Urynary excretion of t-gelsolin diferentiates acquired predisposition to acute injury from nefhrotoxic acute kidney injury.

Quiros-Luis Y[1,2,3], Blanco-Gozalo V [1,2,3], Sancho-Martínez SM [1,2,3], Prieto-García L [1,2,3] , López-Novoa JM [1,2,3], López-Hernández FJ [1,2,3]

[1]Translational Research on Renal and Cardiovascular Diseases (TRECARD), Department of Physiology and Pharmacology, University of Salamanca, Salamanca, Spain.[2]Instituto de Estudios de Ciencias de la Salud de Castilla y León (IECSCYL), Research Unit, University Hospital of Salamanca, Salamanca, Spain. [3]Salamanca Institute for Biomedical Research (IBSAL), University Hospital of Salamanca, Salamanca, Spain.[4]Developmental Biology and Cancer, Institute of Child Health, University College London, UK.

Introduction

Drug nephrotoxicity is a leading cause of acute kidney injury (AKI). Severe AKI leads to acute renal failure, which is associated to high mortality rates, ranging from 50 to 80%, especially in critically ill patients. It is estimate that about 25% of the 100 most used drugs in intensive care units nephrotoxic. Gentamicin is an aminoglycoside antibiotic, is a highly nephrotoxic drug, with 10-25% of therapeutic courses causing some degree of AKI. Early detection AKI is a key determinant for the optimal clinical handling of patients. We have previously demonstrated that a subnephrotoxic treatment with gentamicin predisposes rats to AKI by sensitizing them to the action of other nephrotoxins administered also in subnephrotoxic regimes. Gentamicin induces predisposition correlates with the increased urinary excretion of gelsolin. Gelsolin is a 82 kDa protein involved in cytoskeleton organization. Gelsolin is cleaved apoptosis to render a 43 kDa proteolytic fragment named t-gelsolin.

Aims

The aim of this study is to analyze the capacity of t-gelsolin to differentiate between predisposition to AKI from early renal injury.

Methods/experimental design

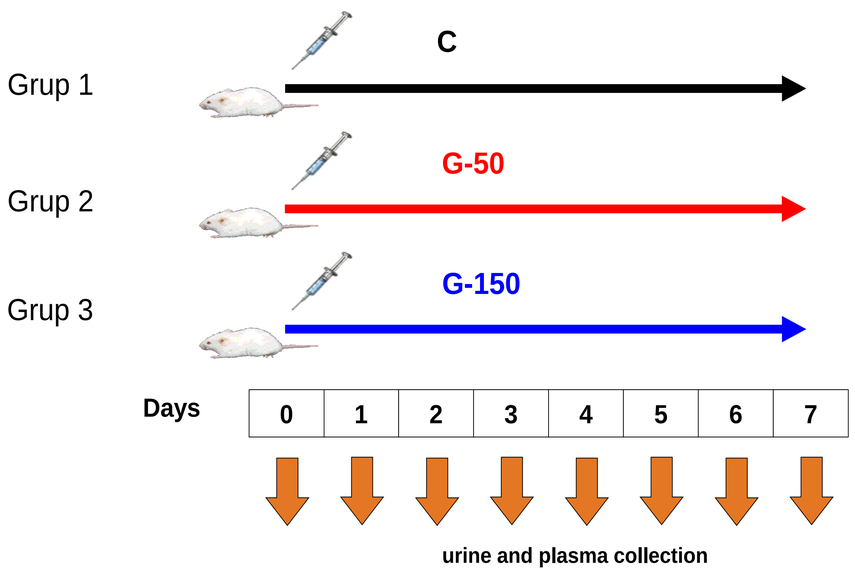
- Experimental Groups (Wistar rats weighing 190-220 g):

- **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).**

- Characterization of renal funtion was evaluated by measuring plasma creatinine and blood urea nitrogen (BUN), and urine proteins and N-acetyl-glucosaminidase (NAG), hematoxilin-eosin stained and urine markers by Western blot.

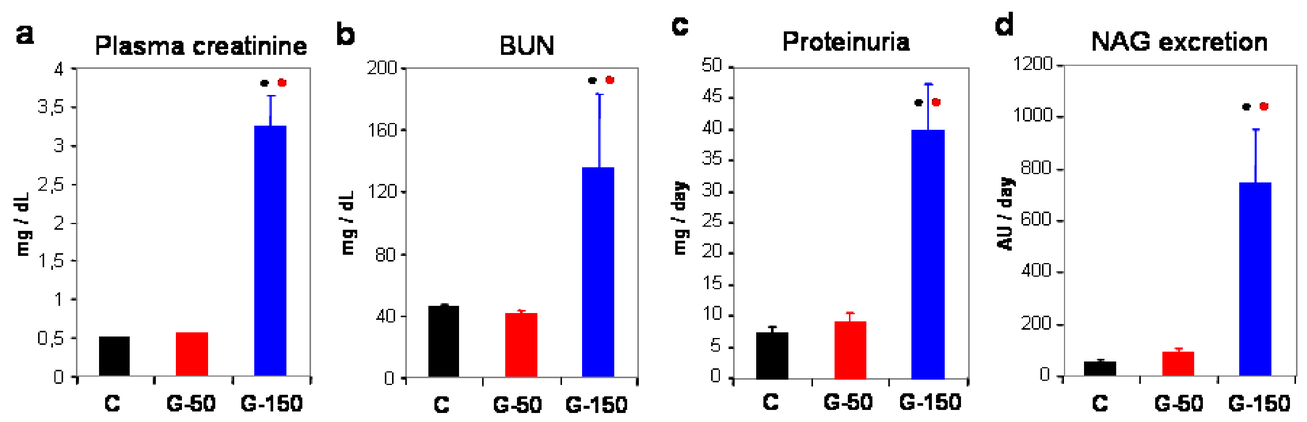
-Western blot were sed to investigate the presence of novel urine markers.

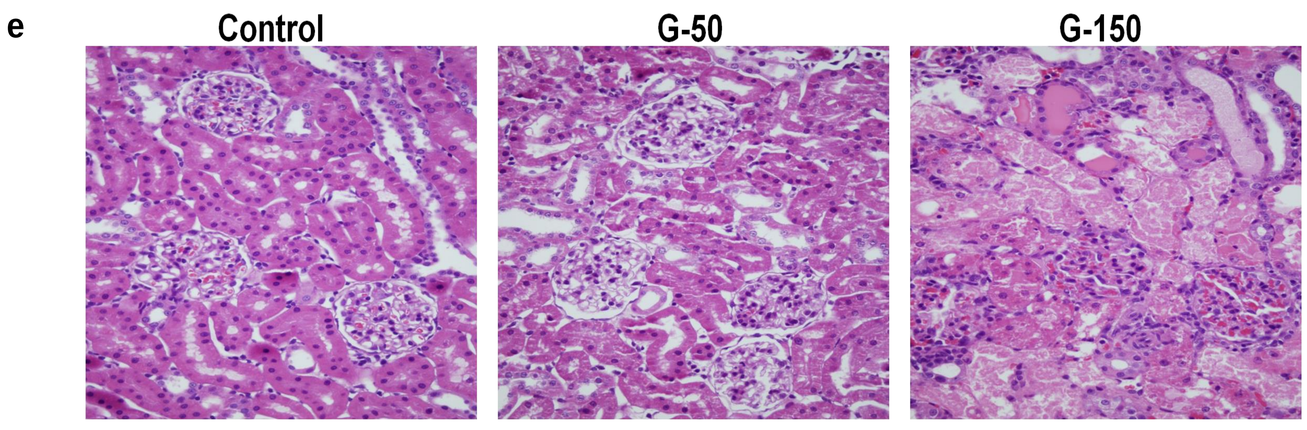
SCHEMATIC REPRESENTATION



Results

Characterization of the renal function





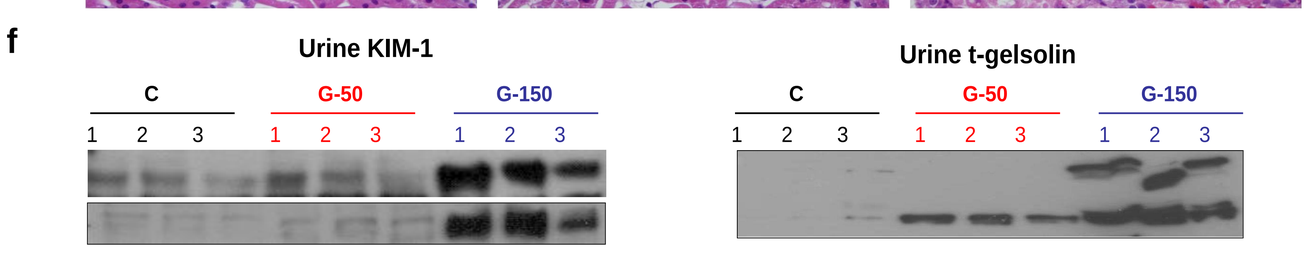


Figure 1. Characterization of the renal function (a) Graphs represent determinations of plasma creatinine, (b) blood urea nitrogen (BUN), (c) urine protein excretion and (d) activity of N-acetyl-glusoaminidase (NAG) after 7 days of treatment. (e) Representative images (400X) of the cortex of hematoxilin–eosin-stained renal sections from C, G-50, and G-150 rats (n=6). (f) Representative images of Western blot analysis of PAI-1, KIM-1 and gelsolin levels in urine from 3 randomly selected animals from C, G-50 and G-150 groups

EVOLUTION OF T-GELSOLIN AND RENAL FUNCTION DURING TREATMENT WITH GENTAMICIN

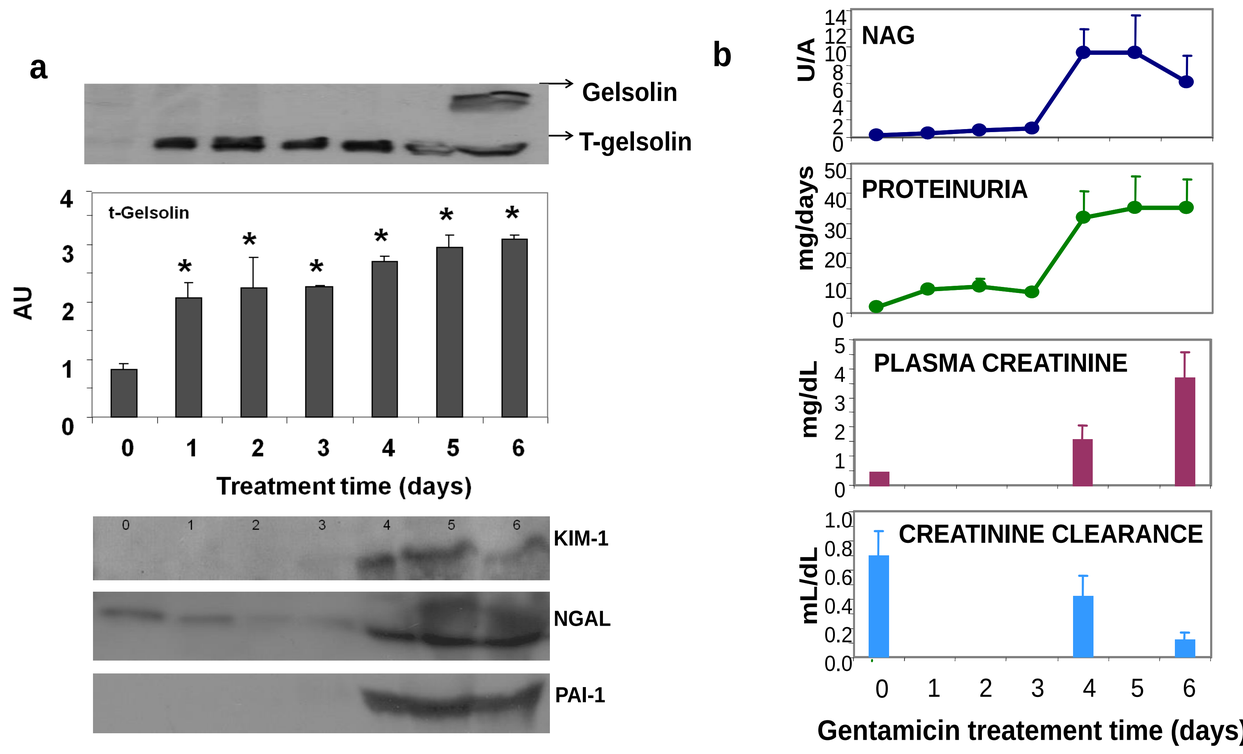


Figure 2. **Time course evolution of urinary gelsolin**. (a) Representative images of Western blot analysis of urinary gelsolin, KIM-1, NGAL and PAI-1, (b) NAG excretion, proteinuria, creatinine clearance and plasma creatinine of rats treated with gentamicin..

Conclusions

This study shows that the excretion urinary level of t-gelsolin might be used to discriminate between rats predisposed to AKI and those undergoing early damage. This capacity may have direct application for the differential diagnosis of gentamicin's nephrotoxicity, which need to be further developed in the preclinical and clinical settings for a better theranostic usage and efficacy of this drug.

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