PARICALCITOL INHIBITED ALDOSTERONE-INDUCED PROINFLAMMATORY FACTORS BY MODULATING EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) PATHWAY IN CULTURED TUBULAR EPITHELIAL CELLS

Jose Luis Morgado Pascual[1], Sandra Rayego-Mateos[1], Carolina Lavoz[1], Matilde Alique[1], Jesús Egido[2], Alberto Ortiz [3] Marta Ruiz-Ortega[1].

1 Renal Research Laboratory, Universidad Autónoma de Madrid, Grupo Redinren; 2 Servicio de Nefrologia.3 Unidad Dialisis, IIS-Fundación Jiménez Díaz. Madrid, Spain.

INTRODUCTION

Chronic kidney disease is characterized by Vitamin D deficiency and activation of the Renin-Angiotensin-Aldosterone system. Increasing data show that Vitamin D receptor agonists (VDRAs) exert beneficial effects in renal disease and possess antinflammatory properties, but the underlying mechanism remains unknown. Emerging evidence suggest that "a disintegrin and metalloproteinase" (ADAM)/epidermal growth factor receptor (EGFR) signalling axis contributes to renal damage. Aldosterone (Aldo) induces EGFR "trans"-activation regulating several processes, including cell proliferation and fibrosis. However, data on tubular epithelial cells is scarce.

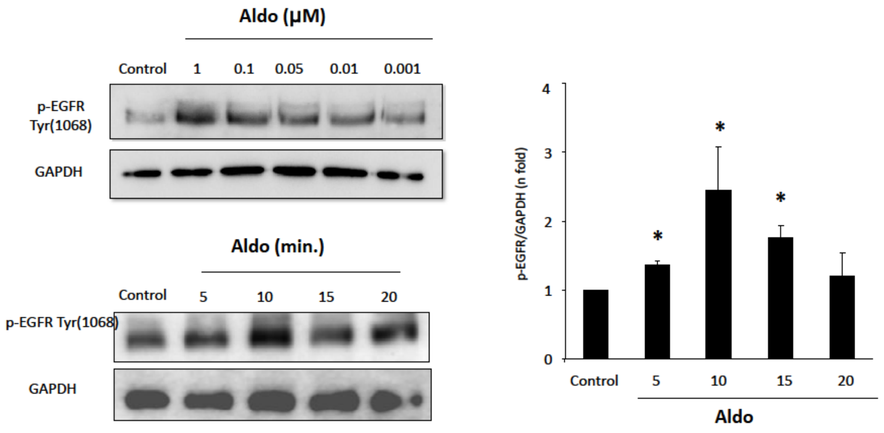
MATHERIAL AND METHODS

The experiments were performed on human and murine renal tubule epithelial cells (HK2 cell line and MCTs, respectively) analyzing the results using different techniques such as Western blot and RT-PCR.

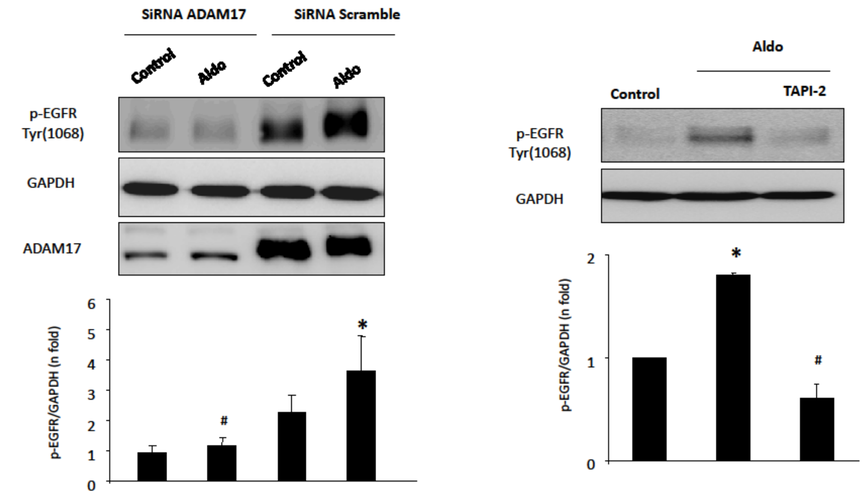
OBJETIVE

To investigate whether the anti-inflammatory effects of VDRAs are mediated by modulation of the EGFR pathway activated by factors involved in renal damage, as Aldosterone.

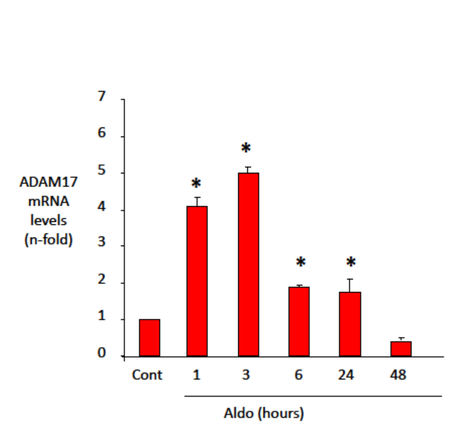
Aldosterone induces EGFR phosphorylation in cultured tubular epithelial cells



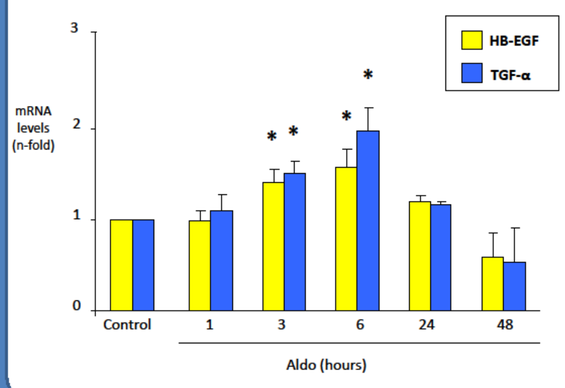
ADAM17 inhibition blocks Aldosterone-mediated EGFR activation in tubular epithelial cells



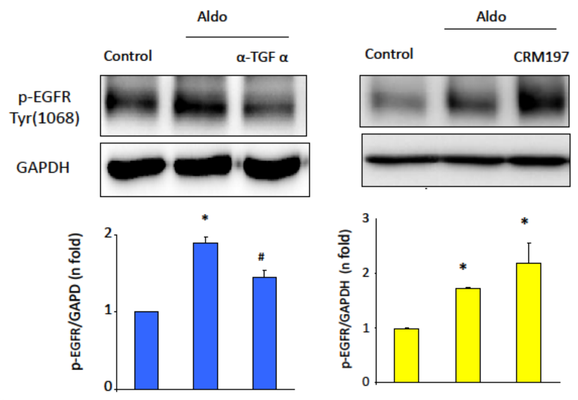
Aldosterone regulates ADAM17 gene expression



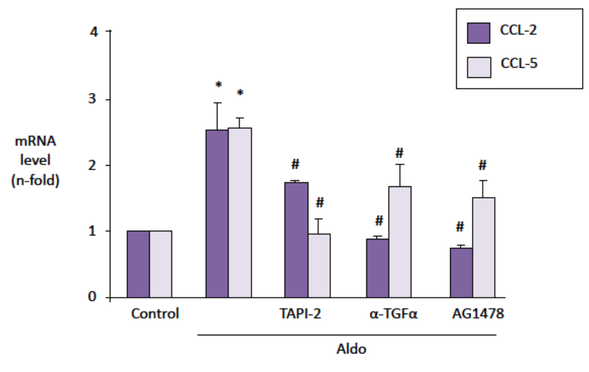
Aldosterone regulates TGF-α and HB-EGF gene expression



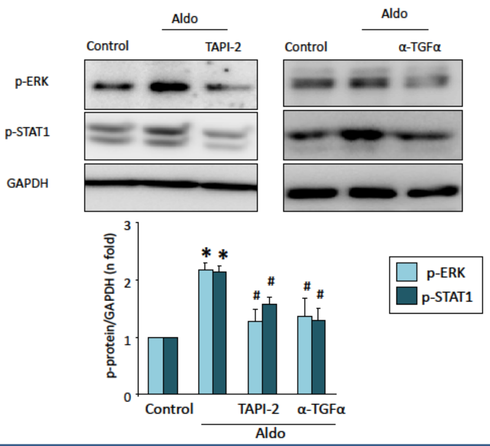
Aldosterone transactivates EGFR via TGFα, but not HB-EGF, shedding

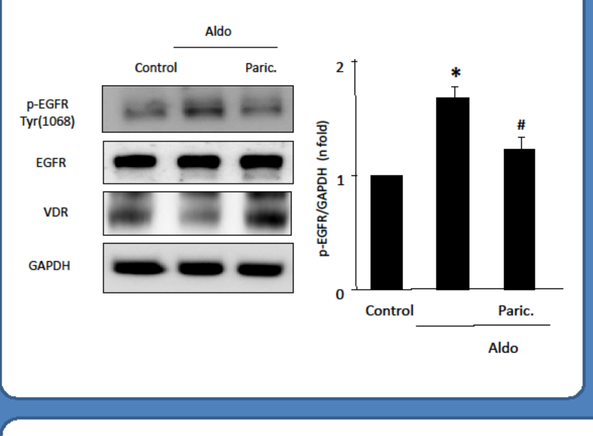


ADAM17/TGF-α/EGFR signaling blockade inhibits Aldo-mediated proinflammatory factors upregulation

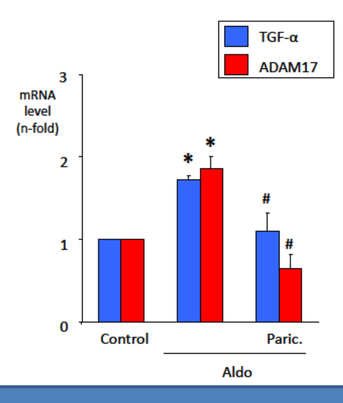


Aldo activates ERK and STAT via ADAM-17/TGF-α/EGFR axis

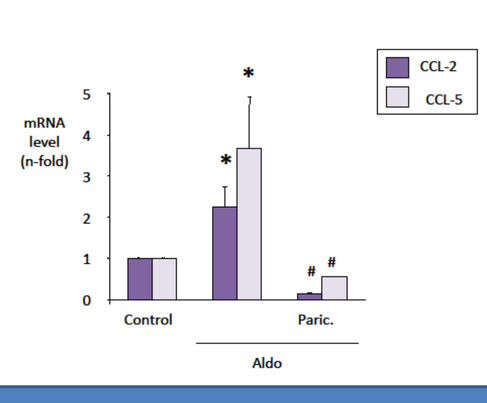


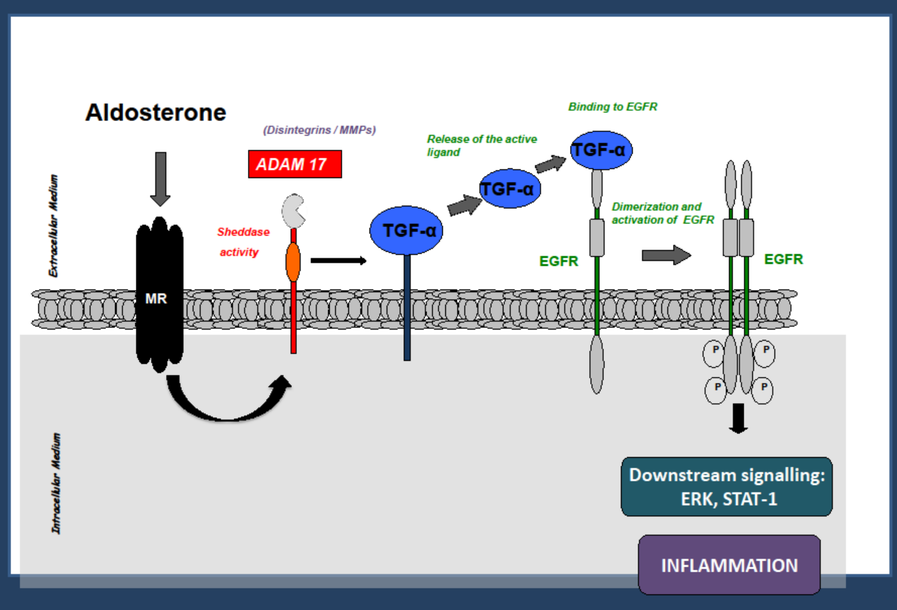


Paricalcitol inhibits gene overexpression of TGFα and HB-EGF

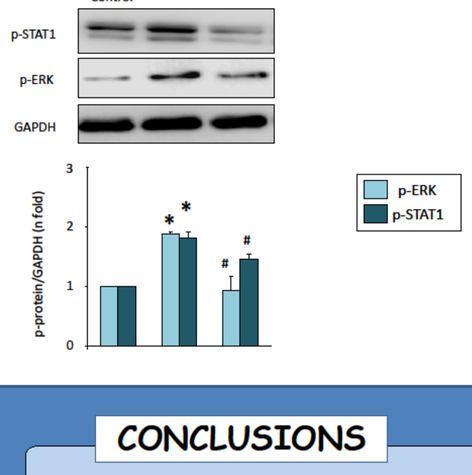


Paricalcitol inhibits Aldo-induced proinflammatory gene expression

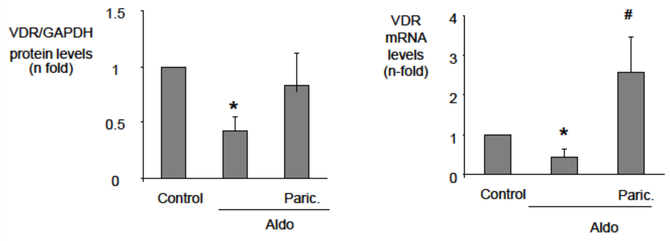


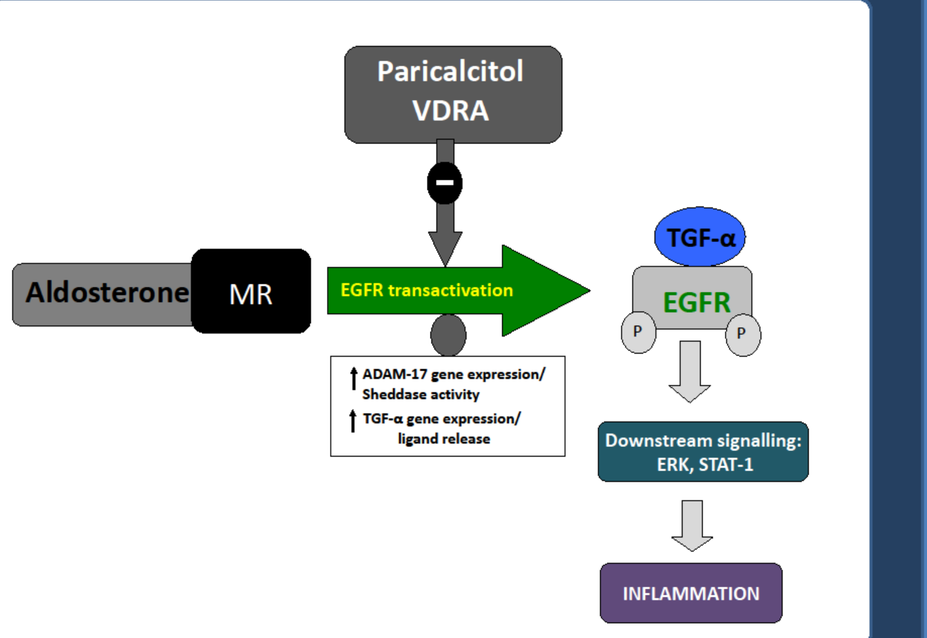


Paricalcitol inhibits Aldo-mediated activation of ERK and STAT-1 pathway



Paricalcitol restores Aldo-induced changes in VDR protein and gene expression levels





CONCLUSIONS

We now demonstrated here that in cultured tubular epithelial cells Aldosterone activates the EGFR pathway via ADAM-17/TGF-α shedding, leading to upregulation of proinflammatoy factors. Our data suggest that the antinflammatory actions of paricalcitol in tubular cells maybe mediated by the inhibition of TGF-α/ADAM17/EGFR signaling pathway.

Unión Europea Fondo Europeo de Desarrollo Regional "Una manera de hacer Europa"
GOBIERNO DE ESPAÑA MINISTERIO DE CIENCIA E INNOVACIÓN Instituto de Salud Carlos III
Red de Investigación Renal redinRen
Dirección General de Universidades e Investigación CONSEJERÍA DE EDUCACIÓN y EMPLEO Comunidad de Madrid
UAM UNIVERSIDAD AUTONOMA DE MADRID
IIS FJD
FIBROTEAM