PARICALCITOL EXERTS ANTINFLAMMATORY EFFECTS IN EXPERIMENTAL MODELS OF RENAL DAMAGE BY THE MODULATION OF THE NON CANONICAL NF-κB PATHWAY.

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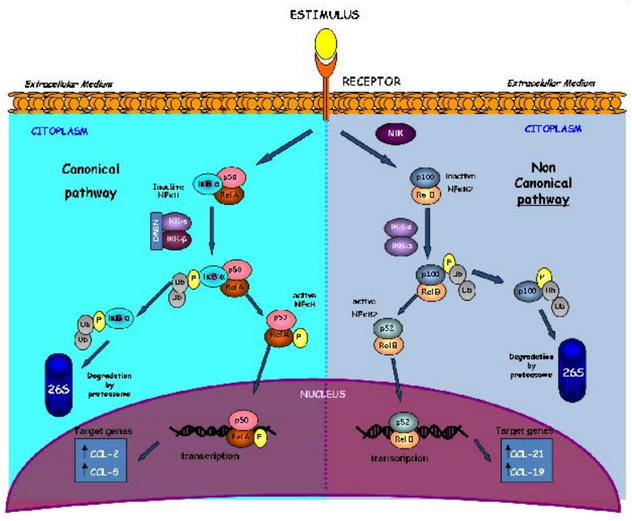
INTRODUCTION

Chronic kidney disease (CKD) is characterized by progressive loss of kidney function that leads to renal failure. Deficiency in Vitamin D or its active metabolites is a common situation in CKD patients. Experimental data in animal models have demonstrated that vitamin D and its analogs (VDRAs) exert beneficial effects independent on their actions on the bone and mineral metabolism, by the regulation of cell proliferation, inflammation and fibrosis. However, the mechanisms involved in their anti-inflammatory actions are not well known. Previous studies have demonstrated the contribution of the canonical pathway of NF-κB1 in kidney damage. However, there is few data about the activation of the non-canonical pathway of NF-κB2 and their contribution to kidney damage.

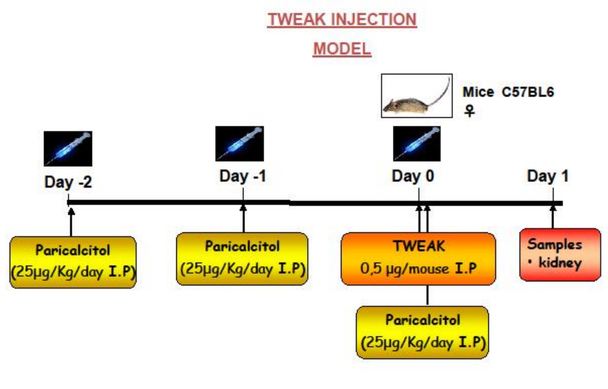


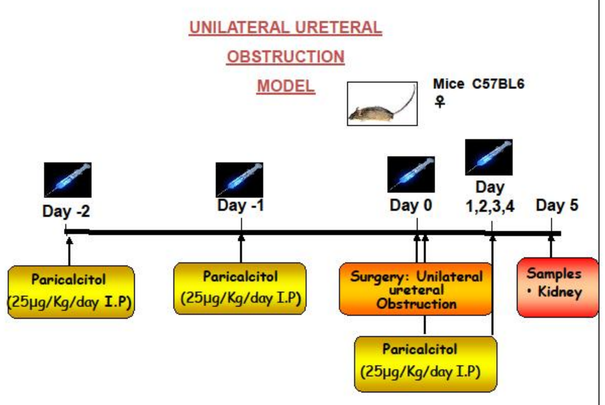
AIM

Our aim was to investigate, in different models of renal damage, the involvement of NF-κB signalling pathway in VDRA anti-inflammatory effects, with special attention to the non-canonical NF-κB pathway and its regulation of several processes including renal inflammation.

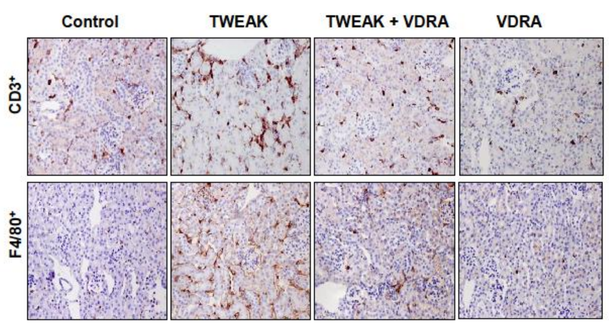
METHODS

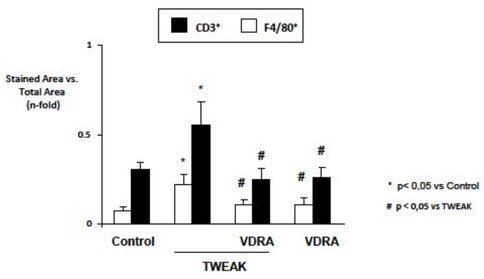
The *in vivo* effect of paricalcitol was studied in different mice models of renal damage. The model of TWEAK-induced renal inflammation was done by intraperitoneal injection of recombinant TWEAK (0.5 mg/ er mouse) and analyzed 24 hours after. The model of unilateral ureteral obstruction (UUO) consist onthe ligation of the left ureter. In each model, animals were treated with the vitamin D receptor agonist (VDRA) Paricalcitol (25 ug/kg/day), starting 48 hours before of injury induction. *In vitro* experiments were performed in tubular epithelial cells.

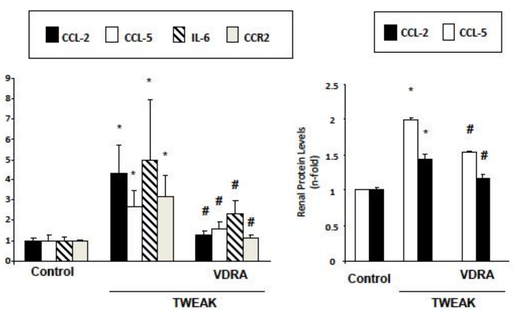




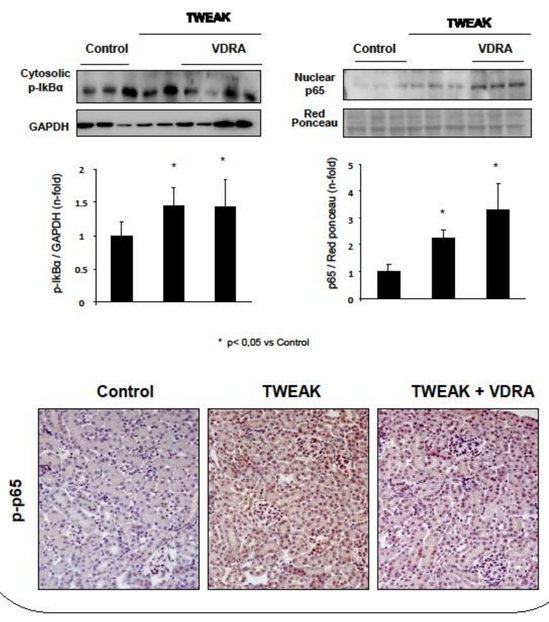
Paricalcitol inhibits the inflammatory response induced by TWEAK in the kidney



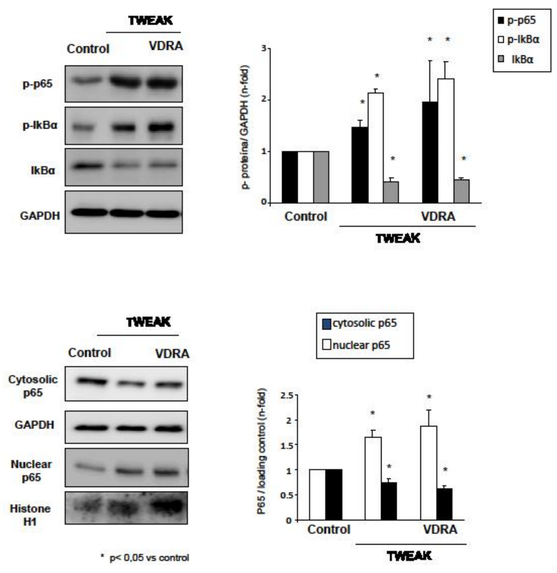




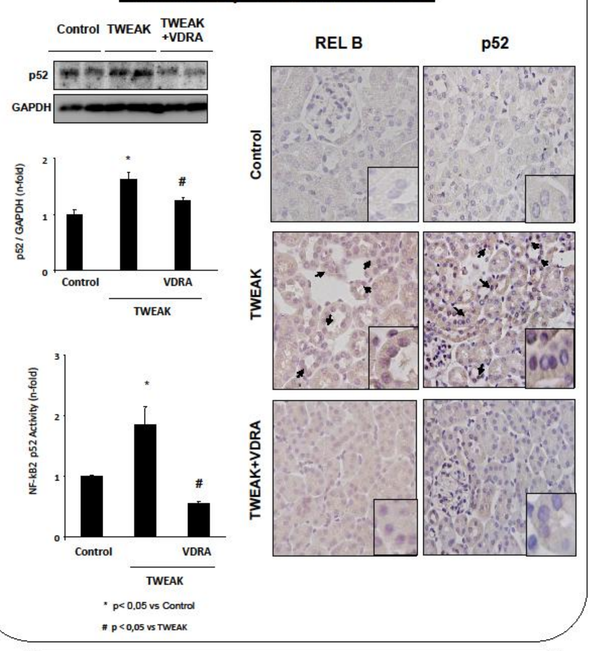
Paricalcitol does not modify the activation of NF-κB1 pathway induced by TWEAK *In vivo*



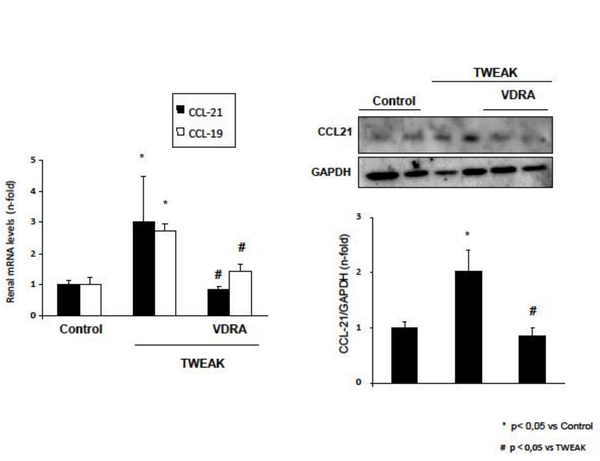
Paricalcitol does not modify the activation of the canonical NF-κB1 pathway induced by TWEAK *In vitro*

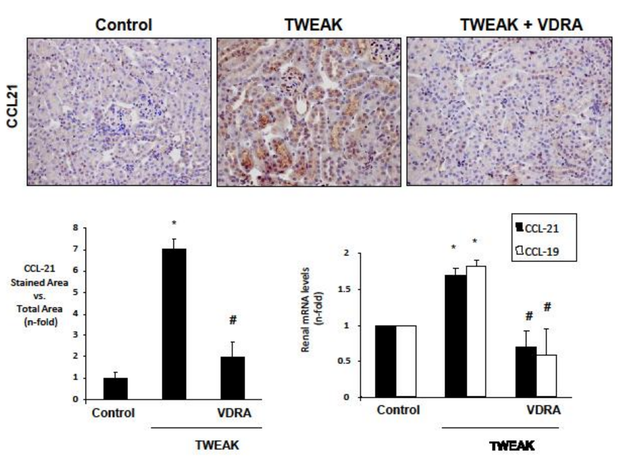


Paricalcitol inhibits the activation of the non canonical NF-κB2 pathway induced by TWEAK *In vivo*

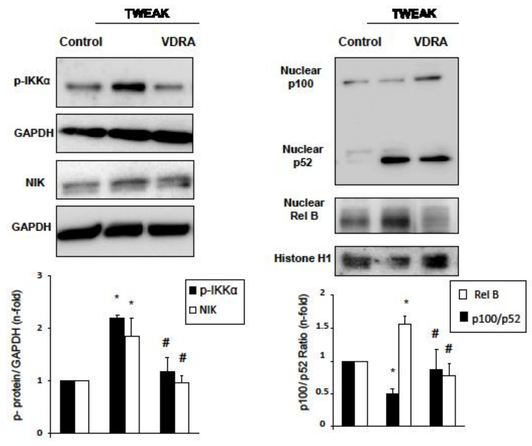


Paricalcitol inhibits NF-κB2-related cytokine expression induced by TWEAK *In vivo*

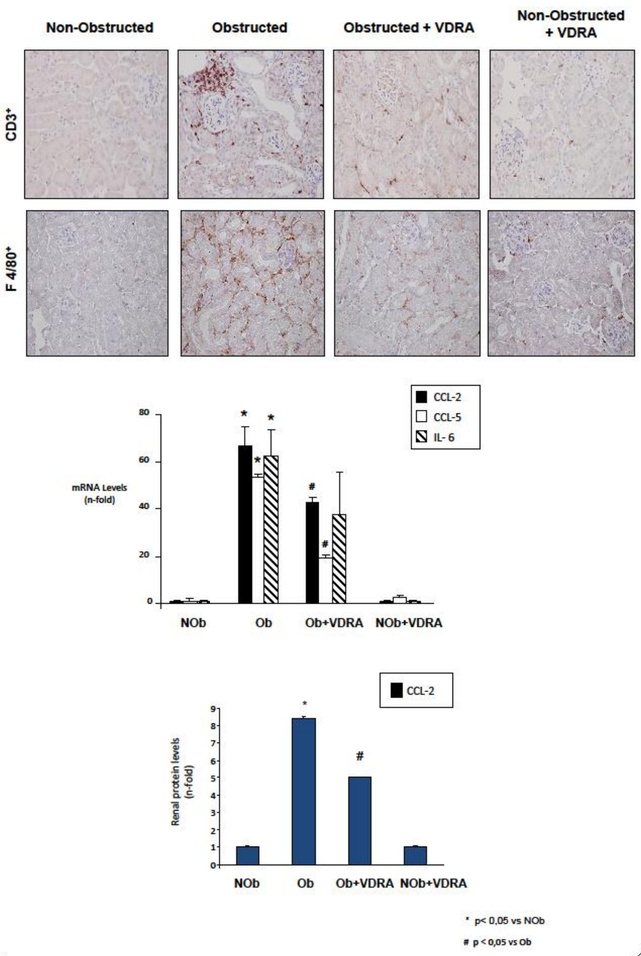




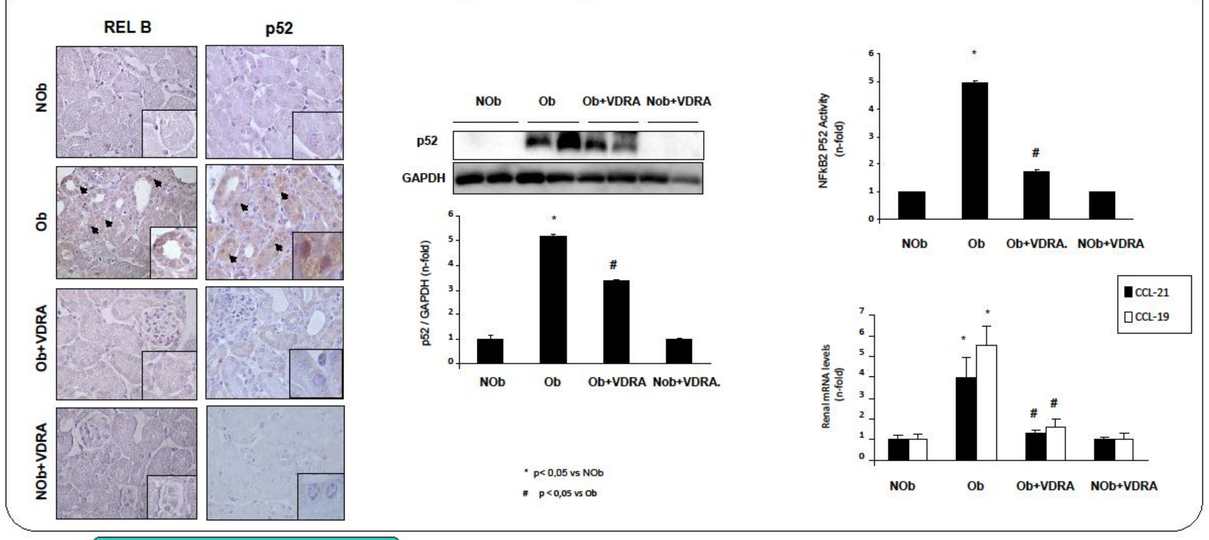
Paricalcitol inhibits the non canonical NF-κB2 activation induced by TWEAK *In vitro*



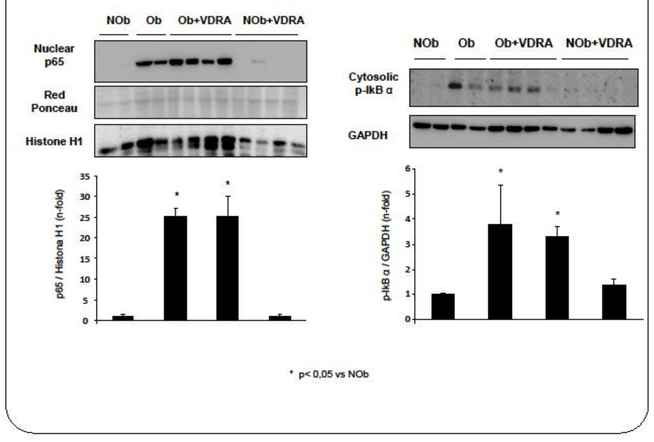
Paricalcitol regulates proinflammatory mediators in unilateral ureteral obstruction model



Paricalcitol inhibits NF-κB2-related cytokine expression in the unilateral ureteral obstruction model



Paricalcitol does not modulate the canonical NFκB1 pathway in the unilateral ureteral obstruction model



CONCLUSIONS

- In both experimental models (unilateral ureteral obstruction model and TWEAK-mediated kidney damage) treatment with the VDRA paricalcitol decreased renal inflammatory response, determined by diminishing renal inflammatory infiltration and the expression of proinflammatory genes (MCP-1, RANTES).
- In both experimental models (UUO and TWEAK-mediated kidney damage), VDRA treatment did not modify the activation of the canonical NF-κB1 pathway (assessed by changes in levels of α-IκB phosphorylation and nuclear translocation of p65). However, Paricalcitol inhibited the activation of non-canonical NF-κB2 pathway (characterized by the regulation of P100/p52, IKK-α or Rel B) and NF-κB2-related cytokines, such as CCL-19 and CCL-21.
- These results were confirmed in cultured tubuloepithelial cells pretreated with Paricalcitol and stimulated with TWEAK.

Our results show that the modulation of the non-canonical NF-κB2 pathway could be a novel mechanism involved in the antinflammatory effects of the VDRA Paricalcitol.

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