Effects of Thyroid Status on Renal Calcium and Magnesium Handling

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ABSTRACT

Renal calcium and magnesium handling was studied in rats with chronic thyroid hormone deficiency or excess, hyperthyroidism. Mean kidney weight of the thyroid deficient rats was 42% of age matched, euthyroid and hyperthyroid animals and glomerular filtration rate was 71% of normal. Fractional sodium excretion was consistently elevated in thyroid deficient rats (0.26%) as compared to euthyroid (0.07%) and hyperthyroid animals (0.07%). Urinary calcium excretion (0.39%) was also elevated and parallel to sodium excretion in thyroid deficiency. Despite this renal leak of sodium and calcium, thyroid deficient animals conserved magnesium much more efficiently than either euthyroid or hyperthyroid rats (5.7% vs 17.4% respectively). Plasma magnesium concentration was elevated by acute $MgCl_2$ infusions to determine the reabsorptive capacity of magnesium. Thyroid deficient rats reabsorbed 15-30% more of the filtered magnesium at any given plasma concentration. Although these effects on electrolyte reabsorption are modest compared to the hemodynamic alterations, the data suggest that thyroid hormone has a direct effect on the tubule which if chronically absent results in subtle sodium and calcium wasting and renal retention of magnesium. Administration of thyroid hormone to euthyroid or thyroid deficient rats twenty-four hours prior to experimentation had no effect on calcium and magnesium handling.

Key words: Hypothyroid, hyperthyroid, rat, calcium, magnesium.

RÉSUMÉ

Cette expérience visait à étudier le métabolisme rénal du calcium et du magnésium, chez des rats atteints d'un hypothyroïdisme ou d'un hyperthyroïdisme chroniques. Le poids moyen des reins des rats hypothyroïdiens équivalait à 42% de celui de congénères euthyroïdiens ou hyperthyroïdiens, de même âge, et le taux de filtration glomérulaire atteignait 71% de la normale. L'excrétion fractionnaire du sodium s'avéra constamment élevée, chez les rats hypothyroïdiens (0,26%), comparativement à leurs congénères euthyroïdiens et hyperthyroïdiens, où elle n'atteignit que 0,07%. L'excrétion urinaire du calcium s'avéra aussi élevée (0,39%) et parallèle à celle du sodium, chez les rats hypothyroïdiens. En dépit de cette perte rénale de sodium et de calcium, les rats hypothyroïdiens retinrent le magnésium beaucoup plus efficacement que leurs congénères euthyroïdiens (5,7%) ou hyperthyroïdiens (17,4%). Des infusions rapides de $MgCl_2$, destinées à déterminer la capacité de réabsorption du magnésium, provoquèrent une élévation de cet électrolyte dans le plasma. Les rats hypothyroïdiens réabsorbèrent de 15 à 30% plus de magnésium filtré, indépendamment de sa concentration plasmatique. Même si ces effets sur la réabsorption des électrolytes semblent modestes, par rapport aux altérations hémodynamiques, les résultats de l'expérience suggèrent que la thyroxine exerce une influence directe sur les tubules rénaux et qu'une absence prolongée de cette influence entraîne une perte subtile de sodium et de calcium, ainsi qu'une rétention de magnésium, par les reins. L'administration de thyroxine à des rats euthyroïdiens, 24 heures avant l'expérience, n'exerça aucune influence sur le métabolisme rénal du calcium et du magnésium.

Mots clés: hypothyroïdien, hyperthyroïdien, rat, calcium, magnésium.

INTRODUCTION

Changes in thyroid function have been associated with alterations of calcium and magnesium metabolism. However the renal effects are not well described and more importantly the mechanisms are incompletely understood. Hypercalcemia occurs not infrequently in hyperthyroidism (1,2) and has been reported as well in thyroid deficiency (1,3). Moreover, hypercalcuria has been reported in hyperthyroidism (4,5) although this is not a uniform finding (6). Plasma magnesium concentration appears to be consistently elevated in thyroid deficiency, possibly due to renal retention (7,8). Serum magnesium levels on the other hand are decreased in hyperthyroidism and urinary excretion of magnesium is increased in these patients. The data are interpreted as thyroid hormone having a direct effect on tubular calcium and magnesium reabsorption in addition to its numerous effects on blood flow, glomerular filtration rate and tubular sodium transport.

The present studies were designed to determine the chronic effect of hyperthyroidism and hypothyroidism on renal calcium and magnesium handling in the rat.

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MATERIALS AND METHODS

Male Wistar rats, with an initial weight of 90-120 g, were used in all experiments. They were maintained on normal laboratory chow containing 1.2% calcium, 0.26% magnesium and 0.86% phosphorus (Ralston Purina Co., St. Louis, Missouri). The animals had free access to the diet and tap water up to the time of experimentation. The sodium content of the regular lab chow was sufficient to keep the hypothyroid rats in sodium balance (9). Hypothyroidism or thyroid deficiency was induced by intraperitoneal injection of 1 mCi of [^{131}I] sodium radioiodide (New England Nuclear, Boston, Massachusetts). Rats subjected to chemical thyroidectomy were given a low iodine diet (ICN Nutritional Biochemicals Div., International Chemical & Nuclear Corp., Cleveland, Ohio) for ten days prior to the radioiodide injection (10). The development of hypothyroidism was suggested by a retardation of growth and the absence of thyroid gland tissue at the time of experimentation. Plasma triiodothyronine (T_3) and thyroxine levels (T_4) were less than 10 ng/100 mL and 1 μg/100 mL, respectively (11). Hyperthyroidism was produced by daily intraperitoneal injections of sodium levothyroxine, 50 μg/100 g body wt (Synthroid, Flint Laboratories Div., Travenol Laboratories).

CLEARANCE STUDIES

All rats were studied 70-90 days after either the ^{131}I administration or the initiation of hyperthyroidism. Age-matched, euthyroid control rats were identically handled and studied simultaneously. The animals had free access to water and food up to the time of surgery. Anesthesia was induced by intraperitoneal injection of 100 mg/kg body weight Inactin (Promonta, Hamburg, W. Germany). In view of their sensitivity to anesthesia, hypothyroid rats received smaller amounts of Inactin (70-80 mg/kg). Thereafter, animals were placed on a temperature-controlled operating table and a tracheostomy was performed. Thyroid deficient animals were parathyroidectomized and euthyroid and hyperthyroid rats were thyroparathyroidectomized with electrocautery, a minimal of one hour prior to experimentation. This procedure was performed to provide a similar background of circulating parathyroid hormone in each of the different experimental groups. Thyroid hormones, T_3 and T_4 have a prolonged half life of 6 and 14 h respectively, and the circulating concentrations would presumably be constant throughout the experiment (1). The jugular and femoral veins were cannulated for fluid infusions and the carotid artery was catheterized for blood pressure measurements and blood sampling. Urine was collected via a PE 90 polyethylene catheter placed in the bladder through a suprapubic incision. Urine was collected into tared polyethylene containers under paraffin oil and quantitated by reweighing the containers. A primary dose (0.5 mL/100 g) of 4% inulin in modified Ringer solution was infused followed by a sustaining infusion given at 20 μL/min. The composition of the modified Ringer in mEq/L was: Na^+ 145, K^+ 4.5, Ca^{2+} 5.0, Mg^{2+} 1.0, Cl^- 110, and HCO_3^- 25 mM. 3H- inulin (New England Nuclear, Boston, Massachusetts) was added to this infusion to produce counts in excess tenfold background in 10 μL of plasma. Animals were equilibrated for one hour prior to performing standard 20-30 min clearance periods. Renal magnesium transport capacity was evaluated by elevating plasma magnesium concentration. Euthyroid and hyperthyroid rats received Ringer solution in the first phase, 160 mEq/L $MgCl_2$ in the second and finally 320 mEq/L $MgCl_2$ in the third phase. The $MgCl_2$ solutions were made up in Ringer solution and infused at 10 μL/min·100 g body weight. Thyroid deficient rats received Ringer solution in the control phase, 120 mEq/L $MgCl_2$ in the second phase, and 240 mEq/L $MgCl_2$ in the third phase. Infusion rates were set at 10 μL/min·100 g body weight. The lower concentrations of magnesium in the infusion solution in the thyroid deficient rats were necessary to achieve plasma magnesium levels comparable to the euthyroid and hyperthyroid rats. This is probably due to the lower levels of exchangeable cellular magnesium previously reported in thyroid deficiency (7,12). Each phase consisted of two consecutive 20-30 min clearance periods which were averaged and reported as the mean result. At the end of the clearance experiments the kidneys were removed and freed of the renal capsule and hilar fat and weighed after light blotting on filter paper.

An additional two series of experiments were performed to determine the acute effects of thyroid hormone. Clearance studies were done on euthyroid (control) and chronic thyroid deficient rats with the same protocol as given above except that levothyroxine (30 mg·hr-1·100 g-1 body wt) was given as a single intraperitoneal injection 21 hours prior to the experiment. The animals in this series of experiments were matched for body weight rather than age-matched. The data from these two groups is indicated by euthyroid +T_4 and thyroid deficient +T_4.

ANALYTICAL METHODS

Inulin -[^{3}H] concentrations in plasma and urine were determined by liquid scintillation in Aquasol (New England Nuclear, Boston, Massachusetts). Plasma protein was determined by refractometry (15). Urine and plasma were analyzed for sodium and potassium by flame photometry (Corning 450, Corning Scientific Instruments Co., Medfield, Massachusetts) and calcium and magnesium by atomic absorption spectrophotometry (Jarrell-Ash 850, Fisher Scientific, Montreal, Quebec). Phosphate was determined by the colorimetric method of Chen *et al* (13). Plasma ultrafiltrates were prepared using Amicon Centriflo ultrafiltration cones (Amicon Co., Lexington, Massachusetts) as previously described (14). Ultrafilterable calcium and magnesium was 65±3% and 72±5% respectively and were similar in the three groups of rats. Thyroxine and triodothyronine concentrations were determined by standard radioimmunoassay techniques. The lower limits of sensitivity for T_4 and T_3 was 1 μg/100 mL and 10 ng/100 mL, respectively.

The glomerular filtration rate (GFR) was determined by the clearance of radioactive inulin and the electrolyte excretion rates were reported as fractional excretion (FE) which is the percent of electrolyte filtered at the glomerulus which appeared in the urine. Statistical analyses included

Student's t test and linear regression analysis where appropriate. All data are presented as mean ± SE.

RESULTS

Table I summarizes the mean body weight, kidney weight and inulin clearance data of the various groups of rats. All animals were initially age-matched and were of the same weight range. The data were obtained at the end of a ten week period. The body weights of the thyroid deficient and hyperthyroid rats were significantly less than euthyroid animals. Kidneys were much smaller in thyroid deficient rats and larger in hyperthyroid rats compared with euthyroid animals. The glomerular filtration rates were significantly lower in the thyroid deficient animals compared to the other groups of animals and not proportional to the kidney weight (12). The present results are based on fractional excretion or glomerular filtration rate, however the interpretations of the data are the same whether based on filtration rate or kidney weight. Arterial hematocrit was lower in thyroid deficient rats compared to euthyroid rats (41 vs 49%) and plasma total protein concentration was higher (6.3 vs 5.9 g/100 mL respectively). There was no difference in these parameters between hyperthyroid and euthyroid animals. The mean blood pressure in thyroid deficient state was somewhat less than in the presence of thyroid hormone (100±8 vs 120±5 mmHg, respectively).

TABLE I. Effect of Chronic Thyroid Deficiency and Hyperthyroidism on Body Weight, Kidney Size and Glomerular Filtration Rate

Group	(n)	age wks	Body wt. g	Kidney wt. g	GFR mL/min
Euthyroid	(6)	12	371 ± 14	1.01 ± 0.10	1.38 ± 0.09
Thyroid deficient	(7)	12	210 ± 3[a]	0.59 ± 0.03[a]	0.41 ± 0.04[a]
Hyperthyroid	(6)	12	315 ± 15[a]	1.25 ± 0.13[a]	1.22 ± 0.21
Euthyroid +T_4	(5)	7	192 ± 10	0.89 ± 0.07	0.91 ± 0.08
Thyroid deficient +T_4	(6)	12	189 ± 9	0.55 ± 0.07[a]	0.42 ± 0.14[a]

Values are means ± SE. The statistics include unpaired Student's t test of experimental animals with the control rats (euthyroid)

[a]Indicates a minimum significance of $p < 0.05$. Euthyroid +T_4 and thyroid deficient +T_4 are control and chronic thyroid deficient rats given acute infusions of levothyroxine in saline, 21 h before experimentation

CONTROL CLEARANCES

Control blood and clearance data for thyroid deficient, euthyroid and hyperthyroid rats is summarized in Table II. Fractional water, sodium and potassium excretion was significantly higher in thyroid deficient animals compared to either euthyroid

TABLE II. Renal Clearance Data of Age-Matched Thyroid Deficient, Euthyroid and Chronic Hyperthyroid Rats

Group	(n)	C_{In} mL/min	FE_{H_2O} %	P_{Na} mEq/L	FE_{Na} %	P_K mEq/L	FE_K %
Thyroid Deficient							
Control	(7)	0.41 ± 0.04[a]	0.47 ± 0.04[a]	152 ± 1	0.26 ± 0.05[a]	4.63 ± 0.20[a]	23 ± 3[a]
Mg infusion I	(7)	0.51 ± 0.06[a]	0.54 ± 0.03[a]	148 ± 1	0.32 ± 0.05[a]	4.25 ± 0.09[a]	22 ± 2
Mg infusion II	(7)	0.56 ± 0.09[a]	0.95 ± 0.11	146 ± 1	0.65 ± 0.17	3.73 ± 0.08[a]	25 ± 2
Euthyroid							
Control	(6)	1.39 ± 0.09	0.29 ± 0.02	151 ± 2	0.08 ± 0.02	5.16 ± 0.19	12 ± 2
Mg infusion I	(6)	1.73 ± 0.25	0.41 ± 0.02	150 ± 2	0.13 ± 0.04	4.56 ± 0.15	25 ± 1
Mg infusion II	(4)	1.73 ± 0.10	1.22 ± 0.02	147 ± 1	1.09 ± 0.40	4.10 ± 0.22	30 ± 2
Hyperthyroid							
Control	(6)	1.22 ± 0.21	0.24 ± 0.02	151 ± 1	0.07 ± 0.01	5.07 ± 0.16	5 ± 1[a]
Mg infusion I	(6)	1.92 ± 0.31	0.27 ± 0.02[a]	152 ± 1	0.07 ± 0.02	5.14 ± 0.24[a]	9 ± 3[a]
Mg infusion II	(5)	1.69 ± 0.36	0.47 ± 0.05[a]	149 ± 1	0.21 ± 0.06[a]	5.10 ± 0.39[a]	15 ± 3[a]

TABLE II. (Cont.) Renal Clearance Data of Age-Matched Thyroid Deficient, Euthyroid and Chronic Hyperthyroid Rats

Group	(n)	P_{Ca} mEq/L	FE_{Ca} %	P_{Mg} mEq/L	FE_{Mg} %	P_{Pi} mM	Fe_{Pi} %
Thyroid Deficient							
Control	(7)	3.75 ± 0.12[a]	0.39 ± 0.05[a]	1.69 ± 0.06	5.7 ± 0.4[a]	2.26 ± 0.10[a]	2.84 ± 1.16[a]
Mg infusion I	(7)	3.48 ± 0.12[a]	1.90 ± 0.60	3.44 ± 0.12[a]	32.4 ± 5.3	2.18 ± 0.14	2.84 ± 1.16[a]
Mg infusion II	(7)	3.32 ± 0.13[a]	5.02 ± 0.85	5.68 ± 0.30[a]	64.9 ± 4.0	2.32 ± 0.15[a]	1.60 ± 0.64[a]
Euthyroid							
Control	(6)	4.64 ± 0.22	0.26 ± 0.04	1.64 ± 0.04	17.4 ± 1.9	3.52 ± 0.06	0.12 ± 0.05
Mg infusion I	(6)	4.44 ± 0.09	2.58 ± 0.71	2.50 ± 0.13	43.5 ± 3.2	3.78 ± 0.06	0.10 ± 0.04
Mg infusion II	(4)	4.18 ± 0.14	8.16 ± 2.12	4.01 ± 0.20	61.6 ± 7.0	4.21 ± 0.34	0.10 ± 0.03
Hyperthyroid							
Control	(6)	4.87 ± 0.09	0.34 ± 0.05	2.07 ± 0.13[a]	17.2 ± 2.1	3.30 ± 0.22	0.18 ± 0.05
Mg infusion I	(6)	4.59 ± 0.14	0.41 ± 0.04[a]	2.77 ± 0.08	29.4 ± 3.3[a]	3.34 ± 0.20	0.11 ± 0.01
Mg infusion II	(5)	4.37 ± 0.15	2.75 ± 1.13[a]	3.86 ± 0.11	46.4 ± 7.4	3.60 ± 0.27	0.33 ± 0.21

[a]Indicates a minimum of $p < 0.01$ significance between the respective clearance periods (control, Mg infusion I, Mg infusion II) of thyroid deficient and hyperthyroid rats compared to the euthyroid, control rats. Abbreviations: C_{In}, glomerular filtration rate; FE_X, fractional excretion of electrolyte X; P_X, plasma concentration of X; Pi, phosphate

or hyperthyroid rats. Absolute urinary water and sodium excretion was about the same for the three series of rats (3.9 ± 0.4 μL/min and 0.32 ± 0.07 μEq/min respectively); however, due to the markedly different filtered loads the thyroid deficient animals had a lower baseline reabsorptive rate (9,12). Plasma sodium concentration was the same in the three experimental groups. Plasma calcium concentration was significantly lower in chronic thyroid deficient animals (3.75 mEq/L) as compared to euthyroid or hyperthyroid rats (4.64 mEq/L) and urinary calcium excretion was higher (0.26 vs 0.39%, respectively). Figure 1 illustrates the control values for each of the three groups of animals. In contrast plasma magnesium was normal in thyroid deficient animals (1.69 mEq/L) and urinary magnesium excretion was markedly lower than euthyroid or hyperthyroid rats (6 vs 17%, respectively). Plasma magnesium concentration was higher in hyperthyroid rats (2.07 mEq/L), however urinary magnesium excretion was the same as euthyroid animals. Figure 2 illustrates the effect of thyroid deficiency on urinary magnesium excretion. Chronic thyroid deficient rats which were parathyroidectomized had a lower plasma phosphate concentration (2.3 vs 3.5 mM) and higher urinary phosphate excretion (2.84 vs 0.12%) compared to either euthyroid or hyperthyroid animals.

In summary, thyroid deficiency resulted in a lower plasma calcium concentration and a higher urinary calcium excretion and a much lower urinary magnesium excretion compared to the normal animals. Hyperthyroidism resulted in slightly higher plasma magnesium concentration, however the urinary magnesium excretion was similar to normal euthyroid rats.

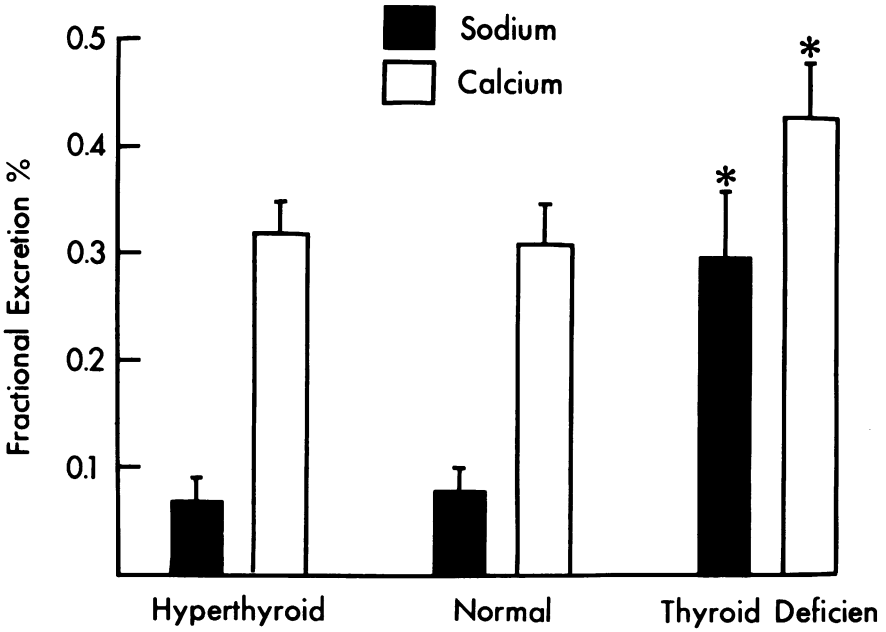

Fig. 1. Effect of chronic thyroid deficiency and hyperthyroidism on urinary excretion of sodium and calcium. * indicates significance ($p < 0.001$) from normal euthyroid rats.

MAGNESIUM TRANSPORT CAPACITY

To determine the effect of chronic thyroid status on magnesium transport capacity, the three series of rats were subjected to graded infusions of $MgCl_2$. Table II summarizes the mean blood values and clearance data. The results of $MgCl_2$ infusion in normal euthyroid rats are similar to that previously reported by our laboratory (15). Fractional water and sodium excretion increased modestly as urinary calcium and magnesium increased in stepwise fashion with graded elevation of plasma magnesium. Normally a close association exists between renal transport of calcium and magnesium such that urinary excretion of the divalent cations increases to a greater extent than can be accounted for by the concurrent natriuresis (15). Plasma calcium concentration fell, presumably due to the markedly increased urinary calcium excretion. Similar observations were observed in the chronic thyroid deficient rats, however the fractional changes were not quantitatively the same. Figure 3 illustrates the effect of graded elevation of plasma magnesium on fractional magnesium excretion. Urinary magnesium excretion was significantly less in thyroid defi-

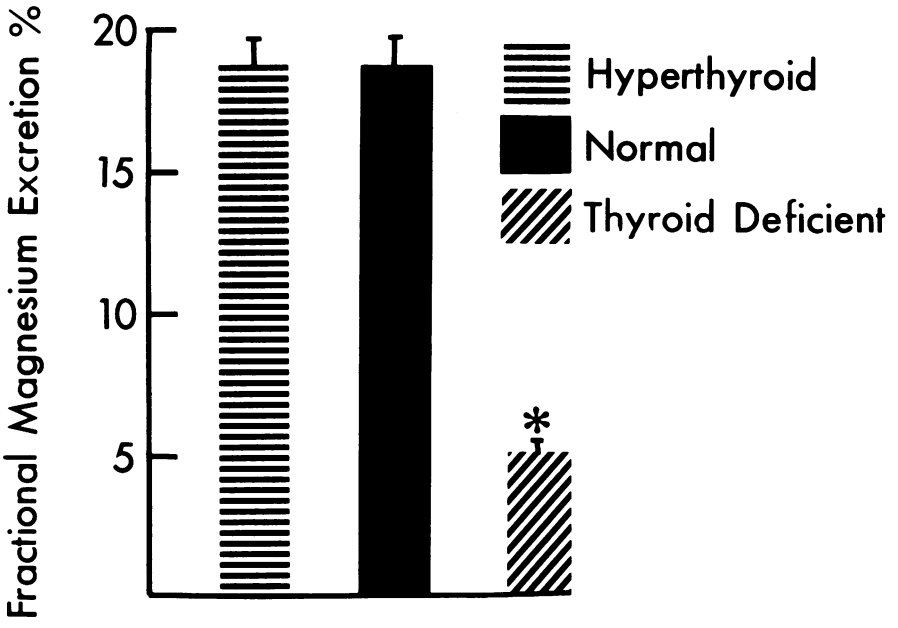

Fig. 2. Effect of chronic thyroid deficiency on the renal conservation of magnesium. * indicates significance ($p < 0.001$) from normal euthyroid rats.

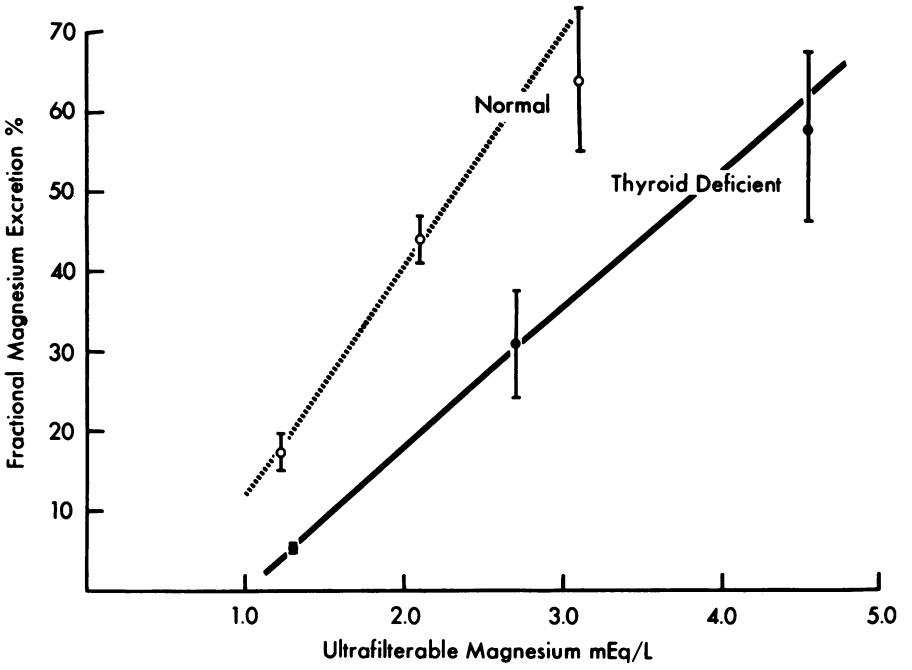

Fig. 3. Capacity of renal magnesium transport in thyroid deficient and euthyroid rats. The plasma magnesium concentration and filtered load was acutely elevated by $MgCl_2$ infusion. Fractional magnesium excretion in thyroid deficient rats was significantly less than normal at all levels of plasma magnesium concentration. Statistical significance was assessed by linear regression analysis.

cient rats at all levels of extracellular magnesium concentration demonstrating the enhanced renal transport capacity for magnesium in thyroid deficiency. On the other hand, urinary calcium excretion increased by similar amounts was observed for euthyroid rats even though the plasma calcium concentration was significantly lower in thyroid deficient animals as compared to the euthyroid rats. Despite the hypocalcemia the renal calcium leak in thyroid deficient rats persisted as observed in the control first phase.

Graded $MgCl_2$ infusion resulted in a very modest rise in both urinary sodium and calcium excretion in hyperthyroid rats as compared to euthyroid or thyroid deficient animals. Urinary magnesium excretion followed a pattern not different from the normal euthyroid animals.

Urinary phosphate excretion was noticeably higher in thyroid deficient parathyroidectomized rats as compared to euthyroid or hyperthyroid experimental groups although plasma phosphate was significantly lower. These values did not change with magnesium infusion. Fractional potassium excretion was significantly lower in all three phases of hyperthyroid rats.

Pharmacological amounts of levothyroxine were acutely administered to euthyroid and thyroid deficient rats 21 h prior to clearance studies to determine the acute response to thyroid hormone. Control plasma and urinary data were not different from the respective groups which did not receive thyroid hormone. Table III summarizes the fractional urinary magnesium excretion as a function of plasma magnesium concentration. The acute administration of thyroid hormone did not alter the transport capacity for magnesium.

TABLE III. Renal Clearance Data of Euthyroid and Chronic Thyroid Deficient Rats Acutely Given T_4 Infusion

Group	(n)	C_{In} mL/min	FE_{H_2O} %	P_{Na} mEq/L	FE_{Na} %	P_K mEq/L	FE_K %
Euthyroid + T_4							
Control	(5)	0.86 ± 0.04[a]	0.40 ± 0.05	143 ± 4	0.16 ± 0.04	4.72 ± 0.18	11 ± 2
Mg infusion I	(5)	0.84 ± 0.11	0.31 ± 0.03	144 ± 5	0.12 ± 0.05	4.74 ± 0.11	12 ± 1
Mg infusion II	(5)	0.94 ± 0.08	0.65 ± 0.12	142 ± 6	0.15 ± 0.06	4.70 ± 0.10	18 ± 3
Thyroid Deficient + T_4							
Control	(6)	0.42 ± 0.09[a]	0.52 ± 0.13	152 ± 2	0.24 ± 0.09[a]	4.87 ± 0.51	18 ± 2[a]
Mg infusion I	(6)	0.52 ± 0.06[a]	0.70 ± 0.04[a]	150 ± 1	0.37 ± 0.06[a]	4.09 ± 0.42	18 ± 2[a]
Mg infusion II	(5)	0.66 ± 0.05[a]	1.01 ± 0.04[a]	145 ± 1	0.93 ± 0.11[a]	3.32 ± 0.06[a]	21 ± 2

TABLE III. (Cont.) Renal Clearance Data of Euthyroid and Chronic Thyroid Deficient Rats Acutely Given T_4 Infusion

Group	(n)	P_{Ca} mEq/L	FE_{Ca} %	P_{Mg} mEq/L	FE_{Mg} %	P_{Pi} mM	Fe_{Pi} %
Euthyroid + T_4							
Control	(5)	4.57 ± 0.07	0.05 ± 0.12	1.59 ± 0.02	23.2 ± 2.1	3.63 ± 0.16	0.29 ± 0.11
Mg infusion I	(5)	4.00 ± 0.15	0.54 ± 0.21	2.24 ± 0.12	27.7 ± 5.2	3.36 ± 0.11	0.08 ± 0.04
Mg infusion II	(5)	3.99 ± 0.11	1.95 ± 0.30	2.94 ± 0.15	42.4 ± 4.3	3.26 ± 0.21	0.09 ± 0.05
Thyroid Deficient + T_4							
Control	(6)	3.37 ± 0.48[a]	0.05 ± 0.21[a]	1.81 ± 0.07[a]	7.1 ± 0.79[a]	2.16 ± 0.05[a]	2.77 ± 0.66[a]
Mg infusion I	(6)	3.54 ± 0.35	1.12 ± 0.12[a]	3.42 ± 0.30[a]	33.8 ± 6.7	3.23 ± 0.63	1.94 ± 0.93[a]
Mg infusion II	(5)	3.73 ± 0.23	2.21 ± 0.40	4.66 ± 0.10[a]	55.3 ± 3.4[a]	2.81 ± 0.26	0.43 ± 0.17[a]

[a]Indicates a minimum of $p < 0.01$ significance between the clearance periods (control, Mg infusion I, Mg infusion II) of thyroid deficient and the respective clearance of euthyroid rats

Abbreviations: C_{In}, glomerular filtration rate; FE_X, fractional excretion of electrolyte X; P_X, plasma concentration of X; Pi, phosphate

DISCUSSION

The present clearance results are expressed as fractional excretions and are therefore based on the glomerular filtration rate (GFR). Thyroid disorders markedly affect body and organ growth and renal hemodynamics however these parameters are altered disproportionately which presents a problem in normalization of clearance data. This has been extensively reviewed by Bradley *et al* (12). Presumably the important parameter is "active renal cell mass". Thus kidney size is perhaps the most useful index in which to normalize the reabsorption data. Disturbances of thyroid function are accompanied by widespread alterations in renal hemodynamics and tubular handling of sodium. In the rat, hypothyroidism is associated with a decrease in renal plasma flow and glomerular filtration rate (12), a limited urinary concentrating ability (16) and an impairment in the renal conservation of sodium (17). The higher urinary sodium excretion leads to a subtle salt wasting (18) and an exaggerated natriuretic response to extracellular volume expansion (19). These responses appear to be independent of mineralocorticoid hormones (20) and chronic treatment with thyroxin restores normal functional responses (21). The effects of hypothyroidism or hyperthyroidism on renal calcium and particularly magnesium handling are largely unknown. Hypercalcemia is frequently observed in patients during the course of hyperthyroidism (2,22). Thyrotoxic patients commonly have an increased urinary magnesium excretion and normal intracellular magnesium concentration (7). Plasma magnesium tends to be elevated in hypothyroidism (7) presumably as a result of renal retention which has been thought to be the result of hypofiltration (1). Intracellular magnesium concentration has been reported to be low in thyroid deficiency (7). The objective of the present study was to characterize the renal handling of calcium and magnesium as it pertains to the alteration in thyroid function.

Calcium reabsorption normally parallels sodium in the proximal convoluted tubule and both are affected in the same way by extracellular fluid expansion or depletion (23). In the more distal tubule, the two processes may be dissociated by such agents as parathyroid hormone, chlorothiazide and acid-base alterations (23). In the present study urinary calcium excretion was significantly greater in thyroid deficient rats compared to euthyroid and hyperthyroid animals. The greater calcium excretion persisted despite markedly lower plasma calcium concentrations indicating the presence of a renal defect in calcium transport in thyroid deficient animals. Moreover the urinary calcium excretion was of a similar magnitude to that observed for sodium transport. Lebwohl *et al* (6) demonstrated that the parallel renal calcium and sodium leak was independent of extracellular volume changes. Michael *et al* (9) performed micropuncture studies to determine the action of thyroid hormone on tubular sodium handling. They reported a direct effect on both proximal and distal sodium reabsorption (9). Sodium and perhaps calcium reabsorption would appear to be depressed throughout the entire nephron in thyroid deficiency.

The renal handling of magnesium in normal animals is noticeably different from calcium. In contrast to calcium, magnesium is reabsorbed to a much less extent in the proximal and distal tubule compared to the loop of Henle (thick ascending limb) which plays a pivotal role in renal magnesium reabsorption and magnesium homeostasis. Thyroid deficiency leads to a marked renal conservation of magnesium. Control urinary excretion was only 25% of the euthyroid animals despite the existing natriuresis and hypercalcemia. Furthermore, the transport capacity for magnesium was greater at all delivery rates as indicated by results from the studies with graded magnesium infusions (Fig. 1). This may suggest that the thick ascending limb of Henle largely retains normal function in thyroid deficiency. Alternatively it may reflect a degree of hypocalcemia in the thyroid deficient rats. We have shown that magnesium reabsorption within Henle's loop is regulated in a major way by the absolute concentration of plasma calcium and/or plasma magnesium (15,24,25). Hypocalcemia would be expected to increase both calcium and magnesium reabsorption. However, this explanation is not supported by the graded hypermagnesemic studies in which calcium excretion rose to a similar extent in the hypocalcemic, thyroid deficient animals as that observed for the normocalcemic, euthyroid rats. Thus the deficiency of thyroid hormones appears to alter the cellular transport of magnesium. This is supported by clinical observations in which plasma magnesium values have been reported to be elevated in hypothyroid patients, presumably as a result of renal retention (7).

In hypothyroid rats the reabsorptive capacity for magnesium is elevated at all levels of magnesium filtration rates despite the inability of the kidney to retain sodium and calcium (15). These were not dependent on changes in circulating parathyroid hormone. The cellular mechanisms responsible for these changes are unknown, but thyroid hormones enhance Na-K ATPase activity (26). This is associated with parallel changes in sodium reabsorption allowing the cell to maintain low intracellular sodium and calcium content and relatively high intracellular magnesium concentrations (27). These cellular changes may provide a common explanation for the alterations in renal handling of sodium, calcium and magnesium in hypothyroidism. Maximal tubular reabsorption of phosphate is increased following chronic administration of T_3 (28). The effect of thyroid hormone on the tubular handling of phosphate appears to be independent of parathyroid hormone or extracellular volume expansion (28). This is supported by the present studies as the urinary phosphate excretion was significantly higher in thyroid deficient rats compared to euthyroid animals in the absence of parathyroid hormone. Hypophosphatemia in these animals may be in part due to this renal tubular phosphate leak and may in part stem from the hypocalcemia and/or the expected chronic elevation of parathyroid hormone levels in the intact thyroid deficient rats. The cellular mechanisms underlying the alteration of tubular phosphate reabsorption by thyroid hormone are not clear. Thyroid hormones enhance Na-K-ATPase activity, a phenomenon which has been shown to be associated with parallel changes in sodium reabsorp-

tion (12,26). Sodium transport may influence phosphate reabsorption, possibly through a membrane co-transport step which thus would be expected to be affected in parallel fastion (29).

In summary, the kidney demonstrates a remarkable capacity to adjust to the marked changes resulting from thyroid disease (12). Overall renal magnesium and calcium balances are not grossly altered but subtle changes do occur. These changes may result in situations such as hypercalcemia which is occasionally observed in hyperthyroidism. In addition, the results presented here indicate an alteration in the homeostasis of calcium and magnesium in the hypothyroid rat. Urinary calcium and sodium excretion are increased in a parallel fashion despite the rather marked hypocalcemia observed in the parathyroidectomized, thyroid deficient rats. Magnesium on the other hand is remarkably conserved at all levels of filtered magnesium suggesting a direct effect of thyroid hormones on tubular magnesium transport. The acute removal of the thyroid glands, which is often performed in clearance and micropuncture studies (14,24,25), does not appreciably alter magnesium and calcium reabsorption over the short duration of study.

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