High salt intake increases copeptin but salt sensitivity is associated with fluid induced reduction of copeptin in women.

Tasevska, Irina; Enhörning, Sofia; Burri, Philippe; Melander, Olle

Published in:
International Journal of Hypertension

DOI:
10.1155/2014/641587

2014

Link to publication

Citation for published version (APA):

Total number of authors:
4

General rights
Unless other specific re-use rights are stated the following general rights apply:
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain.
• You may freely distribute the URL identifying the publication in the public portal.

Read more about Creative commons licenses: https://creativecommons.org/licenses/

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.
Research Article

High Salt Intake Increases Copeptin but Salt Sensitivity Is Associated with Fluid Induced Reduction of Copeptin in Women

Irina Tasevska,1,2 Sofia Enhörning,1,2 Philippe Burri,1,2 and Olle Melander1,2

1 Department of Internal Medicine, Skåne University Hospital, 20502 Malmö, Sweden
2 Department of Clinical Sciences, Lund University, 20502 Malmö, Sweden

Correspondence should be addressed to Irina Tasevska; tasevskairina@gmail.com

Received 8 September 2014; Accepted 8 October 2014; Published 23 October 2014

Academic Editor: Franco Veglio

Copyright © 2014 Irina Tasevska et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

This study investigated if copeptin is affected by high salt intake and whether any salt-induced changes in copeptin are related to the degree of salt sensitivity. The study was performed on 20 men and 19 women. In addition to meals containing 50 mmol NaCl daily, capsules containing 100 mmol NaCl and corresponding placebo capsules were administered during 4 weeks each, in random order. Measurements of 24h blood pressure, body weight, 24h urinary volume, and fasting plasma copeptin were performed at high and low salt consumption. Copeptin increased after a high compared to low dietary salt consumption in all subjects 3.59 ± 2.28 versus 3.12 ± 1.95 (P = 0.02). Copeptin correlated inversely with urinary volume, at both low (r = −0.42; P = 0.001) and high (r = −0.60; P < 0.001) salt consumption, as well as with the change in body weight (r = −0.53; P < 0.001). Systolic salt sensitivity was inversely correlated with salt-induced changes of copeptin, only in females (r = −0.58; P = 0.017). As suppression of copeptin on high versus low salt intake was associated with systolic salt sensitivity in women, our data suggest that high fluid intake and fluid retention may contribute to salt sensitivity.

1. Background

There is strong epidemiological support for a role of high salt intake in hypertension [1–5] and controlled interventions modulating salt intake have shown that high salt intake elevates blood pressure [6, 7]. The degree of blood pressure reduction following a lowering of salt intake (and the degree of blood pressure elevation following an increase of salt intake), that is, the degree of salt sensitivity, varies between individuals. The cause of the interindividual differences in salt sensitivity is unknown. In addition, it is unknown why salt elevates blood pressure. In particular, it is not known what role the increased water intake and water retention that commonly accompany a high salt intake have for salt-induced blood pressure elevation.

The two main stimulants of arginine vasopressin (AVP) secretion are hypovolemia and increased osmolarity. An increased salt intake is likely to lead to elevated AVP in order to retain water and thus sustain normal plasma osmolarity. At the same time, the expected increase in fluid intake and/or fluid retention following increased salt intake would be expected to lower AVP as a consequence of increased intravascular volume status and blood pressure. The net result of these two opposing effects of high salt intake on AVP is unclear. As we have previously found that high activity of the AVP system is related to components of the metabolic syndrome including both diabetes and hypertension [8–10] we here aimed to test whether a high salt intake would alter activity of the AVP system and, if that were the case, in which direction.

In addition, we hypothesized that the amount of water intake or water retention accompanying a standardized increase of salt intake may be reflected in changes of AVP secretion. If this were the case, the effect of water intake and/or retention on salt sensitivity could be estimated by measuring changes of AVP in plasma between low and high salt intake.

There are concerns regarding the reliability of AVP measurements in plasma, as AVP is an unstable molecule both in vivo and ex vivo, which requires complicated handling when
sampling the patients’ blood. Copeptin is a cleavage product of the C-terminal part of the AVP precursor hormone that is produced in equimolar amounts with AVP, a process similar to the generation of insulin and C-peptide. In contrast to AVP, copeptin is stable. Therefore, copeptin is found in considerably higher concentrations in plasma than in AVP and can be expected to be a more reliable marker of the true vasopressin release [11].

2. Methods

The study protocol has been described in detail previously [7]. Briefly, 46 unmedicated study subjects without history of hypertension, diabetes, or kidney disease were recruited via advertisements in local newspapers. Of these, 39 completed the study (20 men and 19 women). The mean age of the 39 subjects who completed the study was 53 ± 11 years and body mass index (BMI) was 26.3 ± 3.1. Clinical characteristics at baseline, low salt, and high salt are shown in Table I. Subjects were examined under baseline conditions (with subjects being on their habitual diets, i.e., on nonstandardized diet). Subjects were then given all meals and drinks containing 50 mmol of NaCl (3 grams) and 50 mmol potassium per day. All meals and drinks were provided by the Department of Clinical Chemistry, Malmö University Hospital. Copeptin was measured in plasma using a commercially available assay in the chemiluminescence/coated tube format (B.R.A.H.M.S AG, Hennigsdorf, Germany) as described previously [12].

Urine and serum concentrations of sodium were measured by standard biochemical methods at the Department of Clinical Chemistry, Malmö University Hospital. Copeptin was measured in plasma using a commercially available assay in the chemiluminescence/coated tube format (B.R.A.H.M.S AG, Hennigsdorf, Germany) as described previously [12].

2.2. Statistics. All data were analyzed with SPSS statistical software (version 21, SPSS Inc., Chicago, IL, USA). Significance of differences of paired variables (i.e., changes induced by different levels of salt intake) was tested by paired t-test or Wilcoxon’s paired rank test, where appropriate, whereas significance of differences between groups was tested with t-test. Pearson’s test of correlations (r) was used to calculate correlations.

3. Results

The 24 h urinary excretion of sodium indicated a good compliance to the high and low salt diets (Table 1). The change of copeptin between the periods of low salt intake versus high salt intake is presented in Table 2. When increasing the dietary salt, copeptin increased significantly in all subjects, a result which was statistically significant in females but not in males. Increasing urinary volume correlated inversely with copeptin both at high and at low dietary salt intake in all

Table I: Clinical characteristics of study subjects.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>High salt</th>
<th>Low salt</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour SBP (mmHg)</td>
<td>139 ± 13,3</td>
<td>136 ± 12,7</td>
<td>131 ± 11,1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>24-hour DBP (mmHg)</td>
<td>86,3 ± 7,4</td>
<td>85,0 ± 7,0</td>
<td>82,3 ± 6,6</td>
<td>0,004</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>79,5 ± 11,2</td>
<td>77,4 ± 10,7</td>
<td>77,3 ± 10,6</td>
<td>0,43</td>
</tr>
<tr>
<td>Urine-Na⁺ (mmol/24 h)</td>
<td>165 ± 67,4</td>
<td>140 ± 39,5</td>
<td>50,7 ± 17,3</td>
<td>&lt;0,0001</td>
</tr>
<tr>
<td>Serum-Na⁺ (mmol/L)</td>
<td>140 ± 1,8</td>
<td>141 ± 1,5</td>
<td>139 ± 1,7</td>
<td>&lt;0,0001</td>
</tr>
</tbody>
</table>

*Refer to individual change of variable on high salt as compared with that on low salt (i.e., variable Δ-value). SBP, systolic blood pressure; DBP, diastolic blood pressure.


4. Discussion

The main finding in our study is that even if copeptin increases after high salt intake, high salt-induced change of copeptin is inversely correlated with degree of salt sensitivity in females.

High level of copeptin in healthy subjects is associated with components of the metabolic syndrome [8, 9] including hypertension and independently predicts development of diabetes mellitus [10]. As it is an open question of whether high level of vasopressin (measured as copeptin) is causally related to diabetes, hypertension, and the metabolic syndrome or not, it is of interest to understand which environmental stimuli alter levels of copeptin. Such environmental stimuli can be used to test if subtraits of the metabolic syndrome can be ameliorated by reduction and worsened by stimulation of factors which elevate copeptin and thus provide information on causality. In the current study we selected the environmental factor of dietary salt, the effect of which on copeptin has never before been studied. We found salt of extra interest as it theoretically may have dual and opposing effects on AVP release by simultaneously increasing blood osmolality and blood volume. We found that 4 weeks of controlled high salt intake as compared to 4 weeks of controlled low salt intake increased plasma concentration of

---

Table 2: Changes in copeptin during low salt consumption and high salt consumption and the changes in between.

<table>
<thead>
<tr>
<th></th>
<th>Copeptin low salt</th>
<th>Copeptin high salt</th>
<th>ΔCopeptin</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>3.12 ± 1.95</td>
<td>3.59 ± 2.28</td>
<td>0.47 ± 1.14</td>
<td>0.02</td>
</tr>
<tr>
<td>Female</td>
<td>2.19 ± 1.38</td>
<td>2.75 ± 1.64</td>
<td>0.56 ± 0.83</td>
<td>0.02</td>
</tr>
<tr>
<td>Male</td>
<td>3.89 ± 2.04</td>
<td>4.29 ± 2.53</td>
<td>0.40 ± 1.37</td>
<td>0.22</td>
</tr>
</tbody>
</table>

ΔCopeptin, the change of copeptin during high salt intake and low salt intake; P, significance.

Table 3: Correlations between copeptin and 24 h urinary volumes during low and high salt consumption, respectively.

(a)

<table>
<thead>
<tr>
<th></th>
<th>Copeptin low salt</th>
<th>Urine volume: all</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>−0.42</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urine volume: female</td>
<td>−0.51</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urine volume: male</td>
<td>−0.39</td>
<td>0.09</td>
</tr>
</tbody>
</table>

P, significance.

(b)

<table>
<thead>
<tr>
<th></th>
<th>Copeptin high salt</th>
<th>Urine volume: all</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>−0.60</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urine volume: female</td>
<td>−0.36</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urine volume: male</td>
<td>−0.65</td>
<td>0.003</td>
</tr>
</tbody>
</table>

P, significance.

Furthermore, Table 4 shows salt-induced changes of body weight. Increasing body weight significantly correlated with a decrease in copeptin in all individuals when changing from high to low salt intake, whereas the change of urinary volume did not significantly correlate with any change in copeptin. When analyzing the change of ambulatory 24-hour blood pressure, systolic salt sensitivity correlated inversely with copeptin when going from low to high salt intake; however, this phenomenon was only seen in females (Table 5). On the other hand, systolic salt sensitivity was correlated neither with the change of body weight nor with the change of urinary excretion. Given the gender difference we divided the women in two categories, premenopausal and postmenopausal, to study whether estrogens contribute to the sensitivity of copeptin [13]. Table 6 shows salt-induced changes of copeptin in women aged below or above 51 [14]. A rise in copeptin with increasing dietary salt was only significant in women aged below 51 years. When comparing relating systolic salt sensitivity to salt-induced change of copeptin, there was no significant correlation in either female age group. Likewise, there was no relationship between salt sensitivity and salt-induced change of body weight and urinary volume in females below and above 51 years of age (Table 7).
Retention in those women. We thus believe that increased intake presumably as a result of high water intake and water opposite, that is, reduction of copeptin following a high salt intake would be related to salt sensitivity. We found that increased salt intake in women on high water intake or water retention or both of these factors. In summary, although increased salt intake in women on high water intake and we thus assumed that low copeptin would be a surrogate marker for high water intake. Furthermore, we interpreted the inverse relationship between change of weight from high to low urinary volume to gradually increasing AVP suppression with increasing fluid consumption as well as fluid retention. Due to the adverse effect of high salt intake needs to be accompanied by increased intake and retention of water in order to lead to elevated blood pressure in women. In contrast, in men plasma concentration of copeptin is not affected by level of salt intake and there is no relationship between any salt-induced changes in copeptin and salt sensitivity of blood pressure, suggesting that different mechanisms underlie salt sensitivity in men.

4.1. Strengths and Limitations. The major limitation of our study is the relatively small number of subjects included, especially in the gender stratified analyses. Not to overestimate the magnitude of the demonstrated associations, our study needs replication. On the other hand, the salt sensitivity testing was performed under controlled conditions including double-blinded placebo versus salt capsule administration and random order of the high and low salt periods. In addition, 24-hour ABP was used to measure blood pressure, resulting in a more exact blood pressure phenotype compared to office blood pressure measurements.

5. Conclusion

The increase in dietary salt consumption significantly correlates with the increase in levels of copeptin in all individuals when calculated together and in females but not in males when calculated separately. An inverted correlation is observed comparing the urinary volume (being an indirect measure of fluid intake) with the levels of copeptin during low and high dietary salt consumption. Comparing the change in body weight (an indirect measure of fluid retention) with the change in levels of copeptin from low dietary salt intake to high salt intake, we can establish a negative correlation being significant in all individuals. Our findings suggest that copeptin can be a useful marker for the amount of fluid consumption as well as fluid retention. Due to the gender differences concerning the sensitivity of copeptin release during low and high dietary salt consumption we also hypothesize that estrogens are contributing factors to the degree of this sensitivity.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

Funding was obtained from the European Research Council (StG-282255), the Swedish Heart and Lung Foundation,

Table 6: Comparison between pre- and postmenopausal women of changes in copeptin during low salt consumption and high salt consumption and the change in between.

<table>
<thead>
<tr>
<th></th>
<th>Copeptin low salt</th>
<th>Copeptin high salt</th>
<th>ΔCopeptin</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female &lt; 52 yrs</td>
<td>2.09 ± 1.84</td>
<td>3.14 ± 2.40</td>
<td>1.05 ± 0.74</td>
<td>0.01</td>
</tr>
<tr>
<td>Female ≥ 52 yrs</td>
<td>2.27 ± 1.02</td>
<td>2.45 ± 0.71</td>
<td>0.18 ± 0.71</td>
<td>0.48</td>
</tr>
</tbody>
</table>

ΔCopeptin, the change of copeptin during high salt intake and low salt intake; N, number of participants in each category; P, significance.

Table 7: Change in systolic salt sensitivity and the change in copeptin, in weight, and in 24 h urinary volumes, during low and high salt consumption in pre- and postmenopausal women.

<table>
<thead>
<tr>
<th></th>
<th>ΔSBP</th>
<th>ΔCopeptin</th>
<th>ΔWeight</th>
<th>ΔUrine volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female &lt; 51 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 7</td>
<td>r = -0.60</td>
<td>P = 0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female ≥ 51 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 9</td>
<td>r = -0.41</td>
<td>P = 0.27</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ΔSBP, systolic salt sensitivity; ΔCopeptin, the change of copeptin during high salt intake and low salt intake; ΔWeight, change in weight; ΔUrine volume, change in urinary volume from high to low urinary volume; N, number of participants in each category; P, significance.
Swedish Research Council, the Novo Nordisk Foundation; the Skåne University Hospital donation funds; the Medical Faculty, Lund University; the governmental funding of clinical research within the National Health Services; and the Albert Pålsson Research Foundation, Region Skåne. All funders represent research grant donors with no influence on the content of the study.

References


