Postnatal development of the renin-angiotensin system in thyroidectomized rats

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ABSTRACT. Postnatal changes in plasma renin activity (PRA), plasma renin concentration (PRC), plasma renin substrate (PRS) and plasma angiotensin II concentration (All) were studied in young thyroidectomized rats from the 4th to the 10th week of life. Although there were no differences in the PRA pattern between thyroidectomized and euthyroid animals, an increase in PRC from the 6th week of life, together with a reduction of the glomerular filtration rate (GFR) and an increase in the fractional excretion of sodium (FE Na\textsubscript{2}) from the 8th week of life, was observed in young hypothyroid animals. Moreover, in thyroidectomized animals, PRS and All declined until the 10th week of age, while in euthyroid animals an increase of PRS and All was observed between the 8th and 10th weeks of life. These results show that the changes in sodium renal handling following thyroidectomy could have an influence on the RAS components.

INTRODUCTION
Previous studies have revealed important alterations of the renin-angiotensin system (RAS) in cases of thyroid dysfunction.

When hypothyroidism is induced in adult animals, a decrease in plasma renin activity (PRA) and plasma renin concentration (PRC) has been observed (1, 2). However, studies performed in animals whose hypothyroidism was induced in the early stages of life showed RAS changes different from those described in adult hypothyroid animals. Some authors have described a decrease in PRA in young thyroidectomized animals with no changes in PRC (3), while others have reported a PRC increase with no changes in PRA (4). Both studies reported the decrease of plasma renin substrate (PRS).

Since the maintenance of adequate thyroid hormones levels is important to ensure correct growth and maturation of the kidney during development, the renal dysfunction caused by a deficiency of thyroid hormones (5) could contribute to the different changes in RAS observed in young and adult hypothyroid animals.

The aim of this work was to study the evolution of RAS in thyroidectomized animals during a brief postnatal period, between the 4th and 10th week of age, in order to determine if they are related to the disturbances of kidney function observed during this period.

MATERIALS AND METHODS

Animals, thyroidectomy, and sample collection
Male Wistar rats, controlled from birth and fed a standard diet, containing 146 mEq/kg of sodium and 192 mEq/kg of potassium, were used for this study. Two groups of animals were selected after birth:
- Test animals: 18 rats were thyroidectomized surgically under ether anesthesia at the end of the 4th week of life. The parathyroid glands were reimplanted before closing the incision. To ensure complete elimination of thyroid tissue each animal received 250 fCi\textsuperscript{131}I ip within 24 h after thyroidectomy. No signs of tetany were seen. The effectiveness of thyroidectomy was confirmed by a marked decrease in both the growth rate and the circulating levels of thyroid hormones, as determined by radioimmunoassay (6). These animals were sacrificed in groups of 6 at 2-week intervals (6, 8 and 10 weeks after birth).
- Control animals: 24 euthyroid rats were also sacrificed in groups of 6 at 2 week intervals, starting on the fourth week after birth (4, 6, 8 and 10 weeks of age). Sacrifice was performed under anesthesia with sodium pentobarbitone (Nembutal, Abbott Lab,) in all cases. One day prior to sacrifice the animals were kept in individual metabolic cages for the collection of 24-h urine samples. Aortic blood samples were taken and divided into two aliquots, one containing 50 µl 6% EDTA. Both aliquots were centrifuged at 2500x g for 15 min at 4 C. The plasma and serum obtained were stored at —20 C until use.

Renin-angiotensin system assay
Plasma renin concentration (PRC), plasma renin substrate (PRS) and plasma renin activity (PRA) were
RESULTS

Hypothyroidism confirmation

In euthyroid rats T₄ increased from the 4th to the 8th week of life, stabilizing until the 10th. However, in hypothyroid animals T₄ decreased sharply between the 4th and the 6th week and gradually until the 10th. In euthyroid animals T₃ was stable between the 4th and 10th week, while in thyroidectomized rats it was undetectable from the 6th week (Fig. 1).

Renin-angiotensin system in thyroidectomized rats

Changes in the kinetic parameters of the renin-angiotensin system are shown in Table 1. No alterations in PRA were observed in euthyroid or hypothyroid animals either during postnatal development, or in the comparison of both groups. However, the PRC of euthyroid animals decreased uniformly until the 8th week of life and increased between the 8th and the 10th week. In thyroidectomized rats an increase in PRC was observed in the 6th week and remained significantly higher than that observed in euthyroid rats.

In both hypothyroid and euthyroid animals PRS decreased gradually between the 4th and the 8th week, but in euthyroid rats it increased from the 8th to the 10th week while in thyroidectomized animals the decrease continued.

In this period of development an increase in ALL was observed in euthyroid animals, while in hypothyroid rats ALL decreased gradually from the fourth week of life.

Renal function in thyroidectomized rats

The effects of thyroidectomy on glomerular filtration rate (GFR) and fractional sodium excretion (FE₉Na) are shown in Figure 2. Thyroidectomy caused a reduction in GFR, which was significantly lower from the eighth week when compared with euthyroid animals. FE₉Na increased gradually in thyroidectomized animals in such a way that at the 8th week of life it was statistically higher than that of euthyroid animals.

DISCUSSION

It is well known that thyroid hormones regulate the growth and development of various tissues and organs in the first period of life. Specifically, the administration of thyroid hormones to normal animals accelerates renal growth, especially when they are administered in hypothyroid states (11). On the contrary, a deficit of thyroid hormones retards cellular differentiation and renal maturation (5), which can cause crucial perturbations in renal hemodynamics and nephron control of salt and water equilibrium.

In agreement with other observations, thyroidectomy in young animals reduced the glomerular filtration rate (GFR) and increased the renal fractional excretion of sodium (FE₉Na) (12, 13). General cardiovascular effects of the hypothyroid state - reduction of both cardiac output and renal plasma flow - seem to be an adequate explanation for GFR reduction (14), and the atrophy of nephron segment and the low tubular Na-K-ATPase activity observed in hypothyroidism seem to be the principal causes of FE₉Na increase (15).