Splanchnic Removal of Human Alpha-Atrial Natriuretic Peptide in Humans: Enhancement After Food Intake

Jens H. Henriksen, Flemming Bendtsen, and Alexander L. Gerbes

In order to assess the effect of food ingestion on splanchnic disposal of human alpha-atrial natriuretic peptide (ANF), hepatic-intestinal removal of ANF was determined before and after a test meal. Hepatic venous and arterial plasma samples were obtained from six subjects, most of whom had only disorders of minor degree. Hepatic blood flow (HBF) increased significantly after meal ingestion (1.10 ± 0.17 [SEM] to 1.51 ± 0.26 L/min, P < .01). Baseline arterial ANF (10.9 ± 3.1 pmol/L, P < .05) and accordingly the splanchnic fractional extraction decreased (0.53 ± 0.09 to 0.35 ± 0.08), although this was not statistically significant. Splanchnic clearance of ANF increased from 347 ± 90 mL/min to a maximal value of 615 ± 168 mL/min (P < .05). Splanchnic removal of ANF was 3.0 ± 0.5 pmol/min before and increased to a maximum value (7.1 ± 2.2 pmol/min, P < .05) 35 minutes after ingestion of the meal. Our results showed enhanced splanchnic removal of ANF after food intake. This is due to increased hepatic-intestinal clearance of the peptide consequent on increased splanchnic blood flow, rather than altered fractional extraction of ANF.

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Atrial natriuretic factor (human alpha-atrial natriuretic peptide [human ANF 99-126], abbreviation in this report: ANF) is important in the regulation of salt-water homeostasis and blood pressure. Since 1981 when de Bold et al.2 reported a natriuretic response to intravenous injection of atrial extracts in rats, a substantial body of reports on synthesis, release, physiological effects, and its possible role in pathophysiology and pharmacology has emerged.3-5 In contrast, studies on degradation and regional removal of ANF are few. Schütten et al.6 found a significant extraction of ANF in kidney, liver-intestine, and limbs of subjects with minor disorders. Organ extraction of ANF has also been reported in patients with heart disease and cirrhosis.8,9 Recently, Vierhapper et al.10 found a basal splanchnic uptake of ANF of 8.5 pmol/min in healthy humans. However, no reports have dealt with the effect of food intake on splanchnic disposal of ANF.

The present study was undertaken to assess the effect of a meal on splanchnic removal of ANF. We studied persons undergoing a liver vein catheterization, the majority who had disorders of minor degree.

MATERIAL AND METHODS

Study Population

The study comprised three women and three men with a mean age of 62 years (range, 50 to 68 years). All subjects were referred to hepatic vein catheterization in order to exclude ischemic mesenteric artery disease. This diagnosis was absent in all, and the majority had disorders of minor degree (Table 1). The patient with chronic hepatitis was in a stable stage with normal biochemical liver function tests. Electrocardiogram (ECG), hemoglobin concentration (mean, 138 mmol/L; range, 136 to 141) were normal in all. The patient had 2,500 kIU of aprotinin and 250 IU of heparin. Plasma was separated.

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Table 1. HBF Rate and Arterial and Hepatic Venous Plasma Concentrations of ANF Before and After Intake of Test Meal in Six Subjects Undergoing Liver Vein Catheterization

<table>
<thead>
<tr>
<th>Subject No./Sex</th>
<th>Age (yr)</th>
<th>Diagnosis</th>
<th>HBF (L/min)</th>
<th>Plasma ANF (pmol/L, a/hv)</th>
<th>HBF (L/min)</th>
<th>Plasma ANF (pmol/L, a/hv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M</td>
<td>68</td>
<td>Intercostal neuralgia</td>
<td>1.18</td>
<td>11.7/5.4</td>
<td>1.68</td>
<td>14.0/5.7</td>
</tr>
<tr>
<td>2/M</td>
<td>50</td>
<td>Dermatomyositis</td>
<td>0.74</td>
<td>23.8/12.3</td>
<td>0.95</td>
<td>23.7/12.3</td>
</tr>
<tr>
<td>3/F</td>
<td>61</td>
<td>Chronic hepatitis</td>
<td>1.17</td>
<td>14.2/10.6</td>
<td>1.45</td>
<td>17.0/11.9</td>
</tr>
<tr>
<td>4/F</td>
<td>62</td>
<td>Irritable bowel syndrome</td>
<td>0.90</td>
<td>0.0/0.7</td>
<td>1.44</td>
<td>3.2/2.9</td>
</tr>
<tr>
<td>5/F</td>
<td>68</td>
<td>Irritable bowel syndrome</td>
<td>0.74</td>
<td>6.7/4.0</td>
<td>0.88</td>
<td>8.1/2.3</td>
</tr>
<tr>
<td>6/M</td>
<td>62</td>
<td>Post cholecystectomy pain</td>
<td>1.83</td>
<td>3.1/1.2</td>
<td>2.64</td>
<td>5.6/0.6</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>1.10</td>
<td>10.9/5.7</td>
<td>1.51†</td>
<td>11.9/6.0</td>
</tr>
</tbody>
</table>

*Numbers denote minutes after intake of test meal.

Abbreviation: a/hv, arterial/hepatic vein.

Significant difference compared with baseline value: †hepatic vein, P < .01; ‡P < .05.

from blood cells immediately by centrifugation at 4°C and frozen (-25°C) until assayed. ANF in plasma was determined by radioimmunoassay as described earlier.15,16 Within- and between-assay coefficients of variation were below 10% and 15%, respectively. Detection limit was 0.5 pmol/mL.

Calculations

Splanchnic removal rate of ANF (J), fractional extraction ratio (E), and clearance (Cl) were determined by the following equations, where \( C_a \) and \( C_v \) are plasma concentrations of ANF in artery and hepatic vein, respectively: \( J = HFP \cdot (C_a - C_v) \); \( E = (C_a - C_v) / C_a \); and \( Cl = (C_a - C_v) / HFP/C_a \).

Statistical Evaluations

Comparisons between paired and grouped differences were performed by Student's paired t test and ANOVA. \( P < .05 \) was considered significant.

RESULTS

Plasma ANF values and HBF are summarized in Table 1. HBF was 1.10 ± 0.17 L/min (mean ± SEM) and increased significantly in all subjects studied to average 1.51 ± 0.26 L/min (\( P < .01 \)) after intake of the test meal. Likewise, splanchnic oxygen uptake increased from 64 ± 8.5 to 89 ± 12 mL O₂/min (\( P < .01 \)). Baseline arterial concentration of ANF (10.9 ± 3.1 pmol/L) was close to the normal average, and did not change significantly after meal ingestion. Hepatic venous concentration of ANF (5.7 ± 2.0 pmol/L) increased to 8.4 ± 1.9 pmol/L (\( P < .05 \)) 60 minutes after meal intake. Arterio-hepatic venous extraction ratios of ANF are shown in Fig 1. Baseline fractional extraction was 0.53 ± 0.09, and this value decreased somewhat after the meal, although not statistically significant. No relationship was found between splanchnic ANF and oxygen extraction. Splanchnic clearance of ANF was 347 ± 81 mL/min and increased significantly (maximum value, 615 ± 158 mL/min \( P < .05 \); average, 441 ± 90 mL/min \( P < .05 \)) after food intake. Hepatic-intestinal removal of ANF was 3.0 ± 0.5 pmol/min before, and reached a maximal value 35 ± 5 minutes after ingestion of the meal (7.1 ± 2.2 pmol/min; \( P < .05 \)). Average time course of clearance and removal are shown in Fig 2.

DISCUSSION

Plasma disappearance of ANF after intravenous infusion is fast, indicating a substantial plasma turnover rate of this peptide.15,16 Other peptides with a fast turnover rate, such as insulin, neurotensin, and vasoactive intestinal polypeptide, have a substantial hepatic degradation,17,18 and this may be influenced by food intake.20 A few reports4,10,21 have dealt...
with the splanchnic disposal of ANF in humans, and the
question of a possible effect of food intake has not been
dressed. The splanchnic uptake of ANF, as found in the present
baseline period (3.0 pmol/min) is somewhat below the value
(8.5 pmol/min) recently published by Vierhapper et al. 10 The
reason for this it not clear, but may be due to (1) the
circulating level of ANF was slightly higher in their study;
(2) they found a splanchnic fractional extraction of 0.76
compared with 0.53 in our study; (3) HBF was higher in their
subjects; and (4) their subjects were younger. The splanchnic
fractional extraction as found in the present study is similar
to that reported by Crozier et al. 11 but somewhat higher than
reported by Schütten et al. 9 and Hollister et al. 10
After intake of the test meal, HBF and splanchnic oxygen
uptake increased in all subjects, mean 37% and 39%,
respectively. This is a normal response. 11 The splanchnic
fractional extraction rate of ANF decreased somewhat,
although not statistically significant. In contrast, the splanchnic
clearance of ANF increased significantly after meal
ingestion. Thus, the increased splanchnic ANF removal after
meal ingestion is most likely due to an increased clearance
secondary to the increased splanchnic blood flow observed
after food intake.
Increased elimination will decrease the circulating level
of ANF if the release rate is unchanged. However, we did not
observe a decrease in arterial ANF. On the contrary, a slight
nonsignificant increase was observed. Food intake may
transitorily enhance the osmotic load of plasma and expand
the plasma volume by displacement of water from the
intracellular pool. 12 Plasma volume expansion may increase
the release of ANF from atrial myocytes. 14, 25 The increased
splanchnic removal of ANF after food intake may, at least in
part, counteract an increased release of ANF, leaving the
arterial level of ANF relatively unchanged. In this context,
however, it should be recalled that the splanchnic removal
only constitutes about one fifth of overall disposal of ANF,
the kidney and lung being the most prominent organs of
ANF removal. 14, 21
In summary, ingestion of food enhances the splanchnic
disposal of ANF as evaluated by the hepatic vein catheterization
technique. The increased hepatic-intestinal removal of
ANF is due to an increased clearance of this peptide consequent
on increased splanchnic blood flow and not to increased
splanchnic fractional extraction of ANF. Increased
splanchnic removal may, in part, oppose any increased
release of ANF after food intake.

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