GLP-1 RECEPTOR ACTIVATION-BASED THERAPY; A PROMISING STRATEGY AGAINST ISCHEMIC STROKE

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ABSTRACT

Hyperglycemia and insulin resistance resulted from uncontrolled diabetes mellitus (DM) had has been consistently associated with poor clinical outcome in patient with ischemic stroke. Hence, early diagnosis of DM, efficient glycemic control, and prevention of its complications, together using credible therapeutic approaches, are essential to avoid the stroke complications and minimize its financial burden. Candidate strategies used to control glycaemia failed to show an efficacy in stroke patients. Glucagon like peptide-1 (GLP-1) receptoragonists are novel antidiabetic agents with a proved neuroprotection effect. Herewith, we review the concept of GLP-1 use as a neuroprotective approachagainstDM-associated stroke.

KEYWORDS: Ischemic stroke; diabetes mellitus; Glucagon-like peptide 1; neuroprotection.

INTRODUCTION

Stroke is a medical emergencywith incidence escalatingalong age.It accounts for most of the disabilities in westernized societies reflecting a serious health and economic threat (1). Although its rate has declined over the last decade, owing to the improved management, it is still one of the most brutal, high-priced health issues with annual direct and indirect healthcare costs (2).

The risk of stroke dramatically increases with hypertension, smoking, atherosclerosis, sedentary lifestyle, obesity and diabetes. Ischemia is the leading cause of stroke being responsible for approximately 85 % of cases. It usually results from cerebral arteryocclusion by a blood clot causing irreversible damage to the neural tissue triggering neurological impairments and disabilities (3).

Therapeutic interventions for stroke require immediate chemical and surgical removal of the cause which is usually a blood clot (4). This should be done within the 3-4 hours period following the onset, in order to obtain the maximum effect with no or the least possible complications. Unfortunately, this is not feasible for the majority of patients, due to late arrival to the hospital, delayed diagnosis, or contraindications to medications (e.g., hypertension) (5). Moreover, thrombolytic drugs used to dissolve the blood clot increase the risk of hemorrhage especially in patients having comorbidities, such as hypertension, atrial fibrillation, and diabetes mellitus (6-7).

To be an ideal treatment for a stroke incident, it should rescue the neural tissue at risk. This is not guaranteed by thrombolytic drugsas its mechanism of action is based on restoring the blood circulation to the affected areas of the brain, providing oxygen and nutrients to the tissue and permitting the spontaneous tissue recovery. These effects are only achievable if the treatment started within a limited time-window following the insult;otherwise, a substantial portion of the neural tissue will never survive. The reperfusion injury is another drawback of the thrombolytic therapy, which is mediated by oxygen radicals liberated upon rapid restoration of oxygen supplyof the ischemic area following clot dissolution (8).

Acute hyperglycemia has been associated with poor clinical outcome in stroke studies, as it was shown to enhance cortical toxicity, increase infarct volumes, promote inflammation, and affect the cerebral vasculature (9). However, conflicting results have been reported regarding the use of intensive glycemic control in stroke patients, with. The initial enthusiasm for intensive insulin therapy in the intensive care unit has disappeared because it was reported that it increases the risk of hypoglycemia(10).

The glucagon-like peptide 1 (GLP-1)can counteract insulin desensitization as it stimulates insulin secretion during episodes of hyperglycemia, decreases

food intake and body weight, and stimulates gastric emptying. This qualified it to be an ideal treatment for diabetes mellitus (DM) (11). Although GLP-1 is primarily known in the context of diabetes, it has been suggested that it exerts an impressive neuroprotective effect in ischemic stroke patients.

This review will focus on the negative impact of chronic DMonthe central nervous system(CNS), with a special emphasis on ischemic stroke and the increasingly promising therapeutic potential of the incretin/glucagon-like peptide-1 (GLP-1) mimetics against DM-associated stroke.

Long-term consequences of DM and hyperglycemia on brain tissues

Over the last three decades, many studies proved that insulin crosses the blood-brain barrier (BBB) via a carrier-mediated and temperature-sensitive active process, exerting multiple neurotrophic effects(12). Chronic peripheral hyperinsulinemia and insulin resistance are major consequences of uncontrolled diabetes (especially DM-related insulin resistance). They result in downregulation of the brain uptake and neuronal signaling of insulin and glycolytic enzymes,hence, decreasing the oxidative glucose metabolismand changing cerebral hemodynamics (13).

Hyperglycemia reduces the cerebral blood flow viaimpairment of adequate vasodilatation of the cerebral blood vessels as vasodilatation is predominantly mediated by endothelium-derived nitric oxide (14). Supporting this point, Quast et al. (1997) showed that the cerebral blood flow is decreased by 37 %in hyperglycemic compared tonormoglycemic rats (15). This rapidly diminishes the brain activitywith progressive impairment of learning, memory, and cognition (16).

Hyperglycemia also increases the lactic acid production turning the intracellular environment acidic, causing mitochondrial dysfunction. It also increases the production of reactive oxygen species (ROS) via increasing the NADPH production causing neuronal death (17). Moreover, Hyperglycemia is usually associated with increased expression of nuclear factor κB, whichinduces endothelial injury and triggers inflammatory function to produce inflammatory mediators ascytokine (18-19), eventuallyaggravating the infarct size and the brain injury.

Furthermore, hyperglycemia stimulates coagulation through offering thrombin–antithrombin complexes and triggering the tissue factor pathway (20), whereas diabetes-induced hyperinsulinemia decreases fibrinolytic activity by increasing the production of plasminogen activator inhibitor (21).

Cross-link between diabetes and stroke

Serious illnesses, including stroke, stresses all body systems leading to the activation of the hypothalamic–pituitary–adrenal axis (22), which inturn increases the glucocorticoids serum level, and activates the sympathetic nervous system (23). The later trigger more glucose production and at the end, insulin resistance and hyperinsulinemia develop (24).

Additionally, stroke is also associated with an inflammatory response with release of cytokines and free radicals such as nitric oxide (NO), which is neurotoxic (25). This responsealso activates the hypothalamic–pituitary–adrenal axis and have also been associated with development of the insulin resistance(26).

Several studies have reported an elevated blood glucose in >40%of patients with acute ischemic stroke at the time of admission;the highest share belongs to patients with a history of diabetes (27). Additionally existence hyperglycemia and hyperinsulinemia decrease the activity of recombinant tissue plasminogen activator (rtPa) treatment in animal models of ischemic stroke (28-29),

The correlation between hyperglycemia and aggravated cerebral injury in stroke yielding a poor clinical outcome has been proved by multiple studies conducted on humans and animals. This correlation is not influenced by other predictors of poor clinical outcome such as age, stroke severity, infarct size, or diabetic status (30-31). Animals with ischemic stroke and hyperglycemia tended to have more brain edema, hemorrhagic transformation of infarcts, brain herniation, and death; the exacerbated damage with hyperglycemia was usually seen with reperfusion and occurs less with permanent occlusion (15, 18).

Evaluation of Tight glycemic control, as a promising neuroprotection features.

The CNS insult caused by chronic uncontrolled DMare mostly caused by the persistent hyperglycemia. This indicates thatthis hassle could be avoided simply by normalization of blood glucose levels(32). The effect ofaggressive reduction of an abnormally elevated blood glucose level has been investigated in various acute illnesses and yielded varied results. Some clinical trials have reported that promptreduction of hyperglycemia in patients with acute stroke is feasible and relatively safe (10).

The study of Van den Berghe et al. (2001) was the most credible study was a study involved patients of the surgical intensive care unit (33). It results proved that patients whom hyperglycemia was treated aggressively had better clinical outcomes than patients received the usual regimen. The benefits associated

with the aggressive hyperglycemia technique decreased the mortality, diminished theduration of ventilator need, minimized the incidence of bloodstream infections, and decreased the risk of critical illness polyneuropathy. On the other hand, the results of a similar trial conducted on patients in the medical intensive care unit showed less promising results with no a statistically significant difference in the mortality rate as a primary outcome (34). While other randomized trials reported that intensive insulin therapy induced a high risk of hypoglycemia in patients with acute stroke (95-98).

Due to conflicting results reported along with Insulin use in stroke patients. New strategies should be considered to provide more glycemic control in stroke victims

The neuroprotective effects of novel GLP-1 receptor agonists in diabetic brain

GLP-1 has been detectedin both neuronal tissues of the brain and microglia. Its receptors are mainlyexpressed by pyramidal neurons in the Purkinje cells in the cerebellum, the hippocampus, and the neocortex (35-36). It wasreported that both activated astrocytes and activated microglia, which participate in the immune/inflammatory response, prompt GLP-1 receptor expression.

The centrally-acting GLP-1 analogs modulate food intake via stimulating insulin secretion in a glucose dependent manner (37).

Over the past few years, experimental evidence has proven that GLP-1 exerts a neuroprotective effect against adverse effects of the stroke. Being able to cross the BBB via simple effusion, it stimulates the paraventricular nucleus to activate glucocorticoid formation without increasing glucose levels afterwardminimizingthe fluctuation of brain glucose levels (38). However, the molecular/cellular mechanisms of these effects are still vague.

The neurotrophic effects of GLP-1 are most probably because it is a growth factor.Hence, it increasesthe expression of genes that control cell growth, repair, and replacement, enhances cell metabolism, inhibitscell apoptosis, reduces inflammatory responses, induces neurite outgrowthand tyrosine hydroxylase expression (39). GLP-1R agonists are also able to enhance synaptic plasticity, stimulate adult neurogenesis and improve cognitive performance (40).

Clinical and experimental studies of glucagon-like peptide-1 receptor agonists.

Exendin-4 (Ex-4) is the first GLP-1R agonist that wasdeveloped by Amylin Pharmaceuticals (San Diego, CA, USA). It shares a 53% amino-acidsequence homology with GLP-, and it can cross the BBB.There are many studies support the neuroprotective effect of GLP-1R agonists have been published.

A transient cerebral ischemia model targeting the CA1 region of the hippocampus was used to study the potential efficacy of Ex-4 against stroke (24). The Ex-4 treatment decreased brain damage and microglia activationmainly through transiently enhanced GLP-1R expression in CA1 hippocampal neurons 24 h after stroke.

The first research to prove that the activation of GLP-1R by Ex-4 permits neuroprotection against stroke, independently of its glycemic regulation action, was published by **Li et al.**(2009)who demonstrated the effect of intracerebral administration of Ex-4 indecreasing the infarct size and enhancing locomotor activity at 48 h post a stroke in the rat. It was.They also proved that the effect was indeed mediated by GLP-1R since Ex-4 was ineffective in GLP-1R knock-out mice. (41)

Teramoto et al. (2011)studiedthe neuroprotective effect ofEx-4 could induce neuroprotection against stroke in rodents (42). They reported that intravenous Ex-4 at the time of stroke or 1 h after stroke onset reduced the infarct size and improved the functional deficit in the mouse. But, when Ex-4 was given at 3 h after stroke, it didn't reduce the infarct size. Although the doses employed in this study (almost 400 μg/kg) are significantly higher than the used clinical dose of Ex-4 to treat DM (0.1 μg/kg), the results were clinically relevant.

On the other side, Briyal et al. (2012)investigated the effect of chronic pretreatment in non-diabetic rats in a model of permanent middle cerebral artery occlusion (43). The results showed that an intraperitoneal 0.5 μg/kg dose of Ex-4 effectively reduced the infarct volume and oxidative stress parameters andminimized the neurological deficits.

Liraglutide is another stable GLP-1 analog,developed by Novonordisk. It is Similar to Ex-4 with ~ 97% homology to GLP-1.It is clinically used as a DM treatment, and its side effects are similar to those of Ex-4.2

According toSato et al. (2013)an intraperitoneal administration of liraglutide2.5 hours post stroke onset induced neuroprotection in the rat in correlation with vascular endothelial growth factor upregulation (44).Also,Briyal et al. (2014)reportedthat pretreatment with liraglutideexerted a neuroprotective effect against stroke in normal and diabetic rats in correlation with decreased apoptosis and oxidative stress (45). These studies could have clinical relevance since they proved that the chronic administration ofliraglutidein DM patients before stroke not only exerted an antidiabetic effect but also improvedthe stroke prognosis.

Conclusion and future direction

Despite the overwhelming evidence that

hyperglycemia is associated with poor functional outcome and increased mortality in patients with acute stroke, the currently published studies do not support the use of intensive insulin therapy and encourage a further search for more efficient and safer methods to control the blood glucose level.

Ex-4 and Liraglutide are GLP-1R agonists with neuroprotective effects already in clinical use for the treatment of T2D; their neuroprotective effect is independent of their glycemic effect. However, the molecular mechanisms of this neurotrophic action are still largely unknown and need further investigations. Moreover, the GLP-1R neuroprotective window, as well as the most efficacious doses and route of administration in relation to anti-stroke efficacy, remain to be determined. Also, adequate testing, on humans with typical comorbidities as diabetes and hypertension to mimic the usual clinical situations, is required.

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