Effect of chronic oral administration of a low dose of captopril on sodium appetite of hypothyroid rats. Influence of aldosterone treatment


Abstract

Rats rendered hypothyroid by treatment with methimazole develop an exaggerated sodium appetite. We investigated here the capacity of hypothyroid rats (N = 12 for each group) to respond to a low dose of captopril added to the ration, a paradigm which induces an increase in angiotensin II synthesis in cerebral areas that regulate sodium appetite by increasing the availability of circulating angiotensin I. In addition, we determined the influence of aldosterone in hypothyroid rats during the expression of spontaneous sodium appetite and after captopril treatment. Captopril significantly increased (P<0.05) the daily intake of 1.8% NaCl (in ml/100 g body weight) in hypothyroid rats after 36 days of methimazole administration (day 36: 9.2 ± 0.7 vs day 32: 2.8 ± 0.6 ml, on the 4th day after captopril treatment). After the discontinuation of captopril treatment, daily 1.8% NaCl intake reached values ranging from 10.0 ± 0.9 to 13.9 ± 1.0 ml, 48 to 60 days after treatment with methimazole. Aldosterone treatment significantly reduced (P<0.05) saline intake before (7.3 ± 1.6 vs day 0, 14.4 ± 1.3 ml) and after captopril treatment. Our results demonstrate that, although hypothyroid rats develop a deficiency in the production of all components of the renin-angiotensin-aldosterone system, their capacity to synthesize angiotensin II at the cerebral level is preserved. The partial reversal of daily 1.8% NaCl intake during aldosterone treatment suggests that sodium retention reduces both spontaneous and captopril-induced salt appetite.

Previous studies have shown a reduction in NaCl aversion in hypothyroid rats with urinary sodium loss and an increase in sodium appetite in different experimental models (1-4). However, controversies still exist regarding the physiological mechanism responsible for sodium appetite, since genetic expression, synthesis and release of the components of the renin-angiotensin-aldosterone system are reduced in hypothyroidism (3,5-9). Moreover, angiotensin II receptor density is altered in hypothyroidism. An increase in

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- Sodium appetite
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- Captopril
- Aldosterone
- Rats
the expression of AT2 receptors was observed in heart, liver, kidney and adrenals, whereas AT1 receptor density was unaltered (7). In this study the influence of hypothyroidism on the density of cerebral AT1 receptors was not investigated (7). Various studies have suggested the involvement of AT1 receptors in the expression of sodium appetite behavior using central administration of antagonists specific for these receptors (10-12). These alterations were revealed concomitantly with the observation of low genetic expression and reduced basal and stimulated release of atrial natriuretic peptide in hypothyroidism (9,13,14) together with the decreased capacity of proximal tubular sodium reabsorption (15). Literature data have led to the conclusion that the sodium appetite of hypothyroid rats is unique because it occurs in the presence of reduced plasma levels of both aldosterone and angiotensin II (3,5-9).

The study of sodium appetite behavior is clearly relevant in view of the water-electrolyte and cardiovascular changes observed in hypothyroidism. There are no reports on the capacity of hypothyroid rats to respond to a natriorexigenic stimulus of low captopril doses.

In the present study we determined the capacity of hypothyroid rats to respond to a low dose of captopril added to the food. This experimental paradigm elevates cerebral angiotensin I availability and induces an increase in sodium intake following neuronal production of angiotensin II (12,16-18), without alterations in water intake. Administration of captopril to rats in the diet (0.7 mg/g of food) or added to the drinking water (about 0.7-1 mg/ml) induced an increase in the ingestion of hypertonic saline (16,17). Low doses of captopril (12 µg/h) infused intracebroventricularly inhibited the sodium appetite which follows oral captopril. Continuous intravenous infusion of high doses of captopril (25-500 mg/day) does not induce sodium appetite. When the dose was reduced to a low value (5 mg/day), NaCl intake increased. These data suggested to the authors that low captopril concentrations do not cross the blood-brain barrier in sufficient amounts to block the angiotensin-converting enzyme, resulting in an increase in the circulating levels of angiotensin I that stimulate sodium appetite upon conversion to angiotensin II in the brain (12,17). The conversion of angiotensin I to angiotensin II, required for the manifestation of sodium appetite after treatment with low captopril doses, probably occurs in the subfornical organ and organum vasculosum lamina terminalis, structures in which angiotensin-converting enzyme has been identified (19,20).

An additional objective was to determine the influence of aldosterone administration on sodium appetite of hypothyroid rats before and during treatment with captopril. In the experimental hypothyroidism induced in rats, hypoaldosteronism occurs, due to deficiency of all the components of the renin-angiotensin system, and this causes urinary sodium loss and compensatory expression of sodium appetite (1,7). For this reason, hypothyroid rats develop an inability to maintain their sodium balance (1-3). Therefore, hormonal replacement by daily administration of aldosterone would restore the capacity to retain sodium in hypothyroid rats (1,3).

Male Wistar rats weighing 235-255 g maintained in the animal house under controlled light and temperature conditions (lights on from 6:00 to 19:00 h) were used. Hypothyroidism was induced by methimazole (0.05% in drinking water; Eli Lilly do Brasil Ltda., São Paulo, SP, Brazil). To test the efficiency of antithyroid treatment, plasma T4 and TSH levels were determined by radioimmunoassay (kits from Abbott do Brasil, São Paulo, SP, Brazil). Thirty and 60 days after treatment with methimazole, plasma T4 and TSH levels were determined by radioimmunoassay (kits from Abbott do Brasil, São Paulo, SP, Brazil). Thirty and 60 days after treatment with methimazole, plasma T4 and TSH levels were determined by radioimmunoassay (kits from Abbott do Brasil, São Paulo, SP, Brazil). Thirty and 60 days after treatment with methimazole, plasma T4 and TSH levels were determined by radioimmunoassay (kits from Abbott do Brasil, São Paulo, SP, Brazil).
methimazole, body weight gain was always lower than 10%, whereas in euthyroid rats an increase higher than 30% was always observed. Euthyroid and hypothyroid rats (N = 12 for each group) received 1.8% NaCl and water and ration ad libitum throughout the experiment. After 32 days of methimazole treatment, captopril, an angiotensin-converting enzyme inhibitor (Bristol-Myers Squibb, São Paulo, SP, Brazil), was added to the food (1 mg/g ration). One of the hypothyroid groups received the mineralocorticoid d-aldosterone (Sigma Chemical Co., St. Louis, MO, USA) for 7 days (100 µg/kg, sc, in corn oil solution) before and during captopril treatment. Under all experimental conditions, water and 1.8% NaCl were offered simultaneously to the animals, which were maintained in metabolic cages fitted with graduated water bottles.

Data are reported as mean ± SEM and were analyzed statistically by analysis of variance for repeated measures followed by the Student-Newman-Keuls test. Differences between means were considered to be significant when P<0.05.

Euthyroid rats treated with captopril showed an increase in 1.8% NaCl intake which reached a peak of 11.9 ± 1.1 ml on the 4th day post-treatment (day 0: 0.5 ± 0.2 ml) without significant alterations in water intake (data not shown).

Figure 1 shows that captopril treatment significantly increased daily intake of 1.8% NaCl (reported as ml/100 g body weight) in hypothyroid rats at 36 days of methimazole administration (day 36: 9.2 ± 0.7 vs day 32: 2.8 ± 0.6 ml, on the 4th day after captopril treatment). After the discontinuation of captopril treatment, daily 1.8% NaCl intake decreased gradually until day 42 and then started to increase, reaching mean values of 10.0 ± 0.9 to 13.9 ± 1.0 ml between 48 and 60 days post-treatment with methimazole. Captopril treatment increased water intake in a more discrete but significant manner (day 36: 9.3 ± 0.6 vs day 32: 6.9 ± 0.6 ml). Hypothyroid rats not treated with captopril also reached levels of 1.8% NaCl intake above 10.0 ml but only from day 56 on and with a less pronounced ascending curve than that observed for hypothyroid rats treated with captopril. Sodium appetite was determined daily in both groups until the 60th day post-treatment with methimazole. In parallel, separate groups of hypothyroid rats previously treated or not with captopril were followed up for 12 months. During this period, both groups showed levels of 1.8% NaCl intake ranging from 10.0 to 14.0 ml/100 g (data not shown).

Figure 2 shows that aldosterone administration drastically decreased the intake of 1.8% NaCl before treatment (7.3 ± 1.6 vs day 0: 14.4 ± 1.3 ml) and attenuated the natriorexigenic response induced by the concomitant administration of a low captopril dose. In this condition water intake was unchanged. The discontinuation of aldosterone treatment led to an elevation in salt intake, reaching values of 20.2 ± 1.9 ml 5 days after

![Figure 1](image-url)
Aldosterone administration to euthyroid rats did not affect the expression of the low salt intake rates but reduced the natriorexigenic response to captopril. On the other hand, the discontinuation of aldosterone administration induced a salt intake response in euthyroid rats which reached a peak of 10.7 – 0.95 ml 4 days after treatment termination (data not shown), whereas in hypothyroid rats this value reached 18.7 – 1.8 ml under the same conditions.

The present results confirm the experimental model of addition of a low captopril dose to rat food as a paradigm of induction of natriorexigenic behavior in euthyroid animals (12,17,18). Furthermore, our data agree with observations of other authors (1-4) showing that hypothyroidism in rats induces an exaggerated sodium appetite. However, controversy might arise since some of these authors used isotonic saline in their studies which may lead to the interpretation that the palatable component constitutes a more predominant factor in salt intake by hypothyroid rats.

Our results demonstrate that hypothyroid rats respond to the natriorexigenic stimulus of a low captopril dose added to the ration. Since the synthesis of components of the renin-angiotensin-aldosterone system is depressed in hypothyroidism one may speculate that the low plasma angiotensin I levels produced in our experimental model represent a stimulus sufficient to induce a natriorexigenic response and a more discrete increase in water intake. These observations lead us to hypothesize that in the model of hypothyroidism used here the cerebral angiotensinergic system involved in the mediation of sodium appetite possesses a component highly sensitive to circulating angiotensin I levels. The reduction in spontaneous sodium appetite intensity and the partial reversal of the natriorexigenic response to captopril observed after aldosterone treatment may suggest that the increase in sodium concentration in the body fluids depresses the conversion of angiotensin I to angiotensin II and/or the expression of AT1 receptors and cerebral angiotensinergic activity in hypothyroidism.

The present results demonstrate that hypothyroid rats develop a more intense sodium appetite after oral captopril treatment. The expression of spontaneous sodium appetite and the natriorexigenic response induced by captopril administration were reduced in hypothyroid rats after aldosterone treatment.

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References


