Activation of Cyclophilin D Induces the Initial Process of Kidney Stone Formation Via Mitochondrial Permeability Transition Pore Opening

Introduction and Objective: Renal tubular cell injury induced by oxidative stress is thought to be the initial process of kidney stone formation. We previously reported that catechin, owing to its anti-oxidative functions, is effective in preventing kidney stone formation. Recently, we discovered mitochondrial collapse, which is regarded as a cause of oxidative stress and renal tubular cell injury. Mitochondrial collapse is generally caused by mitochondrial permeability transition pore opening. That is induced by the activation of cyclophilin D, which is present in the matrix of the inner mitochondrial membrane. However, definite evidence is lacking on the involvement of the activation of cyclophilin D in the initial process of kidney stone formation. In this study, we examined the physiological role of cyclophilin D in kidney stone formation.
Materials and Methods: Male Sprague Dawley rats were divided into the following 3 groups: group 1: rats did not receive treatment (controls); group 2: rats that were administered 1% ethylene glycol (EG) to generate a rat model with kidney stones; and group 3: rats that were administered EG and treated with NIM811 (*N*-methyl-4-isoleucine cyclosporine), a selective inhibitor of cyclophilin D activation, for 14 days. Kidney stone formation was evaluated by polarized-light microscopy and Pizzolato staining. Oxidative stress was evaluated by immunohistochemical staining of the markers Cu-Zn SOD. Mitochondrial structures within the renal tubular cells were observed under a transmission electron microscope. The markers of cell apoptosis, namely cytochrome c and cleaved caspase 3, were evaluated by western blotting and immunohistochemical staining, respectively.
Results: EG administration induced kidney stone formation. However, kidney stone formation was significantly inhibited by NIM811 administration. The expression level of Cu-Zn SOD was high in groups 1 and 3, but it was less in group 2. The mitochondria of group 1 and 3 had a regular internal structure with a continuous double membrane, while group 2 showed mitochondrial collapse. Cytochrome c and cleaved caspase 3 were not expressed in group 1, but they were highly expressed in group 2 as compared to group 3.
Conclusions: Our results provide compelling evidence for the role of cyclophilin D and the associated mitochondrial collapse, oxidative stress and activation of the apoptotic pathway in the initial process of kidney stone formation. This study may offer a new therapeutic strategy for preventing kidney stone formation.