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Neuroprotective Effect of Vildagliptin against Cerebral Ischemia in Rats

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Abstract : The burden of stroke is intensely increasing worldwide. Brain injury following transient or permanent focal cerebral ischemia develops ischemic stroke as a consequence of a complex series of pathophysiological events. The aim of this study is to evaluate the possible neuroprotective effect of a dipeptidyl peptidase-4 inhibitor, vildagliptin, independent on its insulinotropic properties in non-diabetic rats subjected to cerebral ischemia. Anaesthetized Wistar rats were subjected to either left middle cerebral artery occlusion (MCAO) or sham operation followed by reperfusion after 30 min of MCAO. The other three groups were orally administered vildagliptin at 3 dose levels (2.5, 5, 10 mg/kg) for 3 successive weeks before subjected to left focal cerebral ischemia/reperfusion and till the end of the study. Neurological deficit scores and motor activity were assessed 24h following reperfusion. 48h following reperfusion, rats were euthanized and their left brain hemispheres were harvested and used in the biochemical, histopathological, and immunohistochemical investigations. Vildagliptin pretreatment improved neurological score deficit, locomotor activity and motor coordination in MCAO rats. Moreover, vildagliptin reduced malondialdehyde (MDA), elevated reduced glutathione (GSH), phosphotylinosital 3 kinase (PI3K), phosphorylated of protein kinase B (p-AKT), and mechanistic target of rapamycin (mTOR) brain contents in addition to reducing protein expression of caspase-3. Also, vildagliptin showed a dose-dependent attenuation in neuronal cell loss and histopathological alterations in MCAO rats. This study proves that vildagliptin exerted the neuroprotective effect in a dose-dependent manner as shown in amelioration of neuronal cell loss and histopathological damage in MCAO rats, which may be mediated by attenuating neuronal and motor deficits, it’s anti-oxidant property, activation of PI3K/AKT/mTOR pathway and its anti-apoptotic effect.

Keywords : caspase-3, cerebral ischemia, dipeptidyl peptidase-4 inhibitor, oxidative stress, PI3K/AKT/mTOR pathway, rats, vildagliptin
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