The role played by intra-renal Mas receptors in mediating the excretory actions of either endogenous or exogenous Ang (1-7) during the activation of the RAS.

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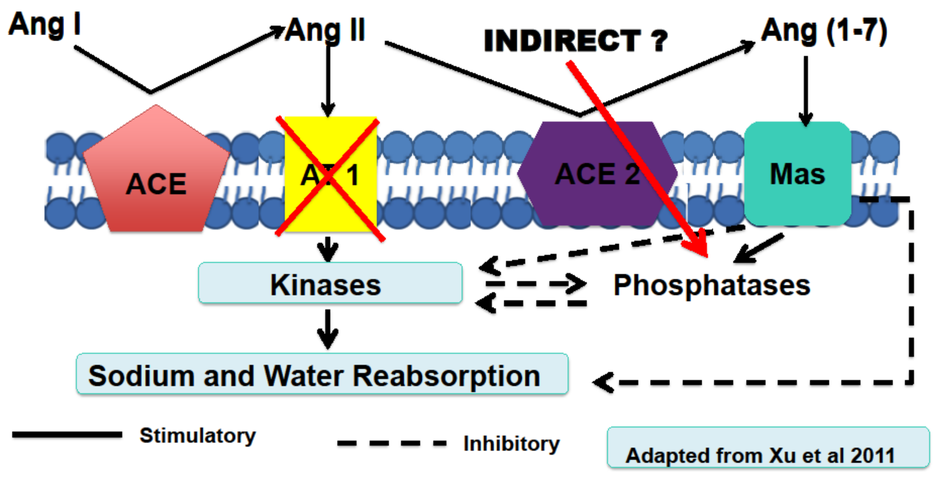
Introduction:

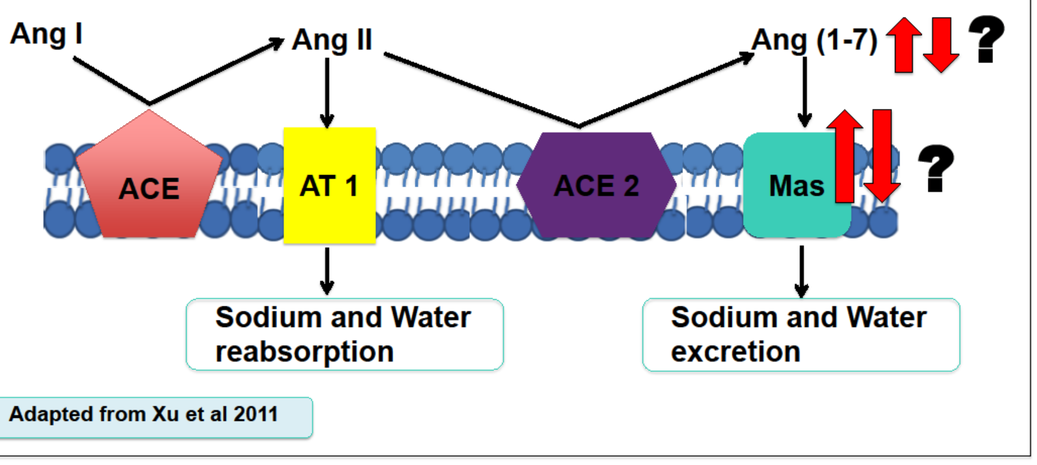
The diuretic and natriuretic responses to intra-renal (IR) Ang (1-7) infusion were enhanced when the RAS was activated by a low sodium diet and blunted when the RAS was suppressed by a high sodium diet and when IR AT1 receptors were antagonized by Losartan.



Aims and Objectives:

Is the altered responsiveness to IR Ang (1-7) infusion during dietary manipulation related to;

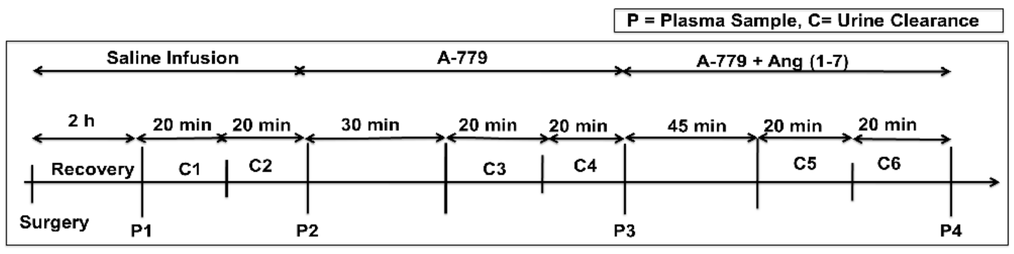
1. Changes in intra-renal Mas receptor activation?
   and/or
2. Changes in endogenous intra renal levels of Ang (1-7)?



Methods:

Functional studies:

-2x Normal sodium group (NNa^+) (0.3% Na^+), 2x Low sodium group (LNa^+) (0.03% Na^+)
-Each receiving either Ang (1-7) (50ng/min) alone or a combination of Ang (1-7) with A-779 (5µg/min)
-General Anesthesia: I.P. administration (1.2ml Chloralose Urethane).
-Mean Arterial Pressure (MAP): Right femoral artery cannula
-Saline and FITC Inulin infusion (3ml/h): Right femoral vein cannula.
-Left Kidney was exposed by a flank incision.
-Urine collection: Left ureter cannula.
-Infusion of Saline, Losartan or Ang (1-7) (1ml/h): Cortico- medullary cannula.



Tissue Preparation:

-Both Kidneys harvested from LNa^+ (low sodium diet) and NNa^+ (normal sodium diet) rats.
-Renal cortex dissected from renal medulla on ice and Protease Inhibitors were added.
-Renal cortex tissue homogenized in Tris (10mM;pH 7.4) Sucrose (25mM) buffer and centrifuged at 12000 rpm for 20 min at 4^0C.
-Protein concentration of the resultant supernatant determined using the BCA assay.

Ang (1-7) Peptide Quantification Protocol:

- Ang (1-7) ELISA kit purchased from, 'My biosource', San Diego, USA.

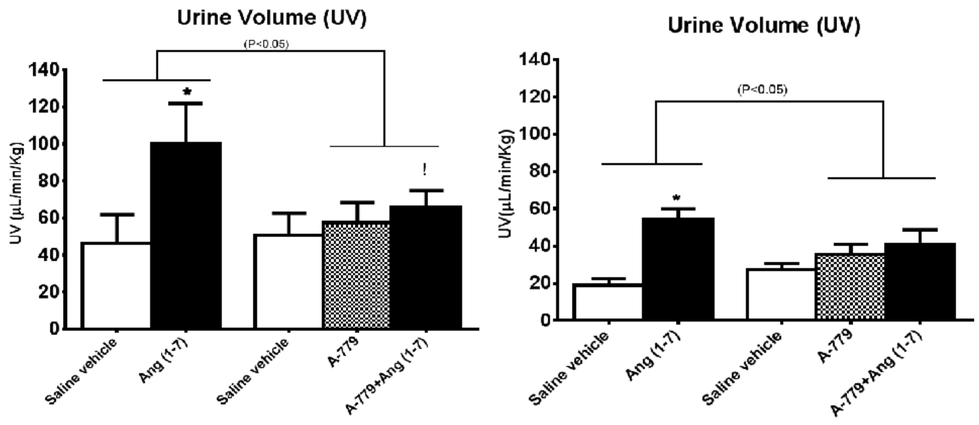
Results:

Table:

	MAP (Normal sodium diet)	GFR (Normal sodium diet)	MAP (Low sodium diet)	GFR (Low sodium diet)
Saline vehicle	93±4	3.1±0.7	91±2	2.6±0.2
Ang (1-7)	90±3	3.2±0.6	92±3	3.5±0.4*
Saline vehicle	98±4	3.7±0.5	88±7	3.1±0.5
A-779	94±3	4.4±0.5 #	86±7	3.6±0.6
A-779+ Ang (1-7)	92±4	4.4±0.5 !	84±5	3.3±0.5

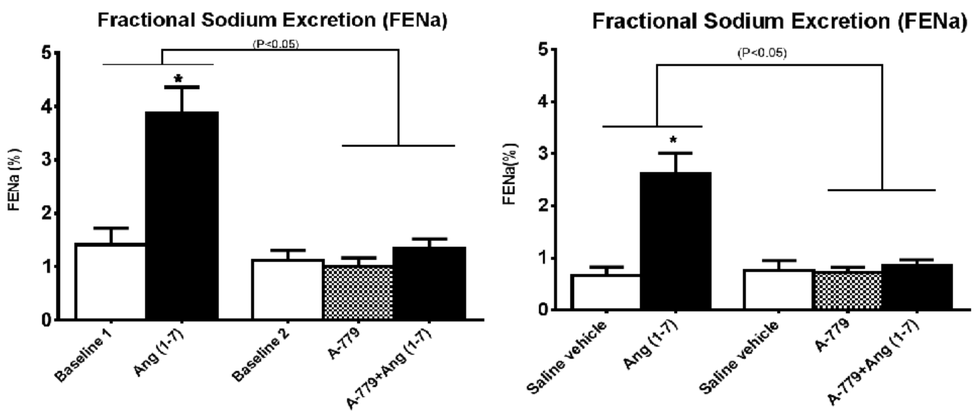
The effect of Ang (1-7), A-779 and Ang (1-7)+A-779 co- infusion on MAP and GFR in both NNa^+ And LNa+ rats.* = P<0.05 compare Ang (1-7) with vehicle. #= P<0.05 compares A-779 with vehicle. ! = P<0.05 compares A-779+ Ang (1-7) with vehicle

Figure 1:



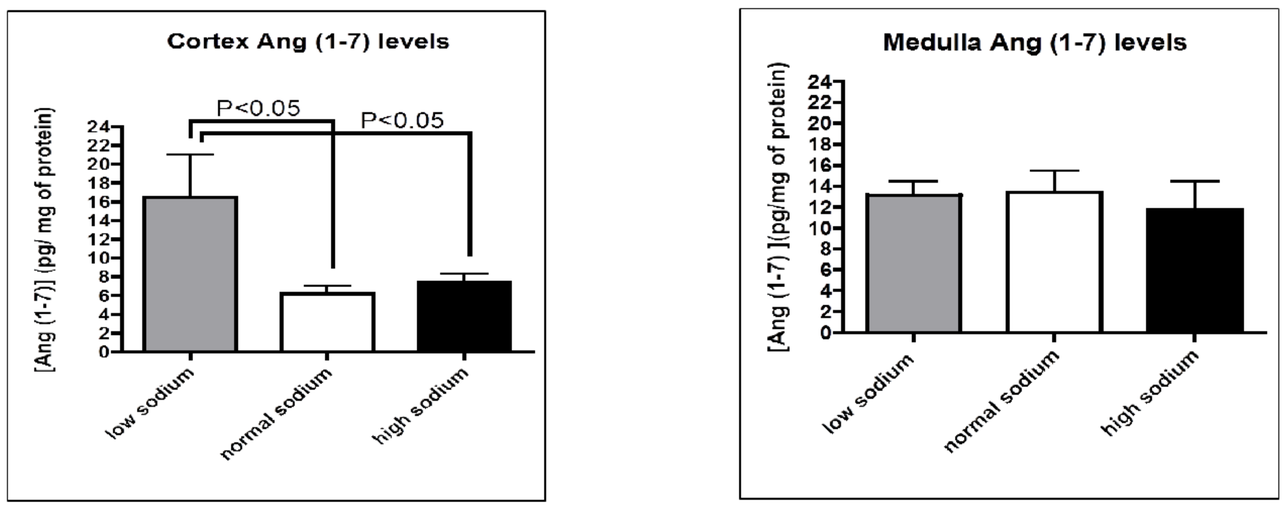
The effect of Ang (1-7), A-779 and Ang (1-7)+A-779 co- infusion on UV in both NNa^+ And LNa+ rats.* = P<0.05 compare Ang (1-7) with vehicle ! = P<0.05 compares A-779+ Ang (1-7) with vehicle

Figure 2:



The effect of Ang (1-7), A-779 and Ang (1-7)+A-779 co- infusionon MAP and GFR in both NNa^+ And LNa+ rats.* = P<0.05 compare Ang (1-7) with vehicle.

Figure 3:



Ang (1-7) levels in the renal cortex were 2 fold greater in LNa^+ rats relative to NNa+ and HNa^+ rats but did not differ between different dietary groups in the renal medulla.

Conclusions:

- Ang (1-7) induced increases in sodium and water excretion were significantly attenuated in the presence of A-779 indicating that the renal excretory actions of exogenous Ang (1-7) are mediated by IR Mas receptors in both dietary groups.
- Conversely, endogenous intra-renal Ang (1-7) does not have a basal inhibitory effect on the renal reabsorption of sodium and water even when the RAS is stimulated by a low sodium diet.
- Furthermore, cortical Ang (1-7) levels were significantly increased in the LNa^+ rats whereas Medullary Ang (1-7) levels did not vary between groups.
- These data indirectly suggest that cortical ACE2 activity and expression may be increased when the endogenous RAS is activated.
- Overall, elevated endogenous Ang (1-7) may act at the level of the renal cortex when the RAS is stimulated to counteract the proliferative and fibrotic effects of Ang II without impinging upon its ability to conserve sodium and water when there is a chronic reduction in dietary sodium.

References: Xu P. , Sriramula S. and Lazartigues E. (2011) ACE 2/ Ang (1-7)/ Mas pathway in the Brain; the axis of good *Am J Physiol Reg Integr Comp Physiol*. 300(4):R804-R817.

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