Low dietary sodium and exogenous angiotensin II infusion decrease plasma adiponectin concentrations in healthy men


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Adiponectin

- Adipocyte
- Adiponectin

- Effect on glucose metabolism
- Effect on lipid metabolism
- Anti-inflammatory action
- Anti-atherogenic action

Adiponectin

- Plasma adiponectin concentration
- Insulin resistance
- Obesity

Risk for development of
- Type 2 D.M
- Hypertension
- Myocardial infarction

Adiponectin

Factors affecting plasma adiponectin level

- Renal clearance (clearance ↓ → ↑ plasma adiponectin)
- Activation of PPARγ adiponectin
- Adipocyte differentiation
- Increases small adipocytes
- Insulin sensitivity

Renin-angiotensin-aldosterone system (RAAS)

angiotensinogen
renin
Angiotensin I
ACE
Angiotensin II

aldosterone↑
Na+ reabsorption↑
Filtration coefficient↓
vasoconstriction
Thirst center
Blood pressure↑

ACE = angiotensin converting enzyme
RAAS may regulate plasma adiponectin in human

Renin-angiotensin-aldosterone system (RAAS)

Patients with - DM - Hypertension

Plasma adiponectin ↑

In rats

Plasma adiponectin ↓

Objective

To investigate the role of RAAS in regulation of adiponectin in humans

By physiological and pharmacological modulations of the RAAS

Shift in dietary Na⁺ intake

• Exogenous Ang II infusion
• ACE inhibitor during high Na⁺

Materials & Methods

Subjects

35 healthy men : 26 ± 9 years

Inclusion criteria

• Normotensive
  - SBP < 140 mmHg
  - DBP < 80 mmHg
• Normal routine physical examination

Exclusion criteria

• Abnormalities during routine physical examination
  - BMI > 30 kg/m²
  - Diabetes mellitus
  - Drug use

Approved by the Ethics Committee of the University Medical Center Groningen

Study protocol

1) Low Na⁺ diet (50 mmol/day)
2) High Na⁺ diet (200 mmol/day)
3) High Na⁺ diet (200 mmol/day) + ACEi

Each intervention : 7 days

✓ Personal food habits
✓ Isocaloric with similar balance between protein, carbohydrate, fat
Study protocol

1) Low Na⁺ diet (50 mmol/d)
2) High Na⁺ diet (200 mmol/d)

UNa24

For assess dietary compliance achievement of a stable Na⁺ balance

Glomerular filtration rate (GFR)

On day

Stabilization period

8.00 am 9.00 am 10.00 am 11.00 am

measure

- Weight
- Height
- Waist & Hip circumference

Insert intravenous canula into both forearms

Baseline GFR

Urine collection

Blood sample

Infuse solution

12 ml/h

Angiotensin II infusion

Record B.P

15-min interval

10.00 am 11.00 am 12.00 am 1.00 pm 2.00 pm 3.00 pm

Infuse Ang II

0.3 ng/kg/min 1 ng/kg/min 3 ng/kg/min

Blood samples

- 11 am for baseline value of adiponectin
- 12 am to 3 pm for PRA, Ang II, aldosterone, adiponectin, and leptin

ACE-inhibition

high Na⁺ + ACEi

Enalapril (ACEi) 20 mg : once daily

At the end of week
- Record blood pressure
- Collect blood sample for adiponectin assay

Blood sampling and analysis

Blood sample

serum

plasma

Glucose oxidase method

Insulin : RIA

Glucose

Aldosterone

Ang II

Renin activity

Adiponectin

Leptin

ng of Ang I produced per ml of plasma per hour

ELISA

HOMA-IR : Homeostasis model assessment for insulin resistance

= [glucose, mmol/l] x [insulin, μU/ml] / 22.5

Data analysis

- Mean ± SD : normal distribution
- Median and quartiles: non normal distribution
- Student paired t-test
- Wilcoxon signed rank test
- P value < 0.05
Results

Effects of altered sodium status

<table>
<thead>
<tr>
<th>BMI</th>
<th>22.5 kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference</td>
<td>81 cm.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low sodium</th>
<th>High sodium</th>
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</thead>
<tbody>
<tr>
<td>(U_{\text{Na}^+}) (mmol/24h)</td>
<td>40 ± 25</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>79.1 ± 9.4</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>85 ± 7</td>
</tr>
<tr>
<td>GFR (ml/min/1.73m²)</td>
<td>103 (99 -113)</td>
</tr>
</tbody>
</table>

* \(p<0.05\), t-test; # \(p<0.05\), Wilcoxon signed rank test

High sodium status suppressed RAAS

<table>
<thead>
<tr>
<th>Low sodium</th>
<th>High sodium</th>
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<tbody>
<tr>
<td>PRA (ng angI/ml/h)</td>
<td>5.9 (4.4-8.1)</td>
</tr>
<tr>
<td>Aldosterone (ng/L)</td>
<td>130 (81-174)</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>4.5 (4.1-4.9)</td>
</tr>
<tr>
<td>Insulin (μU/ml)</td>
<td>8.3 (6.1-13.5)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.7 (1.3-2.5)</td>
</tr>
</tbody>
</table>

PRA = plasma renin activity, * \(p<0.05\), t-test

High sodium status increased adiponectin

Ang II \(\uparrow\) MAP but \(\downarrow\) adiponectin

Ang II \(\uparrow\) MAP/ \(\uparrow\) adiponectin more on high Na*
### Discussion

**Plasma adiponectin**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Baseline</th>
<th>ACEi</th>
</tr>
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<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>88 ± 8</td>
<td>83 ± 8*</td>
</tr>
<tr>
<td>Plasma adiponectin (μg/L)</td>
<td>14.4</td>
<td>16.6*</td>
</tr>
</tbody>
</table>

**High Na+ and ACEi**

- **Exogenous Ang II**
  - **Plasma adiponectin**
    - **↑**
    - **↓**

**RAAS contributes to a relevant extent in plasma adiponectin regulation in humans via Ang II**

**Shift in Na+ intake within the physiological range**

- Modifier of RAAS activity mirrored the changes in plasma adiponectin.
- It seems unlikely that an effect on renal elimination contributed to changes in circulating adiponectin in response to modification of Na+ intake

**Influence of the RAAS on adiponectin is physiologically relevant**

**RAAS blockade increases adiponectin**

- Physiological blockade (HS intake) plus pharmacological blockade (ACEi) of RAAS increased plasma adiponectin concentration
- This has been shown in type 2 DM ([Furuhashi et al., 2003](#)) and hypertensive patients ([Hermann et al., 2006](#)) but not in healthy subjects
Exogenous Ang II suppress adiponectin

- Suppressor effect of Ang II on adiponectin was present during both LS and HS, even at the lowest dose (0.3 ng/kg/min)
- Plasma adiponectin was ~ half of the baseline concentration after 3 h of Ang II infusion in this study
- Half-life of adiponectin is 2.5 h (Hoffstedt et al., 2004)

These suggest that the release of adiponectin from adipocytes may be blocked by Ang II.

Stimulation of Ang II type I receptor blocks the release of adiponectin from adipose tissue

Ang II acts on Ang II type I receptor to inhibit adiponectin release

High Na+ potentiates pressor response to Ang II

- Parallel between the responses of B.P and adiponectin during Ang II infusion is shown in this study
- These responses were enhanced by HS (This study & Hollenberg et al., 1974)
- The mechanism is assumed to be an up-regulation of Ang II type I receptor by HS (Nickenig et al. 1998)

Interrelationship between Ang II, SNS - Adiponectin

Low sodium
Ang II infusion → Activity of SNS ↑
β-adrenergic Stimulation → Inhibits adiponectin gene expression
Central sympathetic blockade → Increases adiponectin concentration

LS / Ang II → SNS activity ↑ → ↓ adiponectin

SNS = Sympathetic nervous system

Implications of an effect of Ang II on circulating adiponectin

- Insulin sensitivity:
  - High Na+ → Adiponectin ↑ + unchanged insulin sensitivity
- Present study
  - High Na+ → Adiponectin ↑ + unchanged insulin sensitivity

Time span of high Na+ Magnitude of changes in sodium balance

MAP

Adiponectin

Low Sod
High Sod

Clasen et al. (2005)
Kurata et al. (2006)
Ran et al. (2006)
Clasen et al. (2005)
Kurata et al. (2006)
Ran et al. (2006)

High Na+ potentiates pressor response to Ang II.
Implications of an effect of AngII on circulating adiponectin

RAAS blockade  ➔ Adiponectin ↑

Therapeutic effects

When endogenous RAAS is low (during HS and volume excess)

Anti-inflammatory and vascular protective effect of adiponectin

RAAS blockade  ➔ Adiponectin ↑

Leptin response to Na⁺ intake and AngII

Present study

<table>
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<tr>
<th>High Na⁺ (Ang II ↓)</th>
<th>Leptin ↑</th>
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<td></td>
<td>Leptin ↓ ~ 15%</td>
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Previous study

- LS  ➔ ↓ leptin concentrations in hypertensive patients
  - Adamczak et al. (2002)
- In vitro studies showed that AngII increased leptin secretion
  - Shurk et al. (2005), Kim et al. (2002)
- Chronic infusion of AngII  ➔ ↓ leptin concentrations in rats
  - Cassis et al. (2004)

Conclusion

- Infusion of Ang II  ➔ ↓ plasma adiponectin in healthy men
- During physiological suppression of RAAS by high Na⁺  ➔ ↑ plasma adiponectin

RAAS

Adiponectin

Metabolic status

Thank You
Routine physical examination

Vital sign: BP, RR, HR, temp
Observation
Palpation
Percussion
Auscultation