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Renal Mechanisms of Hypertension: Intrarenal

Chronic positive salt and water balance

- inability of kidneys to maintain appropriate salt excretion during excess salt intake
- chronic kidney diseases or reduced nephron number
- intrinsic inability to excrete salt efficiently due to over stimulation of reabsorptive mechanisms: gene mutations of transporters

Overactivation of intrarenal renin-angiotensin system
Hypertension Discovered During Routine Check

22 year old white male-presented with ankle injury

<table>
<thead>
<tr>
<th>Routine BP Check:</th>
<th>170/110 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>EKG:</td>
<td>Left ventricular hypertrophy; repolarization abnormalities</td>
</tr>
<tr>
<td>Echo:</td>
<td>Left ventricular hypertrophy</td>
</tr>
<tr>
<td>Blood:</td>
<td>Hemoglobin: 16.8g/dl 47.5</td>
</tr>
<tr>
<td></td>
<td>Hct: 136 mEq/l 47.5</td>
</tr>
<tr>
<td></td>
<td>Plasma Na: 3.0 mEq/l (normal: 3.6-5)</td>
</tr>
<tr>
<td></td>
<td>Plasma K: 1.1 mg/dl</td>
</tr>
<tr>
<td></td>
<td>Creatinine: 94 ml/min</td>
</tr>
<tr>
<td></td>
<td>eGFR: 25 ngAl/ml/hr (normal: .5-3.9)</td>
</tr>
<tr>
<td></td>
<td>Plasma Renin:</td>
</tr>
<tr>
<td></td>
<td>Plasma Aldosterone: 101 ng/dl (normal: &lt;7.2)</td>
</tr>
<tr>
<td>Ultrasound:</td>
<td>4 cm mass in interpolar cortex of left kidney</td>
</tr>
</tbody>
</table>

Enzymes in the Renin Angiotensin System

- Angiotensinogen
  - Renin
    - Prorenin/PR Receptor
    - Neprilysin
      - Prolylendopetidase
  - Neprilysin

- Angiotensin I
  - ACE
    - Ang 1-9
    - Cathepsin A & G
      - Chymase
      - Trypsin, Tonin
    - ACE 2
      - Ang 1-7
      - Neprilysin
  - ACE 2

- Angiotensin II
  - Chymase
  - Aminopeptidases A,N,B
    - Angiotensinase A, C
    - Dipeptidylaminopeptidase
    - Cathepsin
    - Carboxipeptidase
    - Leucylaminopeptidase
  - AT$_1$
  - AT$_2$

- Receptors

- Ang III or Ang (2-8)
- Ang IV or Ang (3-8)
Hypertension Due to a Renin Secreting Juxtaglomerular Cell Tumor

Patient treated with Amlodipine (blocks calcium channels in VSMC) – 10mg
Blood pressure controlled at 135/88

Renal vein renin:
- 20.3 ng Al/ml/hr – right renal vein
- 23.4 ng Al/ml hr – left renal vein

Plasma renin:
- 22.0 ng Al/ml/hr

Surgery:
- open left total nephrectomy
  histology confirmed juxtaglomerular cell tumor

Morning after surgery:
- BP 100/60 (without drugs)
- Plasma Creatinine 1.8 mg/dl
- BUN 28.8 ng/dl

Six Weeks:
- Plasma renin activity 2.3 ng Al/ml/hr
- Blood Pressure 104/61
- Hemoglobin 14.0 g/dl
- eGFR 68 ml/min

Angiotensin Dependent Mechanisms Activated by Unilateral Renal Arterial Stenosis

1. Intrarenal pressure
2. Renin
3. ANG II
4. Na reabsorption
5. Urinary Na excretion
6. Angiotensin
7. Aldosterone
8. Vasoconstriction
9. Arterial Pressure

Stenotic Kidney

Non Stenotic Kidney

Renin but Responsive to Angiotensin Blockers
Plasma and Kidney ANG II Levels in Control and Hypertensive Rats

![Graph showing plasma and kidney ANG II levels in control and hypertensive rats. The graph compares plasma levels and kidney levels with and without clipping and TGR (Ren2) infusion, along with the effects on angiotensin II levels over time.]
Angiotensin II Receptor Subtypes and Renal Actions

**Angiotensin II**

- ↑ Arterial Pressure
- ↑ Aldosterone Release → ↑ Na Reabsorption
- Afferent and Efferent Vasoconstriction
- Mesangial Cell Contraction
- ↑ Sensitivity of TGF Mechanism
- ↑ Na\(^+\)/H\(^+\) Exchanger Activity
- ↑ Proximal and Distal Reabsorption
- ↓ Renin Secretion
- ↑ ET, TxA\(_2\), Reactive Oxygen Species
- Activation of Cytokines and Growth Factors (ICAM1, MCP1, IL-6, TGFβ, PAI-1, NF-κB, VEGF, RhoKinase, PDGF, TNF-α)

**Subtype 1A Receptor**

**Subtype 1B Receptor**

**AT\(_2\) Type Receptor**

- Vasodilator Effect
- Inhibit Cell Proliferation
- Stimulate Bradykinin
- Tubular Reabsorption (?)
- Stimulate Nitric Oxide Synthase (endothelial)

- Pro-inflammatory and pro-fibrogenic in some cells, stimulates RANTES, NF-κB, VEGF, Ang 1, Ang 2
AT$_1$ Receptors on Afferent and Efferent Arterioles

- Afferent Arteriole:
  - AT$_{1A}$ & AT$_{1B}$

- Efferent Arteriole:
  - AT$_{1A}$ only
Angiotensin II Type 1 Receptor Immunohistochemical Localization in the Rat Kidney Cortex

AT_1 Receptors in Kidney Tubules in Cortex and Medulla

Essential Role of $\text{AT}_{1\text{A}}$ Receptor in the Development of 2K1C Hypertension

Luděk Červenka, Vladislav Horáček, Ivana Vaněčková, Jaroslav A. Hubáček, Michael I. Oliverio, Thomas M. Coffman, L. Gabriel Navar

Hypertension 40:735-741, 2002
Tubular and Interstitial Formation, Secretion and Uptake of Angiotensin I

\[ \text{ANG I} \approx 4-8 \text{ pmol/ml} \]

\[ \text{ANG II} \approx 6-10 \text{ pmol/ml} \]

\[ \text{ANG I} \approx 0.4 \text{ pmol/ml} \]

\[ \text{ANG II} \approx 0.2 \text{ pmol/ml} \]

\[ \text{Ao} \approx 300 \text{ pmol/ml} \]

\(<10\%>\)
RIF Ang I and Ang II Concentrations

- Vehicle-infused
- ANG II-infused
- ANG II-infused + candesartan

*P<0.05 vs vehicle
†P<0.05 vs ANG II

Ang II Levels in Rat Kidney Light Endosomes: Effects of Chronic Ang II Infusion and Candesartan

Fluorescent Microscopy Images of Ang II-uptake by NRK-52E Cells

Shown in the figures are positive controls (cells treated only with fluorescent Ang II, GREEN). The nuclei were stained with DAPI (BLUE) and the cell membranes with WGA (RED).
Prominent proximal tubule (PT) localization; Distal tubule (DT) and afferent arteriole (AA) are negative for AGT
Angiotensinogen mRNA Responses to Chronic Ang II Infusions

Cortex AGT & Renin Expression Hypertension

Kobori et al, Hypertension 41:42, 2003
Ang II Mediated Augmentation of Intrarenal Angiotensin II

Ang II Infusion → Circulating Ang II → ↑ AT1 Receptor Mediated Uptake of Ang II → ↑ Intrarenal Ang II levels

↑ AT1 Receptor Mediated Stimulation of Intrarenal AGT mRNA & Protein

Is this an intrarenal mechanism that can be elicited by increased intrarenal Ang II?
Temporal Profile of Systolic Blood Pressure

*, P<0.05 vs. Wild type mice; †, P<0.05 vs. 12 Wks of age.

Kobori et al. AJP Renal 293:F938, 2007
Selective Intrarenal Ang II Production from Human AGT Stimulates Mouse AGT mRNA and Protein in Double Transgenic Mice

Kobori et al. AJP Renal 293:F945, 2007
Intrarenal IL-6 and AGT expression in Ang II-infused mice

IL-6 expression in Ang II-treated macrophages (48 hr)

<table>
<thead>
<tr>
<th>Sham</th>
<th>Ang II-infusion</th>
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<tbody>
<tr>
<td><img src="image" alt="IL-6 Sham" /></td>
<td><img src="image" alt="IL-6 Ang II" /></td>
</tr>
<tr>
<td><img src="image" alt="AGT Sham" /></td>
<td><img src="image" alt="AGT Ang II" /></td>
</tr>
</tbody>
</table>

400 ng/kg/min for 2 weeks

IL-6 mRNA

<table>
<thead>
<tr>
<th>Control</th>
<th>Ang II</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="IL-6/GAPDH Control" /></td>
<td><img src="image" alt="IL-6/GAPDH Ang II" /></td>
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Co-factor (IL-6) Augments Ang II-induced NF-κB and AGT Stimulation in Human Proximal Tubular Cells

**NF-κB activation (EMSA)**

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<tr>
<th>Control</th>
<th>+</th>
<th>-</th>
<th>+</th>
<th>Ang II</th>
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**AGT expression**

<table>
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<tr>
<th>Control</th>
<th>+</th>
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<th>Ang II</th>
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(Satou R. et al. 2008 Am J Physiol Renal Physiol)
Effect of AT₁R Blockade on Urinary Excretion Rates of Ile⁵-Ang II in Val⁵-Ang II Infused Rats

*\( p < 0.05 \), **\( p < 0.01 \) vs. Val⁵-Ang II infused rats + candesartan.

# \( p < 0.01 \) vs. Val⁵-Ang II infused rats at day -1.

Shao et al, Hypertension 56:378-383, 2010
Chronic Ang I Infusions in Mice with ACE Expression only in the Kidneys is Sufficient to Cause Hypertension

Ang II-induced Hypertension in Mice Lacking Kidney ACE

Recordings made by telemetry
Δ WT = 40, Δ No Kidney ACE = 19

Urinary Excretion of Angiotensinogen

Pre-treatment (Day -7)

Post-treatment (Day 13)

Western Blot for Angiotensinogen

Kobori et al, KI 61:579, 2002
AT_{1}R-mediated Enhancement of Kidney and Urinary Angiotensinogen (AGT) in Hypertension

Representative Western blot of urinary AGT

Urinary AGT excretion rate is about 5-fold higher in Ang II-infused rats

1. We developed sensitive and specific quantification systems for human, rat and mouse AGT using sandwich ELISA.

2. The development of AGT ELISA could be a useful tool to investigate the role of intrarenal AGT in hypertension and kidney diseases in human subjects.
Urinary AGT in Experimental Models of Hypertension and Diabetes

**Rat**

- Ang II infusion: 18000% (Kobori, 2003)
- Ang II + High Salt (Male): 14460% (Kobori, 2003)
- Ang II + High Salt (Female): 2770% (Lara, 2011)
- DOCA: 1330% (Rands, 2012)
- SHR + High Salt: 5280% (Kobori, 2003)
- Dahl + High Salt: 413% (Susic, 2011)
- Cyp1a1-Ren2: 2190% (Mirani, 2010)
- STZ: 319% (Kamiyama, 2012)
- Akita T1DM/Hypertension: 550% (Chao-Sheng, 2012)

**Mouse**

- Control (100%)

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*Denotes significant increase compared to control.
Augmentation of Renal Fibrosis in Ang II-infused Rats Fed a High Salt Diet

Lara et al., AJP Renal, 2011
Urinary AGT in Hypertensive Patients

Kobori et al, Hypertension, 2009

*; P < 0.05 vs. Normotensive
†; P < 0.05 vs. HTN - RASB
Urinary AGT in Clinical Studies of Hypertension, Diabetes and Kidney Disease

- Hypertension: Kobori 2008 (182%)
- CKD: Mills 2012 (598%)
- Chronic GN: Urushihara 2010 (318%)
- Type 1 Diabetes: Saito 2009 (280%)
- Type 2 Diabetes: Kim 2012 (733%)
- IgA Nephropathy: Nishiyama 2011 (390%)
- Renal AA amyloidosis: Kutlugün 2012 (430%)
Hypothesis of Distal Spillover for Secreted Proximal Tubule Angiotensinogen (AGT)
Renin is primarily produced by JG cells, however renin-expressing cells have been found outside of JGA in human, mouse, and rat kidneys.

Renin immunoreactivity, mRNA and protein have been shown in PT, connecting tubules (CNT), and in collecting ducts (CD).
Immunofluorescence Labeling of ACE-1 in Collecting Ducts

Collecting Duct Renin Immunoreactivity in Ang II Rats Treated with Olmesartan

Prieto-Carrasquero, MC et al. AJP Renal 289:F632, 2005
Effects of ACE Inhibition during Ang II-dependent Hypertension in Mice

Gonzalez-Villalobos et al, AJP Renal 298:F150-F157, 2010
JG and CD Renin Responses in 2K1C Hypertension

Prieto-Carrasquero, MC et al.
Hypertension 51:1590-1596, 2008
Prorenin Receptor (P)RR

- Cloned by G. Nguyen et al. in 2002
- Expressed in mesangial cells, podocytes, and distal tubules
- Binds renin and prorenin
- Exerts a non-proteolytic activation of prorenin
- Elicits intracellular signaling activation via MAPKs

Nguyen G. et al., Curr Opin Nephrol Hypertens, 16(2) 2007:129–133
(P)RR Localization in the Apical Side of Intercalated Type A Cells

Anti-(P)RR @ 1:400 dilution (DAB, brown); anti AE1 @ 1:500 dilution (Bejoran purple)

Courtesy of Minolfa Prieto
The s(P)RR is Augmented in Renal Medulla and Urine of Ang II-hypertensive Rats

Gonzalez AA et al., Hypertension 2011
Urinary Ang II concentrations and urinary Ang II excretion rates were significantly higher in chronic Ang II infused mice.

Zhao, et al., Hypertension 54:120-126, 2009
Chronic Ang II-infused group had a higher distal sodium reabsorption value.

**DSR=** DSD (Period 3)-Sodium Excretion (Period 1+2)

Zhao, et al., Hypertension 54:120-126, 2009
In Ang II dependent hypertension, the kidney maintains *de novo* intrarenal Ang II formation due to enhancement of CD renin acting on increased AGT spillover.

Renin/Prorenin and PRR Interaction in CD Ang II Formation

Take-Away Message

In angiotensin dependent hypertension, the intratubular renin-angiotensin system is activated leading to stimulation of sodium reabsorption and progressive development of hypertension. Thus, therapeutic measures which block the intratubular system may have greater efficacy in reducing blood pressure. Measurement of urinary angiotensinogen provides an index of efficacy of blockade.
L. Gabriel Navar, Ph.D.
Plasma and Kidney Ang I and Ang II Levels During High and Low Salt Diets

Reciprocal Changes in Kidney Medullary Levels of Ang II/ACE and Ang1-7/ACE2 in 2K1C Rats

Prieto, MC et al. AJP Renal 300:F749, 2009
Chronic Low Salt Diet Does Not Activate Intratubular AGT
We show here that angiotensin II causes hypertension primarily through effects on AT1 receptor in the kidney. We find that renal AT1 receptors are absolutely required for the development of angiotensin II-dependent hypertension and cardiac hypertrophy.

Our finding suggest that AT1 receptors expressed in the kidney are the primary determinants of hypertension and end-organ damage in Ang II-dependent hypertension.
**Effects of Chronic Angiotensin I Infusions in Mice with ACE Expression only in the Kidneys**

*Intrarenal Ang II levels*

![Graph showing Intrarenal Ang II levels for Wild-type mice and ACE 9/9 mice.](image)

- **Wild-type mice**
  - Controls: ~800 fmol/g KW
  - Ang I-infused: ~1100 fmol/g KW

- **ACE 9/9 mice**
  - Controls: ~600 fmol/g KW
  - Ang I-infused: ~1100 fmol/g KW

*Gonzalez-Villalobos, et al. JCI 2013 (In Press)*
Effects of Chronic Angiotensin I Infusions in Mice with ACE Expression only in the Kidneys

24h-Urinary Ang II levels

Wild-Type mice

ACE 9/9 mice

Plasma and Kidney Ang II

Plasma Ang II, fmol/ml

120

90

60

30

0

W
A
D

Kidney Ang II, fmol/g

260

195

130

65

0

W
A
D

*, P<0.05 vs. Wild type mice

Kobori et al. AJP Renal 293:F938, 2007
Mouse AGT mRNA in Kidney and Liver

Kidney Mouse AGT mRNA, Ratio

Liver Mouse AGT mRNA, Ratio

*, P<0.05 vs. Wild type mice

Kobori et al. AJP Renal 293:F938, 2007
Increases in Urinary AGT in Experimental Models and Clinical Studies

- Ang II-infused rats
- DOCA-treated rats
- SHR + High salt diet
- Dahl + High salt diet
- Cyp1a1-Ren2 rats
- ZDF-treated rats
- db/db mouse
- Hypertension
- CKD
- Type 1 Diabetes
- Type 2 Diabetes
- IgA Nephropathy
- Renal AA amyloidosis

Animal study
Clinical study

Control (100 %)
Enhanced Interstitial Fibrosis in Ang II Infused Rats Fed a HS Diet

Lara et al., AJP Renal, 2011
<table>
<thead>
<tr>
<th>Region</th>
<th>Green</th>
<th>Red</th>
<th>Merged</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>AGT mRNA</td>
<td>Segment-specific marker</td>
<td>Co-localization</td>
</tr>
<tr>
<td>S2</td>
<td>AGT protein</td>
<td>Segment-specific marker</td>
<td>Co-localization</td>
</tr>
<tr>
<td>S3</td>
<td>AGT mRNA</td>
<td>Segment-specific marker</td>
<td>Co-localization</td>
</tr>
</tbody>
</table>

**Expression of AGT mRNA and Protein in Normal Rat Kidney**

Masumi Kamiyama, Hiroyuki Kobori, 2012
Kobori et al, Hypertension 41:42, 2003
Proximal Tubular Ang II Concentrations in Control and Hypertensive Rats

Ang II Concentration

pmol/ml

Control JASN 5:1153, 1994
Goldblatt Non-clipped Htn 33:102, 1999
TGR Ren2 AJP:Renal 42:F246, 1997
Role of Internalized Ang II in Proximal Tubule Cells

Extracellular Angiotensin II

- AT$_{1a}$R
- Extracellular Angiotensin II
- AT$_{1a}$R

Cytoplasm

- PLC
- PKC
- Ca$^{2+}$
- Ang II/AT$_{1a}$R

Nucleus

- NFkB?
- mRNA
- NHE3 Expression
- Clathrin/AP-2
- Alternative signaling?
- Angiotensinogen

Classic signaling

Li et al, AJP Renal 291:F375, 2006
Regulation of AGT Expression in Renal Proximal Tubular Cells

Ang II

TNF-α

IL-6

Proximal Tubular Cell

AT₁ receptor

IL-6 receptor

JAK2

NF-κB

p50/p50

p50/p65

STAT3

AGT

Nucleus
Renal Angiotensinogen mRNA on High Salt Diet

Renal Ao mRNA, Ratio to GAPDH mRNA

M: DNA Size Marker
A: H/S+AngII
S: H/S+Sham

Kobori et al, Hypertension 371:1329, 2001
Urinary AGT in Experimental Models of Hypertension and Diabetes

**Rat**
- Ang II infusion
- Ang II + High Salt (Male)
- Ang II + High Salt (Female)
- DOCA
- SHR + High Salt
- Dahl + High Salt
- Cyp1a1-Ren2
- STZ
- Akita T1DM/HTN
- db/db

**Mouse**
- Control (100%)

Sources:
- Kobori 2003
- Rands 2012
- Kobori 2003
- Kobori 2003
- Susic 2011
- Mirani 2010
- Kamiyama 2012
- Chao-Sheng 2012
- Harrison-Bernard Unpublished
Ang II-induced Hypertension in Mice Lacking Kidney ACE

Recordings made by telemetry, Δ WT = 40, Δ No Kidney ACE = 19

Ang II-induced Hypertension in Mice Lacking Kidney ACE

Intrarenal Ang II levels

The Kidney Renin-Angiotensin System in Pathophysiology of Hypertension

L. Gabriel Navar, Ph.D.

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Hypertension and Renal Center of Excellence
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New Orleans, Louisiana
Possibility that Angiotensin Resulting from Unilateral Kidney Disease Affects Contralateral Renal Function

J.C. Fourcade, L.G. Navar, and A.C. Guyton

Department of Physiology and Biophysics,
University of Mississippi School of Medicine, Jackson, MS

...angiotensin formed as a result of unilateral kidney disease will not produce chronic hypertension unless there is also a sodium and fluid retaining effect on the otherwise normal contralateral kidney.

Summary. Evidence from previous theoretical and experimental studies has indicated that

Therefore, the present experiments were conducted in dogs to determine whether or not blood angiotensin concentrations similar to those found in patients with unilateral kidney disease can cause significant water and salt retention by a normal dog kidney. Angiotensin was perfused directly into the renal artery of a semi-isolated perfused kidney preparation, and the effects on renal blood flow, glomerular filtration rate, degree of autoregulation of both renal blood flow and glomerular filtration rate, and rates of excretion of electrolytes and water were all determined at perfusion pressures between 75 and 200 mm Hg. The results showed that angiotensin in reasonably low dosages can cause the normal dog kidney to retain water and salt, but from a quantitative point of view it remains doubtful whether or not enough angiotensin is formed in patients with unilateral kidney disease to produce a similar effect. Studies on the various parameters of kidney function gave an insight into the mechanism of water and salt retention during angiotensin infusion and also explained why angiotensin infusion sometimes causes diuresis rather than anti-diuresis.

Nephron 8:1-16, 1971
AGT expression levels in mouse proximal tubular cells (mPTC) and mesangial cells

Mouse PTC (provided by Dr. Hopfer)

Mesangial cells (MC)

AGT mRNA

AGT protein (cell lysates)

Satou, et al. Unpublished
Effects of Ang II and IL-6 on AGT expression in mPTC

**AGT mRNA**

<table>
<thead>
<tr>
<th></th>
<th>Wild-type mPTC</th>
<th>AT1R dysfunctional mPTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Ang II</td>
<td>1.10</td>
<td>1.00</td>
</tr>
<tr>
<td>IL-6</td>
<td>1.10</td>
<td>1.00</td>
</tr>
<tr>
<td>Ang II + IL-6</td>
<td>1.75*</td>
<td>1.25</td>
</tr>
</tbody>
</table>

Ang II: 100 nM   IL-6: 10 ng/ml   24 hr-treatment   (N = 4)
NF-κB activation (IκB degradation) by Ang II and IL-6 in mPTC

Effect of NF-κB inhibition on the AGT augmentation in mPTC

Satou, et al. Unpublished
AGT expression levels in S2

AGT expression levels in S1, S2 and S3

AGT mRNA

AGT/GAPDH (ratio to control)

N = 4, Mean +/- SE, *P<0.05 vs. Control
Effects of Ang II and IL-6 on AGT expression in mPTC

Satou, et al. Unpublished
Prorenin Responses to Ang II, Ang II + Calphostin C, and PMA Treatments in IMCD Cells

Adapted from Gonzalez et al., 2011
PKA Inhibition with H89 or PKI Prevents Increases of Renin mRNA and Protein Levels by Ang II Treatment

Ang II: 10^-7 M, H89: 10^-6 M, PKI: 10^-6 M, H89, PKI: PKA inhibitor

N=6   * P<0.05 vs. Vehicle, # P<0.05 vs. Ang II

*Liu et al. Manuscript in preparation*
PKC Stimulates cAMP Pathway and Renin Elicited by Ang II in M1 Cells

AT1R → PKC → Yes!

AT1R activates PKC, which then activates cAMP. cAMP activates PKA, which activates CREB, leading to an increase in renin production.
Colleagues, postdoctoral fellows and students who have participated in evaluating the role of the Intrarenal Renin-Angiotensin System in Pathophysiology of Hypertension

Minolfa Prieto, MD, PhD
Alexis Gonzalez, PhD, Weijian Shao, PhD
Romer Gonzalez-Villalobos, PhD*, Ryo Sato, PhD
Hiroyuki Kobori, MD, PhD, Kenneth Mitchell, PhD, Dale Seth, MS

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Tulane University School of Medicine
New Orleans, Louisiana

*Department of Biomedical Sciences, Cedars-Sinai Medical Center Los Angeles, CA
Angiotensin II Induced Hypertension

- Intrarenal pressure decrease
- Renin increase
- ANG II increase
- Na reabsorption increase
- Urinary Na excretion decrease

- Renin decrease
- Angiotensin increase
- Aldosterone increase
- Vasoconstriction increase
- Arterial Pressure increase

- ANG II infusion

- Renin decrease
- ANG II increase
- AGT increase
- ACE increase
Ang II Dependent Mechanisms and Renal Injury in 2K1C GHR

Stenotic Kidney
- Minimal injury
- No proliferation

Non Stenotic Kidney
- Arteriolar hypertrophy
- Mesangial expansion
- Fibrosis
- Vascular injury
- Proliferation

- Renin
- Angiotensin II
- Aldosterone
- Peripheral Resistance
- Sympathetic Tone
- Arterial Pressure

- Renin mRNA
- Urinary Na excretion
- Na reabsorption

- Intrarenal pressure
Model of the Endogenous Secretion of Ang II

Zhuo and Boron. Role of endogenously secreted Ang II in the CO2-induced stimulation of HCO3 reabsorption by renal proximal tubules. AJP Renal 294:F245, 2008
What is the Source of Kidney Ang II?

- AGT mRNA is strongly expressed in S3 segment and weakly expressed in S2 segment in normal rats. In addition, no expression was observed in S1 segment. In contrast, AGT protein is detected mainly S1 segment (Pohl, et al. JBC. 2010, Kamiyama et al. J Hypertens. 2012).

- The part of circulating AGT spill over into the kidney, which contributes to kidney Ang II production under normal condition (Matsusaka, et al. JASN. 2012).

Renin and PRR Interaction in the Collecting Duct