Atrial natriuretic factor
Janssen, Wilbert Martien Theodoor

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
1994

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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CHAPTER 4

INVolvement of ATRIAL NATRIURETIC PePTIDE IN Long-TERM REGULATION OF SODIUM-HOMEOSTASIS IN MAN

Wilbert M T Janssen, Paul E de Jong, Gjalt K van der Hem, and Dick de Zeeuw

Clin Nephrol 30:172, 1988
Chapter 4

SUMMARY

To investigate whether atrial natriuretic factor (ANF) is involved in the long-term regulation of sodium homeostasis and blood pressure control we infused ANF in a low dose (0.2 µg/min) for 48-hours in two female patients with essential hypertension. Mean arterial pressure did not decrease, but tended to increase in both patients during ANF-infusion. No side-effects were observed, particularly no hypotensive periods occurred. In both patients ANF-infusion induced a sustained natriuresis. The cumulative sodium balance was 98 and 244 mmol negative after 2 days of ANF-infusion. These data suggest a physiological role for ANF in the long-term regulation of urinary sodium excretion. It can be hypothesized that an even longer infusion of ANF would (by its sustained natriuretic effect) eventually decrease blood pressure.
ANF and long-term sodium-homeostasis

INTRODUCTION

Atrial natriuretic factor (ANF) has been shown to have an acute natriuretic effect when administered in high (pharmacological) doses by bolus or short-term infusion. Unfortunately, these doses may induce a sudden episode of symptomatic hypotension after some time [1,2]. Only recently it has been shown that ANF has a natriuretic effect at physiological levels in man [3,4]. However, whether ANF is involved in the long-term regulation of sodium- and blood pressure homeostasis is yet unknown. We therefore studied the natriuretic and hypotensive effect of a low dose (0.2 µg/min), 48-hour infusion of ANF in man.

SUBJECTS AND METHODS

Two female patients with essential hypertension (age 52 and 61, diastolic blood pressure > 95 mmHg), who for at least two weeks before the study did not take any drugs and received a diet containing 200 mmol sodium daily, were admitted to hospital, where they held absolute bedrest until the end of the study. After an equilibration period of 3 days, the study was started at noon of the third day (day 1) with a 24 hour solvent infusion, followed by 48 hours of infusion with synthetic α-human ANF(101-126, MSD-RL, Rahway, New Jersey, USA) dissolved in 5 g mannitol/100 ml at a dose of 0.2 µg/min (days 2 and 3), and a one day recovery period with solvent infusion (day 4). During the whole study the patients received a rhythm diet consisting of six portions of equal amounts of sodium, potassium and fluid every 4 hours (total: 200 mmol, 80 mmol, and 2500 ml per day, respectively). Mean arterial pressure (MAP) was recorded every 5 minutes with an automatic non-invasive device (Dinamap®, Criticon Inc, Tampa, Florida, USA). Urine was collected every 4 hours by spontaneous voiding for measurement of sodium excretion. Plasma samples for measurement of immunoreactive ANF (irANF), plasma renin activity (PRA), and plasma aldosterone were taken at 4 PM, midnight, and at 8 AM. Sodium, PRA, and aldosterone were determined using standard techniques, irANF was measured as described previously [4].

RESULTS

ANF-infusion caused a 2-fold increase in irANF-levels (Table 1). MAP did not decrease, but tended to increase in both patients during ANF-infusion. No side-effects were observed, particularly no hypotensive periods occurred as has been reported previously during short-term (30 min to 6 hour) high dose (0.5 to 3.5 µg/min) ANF-infusions [1,2,5,6]. In both patients ANF-infusion induced a sustained natriuresis. Net sodium balance was -56 and -42 mmol on the first and the second day of ANF-infusion for patient 1, and -107 and -137 mmol for patient 2, resulting in a cumulative negative sodium balance of 98 and 244 mmol after 2 days of ANF-infusion. During recovery all values returned to baseline (Table 1).
CHAPTER 4

**TABLE 1.** Values of immunoreactive atrial natriuretic factor (irANF), mean arterial pressure (MAP), urinary volume (U_{vol}) and sodium excretion (U_{NaV}), plasma renin activity (PRA) and plasma aldosterone (Aldo) expressed as mean of the measurements during each study day.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patient</th>
<th>Control</th>
<th>ANF Day 1</th>
<th>ANF Day 2</th>
<th>ANF Day 3</th>
<th>ANF Day 4</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>irANF (pg/ml)</td>
<td>1</td>
<td>56</td>
<td>75</td>
<td>98</td>
<td>33</td>
<td></td>
<td>42</td>
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<td></td>
<td>2</td>
<td>54</td>
<td>131</td>
<td>93</td>
<td>42</td>
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<td>42</td>
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<tr>
<td>MAP (mmHg)</td>
<td>1</td>
<td>94.1</td>
<td>97.7</td>
<td>97.1</td>
<td>87.2</td>
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<td></td>
<td>2</td>
<td>102.3</td>
<td>104.0</td>
<td>107.0</td>
<td>99.8</td>
<td></td>
<td>99.8</td>
</tr>
<tr>
<td>U_{vol} (ml/24 h)</td>
<td>1</td>
<td>1750</td>
<td>2110</td>
<td>1900</td>
<td>1490</td>
<td></td>
<td>1490</td>
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<td></td>
<td>2</td>
<td>1215</td>
<td>1635</td>
<td>2120</td>
<td>1685</td>
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<tr>
<td>U_{NaV} (mmol/24 h)</td>
<td>1</td>
<td>182</td>
<td>238</td>
<td>224</td>
<td>129</td>
<td></td>
<td>129</td>
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<td></td>
<td>2</td>
<td>119</td>
<td>226</td>
<td>256</td>
<td>156</td>
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<td>156</td>
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<tr>
<td>PRA (nmol/l/h)</td>
<td>1</td>
<td>0.4</td>
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<tr>
<td></td>
<td>2</td>
<td>0.5</td>
<td>0.4</td>
<td>0.2</td>
<td>0.4</td>
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<td>0.4</td>
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<tr>
<td>Aldo (nmol/l)</td>
<td>1</td>
<td>0.07</td>
<td>0.11</td>
<td>0.11</td>
<td>0.38</td>
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<td>0.38</td>
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<tr>
<td></td>
<td>2</td>
<td>0.09</td>
<td>0.08</td>
<td>0.09</td>
<td>0.13</td>
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<td>0.13</td>
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</table>

**DISCUSSION**

To date there are no data available on the long-term (that is over more than 6 hours) effects of ANF on blood pressure and sodium excretion in man. Animal studies have shown a marked decrease in MAP already after 2 days of ANF-infusion. Sodium excretion did not change or even decreased during ANF-infusion, which was attributed to the decrease in MAP [7,8]. The results of the present study in man therefore are in contrast with those animal studies, since we found a sustained increase in sodium excretion, which in both patients was similar on both days of the ANF-infusion. During these days irANF-levels only increased 2-fold, thus staying within the physiological range [3], while PRA- and plasma aldosterone-levels did not change. Together, these results suggest a physiological role for ANF in the long-term regulation of urinary sodium excretion. It can be concluded from these data that a low dose 48-hour ANF-infusion causes firstly no symptomatic hypotension, and secondly a sustained natriuresis. It can be hypothesized that an even longer infusion of ANF might by its sustained natriuretic effect eventually decrease MAP. Further studies are needed to clarify the involvement of ANF in the long-term regulation of sodium-homeostasis and blood pressure in man.
ANF and long-term sodium-homeostasis

REFERENCES


