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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[6 7].

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[12] and in rats with experimental chronic Chagas' disease[8].

Kimachi *et al*[9] studying the hypothalamus – pituitary – adrenal cortex axis in chagasic patients showed disturbances in the mechanism of corticotrophin release. Moreira *et al*[15] studying the secretion of luteinizing hormone in men with chronic Chagas' disease demonstrated abnormalities in the secretion of this hormone. Disturbances in the secretory control of growth hormone[17] and prolactin[13] were also found in patients with 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[10].

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[3 4 5 21 22 14 2].

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

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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.*

		Age (years)	*Weight (kg)*	*Height (m)*	*Body surface (m^2)*
Saline infusion	Controls (n = 7)	32,1 ± 10,6	54,5 ± 7,4	1,6 ± 9,4	1,4 ± 0,1
	Patients (n = 11)	33,8 ± 9,1	57,3 ± 8,5	1,6 ± 9,8	1,4 ± 0,1
Dehydration	Controls (n = 9)	30,8 ± 3,9	55,5 ± 6,0	1,6 ± 4,4	1,5 ± 8,4
	Patients (n = 20)	32,7 ± 7,8	56,9 ± 7,6	1,6 ± 9,4	1,6 ± 0,1

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 Helsinki[23].

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 osmolarity was induced in eleven chagasic and in seven control patients by rapid infusion of hypertonic saline at the rate of 0.05 ml/kg/min (Group 1). In twenty others chagasic and nine control subjects, after water diuresis, an increase in plasma osmolarity 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 osmolarity (U_{osm}) and the concentration of urinary creatinine (U_{cr}) determined. Plasma osmolarity (P_{osm}), plasma creatinine (P_{cr}) 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 (C_{H20}) was observed without a significant fall in osmolar clearance (C_{osm}) or in creatinine excretion ($U_{cr}.V$)[16]. Clearances were calculated by the formulas currently used. Urinary and plasma osmolarity 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_{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 (ΔP_{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 (Δ t).

Table 2 – *Increment in plasma osmolar concentration (ΔP_{osm}) to the osmotic threshold (OT) for antidiuretic responses and time dispended to attain the osmotic stimulus (Δ t).*

	Saline infusion		*Dehydration*	
	controls	*patients*	*controls*	*patients*
	(n = 7)	*(n = 11)*	*(n = 9)*	*(n = 20)*
Initial Posm (mOsm/1)	278,60 ± 4,09	278,18 ± 4,75	278,43 ± 3,64	281,43 ± 8,35
Δ Posm (mOsm/1)	5,37 ± 3,22	2,65* ± 2,11	6,21 ± 3,10	3,61* ± 2,14
O. T. (mOsm/1)	283,97 ± 5,09	281,09 ± 5,22	284,64 ± 3,15	285,91 ± 6,10
Δ t (minutes)	38,57 ± 11,80	24,55* ± 13,87	56,67 ± 6,78	42,10* ± 17,11

* $p < 0.05$
(n = individuals)

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_{cr}) before (A) and after (B) the antidiuretic response.*

		C_{cr} (A) ml/min/1,73m²	*C_{cr} (B) ml/min/1,73m²*
Saline infusion	Controls (n = 7)	116,0 ± 8,0	115,4 ± 9,2
	Patients (n = 11)	110,0 ± 14,9	109,4 = 14,9
Dehydration	Controls (n = 9)	118,9 ± 17,8	117,5 ± 19,6
	Patients (n = 20)	116,3 ± 15,0	116,1 ± 14,5

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_{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 (ΔP_{osm}) and the time dispended on attaining it (Δ 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 revelance of this disturbance in the secretion of antidiuretic hormone in chagasic patients with heart failure remains to be determined.

RESUMO

O limiar de sensibilidade osmótica para obtenção de resposta antidiurética foi avaliado em 31 pacientes com a forma crônica da moléstia de Chagas, através de infusão de salina hipertônica ou desidratação. Os resultados, quando comparados com os obtidos em 16 pacientes-controle, mostram uma sensibilidade osmótica aumentada para os chagásicos, dados os menores valores do incremento na osmolaridade plasmática, suficiente para induzir uma queda significativa na depuração de água livre, sem alterações na depuração osmolar ou na excreção de creatinina. Também, o tempo necessário para atingir a antidiurese foi mais curto para os chagásicos do que para os controles. Os resultados sugerem a existência de um distúrbio na osmorregulação, nos pacientes chagásicos, caracterizado por uma sensibilidade osmótica aumentada dos osmorreceptores para liberação da vasopressina. Estes dados interpretam-se como conseqüente à desnervação em áreas hipotalâmicas ou extra-hipotalâmicas, relacionadas com a secreção do hormônio antidiurético, na doença de Chagas.

Palavras chave: Doença de Chagas. Limiar osmótico. Resposta antidiurética. Desnervação hipotalâmica.

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REFERENCES

1. Aubry RH, Nankin HR, Moses AM, Streeten DHP. Measurement of the osmotic threshold for vasopressin release in human subjects and its modification by cortisol. Journal of Clinical Endocrinology 25: 1481-1492, 1965.

2. Britto-Costa R, Gallina RA. Hipotálamo anterior na moléstia de Chagas. Revista do Instituto de Medicina Tropical de São Paulo 13: 92-98, 1971.

3. Chagas C. Novas tripanozomiase humana. Estudos sobre a morfologia e o ciclo evolutivo do Schizotrypanum cruzi n. gen., n. sp., agente etiológico de nova entidade mórbida do homem. Memórias do Instituto Oswaldo Cruz 1: 159-218, 1909.

4. Chagas C. Nova entidade mórbida do homem. Resumo geral de estudos etiológicos e clínicos. Memórias do Instituto Oswaldo Cruz 3: 219-275, 1911.

5. Chagas C. Les formes nerveuses d'una nouvelle trypanosomiase (Trypanosoma cruzi inoculé par Triatoma megista) (Maladie de Chagas). Nouvelle Iconographie Salpétrière 26: 1-9, 1913.

6. Gemert M, Miller M, Carey RJ, Moses AM. Polyuria and impaired ADH release following medial preoptic lesioning in the rat. American Journal of Physiology 228: 1293-1297, 1975.

7. Hayward JN. Neural control of the posterior pituitary. Annual Review of Physiology 37: 191-210, 1975.

8. Lazigi N, Lomonaco DA, Veríssimo JMT, Oliveira HL. Função tireoidiana de ratos com infecção chagásica crônica: influência do teor de iodo na dieta. Revista da Associação Médica Brasileira 17: 227-236, 1971.

9. Kimachi T, Lomonaco AD, Veríssimo TMJ. Exploração funcional do eixo hipotálamo-adeno-hipófise-cortex adrenal na forma crônica da moléstia de Chagas. Revista da Associação Médica Brasileira 20: 57-66, 1974.

10. Kimachi T, Lomonaco AD, Gomes AU, Lima-Filho EC, Azevedo-Marques MM. Distúrbio do mecanismo de concentração urinária em pacientes com a forma crônica da moléstia de Chagas. Revista do Instituto de Medicina Tropical de São Paulo 20: 6-14, 1978.

11. Kimachi T, Veiga JPR, Lima-Filho EC. Effects of plasma corticosteroid concentration on the osmotic threshold for vasopressin releasing in Chagas' disease. Revista da Sociedade Brasileira de Medicina Tropical 16: 139-143, 1983.

12. Lomonaco DA, Oliveira HL, Kieffer J, Pieroni RR. Abnormal regulation of thyroid function in patients with chronic Chagas' disease. Acta Endocrinológica 53: 162-176, 1966.

13. Medeiros MS. Regulação da secreção da prolactina na forma crônica da doença de Chagas humana. Dissertação de Mestrado. Faculdade de Medicina de Ribeirão Preto, USP, 1983.

14. Menezes H, Alcântara FG. Distribuição dos parasitas (pseudo-cistos) no sistema nervoso central de ratos infectados experimentalmente pelo T. cruzi. Revista Goiana de Medicina 11: 21-25, 1965.

15. Moreira AC, Antunes-Rodrigues J, Lima-Filho EC, Foss MC, Iazigi N, Veríssimo JMT. Luteinizing hormone secretion in men with chronic Chagas' disease. Revista do Instituto de Medicina Tropical de São Paulo 24: 148-156, 1982.

16. Moses AM, Miller M. Osmotic threshold for vasopressin release as determined by saline infusion and by dehydration. Neuroendocrinology 7: 219-226, 1971.

17. Oliveira ML. Estudo da regulação do hormônio de crescimento na moléstia de Chagas crônica. Dissertação de Mestrado. Faculdade de Medicina de Ribeirão Preto, USP, 1980.

18. Robertson GL, Shelton RL, Athar S. The osmoregulation of vasopressin. Kidney International 10: 25-37, 1976.

19. Robertson GL. Thirst and vasopressin function in normal and disordered states of water balance. Journal of Laboratory and Clinical Medicine 101: 351-371, 1983.

20. Schrier RW, Berl T, Anderson RJ. Editorial Review. Osmotic and non-osmotic control of vasopressin release. American Journal of Physiology 236: F 321 – F 332, 1979.

21. Vianna G. Contribuição para o estudo da anatomia patológica da "Moléstia de Carlos Chagas". Memórias do Instituto Oswaldo Cruz 3: 276-294, 1911.

22. Villela E, Torres CM. Estudo histopatológico do sistema nervoso central em paralisia experimental determinada pelo Schizotripanum cruzi. Memórias do Instituto Oswaldo Cruz 19: 175-219, 1926.

23. World Health Organization. Biomedical research: a revised code of ethics. W. H. O. Chronicle 30: 360-362, 1976.