

Lack of Functional Interaction between Nitric Oxide and ET-A Receptors in Cisplatin-Induced Acute Renal Failure

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Abstract : Although the role of either nitric oxide (NO) or endothelin receptors modulation in the severity of cisplatin-induced nephrotoxicity has been recognized in previous studies including our own, the possible interaction between the two pathways remains obscure. In this study, we tested the possible interaction between the nitrergic and endothelin pathways in cisplatin-induced nephrotoxicity in male rats. Sprague Dawley male rats (200 to 250 g) were divided into four groups: Control (given a single dose of normal saline, i.p.), cisplatin (6 mg/kg, i.p.), cisplatin+Sildenafil (2 mg/kg, i.p.), cisplatin+Sildenafil+BQ-123 (1 mg/kg, i.p.). Each of the co-administered drugs was given in two doses; one hour before and one day after the cisplatin dose. Acute cisplatin administration resulted in significant increases in BUN and serum creatinine levels at 96 h following cisplatin injection. Increased levels of MDA, TNF- α and caspase-3, decreased nitrite/nitrate level and SOD activity in kidney homogenates were also observed following cisplatin injection. According to the obtained results, the co-administration of sildenafil alone with cisplatin offered a reno-protective effect comparable to that obtained following the concurrent administration of both sildenafil and the selective ETAR antagonist BQ-123. Thus, the current study is the first to reveal that the presence of an intact NO/cGMP system may offer a moderate reno-protective effect against cisplatin-induced nephrotoxicity even in the presence of ETAR-mediated vasoconstriction, suggesting the absence of obvious functional interaction between the nitrergic and endothelin pathways in cisplatin-induced nephrotoxicity in male rats.

Keywords : BQ-123, cisplatin, endothelin-1, nephrotoxicity, sildenafil

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