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Berberine activates Nrf2 nuclear translocation and inhibits apoptosis induced by high glucose in renal tubular epithelial cells through a phosphatidylinositol 3-kinase/Akt-dependent mechanism.

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Abstract

Apoptosis of tubular epithelial cells is a major feature of diabetic kidney disease, and hyperglycemia triggers the generation of free radicals and oxidant stress in tubular cells. Berberine (BBR) is identified as a potential anti-diabetic herbal medicine due to its beneficial effects on insulin sensitivity, glucose metabolism and glycolysis. In this study, the underlying mechanisms involved in the protective effects of BBR on high glucose-induced apoptosis were explored using cultured renal tubular epithelial cells (NRK-52E cells) and human kidney proximal tubular cell line (HK-2 cells). We identified the pivotal role of phosphatidylinositol 3-kinase (PI3K)/Akt in BBR cellular defense mechanisms and revealed the novel effect of BBR on nuclear factor (erythroid-derived 2)-related factor-2 (Nrf2) and heme oxygenase (HO)-1 in NRK-52E and HK-2 cells. BBR attenuated reactive oxygen species production, antioxidant defense (GSH and SOD) and oxidant-sensitive proteins (Nrf2 and HO-1), which also were blocked by LY294002 (an inhibitor of PI3K) in HG-treated NRK-52E and HK-2 cells. Furthermore, BBR improved mitochondrial function by increasing mitochondrial membrane potential. BBR-induced anti-apoptotic function was demonstrated by decreasing apoptotic proteins (cytochrome c, Bax, caspase3 and caspase9). All these findings suggest that BBR exerts the anti-apoptosis effects through activation of PI3K/Akt signal pathways and leads to activation of Nrf2 and induction of Nrf2 target genes, and consequently protecting the renal tubular epithelial cells from HG-induced apoptosis.

KEYWORDS: Apoptosis; Berberine; High glucose; NF-E2-related factor 2; Phosphatidylinositol 3-kinase (PI3K)/Akt; Renal tubular epithelial cells

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