cell proliferation ↑ |
| | β-Cell apoptosis ↓ | β-Cell apoptosis ↓ |
| | Glucagon-dependent glucagon ↓ | Glucagon secretion ↑ |
| Food intake and weight | Food intake ↓ | |
| Gastrointestinal system | Promotion of weight loss | |
| | Gastric emptying ↓ | |
| Cardiovascular effects | Blood pressure ↓ | |
| | Endothelial function ↑ | Cardioprotective |
| Bone | Bone formation ↑ | Bone absorption ↓ |
| | Bone absorption ↓ | |
| Lipid metabolism | Fatty acid synthesis ↓ | Lipogenesis ↑ |
| | Fatty acid oxidation ↑ | |

GLP-1, glucagon-like-peptide-1.

Studies on the extrapancreatic effects of GIP are relatively scarce, but it is known that GIP is involved in lipogenesis in adipose tissue. Incretins also act on the brain; peripherally secreted GLP-1 can cross the blood–brain barrier (BBB) by passive diffusion. Furthermore, within the brain, a small amount of GLP-1 is produced in the nucleus of the solitary tract in the caudal brainstem, thus functioning as a neurotransmitter.
sites for GLP-1Rs in the brain are located in the hypothalamus, hippocampus, striatum, brain stem, substantia nigra and subventricular zone, among other structures. The GIP-R is expressed in the cerebral cortex, hippocampus and the olfactory bulb. It seems that peripherally administered GLP-1 also plays a role in glucose homeostasis, food intake and satiety through brain GLP-1R.

There is evidence in animals that direct administration of GLP-1 in the brain leading to brain GLP-1R signaling influences peripheral glucose metabolism. Under hyperglycemic conditions, intracerebroventricular (ICV) administration of a GLP-1 agonist through stimulation of brain GLP-1R induces insulin secretion, and activates peripheral pathways inhibiting glucose uptake and promotes glycogen storage in the liver. Another study showed that hindbrain administration of GLP-1 increased glucose-stimulated insulin secretion and reduced hepatic glucose production. Some animal studies have shown that direct administration of a GLP-1-agonist in the brain leading to GLP-1R signaling leads to a decrease in food intake and to induction of satiety or anorexia.

**Pleiotropic effects of incretins and incretin-based therapies on the brain**

Incretins appear to have additional effects on the brain that are not directly related to glucose metabolism. In several neuronal cell line studies, GLP-1 induced neurite outgrowth. One study found that ICV infusion of GIP stimulated progenitor cell proliferation in the rat hippocampus. Furthermore, a study of GIPR-knockout mice showed that disruption of the GIP signaling pathways leads to a diminished number of progenitor cells in the dentate gyrus. These findings suggest that incretins have neurotrophic properties in the brain.

In addition to these neurotrophic properties, GLP-1 appears to have neuroprotective properties. Neuronal cell line studies showed that GLP-1 protected against H2O2-induced toxicity by raising the expression of anti-apoptotic proteins. In another cell line study, GLP-1 also protected against oxidative stress-induced neuronal cell apoptosis. Also, GLP-1 protected rat cultured hippocampal cells in vitro against glutamate-induced apoptosis.

Another interesting observation is that incretins could influence synaptic plasticity; that is, long-term potentiation (LTP) and cognition. LTP is the cellular correlate of memory formation, and is defined as a persisting enhancement in signal transmission between two neurons, resulting from their synchronous activity. In rodent models, ICV injection of GLP-1 or GIP enhanced LTP in the hippocampus. In contrast, administration of a GIP-antagonist induced inhibition of LTP. On a behavioral level, ICV administration of a GLP-1 agonist in mice enhanced associative and spatial learning through GLP-1R. Additional evidence for incretin involvement in plasticity and cognition came from studies in GLP-1R or GIP-R knockout mice, in which LTP and cognition were impaired.

In mice, the GLP-1 agonists exenatide, lixisenatide and liraglutide can all cross the BBB after peripheral administration. Some studies have shown that the DPP-4 inhibitors linagliptin and vildagliptin do not pass the BBB. However, other studies have suggested that an increased plasma level of GLP-1 or inhibition of DPP-4, enhance transport of GLP-1 across the BBB. DPP-4 inhibitors might also influence the brain through vascular effects. This potential mode for modulation was suggested in a study wherein oral linagliptin treatment in type 2 diabetes mellitus rats restored insulin-mediated vasorelaxation of middle cerebral arteries. This result implies that linagliptin acts on the brain through the vasculature.

The direct neuronal effects that are reported for the incretins themselves have also been observed for incretin-based therapies. Neuronal cell line studies showed that the GLP-1 agonist exendin-4 promotes cell proliferation, neuronal differentiation and neurite outgrowth. Furthermore, a number of rodent studies on peripheral administered GLP agonists found an increased rate of neuronal cell proliferation and stimulation of neurogenesis.

Neuronal cell line studies on GLP-agonists showed protection against H2O2-induced toxicity. In a cell line study on human neuroblastoma cells, liraglutide enhanced cell viability and stimulated a range of growth-factor related protective processes, which resulted in a reduced rate of apoptosis.

GLP-1 agonists and DPP-4 inhibitors might have beneficial effects on LTP and cognition as well. In one study, ICV injection of liraglutide was effective in LTP. Subcutaneous injections of exendin-4 and liraglutide in obese mice improved disturbances of LTP. Peripheral administration of DPP-4 inhibitors (sitagliptin and vildagliptin) in high-fat diet rats led to improvement of cognitive functioning in several studies.

**TYPE 2 DIABETES MELLITUS, DEMENTIA AND INCRETIN-BASED THERAPIES**

Cognitive impairment and dementia are increasingly recognized as important complications of type 2 diabetes mellitus. For instance, patients with type 2 diabetes mellitus perform slightly worse on a range of cognitive tasks, compared with patients without type 2 diabetes mellitus. The rate of cognitive decline in patients with type 2 diabetes mellitus can be up to twofold faster compared with normal aging. Patients with type 2 diabetes mellitus have an increased risk for MCI, compared with patients without type 2 diabetes mellitus. The proportion of patients who convert from MCI to dementia is 1.5–3-fold higher in patients with than in those without type 2 diabetes mellitus. Type 2 diabetes mellitus also increases the risk of dementia. A meta-analysis including more than 30,000 people of whom 16% had type 2 diabetes mellitus showed that the relative risk (RR) for dementia was 1.5 (95% confidence interval [CI] 1.3–1.7). This increased risk for dementia applies to both AD, with a RR of 1.5 (95% CI 1.4–1.7) and vascular dementia, with a RR of 2.5 (95% CI 2.1–3.0). However, despite the fact that the relative risk of vascular dementia is higher.
than that of AD in patients with type 2 diabetes mellitus, AD is the most common type of dementia in type 2 diabetes mellitus patients, because the absolute risk of AD is higher than that of vascular dementia.

The question is what causes accelerated cognitive decline and increased dementia risk in patients with type 2 diabetes mellitus. Glycemic control is an obvious candidate, and has been investigated in a substantial number of studies. A systematic review of cross-sectional and longitudinal observational studies in people with type 2 diabetes mellitus reported that measures of glycemia, particularly high glycated hemoglobin concentration and glucose variability, are negatively associated with cognitive function. However, the strength of the association is weak, and glycated hemoglobin generally accounted for less than 10% of the variance in cognition in the included studies. With regard to glucose-lowering treatment, available randomized controlled trials (RCTs) report no consistent beneficial effects of intensified vs standard glucose-lowering treatment on cognitive functioning in patients with type 2 diabetes mellitus. A Cochrane systematic review found no evidence for cognitive benefit in relation to types and intensity of glucose-lowering treatments. In concordance, a recent meta-analysis of 24,000 patients with type 2 diabetes mellitus reported that intensive glycemic control was not associated with a slower rate of cognitive decline compared with regular treatment (standardized mean difference 0.02 95% CI –0.03 to 0.08). Nevertheless, some glucose-lowering drugs might improve cognitive functioning independent of glucose lowering through other drug class effects. Rodent models have suggested beneficial glycemia-independent effects of biguanides and TZD on cognition, and has been investigated in a substantial number of studies. A systematic review of cross-sectional and longitudinal observational studies in people with type 2 diabetes mellitus reported that measures of glycemia, particularly high glycated hemoglobin concentration and glucose variability, are negatively associated with cognitive function. However, the strength of the association is weak, and glycated hemoglobin generally accounted for less than 10% of the variance in cognition in the included studies. With regard to glucose-lowering treatment, available randomized controlled trials (RCTs) report no consistent beneficial effects of intensified vs standard glucose-lowering treatment on cognitive functioning in patients with type 2 diabetes mellitus. A Cochrane systematic review found no evidence for cognitive benefit in relation to types and intensity of glucose-lowering treatments. In concordance, a recent meta-analysis of 24,000 patients with type 2 diabetes mellitus reported that intensive glycemic control was not associated with a slower rate of cognitive decline compared with regular treatment (standardized mean difference 0.02 95% CI –0.03 to 0.08). Nevertheless, some glucose-lowering drugs might improve cognitive functioning independent of glucose lowering through other drug class effects. Rodent models have suggested beneficial glycemia-independent effects of biguanides and TZD on AD pathology. However, whereas some clinical studies on AD patients reported beneficial effects of TZD, other studies did not confirm these results. In the context of the present review, we focus on possible drug class effects of incretin-based therapies on cognition.

Preclinical studies on the effects of incretin-based therapies on dementia have focused on AD. The core etiological processes in AD are considered to be aberrant amyloid-β (Aβ) processing, leading to formation of toxic Aβ oligomers and aggregation of microtubule-associated protein tau (MAPT). Aβ oligomers are derived from amyloid precursor protein (APP) by cleavages by two membrane-bound proteases. These Aβ oligomers can cause synaptic dysfunction, inflammation and neuronal cell death. Phosphorylation of MAPT induces the formation of neurofibrillary tangles (NFT). Hyperphosphorylation of MAPT leads to a dissociation of NFTs, resulting in neuron damage. Interestingly, disturbances in amyloid or MAPT processing have been linked to brain insulin resistance in AD. In rodent models of AD, ICV administered (Val8)GLP-1, D-Ala2GIP facilitated synaptic plasticity in mice at an advanced state of AD. Two studies showed that centrally-administered (Val8)GLP-1 and D-Ala2GIP reversed impairment of LTP induced by Aβ. In another study, centrally-administered liraglutide enhanced LTP in late-stage AD rodents as well as in wild-type rodents. In addition, a number of studies showed prevention of synaptic loss.

Several preclinical studies have also explored effects of incretins on the core etiological processes of AD. Neuronal cell line studies showed that exendin-4 reduced the levels of Aβ, other neuronal cell line studies found that exendin-4 reduced levels of APP, but had no impact on Aβ levels. In rodent models of AD, peripherally-administered geniposide and D-Ala2GIP reduced levels of Aβ plaque load. However, two other studies reported no reduction of both APP and Aβ levels, despite the fact that treatment did have beneficial effects on memory or LTP. Peripherally-administered liraglutide reduced both Aβ and APP levels, even in a late-stage AD rodent model. Furthermore, peripherally-administered sitagliptin, saxagliptin and vildagliptin lowered the levels of Aβ and reduced tau phosphorylation. Peripherally-administered saxagliptin and vildagliptin reduced tau phosphorylation, whereas one study reported that sitagliptin was not effective against tau phosphorylation, and instead worsened it.

Neuronal cell line studies and AD rodent models showed that GLP-1 and GIP ameliorated oxidative stress-induced injury, and protected against cell death induced by Aβ. Furthermore, various studies reported that D-Ala2GIP reduced the inflammatory response in rodent AD models. Also, sitagliptin, saxagliptin and vildagliptin showed anti-inflammatory properties, as well as liraglutide in a late-stage AD rodent model. Moreover, peripherally-administered liraglutide and D-Ala2GIP increased neuronal progenitor cell proliferation and neurogenesis in AD rodent models.

The key question is of course whether these promising results in experimental studies also translate into clinically relevant treatment effects in humans. The results of two RCTs in people with MCI or early AD, but without type 2 diabetes mellitus are awaited (Table 3). As patients with type 2 diabetes mellitus...
mellitus are at increased risk for MCI and dementia, possibly through mechanisms that are influenced by incretin-based therapies, there is a particular need for additional RCTs, especially in this group.

**TYPE 2 DIABETES MELLITUS, STROKE AND INCRETIN-BASED THERAPIES**

**Type 2 diabetes mellitus and prevention of stroke**

Diabetes is a risk factor for stroke, and is linked to worse stroke outcome. In a meta-analysis of prospective studies, the reported hazard ratio (HR) for ischemic stroke in patients with diabetes was 2.3 (95% CI 2.0–2.7). Assuming a population-wide prevalence of diabetes of 10% in adults aged over 50 years, the diabetes-attributable risk of stroke is at 12%.

Again, the question is whether glyceremia is the causal link between type 2 diabetes mellitus and the increased risk of stroke. Indeed, glyceremia has been studied extensively in this context. Two landmark RCTs reported that the risk of stroke was not affected by intensive glycemic control in patients with longstanding type 2 diabetes mellitus. A subsequent meta-analysis including 34,533 type 2 diabetes mellitus patients also showed that intensive glycemic control did not reduce stroke risk compared with regular treatment (HR 5-year stroke risk 0.96, 99% CI 0.8–1.1). A Cochrane meta-analysis including 34,912 type 2 diabetes mellitus patients reported the same finding (RR 1, 95% CI 0.84–1.19). Apparently, levels of glyceremia by itself have no major impact on stroke risk in type 2 diabetes mellitus. However, some glucose-lowering drugs might affect stroke risk independent of glucose lowering. In the context of the present review, we consider such potential class effects for incretin-based therapies in the primary and secondary prevention of stroke. Two RCTs on saxagliptin or alogliptin vs a placebo in patients with type 2 diabetes mellitus and a previous history of cardiovascular events (including stroke) showed a similar incidence of non-fatal ischemic stroke in the treatment and placebo groups (HR 0.91, 95% CI 0.55–1.50 and HR 1.11, 95% CI 0.88–1.39). As a subsequent RCT on sitagliptin vs a placebo in patients with type 2 diabetes mellitus and established cardiovascular disease, including ischemic stroke, also showed no difference in incidence of stroke (HR 0.97, 95% CI 0.79–1.19). In contrast, a recent prospective meta-analysis pooled data of RCTs on the effects of linagliptin vs other therapies (gliipemide, voglibose or placebo) on major cardiovascular events in 5,847 patients with type 2 diabetes mellitus and low prevalence of prior cardiovascular events. The incidence rate of non-fatal stroke was significantly reduced in the linagliptin group compared with the other groups (HR 0.34, 95% CI 0.15–0.75). The results of six ongo-
ing trials are still awaited (Table 4). In sum, for secondary prevention of stroke, there is currently no evidence for a class effect of DPP-4 inhibitors. However, preliminary data do show that incretin-based therapies might be effective in primary prevention of stroke, and results of further RCTs are awaited.

Type 2 diabetes mellitus and outcome of stroke

Diabetes is associated with poor functional outcome after ischemic stroke (odds ratio [OR] 1.5, 95% CI 1.1–1.9)\(^9\), and with an increased mortality 1 year after ischemic stroke (HR 1.2, 95% CI 1.1–1.2)\(^9\). Diabetes also increases the risk of post-stroke dementia (OR 1.4, 95% CI 1.2–1.7)\(^\text{100}\). Furthermore, hyperglycemia in the acute phase of stroke is associated with poor outcome, also in people without diabetes. Hyperglycemia is present in 30–40% of the patients with acute ischemic stroke\(^3\). A systematic review found that admission hyperglycemia occurred in 8–63% of non-diabetic stroke patients, and in 39–83% of diabetic patients\(^101\). A recent systematic review on the association between hyperglycemia at admission and outcome after ischemic stroke showed that hyperglycemia at admission is a predictor of neurological deterioration occurring within 24 h after ischemic stroke\(^102\).

Table 4 | Randomized controlled trials on the effect of incretin-based agents on incidence of stroke

| Study          | Agent | Study population | End-point | Results (if applicable) |
|----------------|-------|------------------|-----------|-------------------------|
| EXAMINE trial (2013)\(^95\) | Agent: alogliptin Comparator: placebo | 5,380 T2DM patients with a recent ACS | Primary end-point: a composite of death from CV disease, non-fatal myocardial infarction or non-fatal stroke | Similar incidence in both groups for non-fatal stroke (HR 0.91, 95% CI 0.55–1.50, \(P = 0.71\)) |
| SAVOR-TIMI 53 (2013)\(^95\) | Agent: saxagliptin Comparator: placebo | ≥16,000 T2DM patients with a history of, or were at risk for a CV event | Primary end-point: a composite of CV death, myocardial infarction or ischemic stroke | Similar incidence in both groups for non-fatal ischemic stroke (HR 1.11, 95% CI 0.88–1.39, \(P = 0.38\)) |
| TECOS\(^96\) | Agent: sitagliptin Comparator: placebo | 14,671 T2DM patients with established CV disease | Primary endpoint: a composite defined as CV-related death, non-fatal MI, non-fatal stroke, or unstable angina requiring hospitalizations | Similar incidence in both groups for fatal or non-fatal stroke (HR 0.97, 95% CI 0.79–1.19, \(P = 0.76\)) |
| ELIXA (NCT01147250) | Agent: lixisenatide Comparator: placebo | Phase 3 study Period: 2010–2015 6,000 T2DM patients after ACS | Primary end-point: a composite of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina | |
| LEADER (NCT01179048) | Agent: liraglutide Comparator: placebo | Phase 3 study Period: 2010–October 2015 9,340 T2DM patients | Primary end-point: a composite of CV death, non-fatal MI and non-fatal stroke | |
| CAROLINA (NCT01243424) | Agent: linagliptin Comparator: glimepiride | Phase 3 study Period: 2010–2018 6,000 T2DM patients with a high CV risk profile | Primary end-point: a composite of CV death non-fatal myocardial infarction, non-fatal stroke and hospitalization for unstable angina pectoris | |
| REWIND (NCT01394952) | Agent: dulaglutide Comparator: placebo | Phase 3 study Period: 2011–2019 9,622 T2DM patients | Primary end-point: a composite of CV death, non-fatal MI and non-fatal stroke | |
| CARMELINA (NCT01897532) | Agent: linagliptin Comparator: placebo | Phase 4 study Period: 2013–2018 8,300 T2DM patients with a high risk of CV events | Primary end-point: a composite of CV death, non-fatal MI and non-fatal stroke | |
| EXSCEL (NCT01144338) | Agent: exenatide Comparator: placebo | Phase 4 study Period: 2010–2017 14,000 T2DM patients | Primary end-point: a composite of CV death, non-fatal MI and non-fatal stroke | |

ACS, acute coronary syndrome; CV, cardiovascular; MI, myocardial infarction; T2DM, type 2 diabetes.
unadjusted relative risk of in-hospital or 30-day mortality after an ischemic stroke in patients with hyperglycemia at admission is 3.3 (95% CI 2.3–4.7) in those without known diabetes, and 2.0 (95% CI 0.40–9.01) in patients with diabetes. This elevated risk is independent of other predictors of poor outcome. Often, hyperglycemia at admission is the result of a stress response rather than reflecting pre-existing unrecognized diabetes.

The question is of course whether the relationship between hyperglycemia and outcome after stroke is causal, or whether hyperglycemia is mostly an epiphenomenon that reflects stroke severity or other concomitant adverse factors. Several pathophysiological processes have been identified through which hyperglycemia could increase cerebral damage. Furthermore, experimental studies in hyperglycemic rodents found an association between treatment with antidiabetic agents and outcome of ischemic stroke. Several RCTs have therefore explored if tight glycemic control in the acute phase of stroke can improve stroke outcome. A Cochrane meta-analysis of 11 of such studies, involving 1,583 patients with stroke and admission hyperglycemia, showed no difference in outcome after stroke between intensively monitored intravenous insulin treatment and usual care (OR 1.0 95% CI 0.8–1.2).

Although the currently available data show that tight glycemic control offers no benefit for stroke outcome, glucose-lowering drugs might affect outcome of stroke through class effects independent of glucose lowering. Rodent studies have suggested beneficial glycemia-independent effects of biguanides, sulfonylureas and TZD on outcome of ischemic stroke.

Preclinical studies have investigated the effects of incretin-based therapies on outcome of stroke. Pre-stroke treatment with ICV-administered exendin-4 or peripherally-administered alogliptin effectively reduced neurological deficits and infarct volume in normoglycemic rodents. Post-stroke treatment with peripherally-administered exendin-4 or lixagliptin also showed protection against motor impairment, and led to reduction of infarct volume in normoglycemic rodents. Combined pre- and post-stroke treatment with peripherally-administered exendin-4 led to increased spontaneous motor activity in normoglycemic rodents.

The effects of incretin-based therapies have also been studied in diabetic rodent models of ischemic stroke. Post-stroke treatment with peripherally-administered exendin-4 in diabetic rodents resulted in a reduction of infarct volume in a dose-dependent manner. Combined pre- and post-treatment with peripherally-administered lixagliptin in diabetic rodents showed a trend toward a decrease in infarct volume. In a recent rodent model, post-stroke treatment with peripherally-administered lixagliptin improved stroke-induced cognitive impairment, independent of glucose-lowering effects.

These apparent beneficial effects of incretin-based therapies on outcome of ischemic stroke could involve several mechanisms. Incretin-based therapies might act on salvage of the penumbra. The penumbra is the part of the ischemic zone that can recover if adequate reperfusion is re-established in the early stage of ischemic stroke. Two studies found increased expression of GLP-1Rs and protein levels in the penumbra after induction of ischemia.

Inflammation or oxidative stress might also play a role. After stroke, microglial activation, an inflammatory response, induces various neurotoxic free radicals, cytoxic and pro-inflammatory mediators, and contributes to infarct progression. Rodent models showed inhibited microglial activation and microglial migration, thereby suppressing the inflammatory response induced by ischemic stroke. In addition, rodent models of ischemic stroke showed that incretin-based therapies might protect against oxidative stress and neuronal cell death.

Incretin-based therapies have shown neurotrophic properties after ischemic stroke by increasing neuroblast formation and neuronal stem cell (NSC) proliferation, thereby not affecting stroke-induced neurogenesis. Pre-treatment of peripherally-administered linagliptin has been shown to enhance NSC proliferation only in diabetic mice, but not in non-diabetic mice. However, linagliptin did not ameliorate NSC in vitro, suggesting that the effect of linagliptin on NSC in diabetic mice is indirect.

RCTs in patients with stroke are required to investigate the clinical effects of incretin-based therapies on stroke outcome. Because possible effects of such therapies do not appear to be primarily mediated through glucose-lowering effects, such trials need not be limited to patients with ischemic stroke and hyperglycemia or type 2 diabetes mellitus. A RCT could involve patients with a stroke regardless of the presence of admission hyperglycemia. Nevertheless, if such trials would show benefit of incretin-based therapies on stroke outcome, this might be particularly relevant for patients with type 2 diabetes mellitus. Patients with type 2 diabetes mellitus already on incretin-based therapy would then be “protected” from the moment of stroke onset onwards, rather than from the moment the first dose of the drug is given after admission for stroke, as would be the case in other patients.

CONCLUSION

In conclusion, preclinical studies show that incretin-based therapies might hold promise in the treatment of dementia, in particular AD, and stroke. In AD models, incretin-based therapies improve cognition and synaptic plasticity, show anti-inflammatory and anti-oxidative properties, and reduce Aβ levels and tau phosphorylation. RCTs of incretin-based therapies on stroke prevention showed no reduction of stroke risk, although a recent prospective meta-analysis showed promising results. The results of ongoing RCTs on stroke prevention are still awaited. In addition, experimental studies on stroke outcome show beneficial effects on functional outcome, infarct volume, inflammation and oxidative stress.

If the results of the experimental studies are confirmed in RCTs, this would be particularly relevant for patients with
type 2 diabetes mellitus, who are at increased risk of stroke and dementia, and who of course also require a form of glucose-lowering treatment. If class effects of incretin-based therapies in treatment of dementia or stroke would indeed be established, this is likely to have a substantial impact on treatment recommendations. Nevertheless, at this stage, we should be somewhat cautious in our optimism, as both in the field of dementia and in stroke it has proven difficult to translate treatments with great promise in rodents to evidence-based therapies in humans.

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GJB consults for and receives research support from Boehringer Ingelheim, and consults for Takeda Pharmaceuticals. Compensation for these services is transferred to his employer, the UMC Utrecht. The other authors declare no conflict of interest.

REFERENCES
1. International Diabetes Federation. IDF Diabetes Atlas, 6th edn. 2013.
2. Koekkoek PS, Kappelle LJ, van den Berg E, et al. Cognitive function in patients with diabetes mellitus: guidance for daily care. Lancet Neurol 2015; 14: 329–340.
3. Luitse MJA, Biessels GJ, Rutten GEHM, et al. Diabetes, hyperglycaemia, and acute ischaemic stroke. Lancet Neurol 2012; 11: 261–271.
4. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. Lancet 2014; 383: 1068–1083.
5. Gonzalez C, Beruto V, Keller G, et al. Investigational treatments for Type 2 diabetes mellitus: exenatide and liraglutide. Expert Opin Investig Drugs 2006; 15: 887–895.
6. Ahren B, Landin-Olsson M, Jansson PA, et al. Inhibition of dipeptidyl peptidase-4 reduces glycemia, sustains insulin levels, and reduces glucagon levels in type 2 diabetes. J Clin Endocrinol Metab 2004; 89: 2078–2084.
7. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015; 38: 140–149.
8. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006; 368: 1696–1705.
9. Nauck MA. Incretin-based therapies for type 2 diabetes mellitus: properties, functions, and clinical implications. Am J Med 2011; 124(Suppl): S3–S18.
10. Karagiannis T, Paschos P, Paletas K, et al. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ 2012; 344: e1369.
11. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology 2007; 132: 2131–2157.
12. Phillips LK, Prins JB. Update on incretin hormones. Ann N Y Acad Sci 2011; 1243: E55–E74.
13. Figueiredo CP, Pamplona FA, Mazzuco TL, et al. Role of the glucose-dependent insulinotropic polypeptide and its receptor in the central nervous system: therapeutic potential in neurological diseases. Behav Pharmacol 2010; 21: 394–408.
14. Seino Y, Yabe D. Glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1: Incretin actions beyond the pancreas. J Diabetes Investig 2013; 4: 108–130.
15. Malmgren S, Ahren B. DPP-4 inhibition contributes to the prevention of hypoglycaemia through a GIP-glucagon counterregulatory axis in mice. Diabetologia 2015; 58: 1091–1099.
16. Williams DL. Minireview: finding the sweet spot: peripheral versus central glucagon-like peptide 1 action in feeding and glucose homeostasis. Endocrinology 2009; 150: 2997–3001.
17. Baggio LL, Huang Q, Brown TJ, et al. A recombinant human glucagon-like peptide (GLP)-1–albumin protein (albugon) mimics peptidergic activation of GLP-1 receptor-dependent pathways Coupled with satiety, gastrointestinal motility, and glucose homeostasis. Diabetes 2004; 53: 2492–2500.
18. Kastin A, Akerstrom V, Pan W. Interactions of glucagon-like peptide-1 (GLP-1) with the blood-brain barrier. J Mol Neurosci 2002; 18: 7–14.
19. Salcedo I, Tweedie D, Li Y, et al. Neuroprotective and neurotrophic actions of glucagon-like peptide-1: an emerging opportunity to treat neurodegenerative and cerebrovascular disorders. Br J Pharmacol 2012; 166: 1586–1599.
20. Harkavy A, Whitton PS. Glucagon-like peptide 1 receptor stimulation as a means of neuroprotection. Br J Pharmacol 2010; 159: 495–501.
21. Knau C, Cani PD, Perrin C, et al. Brain glucagon-like peptide-1 increases insulin secretion and muscle insulin resistance to favor hepatic glycogen storage. J Clin Invest 2005; 115: 3554–3563.
22. Sandoval DA, Bagnol D, Woods SC, et al. Arcuate glucagon-like peptide 1 receptors regulate glucose homeostasis but not food intake. Diabetes 2008; 57: 2046–2054.
23. Hayes MR, Leichner TM, Zhao S, et al. Intracellular signals mediating the food intake-suppressive effects of hindbrain

http://onlinelibrary.wiley.com/journal/jdi
glucagon-like peptide-1 receptor activation. Cell Metab 2011; 13: 320–330.
24. Perry T, Haughey NJ, Mattson MP, et al. Protection and reversal of excitotoxic neuronal damage by glucagon-like peptide-1 and exendin-4. J Pharmacol Exp Ther 2002; 302: 881–888.
25. Liu J, Zheng X, Yin F, et al. Neurotrophic property of geniposide for inducing the neuronal differentiation of PC12 cells. Int J Dev Neurosci 2006; 24: 419–424.
26. Nyberg J, Anderson MF, Meister B, et al. Glucose-dependent insulinotropic polypeptide is expressed in adult hippocampus and induces progenitor cell proliferation. J Neurosci 2005; 25: 1816–1825.
27. Faire E, Gault VA, Thorens B, et al. Glucose-dependent insulinotropic polypeptide receptor knockout mice are impaired in learning, synaptic plasticity, and neurogenesis. J Neurophysiol 2011; 105: 1574–1580.
28. Liu J, Yin F, Zheng X, et al. Geniposide, a novel agonist for GLP-1 receptor, prevents PC12 cells from oxidative damage via MAP kinase pathway. Neurochem Int 2007; 51: 361–369.
29. Liu JH, Yin F, Guo LX, et al. Neuroprotection of geniposide against hydrogen peroxide induced PC12 cells injury: involvement of PI3 kinase signal pathway. Acta Pharmacol Sin 2009; 30: 159–165.
30. Kimura R, Okouchi M, Fujioka H, et al. Glucagon-like peptide-1 (GLP-1) protects against methylglyoxal-induced PC12 cell apoptosis through the PI3K/Akt/mTOR/GCCL/redox signaling pathway. Neuroscience 2009; 162: 1212–1219.
31. McClean PL, Gault VA, Harrriott P, et al. Glucagon-like peptide-1 analogues enhance synaptic plasticity in the brain: a link between diabetes and Alzheimer’s disease. Eur J Pharmacol 2010; 630(1–3): 158–162.
32. Gault VA, Holscher C. GLP-1 agonists facilitate hippocampal LTP and reverse the impairment of LTP induced by beta-amyloid. Eur J Pharmacol 2008; 587: 112–117.
33. Gault VA, Holscher C. Protease-resistant glucose-dependent insulinotropic polypeptide agonists facilitate hippocampal LTP and reverse the impairment of LTP induced by beta-amyloid. J Neurophysiol 2008; 99: 1590–1595.
34. During MJ, Cao L, Zuzga DS, et al. Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. Nat Med 2003; 9: 1173–1179.
35. Abbas T, Faire E, Holscher C. Impairment of synaptic plasticity and memory formation in GLP-1 receptor KO mice: Interaction between type 2 diabetes and Alzheimer’s disease. Behav Brain Res 2009; 205: 265–271.
36. Kastin AJ, Akervast V. Entry of exendin-4 into brain is rapid but may be limited at high doses. Int J Obes Relat Metab Disord 2003; 27: 313–318.
37. Hunter K, Holscher C. Drugs developed to treat diabetes, liraglutide and lixisenatide, cross the blood brain barrier and enhance neurogenesis. BMC Neurosci 2012; 13: 33.
38. Fuchs H, Binder R, Greischel A. Tissue distribution of the novel DPP-4 inhibitor BI 1356 is dominated by saturable binding to its target in rats. Biopharm Drug Dispos 2009; 30: 229–240.
39. Boschmann M, Engeli S, Dobberstein K, et al. Dipeptidyl-peptidase-IV inhibition augments postprandial lipid mobilization and oxidation in type 2 diabetic patients. J Clin Endocrinol Metab 2009; 94: 846–852.
40. Gallwitz B. Therapies for the treatment of type 2 diabetes mellitus based in incretin action. Minerva Endocrinol 2006; 31: 133–147.
41. Hardigan YA T, Abdelsaid M, Cougha M, Ergul A. Treatment with DPP-IV inhibitor linagliptin restores insulin-mediated vasorelaxation in middle cerebral arteries from type-2 diabetic Goto-Kakizaki rats. Exp Biol 2015; poster number: W155 1044.8.
42. Perry T, Lahiri DK, Sambamurti K, et al. Glucagon-like peptide-1 decreases endogenous amyloid-beta peptide (Abeta) levels and protects hippocampal neurons from death induced by Abeta and iron. J Neurosci Res 2003; 72: 603–612.
43. Luciani P, Deledda C, Benvenuti S, et al. Differentiating effects of the glucagon-like peptide-1 analogue exendin-4 in a human neuronal cell model. Cell Mol Life Sci 2010; 67: 3711–3723.
44. Belsham DD, Fick LJ, Dalvi PS, et al. Ciliary neurotrophic factor recruitment of glucagon-like peptide-1 mediates neurogenesis, allowing immortalization of adult murine hypothalamic neurons. FASEB J 2009; 23: 4256–4265.
45. Li Y, Tweetide D, Mattson MP, et al. Enhancing the GLP-1 receptor signaling pathway leads to proliferation and neuroprotection in human neuroblastoma cells. J Neurochem 2010; 113: 1621–1631.
46. Bertilsson G, Patrone C, Zachrishon O, et al. Peptide hormone exendin-4 stimulates subventricular zone neurogenesis in the adult rodent brain and induces recovery in an animal model of Parkinson’s disease. J Neurosci Res 2008; 86: 326–338.
47. Li H, Lee CH, Yoo KY, et al. Chronic treatment of exendin-4 affects cell proliferation and neuroblast differentiation in the adult mouse hippocampal dentate gyrus. Neurosci Lett 2010; 486: 38–42.
48. Hamilton A, Patterson S, Porter D, et al. Novel GLP-1 mimetics developed to treat type 2 diabetes promote progenitor cell proliferation in the brain. J Neurosci Res 2011; 89: 481–489.
49. Sharma MK, Jalewa J, Holscher C, et al. Neuroprotective and anti-apoptotic effects of liraglutide on SH-SYSY cells exposed to methylglyoxal stress. J Neurochem 2014; 128: 459–471.
50. Gault VA, Porter WD, Flatt PR, et al. Actions of exendin-4 therapy on cognitive function and hippocampal synaptic plasticity in mice fed a high-fat diet. Int J Obes 2010; 34: 1341–1344.
51. Porter WD, Flatt PR, Hölischer C, et al. Liraglutide improves hippocampal synaptic plasticity associated with increased expression of Mash1 in ob/ob mice. *Int J Obes* 2013; 37: 678–684.

52. Pipatpiboon N, Pintana H, Pratchayasakul W, et al. DPP4-inhibitor improves neuronal insulin receptor function, brain mitochondrial function and cognitive function in rats with insulin resistance induced by high-fat diet consumption. *Eur J Neurosci* 2013; 37: 839–849.

53. Sakr HF. Effect of sitagliptin on the working memory and reference memory in type 2 diabetic Sprague-Dawley rats: possible role of adiponectin receptors 1. *J Physiol Pharmacol* 2013; 64: 613–623.

54. Pintana H, Apaiaj N, Chattipakorn N, et al. DPP-4 inhibitors improve cognition and brain mitochondrial function of insulin-resistant rats. *J Endocrinol* 2013; 218: 1–11.

55. van den Berg E, Kloppenborg RP, Kessels RP, et al. Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: A systematic comparison of their impact on cognition. *Biochim Biophys Acta* 2009; 1792: 470–481.

56. Cheng G, Huang C, Deng H, et al. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Intern Med J* 2012; 42: 484–491.

57. Geijselaers SLC, Sep SJS, Stehouwer CDA, et al. Glucose regulation, cognition, and brain MRI in type 2 diabetes: a systematic review. *Lancet Diabetes Endocrinol* 2015; 3: 75–89.

58. Luchsinger JA, Palmas W, Teresi JA, et al. Improved diabetes control in the elderly delays global cognitive decline. *J Nutr Health Aging* 2011; 15: 445–449.

59. Evans GJ, Sastre AA. Effect of the treatment of Type II diabetes mellitus on the development of cognitive impairment and dementia (Review). *Cochrane Database Syst Rev* 2003; 4: CD003804.

60. Tuligenga RH. Intensive glycaemic control and cognitive decline in patients with type 2 diabetes: a meta-analysis. *Endocr Connect* 2015; 4: R16–R24.

61. Patrone C, Eriksson O, Lindholm D. Diabetes drugs and neurological disorders: new views and therapeutic possibilities. *Lancet Diabetes Endocrinol* 2014; 2: 256–262.

62. Moreira RO, Campos SC, Soldera AL. Type 2 Diabetes Mellitus and Alzheimer’s Disease: from physiopathology to treatment implications. *Diabetes Metab Res Rev* 2013; doi: 10.1002/dmrr.2442.

63. Ballard C, Gauthier S, Corbett A, et al. Alzheimer’s disease. *Lancet* 2011; 377: 1019–1031.

64. Heneka MT, Carson MJ, Khoury JE, et al. Neuroinflammation in Alzheimer’s disease. *Lancet Neurol* 2015; 14: 388–405.

65. Boutajangout A, Sigurdsson EM, Krishnamurthy PK, et al. Tau as a therapeutic target for Alzheimer’s disease. *Curr Alzheimer Res* 2011; 8: 666–677.

66. Cholerton B, Baker LD, Craft S. Insulin, cognition, and dementia. *Eur J Pharmacol* 2013; 719(1–3): 170–179.

67. Talbot K, Wang HY, Kazi H, et al. Demonstrated brain insulin resistance in Alzheimer’s disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. *J Clin Invest* 2012; 122: 1316–1338.

68. Li L, Zhang ZF, Holscher C, et al. (Val8) glucagon-like peptide-1 prevents tau hyperphosphorylation, impairment of spatial learning and ultra-structural cellular damage induced by streptozotocin in rat brains. *Eur J Pharmacol* 2012; 674: 280–286.

69. Han WN, Holscher C, Yuan L, et al. Liraglutide protects against amyloid-beta protein-induced impairment of spatial learning and memory in rats. *Neurobiol Aging* 2013; 34: 576–588.

70. Wang XH, Li L, Holscher C, et al. Val8-glucagon-like peptide-1 protects against Abeta1-40-induced impairment of hippocampal late-phase long-term potentiation and spatial learning in rats. *Neuroscience* 2010; 170: 1239–1248.

71. Gao C, Liu Y, Jiang Y, et al. Geniposide ameliorates learning memory deficits, reduces tau phosphorylation and decreases apoptosis via GSK3beta pathway in streptozotocin-induced alzheimer rat model. *Brain Pathol* 2014; 24: 261–269.

72. McClean PL, Parthsarathy V, Faivre E, et al. The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer’s disease. *J Neurosci* 2011; 31: 6587–6594.

73. Bomba M, Ciavardelli D, Silvestri E, et al. Exenatide promotes cognitive enhancement and positive brain metabolic changes in PS1-KI mice but has no effects in 3xTg-AD animals. *Cell Death Dis* 2013; 4: e612.

74. Xiong H, Zheng C, Wang J, et al. The neuroprotection of liraglutide on Alzheimer-like learning and memory impairment by modulating the hyperphosphorylation of tau and neurofilament proteins and insulin signaling pathways in mice. *J Alzheimers Dis* 2013; 37: 623–635.

75. McClean PL, Holscher C. Liraglutide can reverse memory impairment, synaptic loss and reduce plaque load in aged APP/PS1 mice, a model of Alzheimer’s disease. *Neuropharmacology* 2014; 76 (Pt A): 57–67.

76. Chen S, Liu AR, An FM, et al. Amelioration of neurodegenerative changes in cellular and rat models of diabetes-related Alzheimer’s disease by exendin-4. *Age (Dordr)* 2012; 34: 1211–1224.

77. D’Amico M, Di Filippo C, Marfella R, et al. Long-term inhibition of dipeptidyl peptidase-4 in Alzheimer’s prone mice. *Exp Gerontol* 2010; 45: 202–207.

78. Kosaraju J, Murthy V, Khatwal RB, et al. Vildagliptin: an anti-diabetes agent ameliorates cognitive deficits and pathology observed in streptozotocin-induced Alzheimer’s disease. *J Pharm Pharmacol* 2013; 65: 1773–1784.

79. Kosaraju J, Gali CC, Khatwal RB, et al. Saxagliptin: a dipeptidyl peptidase-4 inhibitor ameliorates streptozotocin
induced Alzheimer’s disease. *Neuropharmacology* 2013; 72: 291–300.

80. Li Y, Duffy KB, Ottinger MA, et al. GLP-1 receptor stimulation reduces amyloid-beta peptide accumulation and cytotoxicity in cellular and animal models of Alzheimer’s disease. *J Alzheimers Dis* 2010; 19: 1205–1219.

81. Fairev E, Holscher C. D-Ala2GIP facilitated synaptic plasticity and reduces plaque load in aged wild type mice and in an Alzheimer’s disease mouse model. *J Alzheimers Dis* 2013; 35: 267–283.

82. Gengler S, McClean PL, McCurtin R, et al. Val8GLP-1 rescues synaptic plasticity and reduces dense core plaques in APP/PS1 mice. *Neurobiol Aging* 2012; 33: 265–276.

83. Fairev E, Holscher C. Neuroprotective effects of D-Ala2GIP on Alzheimer’s disease biomarkers in an APP/PS1 mouse model. *Alzheimers Res Ther* 2013; 5: 20.

84. He P, Li P, Hua Q, et al. Chronic administration of antistroke herbal medicine TongLuOJuNao reduces amyloidogen processes of amyloid precursor protein in a mouse model of Alzheimer’s disease. *PLoS ONE* 2013; 8: e58181.

85. Duffy AM, Holscher C. The incretin analogue D-Ala2GIP reduces plaque load, astrogliosis and oxidative stress in an APP/PS1 mouse model of Alzheimer’s disease. *Neuroscience* 2013; 228: 294–300.

86. Ma T, Du X, Pick JE, et al. Glucagon-like peptide-1 cleavage product GLP-1(9–36) amide rescues synaptic plasticity and memory deficits in Alzheimer’s disease model mice. *J Neurosci* 2012; 32: 13701–13708.

87. Kim DH, Huh JW, Jang M, et al. Sitagliptin increases tau phosphorylation in the hippocampus of rats with type 2 diabetes and in primary neuron cultures. *Neurobiol Dis* 2012; 46: 52–58.

88. Qin Z, Sun Z, Huang J, et al. Mutated recombinant human glucagon-like peptide-1 protects SH-SY5Y cells from apoptosis induced by amyloid-beta peptide (1–42). *Neurosci Lett* 2008; 444: 217–221.

89. Collaboration ERF. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; 375: 2215–2222.

90. Group AC. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; 358: 2560–2572.

91. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; 360: 129–139.

92. Boussageon R, Bejan-Angouvant T, Saadadian-Elahi M, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. *BMJ* 2011; 343: d4169.

93. Hemmingsen B, Lund SS, Gluud C. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2013; 11: CD008143.

94. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013; 369: 1317–1326.

95. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013; 369: 1327–1335.

96. Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2015; 373: 232–242.

97. Rosenstock J, Marx N, Neubacher D, et al. Cardiovascular safety of linagliptin in type 2 diabetes: a comprehensive patient-level pooled analysis of prospectively adjudicated cardiovascular events. *Cardiovasc Diabetol* 2015; 14: 57.

98. Megherbi SE, Milan C, Minier D, et al. Association between diabetes and stroke subtype on survival and functional outcome 3 months after stroke: data from the European BIOMED Stroke Project. *Stroke* 2003; 34: 688–694.

99. Kamalesh M, Shen J, Eckert GJ. Long term postischemic stroke mortality in diabetes: a veteran cohort analysis. *Stroke* 2008; 39: 2727–2731.

100. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol* 2009; 8: 1006–1018.

101. Capes SE, Hunt D, Malmberg K, et al. Stress hyperglycaemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke* 2001; 32: 2426–2432.

102. Seners P, Turc G, Oppenheim C, et al. Incidence, causes and predictors of neurological deterioration occurring within 24 h following acute ischaemic stroke: a systematic review with pathophysiological implications. *JNNP* 2015; 86: 87–94.

103. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet* 2009; 373: 1798–1807.

104. Kruyt ND, Biessels GJ, Devries JH, et al. Hyperglycemia in acute ischemic stroke: pathophysiology and clinical management. *Nat Rev Neurol* 2010; 6: 145–155.

105. Tureyen K, Kapadia R, Bowen KK, et al. Peroxisome proliferator-activated receptor-gamma agonists induce neuroprotection following transient focal ischemia in normotensive, normoglycemic as well as hypertensive and type-2 diabetic rodents. *J Neurochem* 2007; 101: 41–56.

106. Simard JM, Yurovsky V, Tsymbaluk N, et al. Protective effect of delayed treatment with low-dose glibenclamide in three models of ischemic stroke. *Stroke* 2009; 40: 604–609.

107. Culman J, Nguyen-Ngoc M, Glatz T, et al. Treatment of rats with pioglitazone in the reperfusion phase of focal cerebral ischemia: a preclinical stroke trial. *Exp Neurol* 2012; 238: 243–253.
108. Bellolio MF, Gilmore RM, Ganti L. Insulin for glycaemic control in acute ischaemic stroke. *Cochrane Database Syst Rev* 2014; 23: CD005346.

109. Abdelsaid M, Prakash R, Li W, et al. Metformin treatment in the period after stroke prevents nitrative stress and restores angiogenic signaling in the brain in diabetes. *Diabetes* 2015; 64: 1804–1817.

110. Caffes N, Kurland DB, Gerzanich V, et al. Glibenclamide for the treatment of ischemic and hemorrhagic stroke. *Int J Mol Sci* 2015; 16: 4973–4984.

111. White AT, Murphy AN. Administration of thiazolidinediones for neuroprotection in ischemic stroke: a pre-clinical systematic review. *J Neurochem* 2010; 115: 845–853.

112. Li Y, Perry T, Kindy MS, et al. GLP-1 receptor stimulation preserves primary cortical and dopaminergic neurons in cellular and rodent models of stroke and Parkinsonism. *Proc Natl Acad Sci USA* 2009; 106: 1285–1290.

113. Briyal S, Gulati K, Gulati A. Repeated administration of exendin-4 reduces focal cerebral ischemia-induced infarction in rats. *Brain Res* 2012; 1427: 23–34.

114. Teramoto S, Miyamoto N, Yatomi K, et al. Exendin-4, a glucagon-like peptide-1 receptor agonist, provides neuroprotection in mice transient focal cerebral ischemia. *J Cereb Blood Flow Metab* 2011; 31: 1696–1705.

115. Sato K, Kameda M, Yasuhara T, et al. Neuroprotective effects of liraglutide for stroke model of rats. *Int J Mol Sci* 2013; 14: 21513–21524.

116. Lee CH, Yan B, Yoo KY, et al. Ischemia-induced changes in glucagon-like peptide-1 receptor and neuroprotective effect of its agonist, exendin-4, in experimental transient cerebral ischemia. *J Neurosci Res* 2011; 89: 1103–1113.

117. Darsalia V, Mansouri S, Ortsäter H, et al. Glucagon-like peptide-1 receptor activation reduces ischaemic brain damage following stroke in Type 2 diabetic rats. *Clin Sci* 2012; 122: 473–483.

118. Darsalia V, Ortsäter H, Olverling A, et al. The DPP-4 inhibitor linagliptin counteracts stroke in the normal and diabetic mouse brain: a comparison with glimepiride. *Diabetes* 2013; 62: 1289–1296.

119. Ma M, Hasegawa Y, Koibuchi N, et al. DPP-4 inhibition with linagliptin ameliorates cognitive impairment and brain atrophy induced by transient cerebral ischemia in type 2 diabetic mice. *Cardiovasc Diabetol* 2015; 14: 54.

120. Chowen JA, de Fonseca FR, Alvarez E, et al. Increased glucagon-like peptide-1 receptor expression in glia after mechanical lesion of the rat brain. *Neuropeptides* 1999; 33: 212–215.