REFERÊNCIA

INCREASED OSMOTIC SENSITIVITY FOR ANTIDIURETIC RESPONSE IN CHRONIC CHAGAS' DISEASE

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The osmotic threshold for attaining the antidiuretic response to hypertonic saline infusion and progressive dehydration was studied in 31 patients with the chronic form of Chagas' disease and 16 control patients. The chagasic patients exhibited enhanced osmotic sensitivity to the antidiuretic response. This was demonstrated by lower values of the increments in plasma osmolarity sufficient to induce a significant fall in water clearance, without alterations in the osmolar clearance or creatinine excretion. The time needed to attain the antidiuretic response was shorter for chagasics in relation to normal subjects. The results suggest the existence of a disturbance in the fine control of osmoregulation in the chagasic patients. They are interpreted to be a consequence of the denervation in hypothalamic or extrahypothalamic areas that regulate the secretion of vasopressin in chronic Chagas' disease.

Key words: Chagas' disease. Osmotic threshold. Antidiuretic response. Hypothalamic denervation.

The secretion of antidiuretic hormone is a function dependent on the integrity of hypothalamic structures."}

Abnormalities in secretory function of the hypothalamus have been demonstrated by different authors to be associated with chronic Chagas' disease. Thus, alterations in thyroid function, interpreted as consequent of a hypothalamic defect in the control of thyrotrophic hormone release was detected in chagasic patients and in rats with experimental chronic Chagas' disease. Alterations in the control of osmolar concentration of extracellular fluid, probably due to changes in the sensitivity for the release of antidiuretic hormone of osmoreceptors, were also exhibited by chagasic patients.

All these functional abnormalities were concluded to be the result of hypothalamic neuronal destruction produced by Chagas' disease in the context of the involvement of the central nervous system in this disease.

In order to further evaluate the hypothalamic control of antidiuretic response to variations in plasma osmolar concentration in chronic Chagas' disease we studied the threshold of osmotic sensitivity for antidiuretic response to hypertonic saline infusion and to dehydration.

MATERIAL AND METHODS

Investigations were done in sixteen (four female and twelve male) healthy subjects and in thirty-one (twelve female and nineteen male) patients all with positive serology for Chagas' disease. Eight patients...
showed exclusive heart disease on the basis of electrocardiographic changes, without past or present heart failure. Two presented only an abnormality in esophageal function characterized by slight dysphagia without overt megaesophagus on radiologic study. Two other patients showed associated heart disease and slight dysphagia, and nineteen were classified as the indeterminate form of the disease with no clinically detectable abnormalities, except for the positive serology. The anthropometric data of the control subjects and chagasic patients are showed in the Table 1. No significant change was observed between these anthropometric data and the nutritional status when we compared the two groups.

Table 1 – Anthropometric data of the control and chagasic patients.

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Height (m)</th>
<th>Body surface (m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Saline infusion</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Controls (n = 7)</td>
<td>32.1 ± 10.6</td>
<td>54.5 ± 7.4</td>
<td>1.6 ± 9.4</td>
<td>1.4 ± 0.1</td>
</tr>
<tr>
<td>Patients (n = 11)</td>
<td>33.8 ± 9.1</td>
<td>57.3 ± 8.5</td>
<td>1.6 ± 9.8</td>
<td>1.4 ± 0.1</td>
</tr>
<tr>
<td><strong>Dehydration</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Controls (n = 9)</td>
<td>30.8 ± 3.9</td>
<td>55.5 ± 6.0</td>
<td>1.6 ± 4.4</td>
<td>1.5 ± 8.4</td>
</tr>
<tr>
<td>Patients (n = 20)</td>
<td>32.7 ± 7.8</td>
<td>56.9 ± 7.6</td>
<td>1.6 ± 9.4</td>
<td>1.6 ± 0.1</td>
</tr>
</tbody>
</table>

The data are expressed as mean ± sd.

The study was performed under consent and all subjects were informed about the general objectives according to the Declaration of Helsinki²³.

All subjects were hospitalized and allowed to adapt for three days before the experiments. During this period they were maintained on a standard diet of 3,000 – 3,200 calories (about 120 g of protein and 200 mEq/day of sodium). The females were studied in the preovulatory phase of the menstrual cycle.

The study was performed in the morning with the subjects in fasting state. After emptying their bladders all subjects received an oral water overload of 20 ml/kg for 15-20 minutes. A brachial intravenous line was maintained to obtain blood samples. In a contralateral vein an infusion of 5% NaCl solution at 0.005 ml/kg/min was given using a model 950 Harvard pump.

When constant water diuresis was established (basal conditions) maintaining the water overload, an increase in plasma osmolality was induced by progressive dehydration (Group 2). In all patients the diuresis of each 15 minute period was noted and the urinary flow (V), the urinary osmolality (Uosm) and the concentration of urinary creatinine (Ucr) determined. Plasma osmolality (Posm), plasma creatinine (Pcr) and the hematocrit were obtained from blood samples collected in the middle of each period. An antidiuretic response was assumed to have started when a fall in free water clearance (Cf20) was observed without a significant fall in osmolar clearance (Cosm) or in creatinine excretion (Ucr.V)¹⁶. Clearances were calculated by the formulas currently used. Urinary and plasma osmolality were determined by the Fiske osmometer. Plasma and urinary creatinine levels were obtained by colorimetric method. The osmotic threshold for antidiuretic response was calculated by regression of plasma osmolar concentration over the time. All data are expressed as mean ± sd. The values from chagasic patients were analyzed by the Students’ t test with an accepted significance level of 5% (p < 0.05).

RESULTS

The mean plasma osmolar concentration before the hypertonic saline infusion in group 1 patients

and before the dehydration in group 2 (Initial $P_{\text{osm}}$) with the respective attained mean osmotic threshold (O. T.) in comparison with control groups are shown in Table 2. The table also shows the mean increase in plasma osmolarity to induce the antidiuretic responses ($\Delta P_{\text{osm}}$) and the average time that elapsed from the beginning of saline infusion or dehydration (zero time) to the moment when the antidiuretic responses were calculated ($\Delta t$).

Table 2 – Increment in plasma osmolar concentration ($\Delta P_{\text{osm}}$) to the osmotic threshold (OT) for antidiuretic responses and time dispended to attain the osmotic stimulus ($\Delta t$).

<table>
<thead>
<tr>
<th></th>
<th>Saline infusion controls</th>
<th>Saline infusion patients</th>
<th>Dehydration controls</th>
<th>Dehydration patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial $P_{\text{osm}}$ (mOsm/1)</td>
<td>(n = 7) 278,60 ± 4,09</td>
<td>(n = 11) 278,18 ± 4,75</td>
<td>(n = 9) 278,43 ± 3,64</td>
<td>(n = 20) 281,43 ± 8,35</td>
</tr>
<tr>
<td>$\Delta P_{\text{osm}}$ (mOsm/1)</td>
<td>5,37 ± 3,22</td>
<td>2,65* ± 2,11</td>
<td>6,21 ± 3,10</td>
<td>3,61* ± 2,14</td>
</tr>
<tr>
<td>O. T. (mOsm/1)</td>
<td>283,97 ± 5,09</td>
<td>281,09 ± 5,22</td>
<td>284,64 ± 3,15</td>
<td>285,91 ± 6,10</td>
</tr>
<tr>
<td>$\Delta t$ (minutes)</td>
<td>38,57 ± 11,80</td>
<td>24,55* ± 13,87</td>
<td>56,67 ± 6,78</td>
<td>42,10* ± 17,11</td>
</tr>
</tbody>
</table>

* p < 0.05  
(n = 7)

Endogenous creatinine clearance varied within a narrow range both during the periods of stable water diuresis and after the onset of antidiuresis, both for controls and chagasic patients (Table 3). Hematocrit tended to decrease after administration of water overload, and reached normal levels during the final testing periods for both groups.

Table 3 – Endogenous creatinine clearance ($C_{\text{cr}}$) before (A) and after (B) the antidiuretic response.

<table>
<thead>
<tr>
<th></th>
<th>$C_{\text{cr}}(A)$ ml/min/1,73m²</th>
<th>$C_{\text{cr}}(B)$ ml/min/1,73m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline infusion controls (n = 7)</td>
<td>116,0 ± 8,0</td>
<td>115,4 ± 9,2</td>
</tr>
<tr>
<td>Saline infusion patients (n = 11)</td>
<td>110,0 ± 14,9</td>
<td>109,4 = 14,9</td>
</tr>
<tr>
<td>Dehydration controls (n = 9)</td>
<td>118,9 ± 17,8</td>
<td>117,5 ± 19,6</td>
</tr>
<tr>
<td>Dehydration patients (n = 20)</td>
<td>116,3 ± 15,0</td>
<td>116,1 ± 14,5</td>
</tr>
</tbody>
</table>

The data are expressed as mean ± sd
DISCUSSION

In the present study, the osmotic threshold (O. T.) obtained under control conditions were similar to those showed by other investigators\(^1\) \(16\) \(18\) \(19\). However the O. T. and Initial \(P_{\text{osm}}\) for chagasic patients showed more variability when compared with the control group and this is suggestive of the existence of a disturbance in the fine control of plasma osmolar concentration. On the other hand, the increments in plasma osmolarity sufficient to induce antidiuresis (\(\Delta P_{\text{osm}}\)) and the time dispended on attaining it (\(\Delta t\)) was significantly lower for chagasic patients as showed in Table 2.

These results suggest the existence of a disturbance in osmoregulation in chronic chagasic patients, characterized by increased osmotic sensitivity to the antidiuretic response. The date are in general agreement with those obtained by Kimachi et al\(^{10}\) in their investigation of urine concentration in chronic chagasic patients, where parameters such as urinary flow, osmolar clearance and free water clearance appeared to be altered suggesting the presence of abnormalities in osmoregulation.

These alterations presented by chagasic patients are interpreted as the consequence of denervation in hypothalamic or extrahypothalamic areas affecting the secretory control of vasopressin. An afferent denervation is present in chagasic patients which blocks the arrival to the central nervous system of stimuli from stretch-sensitive receptors. These are located in the atria and large blood vessels. With changes in the resetting level of osmoreceptors, these may be precociously sensitized to increase in plasma osmolarity. This could explain the results obtained in the present study. Probably the abnormal antidiuretic response, found in chagasic patients, is associated with a dysfunction in the hypothalamus-pituitary-cortex adrenal axis as suggested by Kimachi et al\(^{11}\).

The relevance of this disturbance in the secretion of antidiuretic hormone in chagasic patients with heart failure remains to be determined.

ACKNOWLEDGEMENTS

The authors gratefuly acknowledge the technical assistance of Fernando V. Padua, Hidenori A. Owa, Baltazar Nunes, Milton Cunha and Waldecy Correia.

REFERENCES


