Antioxidation and anti-inflammation by haem oxygenase-1 contribute to protection by tetramethylpyrazine against gentamicin-induced apoptosis in murine renal tubular cells. Nephrology Dialysis Transplantation

蘇裕謀
Sue YM;Cheng CF;Chang CC;Chou Y;Chen CH;Juan SH

摘要

Abstract

Gentamicin, a widely used antibiotic for the treatment of bacterial infection, can cause nephrotoxicity. Tetramethylpyrazine (TMP) is a compound purified from the rhizome of Ligusticum wallichi (called chuanxiong in Chinese). Besides its protection against ischaemia-reperfusion injury and nephritis in mice, we previously reported that TMP reverses gentamicin-induced apoptosis in rat kidneys. Haem oxygenase-1 (HO-1) induction by TMP has also been shown to attenuate myocardial ischaemia/reperfusion injury in rats. METHODS: We used rat renal tubular (NRK-52E) cells, transformed cells with HO-1 overexpression or knockdown, and an adenovirus carrying the HO-1 gene (Adv-HO-1) as gene therapy targeting murine kidneys to explore the role of HO-1 in protection by TMP against gentamicin-induced toxicity both in vitro and in vivo. We evaluated the protective effects of HO-1 on several apoptotic parameters induced by gentamicin: cleaved caspases-3 and -9, cycloxygenase-2 (Cox-2) and subcellular localization of nuclear factor kappa B-p65 (NF-kappaB-p65), Bcl-xl and HS-1-associated protein (Hax-1) in NRK-52E cells. RESULTS: NRK-52E cells treated with TMP exhibited transcriptional upregulation of the HO-1 protein by approximately twofold. Overexpression of HO-1 in NRK-52E cells significantly increased mitochondrial protein levels of the antiapoptotic molecules, Bcl-xL and Hax-1, and markedly decreased the NADPH oxidase activity and proinflammatory molecules, NF-kappaB-p65 and Cox-2, which might decrease gentamicin-induced activation of caspases-9 and -3. Conversely, NRK-52E cells with HO-1 knockdown significantly exacerbated gentamicin-induced tubular cell apoptosis. Additionally, the concomitant HO-1 induction by TMP was also evident in vivo, and HO-1 therapy markedly attenuated gentamicin-induced renal apoptosis to

a similar extent as TMP pretreatment. CONCLUSIONS: Collectively, we suggest that HO-1 induced by TMP might, at least in part, protect against gentamicin-induced nephrotoxicity through antiapoptotic and anti-inflammatory mechanisms, and that it may have therapeutic potential for patients with renal disease. This is also the first demonstration that HO-1 increases Hax-1 mitochondrial localization.