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시스플라틴 유발 신손상 백서 모델에서 산화질소와 나트륨이뇨펩티드의 변화

전남대학교 의과대학 내과[1], 전남대학교 의과대학 생리학과[2]

김창성[1], 정미연[1], 이주란[1], 최준석[1], 박정우[1], 배은희[1], 마성권[1], 이종은[2], 김수완[1]

Changes of Nitric Oxide and Natriuretic Peptide System in Cisplatin-induced Kidney Injury in Rats

Chang Seong Kim[1], Mi Youn Chung[1], Ju Ran Lee[1], Joon Seok Choi[1], Jeong Woo Park[1]
Eun Hui Bae[1], Seong Kwon Ma[1], JongUn Lee[2], Soo Wan Kim[1]

Department of Internal Medicine[1] Chonnam National University Medical School
Department of Physiology[2] Chonnam National University Medical School

Introduction: Cisplatin is a chemotherapeutic agent used in the treatment of solid tumors. However, nephrotoxicity is the dose-limiting factor in its clinical use. The present study was aimed to determine whether altered regulation of the local nitric oxide and natriuretic peptide systems is involved in the pathogenesis of cisplatin-induced nephropathy.
Methods: Cisplatin (6 mg/kg) was injected intraperitoneally into male Sprague-Dawley rats. The control group was not treated with cisplatin. Expression levels of nitric oxide synthase, nitrotyrosine, soluble guanylyl cyclase and neutral endopeptidase in the kidneys were determined 4 days after treatment by semiquantitative immunoblotting. mRNA expression of natriuretic peptides and their receptors was determined by real-time polymerase chain reaction. The activities of soluble and particulate guanylyl cyclase were determined by measuring the amount of cyclic 3', 5'-guanosine monophosphate generated in response to sodium nitroprusside and atrial natriuretic peptide, respectively.
Results: In cisplatin treated rats, creatinine clearance was decreased, while sodium and water excretion were increased. The expression of inducible nitric oxide synthase and nitrotyrosine was increased in the cortex/outer stripe of outer medullar and inner medullar, while that of endothelial and neuronal nitric oxide synthase was decreased in the inner medullar. Excretion of nitric oxide metabolites was increased in cisplatin treated rats. The catalytic activity of soluble guanyly cyclase was blunted in the papilla after cisplatin was administered. The mRNA expression of atrial natriuretic peptide, brain natriuretic peptide, and C-type natriuretic peptide was increased, while that of natriuretic peptide receptors-A and C were decreased in the test rats. The catalytic activity of particulate guanylyl cyclase in the papilla was blunted after cisplatin was administered.
Conclusions: Increased production of nitric oxide by inducible nitric oxide synthase may contribute to cytotoxic injury, resulting in cisplatin-induced nephropathy, while the up-regulation of renal natriuretic peptide synthesis together with the down-regulation of neutral endopeptidase and natriuretic peptide receptor-C may contribute to the natriuresis and diuresis seen in cisplatin-induced nephropathy.

Key Words: 시스플라틴, Guanylyl cyclase,산화 질소
Cisplatin, Guanylyl cyclase, Natriuretic peptide, Nitric oxide