Glucagon-Like Peptide-1 Receptor Agonist Exendin-4 Ameliorates Stroke-Induced Brain and Bladder Injury in Type I Diabetic Rats

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Abstract

Background and Purpose: The risk for stroke is higher in patients with diabetes by hyperglycemia induced oxidative stress and is commonly associated with diabetic cystopathy. We hypothesized glucagon-like peptide-1 receptor agonist exendin-4 (Ex-4) with hypoglycemic effect and neuroprotection may attenuate global cerebral ischemia (IR) induced brain and bladder injury in diabetic rats. Experimental Approach: Ten minutes of bilateral carotid artery occlusion combined with hemorrhage-induced hypotension (30 mmHg) (IR) was induced in female Wistar rats with streptozotocin-induced type I diabetes. Prefrontal cortex edema was evaluated by T2-weighted magnetic resonance. Voiding function was determined by a transcystometry. Endoplasmic reticulum (ER) stress, apoptosis, autophagy and pyroptosis were determined by western blot and immunohistochemistry. Key Results: Diabetes increased the levels of ER stress associated proteins including pIRE-1, cleaved caspase-12, pJNK, ATF4, ATF6 and CHOP, apoptosis associated caspase 3 and PARP proteins expression, autophagy associated proteins Beclin-1 and LC3-II proteins expression and pyroptosis associated caspase 1 and IL-1β proteins expression in the prefrontal cortex and bladders. IR led to a significantly prefrontal cortex edema and voiding dysfunction and further enhanced ER stress, apoptosis, autophagy and pyroptosis in brain and bladder of the diabetic rats. Diabetes thickened the lamina propria layers and increased bladder Masson's trichrome stain. Intraperitoneal Ex-4 treatment significantly attenuated prefrontal cortex edema, ER stress, apoptosis, autophagy and pyroptosis in brains and bladders and improved bladder dysfunction. Conclusion and Implications: Glucagon-like peptide-1 receptor agonist Ex-4 ameliorates stroke-induced brain injury and bladder dysfunction in diabetic rats through inhibiting ER stress, apoptosis, autophagy and pyroptosis signaling.

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