Ruprecht-Karls-Universität Heidelberg

Fakultät für Klinische Medizin Mannheim

Dissertations-Kurzfassung

Impact of Hypoxia and Hypercapnia on Calcium Oxalate Induced Toxicity on Renal Cells

Autor: Yanwei Cao
Institut / Klinik: Urologische Universitätsklinik
Doktorvater: Priv.-Doz. Dr. T. Knoll

Although most urinary stones are formed of calcium oxalate (CaOx), there is an ongoing controversy about the pathogenesis and the primary site of calcium oxalate stone formation. While most studies have proposed an intratubular crystallization, recent studies have implied a primary interstitial calcification within the renal papilla. Anatomical studies have demonstrated a close association between the renal vasculature and renal tubules. It has been hypothesized that disorders of the vasculature may contribute to renal stone formation. So far, the unique, chronic ischemic papillary environment has not been included in investigations on calcium oxalate toxicity. Aim of this study was therefore to investigate the influence of local hypoxia and hypercapnia on the vulnerability of both renal epithelial and interstitial cell lines to calcium oxalate crystals.

Two renal tubular cell lines (LLC-PK1 and MDCK), human umbilical vein endothelial cells (HUVEC) and fibroblast cell lines were exposed to hypoxia (3% O_2) alone, hypercapnia combined with hypoxia (3% O_2, 18% CO_2) or standard culture conditions (20% O_2) for 72 hours. Cell survival rates were determined microscopically after incubation with CaOx for 4 hours at final concentrations of 1, 2 and 4 mM. DAPI staining and western blot for caspase-3 were applied to evaluate an induction of apoptosis.

Our data confirmed that CaOx produced concentration dependent toxicity on the viability of the cell lines. HUVECs were most vulnerable to CaOx among the investigated cell lines. Hypoxia alone did not increase oxalate toxicity. However, at combined hypoxia and hypercapnia, all cell lines displayed a significant reduction of cell survival. Again, this effect was most pronounced in HUVECs. We could not demonstrate the induction of apoptosis in any cell lines, indicating cell deaths being a result of cell necrosis.

Our results clearly demonstrate an increased CaOx toxicity to renal cells at chronic ischemia. Based on the idea of primary extratubular crystallization, a hypoxic and hypercapnic environment might influence the process of CaOx stone formation. An involvement of the renal vasculature, that has been proposed recently, is conceivable considering the significant vulnerability of endothelial cells to CaOx crystals. Diseases of the vasculature, like arteriosclerosis, may further increase cell vulnerability to CaOx and promote stone formation. This issue has to be clarified by further experimental epidemiologic studies. The identification of the processes leading to urinary stone formation would allow the development of specific preventive measures. The need for such investigations is underlined by a worldwide increasing incidence of urolithiasis.