Study of the role of pro-inflammatory and anti-inflammatory cytokines in acute kidney injury induced by gentamicin.

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Introduction

Acute kidney injury (AKI) occurs in response to certain drugs, metals and a variety of other insults, however, AKI is nowadays diagnosed when the patient presents evident alterations of renal excretory, which show clinically detectable signs and symptoms. At this a point, the damage is very extensive and the treatment is more difficult. Studies have correlated long-term morbidity and mortality in AKI cases to chronic inflammatory conditions created by the action of various inflammatory cytokines that contribute to renal vascular and tubular injury with consequent development of AKI. Inflammatory response is coordinated by pro-inflammatory cytokines such as TNF- α, IL-6 and IFNg, which stimulates the synthesis of other pro-inflammatory cytokines, adhesion molecules, and anti-inflammatory cytokines, particularly IL-10 that inhibits the secretion of IL-1β, TNF-α, and IL-6, thus regulates pro-inflammatory cytokines production. The balance between pro- and anti-inflammatory cytokines affects the clinical outcome of various inflammatory conditions including AKI.

Aims

The aim of this work, we studied the presence or absence of inflammation-related molecules in the urine of AKI rats, and their association to pathological events for potential diagnostic purposes.

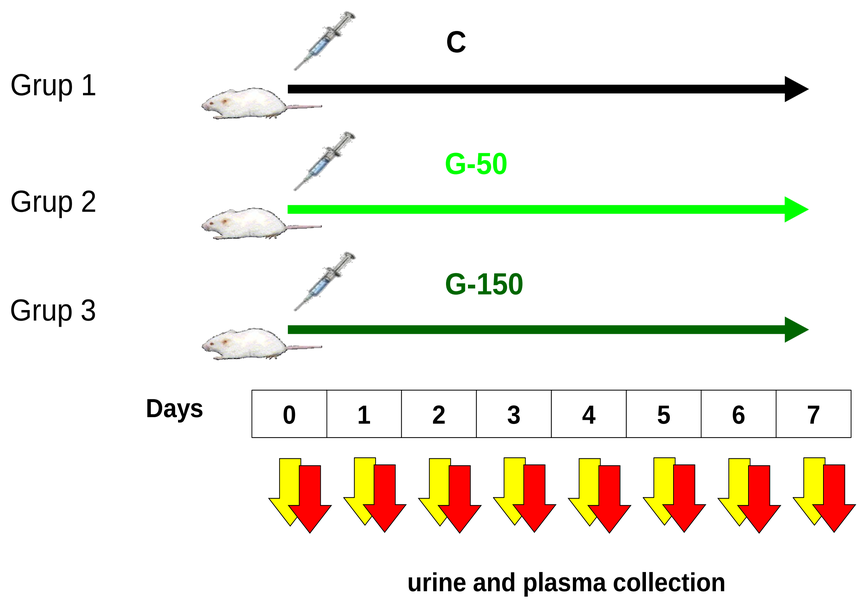
Methods/ experimental design

- Experimental Groups (female Wistar rats weighing 190-220 g):
  - Group 1: daily saline (C) i.p. (day 0-6)
  - Group 2: daily 50 mg/kg body weight Gentamicin (G-50) i.p. (day 0-6)
  - Group 3: daily 150 mg/kg body weight Gentamicin (G-150) i.p. (day 0-6).

-Renal toxicity was evaluated by measuring plasma creatinine and blood urea nitrogen (BUN), and urine proteins and N-acetyl-glucosaminidase (NAG).

-IFNg, intercellular adhesion molecule (ICAM-1) and IL-10 were measured by a multiplex Quantibody® Array method.

Schematic representation of the experimental design



Results

Classical diagnostic markers of nephrotoxicity

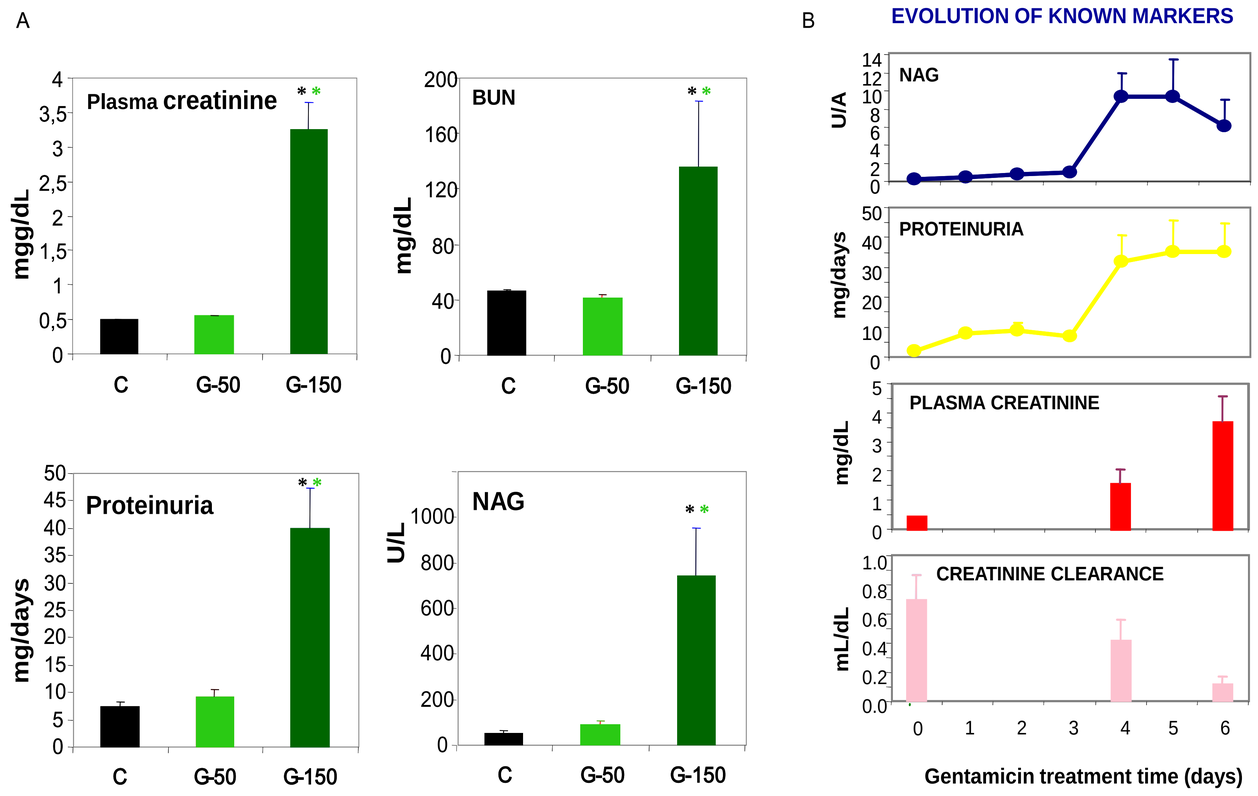


Figure 1. Figure 1. Classical diagnostic markers of nephrotoxicity. (A) Graphs represent determinations of plasma creatinine and blood urea nitrogen, urine protein daily excretion and daily urine activity of N-acetyl-glusoaminidase (NAG), measured in urine from rats treated during 7 days with 0 (Control), 50 (G-50) or 150 (G-150) mg/day gentamacin (per Kg of body weight). (B) Evolution of plasma creatinine concentration, creatinine clearance, proteinuria and N-acetyl-glucosaminidase (NAG) during all tratreament whit gentamacin 150 mg/day (G-150).

Urinary levels of cytokines is associated to AKI induced by gentamicin

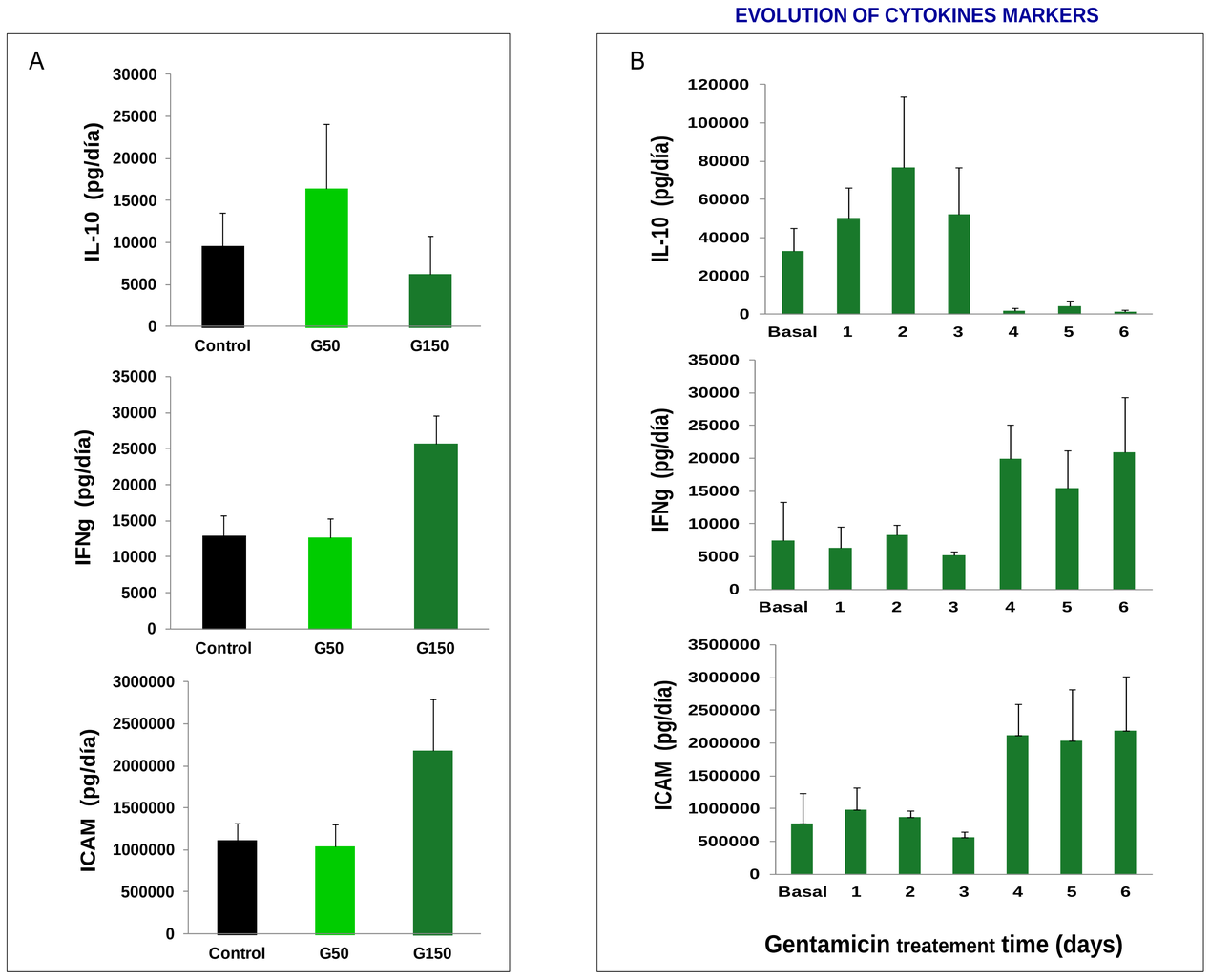


Figure 2. Urinary levels of pro-inflammatory and anti-inflammatory cytokines. (A) IL-10, IFN-γ and ICAM measured in urine from rats treated during 7 days with 0 (Control), 50 (G-50) or 150 (G-150) mg/day gentamacin (per Kg of body weight). (B) IL-10, IFN-γ and ICAM measured during all tratreament whit gentamacin 150 mg/day (G-150).

Conclusions

These findings indicate that a urinary profile posed by low levels of IL-10 and high levels of INFg and ICAM-1 is associated to nephrotoxic AKI, and reveals that renal inflammatory processes may be monitored through the analysis of the urine.

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