

A putative mechanism explaining sepsis-induced kidney failure in experimental sepsis

Thiele Osvaldt Rosales, Daiane Mara Bobermin, Jamil Assreuy

Universidade Federal de Santa Catarina – UFSC, Florianopolis (SC), Brazil.

Objective: Renal vascular reactivity to catecholamines is preserved in sepsis whereas the opposition to what takes place in the systemic circulation. We aimed to study whether this distinct behavior of the kidney was related to G protein-coupled receptor kinase 2 (GRK2), α_1 adrenergic receptor density and the putative role of nitric oxide (NO).

Methods: Female Swiss and Black C57BL/6 NOS-2-KO mice were submitted to sepsis by cecal ligation and puncture (CLP). Swiss mice were treated with a NOS-2 inhibitor (1400W; 1 mg/kg), 30 min before and 6 and 12 hours after sepsis induction or with a NO donor (SNAP, 10 mg/Kg). Alpha 1 adrenergic-receptor fluorescent binding assay and Western blot analysis (GRK2 and NOS-2) were performed 24 hours after CLP or 4 hours after SNAP treatment. Swine kidney epithelial cell line (LLC-PK1) were treated with SNAP (100 μ M) in the presence or not of an inhibitor of soluble guanylate cyclase (ODQ, 1 μ M). All procedures were approved by the institutional Animal Ethics Committee (CEUA 8443190617).

Results: Our results show that i) sepsis reduced GRK2 levels to almost nil and induced a simultaneous increase (75%) in α_1 adrenergic receptor density in the kidney; ii) NOS-2 protein expression increased in septic kidney; iii) decrease of GRK2 levels was prevented in NOS-2-KO mice or with 1400W treatment; iv) treatment with the NO donor reduced the GRK2 content in kidney and in LLC-PK1 cells; v) the decrease in LLC-PK1 cells was prevented by the inhibition of soluble guanylate cyclase.

Conclusions: Our findings show that sepsis induced a decrease in GRK2 levels together with an increased density of α_1 adrenergic receptors in kidney. Furthermore, our results indicated that GRK2 levels are highly dependent of NO pathway in septic kidney and in LLC-PK1 cells. The permanence of the vasoconstrictor response in the kidney may help to explain the sepsis-induced kidney failure.

Financial support: CNPq, CAPES and FINEP.