REGIIIβ IS A POTENTIALLY DIFFERENTIAL URINARY MARKER IN TWO ANIMAL MODELS OF ACUTE KIDNEY INJURY INDUCED BY CISPLATIN OR GENTAMICIN

Blanco-Gozalo V[1,2,3], Quirós-Luis Y[1,2], 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.

Introduction

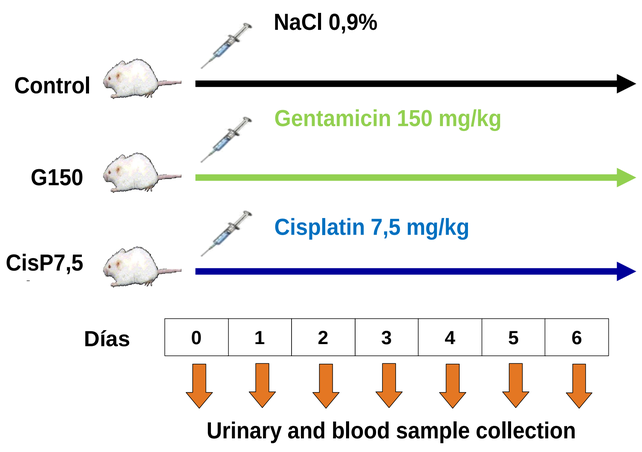
Nephrotoxicity poses a considerable health and economic problem worldwide. It is an important reason of failure along the drug discovery process, which leads to discarding otherwise clinically interesting molecules. Most importantly, about 25% of the 100 most used drugs in intensive care units are potentially nephrotoxic. Overall, it is estimated that nephrotoxicity is responsible for 10-20% of the acute renal failure cases. A critical aspect for the optimal clinical handling of AKI is an early diagnosis. Important progress has been made in the last decade towards an increasingly earlier detection based on novel and more sensitive urinary markers. However, AKI diagnosis may still be improved in an individual-drug basis, for enhanced theranostics and a more individualized medicine.

Aims

We decided to study the regenerating islet-derived protein III beta (REGIIIβ) as potentially differential urinary markers of gentamicin and cisplatin nephrotoxicity.

Methods / experimental design

We studied two animal models of AKI induced by gentamicin or cisplatin (and saline as control). Renal function was monitored by means of serum creatinine, BUN, creatinine clearance and proteinuria. Renal morphology and tissue integrity were assessed by histological studies and tissue and urine renal markers were determinate by Western blot.



To do this, we treat Wistar rats with:

Group 1: Control (C). Rats given physiological saline for 6 days.

Group 2: Gentamicin 150 (G150). Rats given a toxic dose of gentamicin (150 mg / kg / day) for 6 days intraperitoneally.

Group 3: Cisplatin 7,5 (Csp7,5). Rats given a single toxic dose of cisplatin (5 mg / kg / day) intraperitoneally.

Conclusions

REGIIIβ is a potentially differential or etiological urinary marker of gentamicin´s nephrotoxicity. It will help to better delineate the pharmacological profile of gentamicin and, in turn, to improve its clinical utility.

Results

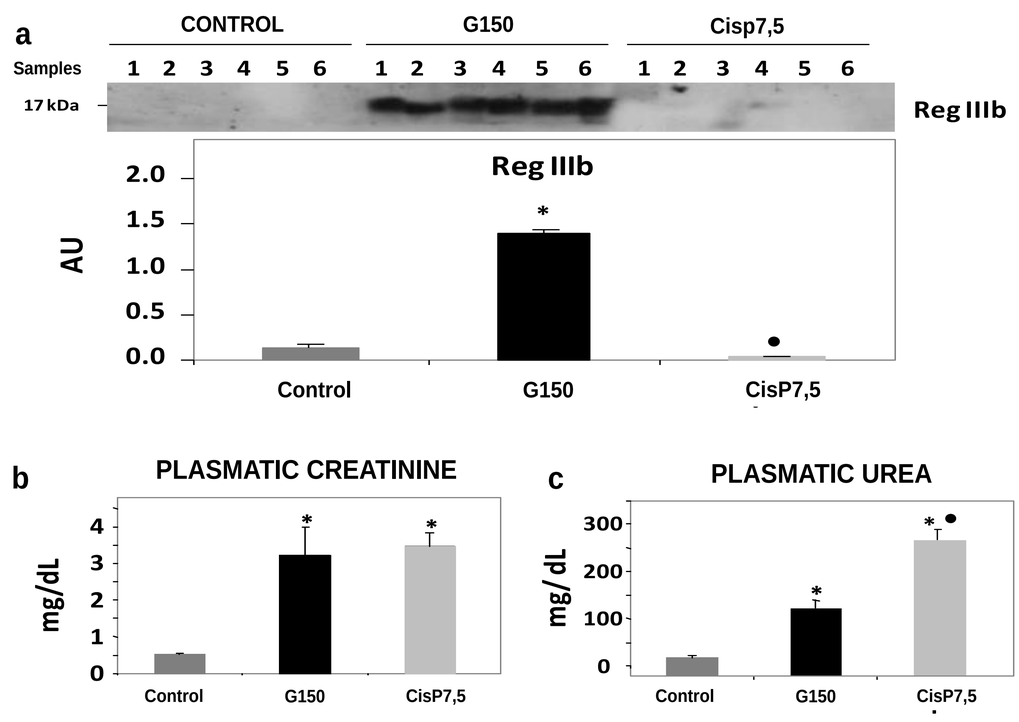


Fig 1. Western blot analysis of RegIIIb in urine samples from 6 randomly selected rats with vehicle (control), gentamicin or cisplatin (a), plasma creatinine (b) and plasma urea (c). * p <0.05 vs control; • p <0.05 vs gentamicin

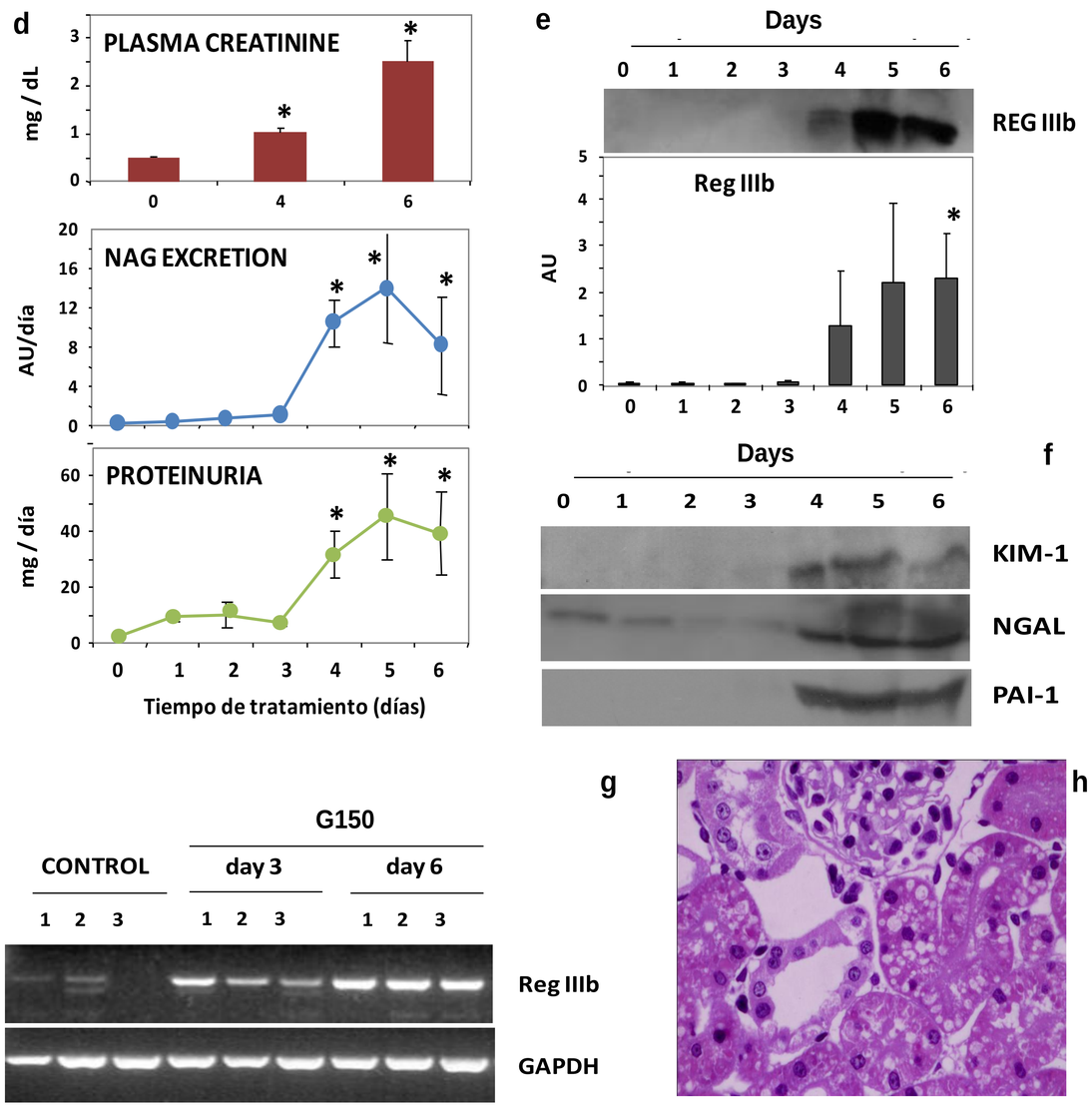


Fig 2. Evolution in time of RegIIIb. Plasma creatinine concentration, excretion of N-acetyl-β-D-glucosaminidase (NAG) and proteinuria (d), Western blot analysis of urinary excretion of RegIIIb (e), Western blot analysis of KIM-1, NGAL and PAI-1 (f) and gene expression of RegIIIb and GAPDH in renal tissue by RT-PCR of 3 randomly selected rats treated with vehicle (control) or gentamicin for 3 and 6 days (g), representative image of renal sections Stained with hematoxylin-eosin from G-150 rats treated for 3 days (h). * p <0.05 vs control.00

Supported by the Kidney Research Network REDINREN of the Instituto de Salud Carlos III (ISCIII), Spain, co-funded by FEDER