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POSSIBLE NEW UTILITY OF VDBP PROTEIN AS BIOMARKER OF CHRONIC PREDISPOSITION TO ACUTE KIDNEY INJURY

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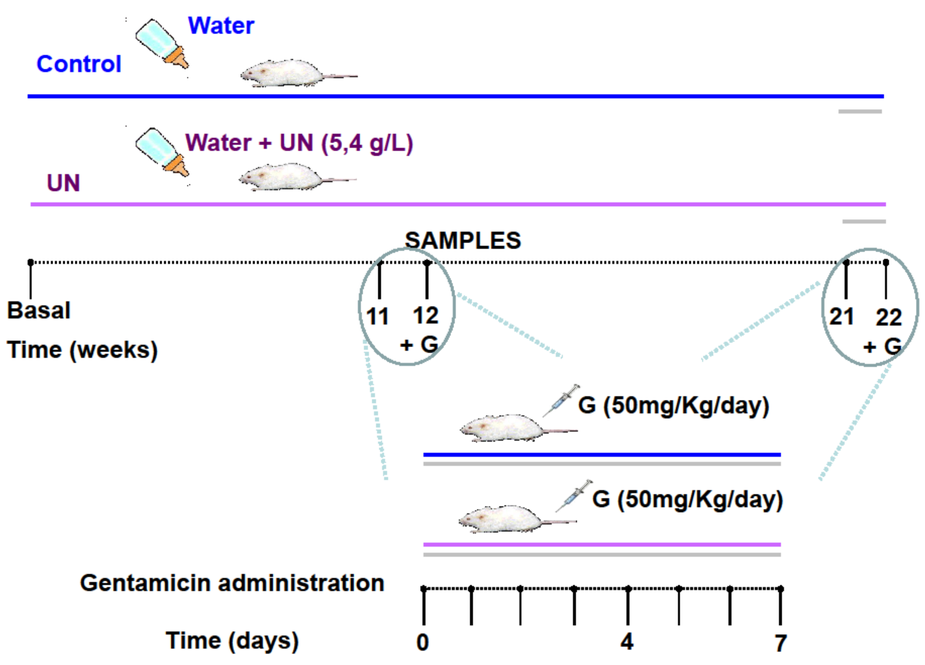
INTRODUCTION

In the last years, the new concept of predisposition to acquire acute kidney injury (AKI) is emerging. This concept was observed in our group when experimental animals exposed to an absolutely subnephrotoxic acute treatment with certain drugs (e.g. gentamicin and cisplatin) developed AKI when they were treated with a second insult with another drug, while control animals exposed to the same second drug experimented no toxicity.

OBJETIVE

We decide to study if chronic exposure to nephrotoxicants might induce this predisposition to acute kidney injury and investigate how to detect this condition by the search of predisposition biomarkers.

EXPERIMENTAL METHOD



Experimental groups (Sprague Dawley rats):

• **Control group (C):** free access to drinking water. After 11 or 21 weeks gentamicin (G, sub-toxic doses: 50 mg/Kg/day) was administered i.p. during 7 days.

• **Experimental nephrotoxic, Uranyl Nitrate (UN):** free access to drinking water which contains UN (doses that apparently do not produce kidney damage: 5,4 g/L). After 11 or 21 weeks gentamicine (G, sub-toxic doses: 50 mg/Kg/day) was administered i.p. during 7 days.

1. Renal function studies:

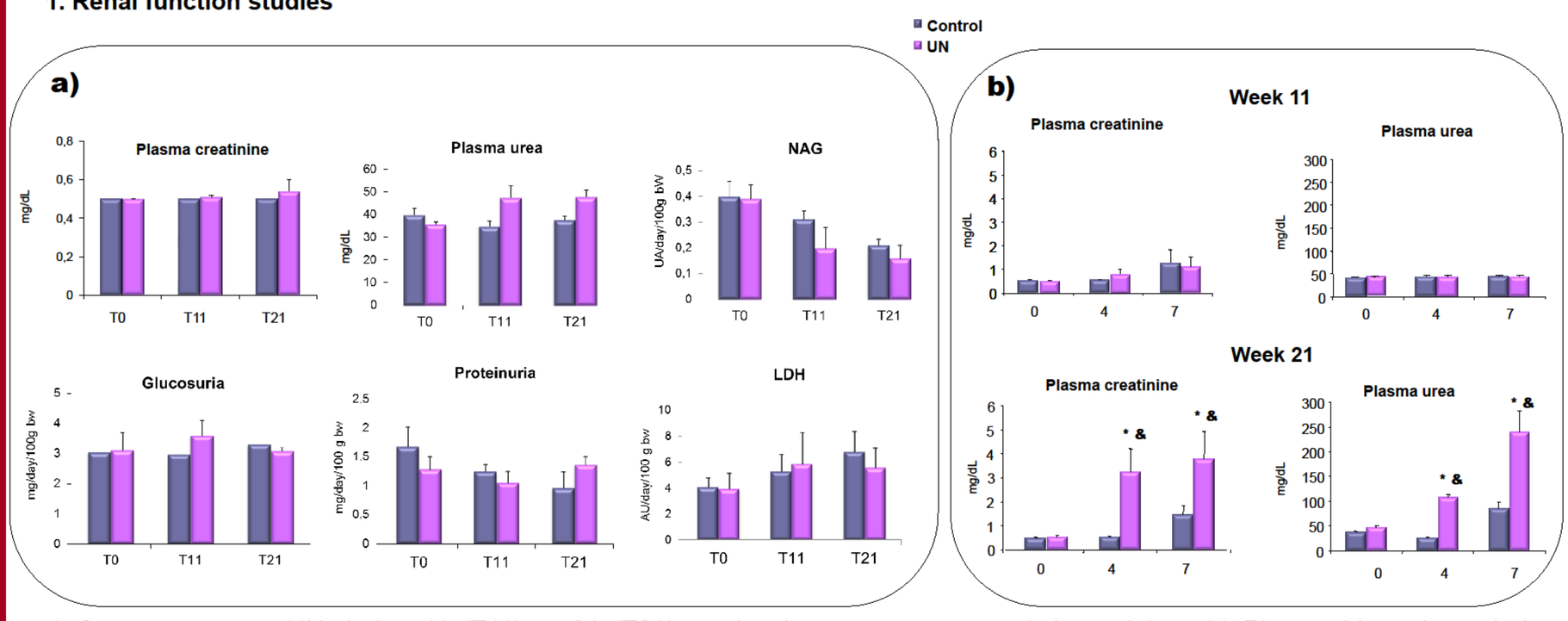
• Serum: Creatinine (Crs) and Urea using auto-analizer Reflotron Plus®.
• Urine: proteinuria, glucosuria, activity of enzime N-acetyl-β- D-glucosaminidase (NAG) and lactate deshidrogenase (LDH), by especific colorimetric methods.
• Kidney: histological study by hematoxilin and eosin

2. Search of predisposition biomarkers:

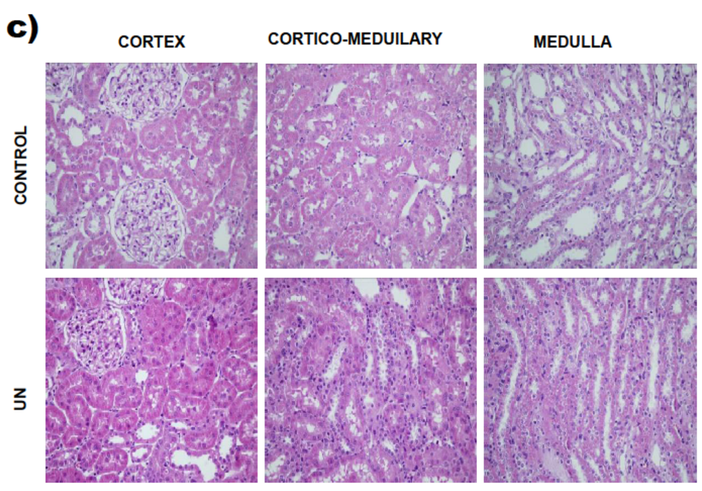
• Urinary proteomic analysis.
• Western Blot confimation of VDBP (vitamin-D-binding protein) excretion in urine.

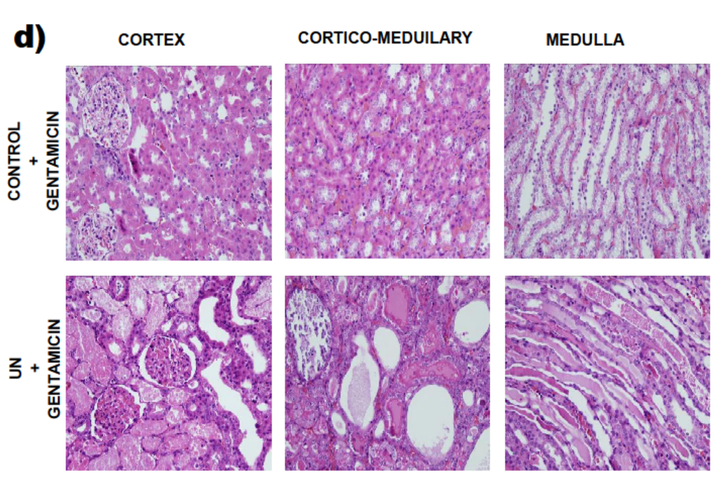
RESULTS

1. Renal function studies



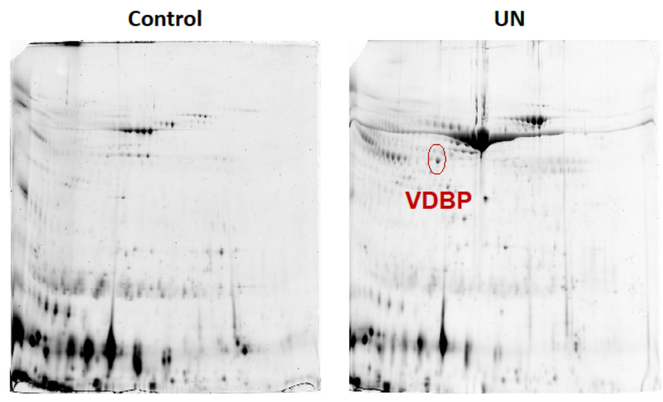
a) Overexposure to UN during 11 (T11) or 21 (T21) weeks does not cause renal tissue injury. b) Plasma biomarkers during gentamicin administration (days 0, 4 and 7) at week 11 or week 21. Data expressed as mean ± EEM. Statistically significant differences, p<0,05 according to the Scheffé test: & vs basal same group; * vs control same time.



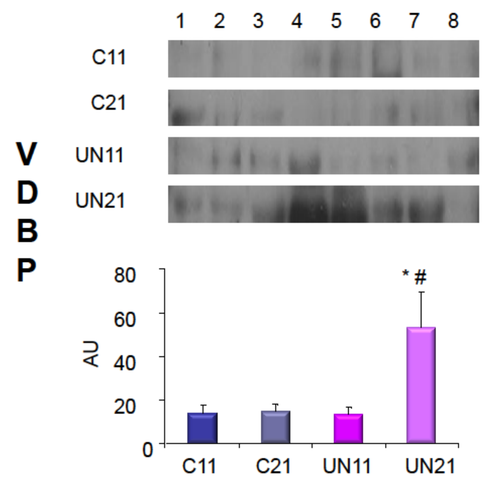


Representative photographs of renal slices stained with hematoxylin and eosin c) at 21 weeks of exposure or d) after gentamicin administration (d7)

2. Search of predisposition biomarkers



Representative 2-DE gel of each group.



Western blot cuantification. Data expressed as mean ± EEM. Statistically significant differences, p<0,05 according to the Scheffé test * vs control same time; # vs T11 same group.

CONCLUSIONS

Our results suggest that chronic exposure to UN, at doses that apparently does not produce damage, predisposes to acute kidney injury when animals were subjected to a second insult at subtoxic doses. The protein VDBP appears increased in urine of predisposed animals at 21 weeks but not at 11 which means that this increase is associated with hidden injury but not with the exposition to uranium. VDBP protein might be potentially used as marker of chronic predisposition to ARF. This new diagnostic tool might help to reduce AKI incidence and severity, and also the associated sanitary and socioeconomic costs.

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AKI - experimental models
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