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Research article

Delayed administration of the GLP-1 receptor agonist liraglutide improves metabolic and functional recovery after cerebral ischemia in rats

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HIGHLIGHTS

- We demonstrated metabolic and functional recovery after delayed treatment with the GLP-1R agonist liraglutide after cerebral ischemia in rats.
- Liraglutide improves metabolic and functional recovery after cerebral ischemia in a dose-dependent manner.
- Liraglutide improves metabolic and functional recovery by promoting neurovascular remodeling through its receptor, GLP-1R.

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ABSTRACT

Glucagon-like peptide 1 receptor (GLP-1R) agonists administered before or immediately after induction of experimental stroke have been shown to provide acute neuroprotection. Here, we determined whether delayed treatment with a GLP-1R agonist could improve metabolic and functional recovery after stroke. Rats were subjected to middle cerebral artery occlusion (MCAO) and given the well-established GLP-1R agonist liraglutide (50, 100, or 200 μg/kg) or normal saline (NS) daily for 4 weeks, starting 1 day after MCAO. Cerebral glucose metabolism and neurological deficits were evaluated using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) imaging and modified neurological severity score (mNSS) test. Levels of neuronal nuclei (NeuN), glial fibrillary acidic protein (GFAP), von Willebrand factor (vWF), and GLP-1R were assessed by immunohistochemical staining and Western blot analysis. PET imaging showed that animals treated with liraglutide had significantly higher ^{18}F-FDG accumulation in the cerebral infarction compared with animals treated with NS. Liraglutide significantly reduced the mNSS score. It also greatly increased the expression of NeuN, GFAP, vWF, and GLP-1R in the cerebral ischemic area at postoperative week 4. These results demonstrated metabolic and functional recovery after delayed treatment with liraglutide in a rat model of cerebral ischemia.

1. Introduction

Stroke is one of the chief causes of disability and death worldwide. About 80% of strokes are ischemic, which is caused by blockage of blood supply to the brain [9]. Despite years of focused research, the only FDA approved drug for brain ischemia is tissue plasminogen activator (tPA). However, this treatment benefits <10% of ischemic stroke patients, because tPA must be given within 4.5 h of stroke onset [16]. Thus, it is urgent to develop novel strategies that can be executed outside of this therapeutic window. To extend the therapeutic window for stroke therapy, several strategies are being studied. One strategy that is emerging as a viable option is improving functional recovery after stroke.

Glucagon-like peptide 1 (GLP-1) is an incretin hormone that is secreted by the gut and binds to the GLP-1 receptor (GLP-1R), which is found throughout the brain and plays a crucial role in control of neuronal structure and function [17]. Recent studies have highlighted acute neuroprotective effects of GLP-1R agonists administered either before or several hours after experimental

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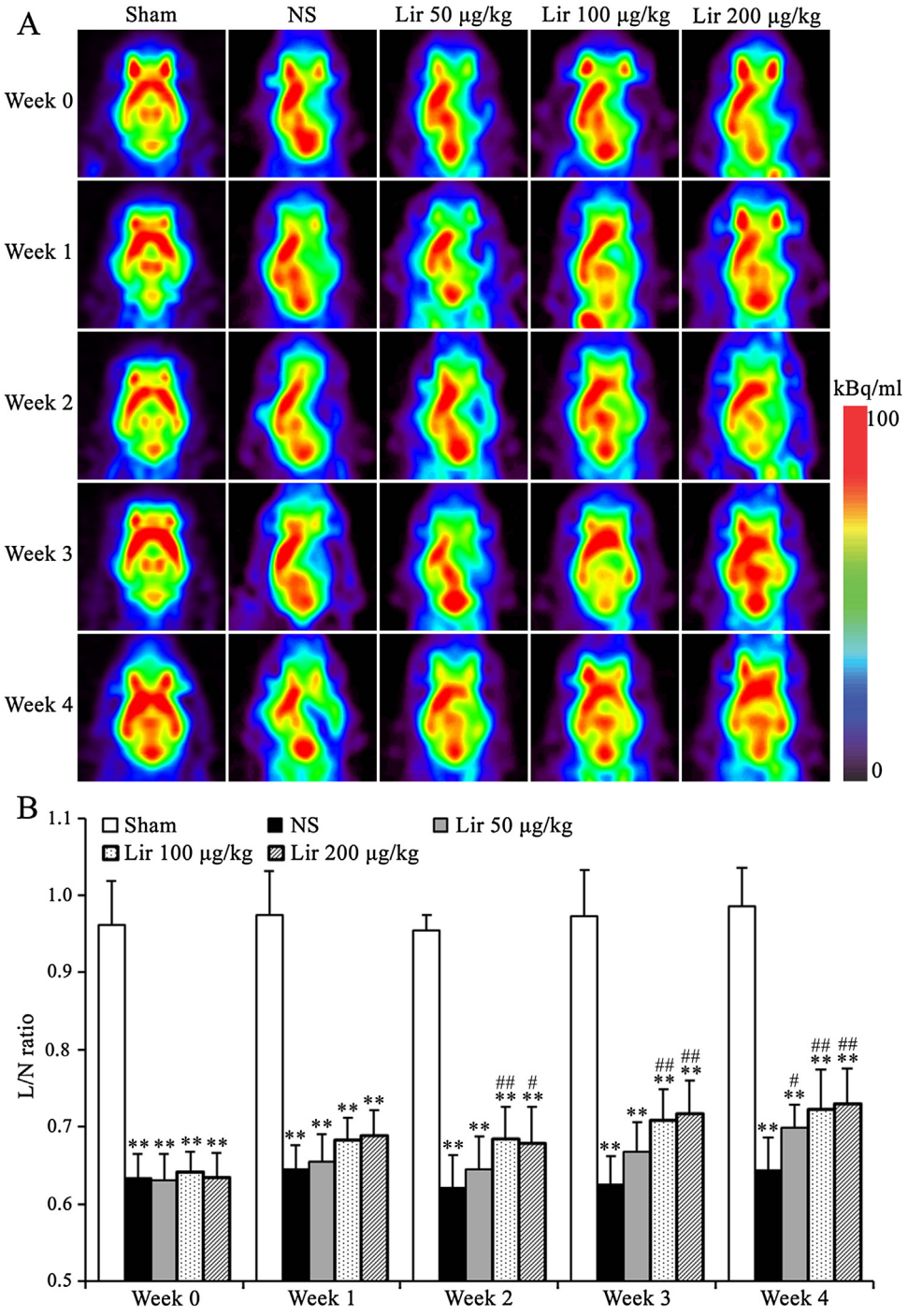

Fig. 1. Liraglutide (Lir) enhanced glucose metabolism in the cerebral ischemic area. (A) Serial ^{18}F FDG microPET images demonstrating metabolic recovery after liraglutide treatment for MCAO in rats. Images show the brain in axial view. Scale was set in accordance with signal intensity. (B) Semi-quantitative analysis of glucose metabolic changes in each group (shown as L/N ratio). Values are mean ± SD, n = 6, $^{**}P < 0.01$ *vs.* sham group, $^{\#}P < 0.05$ and $^{\#\#}P < 0.01$ *vs.* NS group.

stroke [2,3,5,13,24]. GLP-1R may hold promise as a restorative target. Emerging evidence has shown that GLP-1R agonists induce neurite outgrowth and protect synaptic plasticity after neuronal injury [19,23]. However, it is currently not known whether the therapeutic window for GLP-1R agonists can exceed 4.5 h after stroke onset or whether GLP-1R agonists improve long-term functional recovery after ischemic stroke. For this reason, delayed administration of a well-established GLP-1R agonist, liraglutide, was assessed for effects on functional recovery after cerebral ischemia.

Liraglutide has been shown to improve glucose metabolism [14]. However, the role of liraglutide in the brain after stroke is still unclear. Glucose metabolism is critical to brain function [22]. Exploration of metabolic changes and efficacy after liraglutide treatment is necessary for development of a noninvasive, accurate, and sensitive approach.

Positron emission tomography (PET) can perform both functional and molecular imaging, which can be utilized to monitor neurofunctional alterations [10]. PET with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) has been used to detect subtle changes of glucose metabolism in rats following ischemic stroke [27]. In this study, ^{18}F FDG microPET and modified neurological severity score (mNSS) test were used to evaluate metabolic changes and neurological func-