PERSPECTIVE

# Can glucagon-like peptide-1 (GLP-1) analogues make neuroprotection a reality?

Currently, ischemic stroke remains one of the most costly and devastating clinical syndromes, accounting for 9% of all deaths and being the second leading cause of death in the world (Davidson et al., 2018). Approximately 20% of strokes are caused by intracerebral hemorrhage, while the other ~80% are classified as ischemic. With the discovery of thrombolysis, reperfusion therapy became an option for the treatment of ischemic stroke. More recently, endovascular recanalization with mechanical thrombectomy has brought about a paradigm shift in the optimal management of patients with large vessel occlusion. Importantly, early reperfusion is the only therapy that is proven to limit infarct size in patients with acute ischemic stroke. However, despite a successful recanalization being achieved in more than 70% of patients treated with mechanical thrombectomy +/– intravenous tissue recombinant plasminogen activator, functional independence (modified Rankin score 0–2 at 3 months after ischemic stroke) is obtained only in ~45% of cases. This reveals the further need to develop new adjunctive neuroprotective treatment strategies alongside reperfusion therapy.

While reperfusion is the prerequisite to salvage ischemic tissue, the restoration of cerebral circulation may paradoxically cause further damage to jeopardized tissue. Though it was discovered and mostly studied in the heart (Yellon and Hausenloy, 2007), reperfusion injury has also been suggested to occur in the brain (Davidson et al., 2018). As such, targeting reperfusion injury should be considered as an effective means of developing additional adjunctive therapies in patients with acute ischemic stroke. The overall aim of these adjunctive therapies would be both to delay cell death until reperfusion can take place, and to continue protecting the brain in the hours after reperfusion therapy has been initiated.

A recent review describes a number of obvious commonalities between acute ST-elevated myocardial infarction (STEMI) and ischemic stroke, which raise the interesting possibility that protective modalities, which are successful in one scenario, may also be effective in the other. On the other hand, although the mechanisms of cellular injury caused by ischemia/reperfusion are very similar in the heart and brain, the brain is uniquely sensitive to damage by glutamate released from depolarized cells which causes glutamate excitotoxicity (Davidson et al., 2018).

Another clinically important difference between STEMI and acute stroke addresses the phenomenon of "no reflow", which is known to take place in both the heart and the brain but with very different kinetics and a partially distinct mechanism (Davidson et al., 2018). No reflow can occur within 5–10 minutes of ischemia in the brain, and may, therefore, contribute to neuronal death, whereas in the heart it only occurs after 30+ minutes and its contribution to cell death is less clear. Therefore, the time window for neuroprotection at reperfusion is presumably wider than that for cardioprotection.

In addition, there is an *a priori*, mechanistically justified, fundamental difference in the pharmacological approach in patients with an acute ischemic stroke *versus* STEMI. While nearly all STEMI patients receive $P2Y_{12}$ platelet inhibitors, this medication is not routinely used at the time of recanalization in stroke patients for fear of causing hemorrhagic conversion.

Concerning these peculiarities in the mechanisms of ischemia/reperfusion brain injury, treatment with glucagon-like peptide-1 (GLP-1) analogues appears to be a promising neuroprotective strategy. Although this peptide first emerged and is now being routinely used as a therapy for type 2 diabetes mellitus, its pleiotropic effects have attracted the attention of specialists from other areas of basic science and clinical medicine, specifically cardiologists.

Importantly, endogenous GLP-1 has been demonstrated to be involved in the mechanism alleviating ischemia/reperfusion injury of the heart (Basalay et al., 2016). In line with this, three out of four clinical trials in STEMI patients have demonstrated the efficacy of the infusion of short-acting GLP-1 receptor (GLP-1R) agonist exenatide and its longer-acting analogue liraglutide, initiated shortly before the onset of reperfusion, in reducing final infarct size (Huang et al., 2017). More recently, Chen et al. (2016b) reported the results of a randomized, controlled trial conducted in 210 subjects, which demonstrated the potential for the liraglutide to reduce no reflow in STEMI patients. As the effect of GLP-1 on the gravity of no reflow has never been clearly described in the brain subjected to ischemia and reperfusion, further studies are undoubtedly warranted in this direction. In addition, this suggests an immense potential of this class of drugs for the patients presenting with acute stroke. The suggested mechanisms of the anti-no reflow effect of GLP-1 include the modulation of glucose levels, reduction in inflammation, and improvement in vascular endothelial function (Chen et al., 2016b).

GLP-1 is known to be a growth factor with its classical inherent effects, i.e. activation of the expression of genes responsible for cell growth, repair and replacement, increase of cell metabolism, and inhibition of apoptosis and inflammatory responses (Hölscher, 2014). Regarding the rationale of using the same pharmacological approach based on GLP-1 analogues for neuroprotection as for cardioprotection, there are important data from *in vitro* studies, which indicate that the GLP-1R agonists possess a neurotrophic property, reduce oxidative stress, and protect cortical neurons from hypoxia-triggered cell death (Salcedo et al., 2012). In addition, they can prevent and reverse exitotoxic neuronal damage (Salcedo et al., 2012). All these effects of GLP-1 seem to be in accordance with the specific mechanisms of ischemia/reperfusion injury of the brain in the setting of acute ischemic stroke.

Most of the known GLP-1 mimetics have been shown to be able to cross the blood-brain barrier, even in the normoxic state, though at relatively high doses (Hölscher, 2014). This allows one to expect that sufficiently high concentrations of systemically administered GLP-1 analogue will reach the brains of patients, particularly during the acute phase of ischemic stroke, when the blood-brain barrier is known to be disrupted (Davidson et al., 2018).

To date, more than twenty preclinical studies have demonstrated the reduction of infarct volume in the brain by recombinant human GLP-1 as well as GLP-1 analogues, exenatide and liraglutide, in non-diabetic and diabetic models of acute ischemic stroke, when administered systemically before ischemia, acutely at reperfusion or with some delay after the onset of reperfusion (Marlet et al., 2018). Taken together, these studies suggest that administration of GLP-1R agonists is one of the most promising treatments to pursue for patients immediately after stroke. Importantly, the neuroprotective effect of liraglutide was shown to be independent of glycaemia normalisation (Filchenko et al., 2018). This fact, together with the effects of GLP-1 on cortical neurons *in vitro* (Salcedo et al., 2012), indicate the potential of using GLP-1 analogues for neuroprotection in patients without type 2 diabetes. A recent experimental study by Basalay et al. (2019) compared the effects of two GLP-1 analogues – liraglutide and semaglutide – in non-diabetic rats. It was hypothesized that the long-acting semaglutide would confer prolonged neuroprotection by covering a longer duration of the reperfusion process, compared to its shorter-acting GLP-1 analogue, liraglutide. However, the neuroprotective effect of the two drugs was shown to be comparable. Besides, the infarct-limiting effect was seen only if the drug was administered after 90-minute ischemia, but not after longer time periods. In addition, they and others demonstrated that the neuroprotective effects of this class of GLP-1 analogue drugs were dose-dependent (Salcedo et al., 2012; Basalay et al., 2019). However, further experimental and clinical studies are required to directly compare the beneficial effects of different GLP-1 analogues in the setting of acute ischemic stroke.

Although the downstream pathways underlying the infarct-limiting effect of GLP-1 in the model of ischaemia and repefusion of the brain has not been extensively studied, the ability of GLP-1 to activate pro-survival pathways in the model of myocardial infarction is well known (Hausenloy and Yellon, 2008). The mechanism underlying the cardioprotection by GLP-1 has been shown to be independent of any effect on glucose and to recruit the intracellular signaling pathways involving Akt, Erk1/2, p70S6K, and AMPK as well as the downstream phosphorylation and inhibition of the pro-apoptotic protein BAD (Hausenloy and Yellon, 2008). In addition, as demonstrated by Basalay

et al. (2016), cardioprotection induced by GLP-1R agonist Exendin-4 is mediated by a mechanism involving M3 muscarinic receptors.

Importantly, it has been shown that GLP-1R agonist exendin-4 ameliorates warfarin-associated, hemorrhagic transformation after cerebral ischemia (Chen et al., 2016a). This effect of GLP-1 analogues, if confirmed in clinical trials, could be of particular importance, as hemorrhagic transformation is undoubtedly a major fear of neurologists, sometimes counterbalancing the potential benefits of reperfusion therapy.

Interestingly, two of the clinical trials conducted so far, investigating the benefits of GLP-1 analogues in patients with type 2 diabetes, have shown a benefit of semaglutide and dulaglutide, achieved by a reduction in the rate of non-fatal stroke (Kristensen et al., 2019). However, to date, all the clinical trials investigating the effects of GLP-1 analogues have been conducted in patients with type 2 diabetes, and evaluated the incidence, rather than outcomes, of an acute ischemic stroke. In addition, the doses of the drugs in these trials were substantially lower than those that have been used in *in vivo* experimental studies (Marlet et al., 2018; Basalay et al., 2019). This indicates the need for further clinical trials, possibly using higher doses of GLP-1 analogues and aiming to assess brain salvage and functional outcome in both diabetic and non-diabetic patients presenting with acute ischemic stroke.

One potential restricting factor that might limit the benefits of GLP-1 analogues in patients with an acute stroke is the time interval from the onset of brain ischemia to repefusion, which is typically longer in this setting than the duration of an ischemic insult in the hearts of STEMI patients. The precise relationship between the duration of focal brain ischemia in rats and the corresponding ischemic period in humans is not known. However, infarct progression in the brains of humans is presumed to be ~2–3 times slower *vs*. in the brains of rats (Basalay et al., 2019). This implies that the ischemic time of an 'ideal patient' with acute ischemic stroke, who may be able to benefit from treatment with GLP-1 analogue, should lie within an upper limit of 4.5 hours. According to this criterion, ~50% of patients presenting with acute ischemic stroke would be eligible for such therapy.

On the other hand, the potential benefit of treatment with GLP-1 analogues as an adjunct to reperfusion therapy in patients with acute ischemic stroke is expected to be higher than in STEMI patients. This arises from the fact that the positive effects of any newly tested therapeutic strategies in STEMI patients can appear to be partially or completely masked by the medication commonly administered in the acute phase, such as beta-blockers and antiplatelet therapy, especially the third-generation $P2Y_{12}$ antagonists, which are known to exhibit coagulation-independent cardioprotection in their own right. Conversely, in patients with acute stroke who undergo reperfusion therapy, beta-blockers are not routinely administered, and antiplatelet treatment, normally confined to aspirin or clopidogrel, is generally introduced secondarily, especially in those treated with alteplase. For these reasons, we suggest that the potential benefit of using GLP-1 agonists in patients with ischemic stroke may be higher than in the setting of myocardial infarction (**Figure 1**).

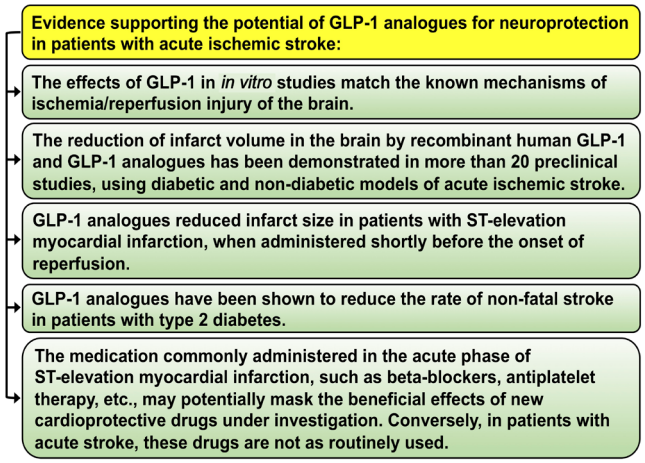


**Figure 1 The existing evidence, indicating the potential of using glucagon-like peptide (GLP-1) analogues for neuroprotection in patients presenting with acute ischemic stroke.**

In conclusion, we believe that the potential for treatment with GLP-1 analogues alongside reperfusion therapy may offer a way forward in developing neuroprotective strategies aimed at reducing reperfusion injury in patients who present with an acute ischemic stroke.

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