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Biochemistry

Thyroid hormones increase Na^+–H^+ exchange activity in renal brush border membranes

(**Na^+ reabsorption/Na^+-dependent phosphate uptake/hyperthyroid animals/increase in phosphate transport**)

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ABSTRACT **Na^+–H^+ exchange activity, i.e., amiloride-sensitive Na^+ and H^+ flux, in renal proximal tubule brush border (luminal) membrane vesicles was increased in the hyperthyroid rat and decreased in the hypothyroid rat, relative to the euthyroid animal. A positive correlation was found between Na^+–H^+ exchange activity and serum concentrations of thyroxine (T4) and triiodothyronine (T3). The thyroid status of the animal did not alter amiloride-insensitive Na^+ uptake. The rate of passive pH gradient dissipation was higher in membrane vesicles from hyperthyroid rats compared to the rate in vesicles from hypothyroid animals, a result which would tend to limit the increase in Na^+ uptake in vesicles from hyperthyroid animals. Na^+-dependent phosphate uptake was increased in membrane vesicles from hyperthyroid rats; Na^+-dependent D-glucose and L-proline uptakes were not changed by the thyroid status of the animal. The effect of thyroid hormones in increasing the uptake of Na^+ in the brush border membrane vesicle is consistent with the action of the hormones in enhancing renal Na^+ reabsorption. Further, the regulation of transtubular Na^+ flux has now been shown to be concomitant with modulation of the entry of Na^+ into the tubular cell across its luminal membrane, mediated by the exchange reaction, and with the previously reported control of the pumping of Na^+ out of the cell across its basolateral membrane, mediated by the Na^+,K^+-ATPase.**

Thyroid hormones (thyroxine, T4; triiodothyronine, T3) have a significant role in controlling kidney growth and function. The hormones are important regulators of renal plasma flow, glomerular filtration rate, concentration and dilution of urine, oxygen consumption, and the reabsorption of phosphate, Ca^{2+}, and Na^+ (1, 2). Thyroid hormones stimulate Na^+,K^+-ATPase activity (3), and changes in renal Na^+,K^+-ATPase activity closely parallel alterations in net transport of Na^+ (4). T3 is known to induce the synthesis of Na^+,K^+-ATPase (5). It also has been proposed that thyroid hormones augment renal Na^+,K^+-ATPase activity by an adaptive mechanism responding to changing resorptive Na^+ loads (4). Both mechanisms, the induction of Na^+ pump elements and the adaptive response to increased filtered Na^+, could operate together in mediating the action of thyroid hormones on Na^+ reabsorption (1). Another hypothesis, that thyroid hormones enhance the entry of Na^+ from the filtrate to the tubular cell across the luminal membrane, merits consideration.

Na^+, at physiological concentrations, crosses the luminal brush border membrane of the proximal tubule mostly by Na^+–H^+ exchange (6, 7). The carrier mediates the electroneutral antiport of Na^+ for H^+, Na^+ entering the cell as H^+ migrates from cell to lumen (8–10). Amiloride at relatively high concentrations (K_i = 5 × 10^{-5}M) competitively inhibits exchange activity (10). In contrast, the ouabain-sensitive Na^+,K^+-ATPase, which serves to pump Na^+ from cell to interstitium, is located on the basolateral membrane of the tubular cell (11).

We have reported recently that renal Na^+–H^+ exchange activity is subject to hormonal regulation. Glucocorticoids increase the activity of the carrier in brush border membrane vesicles (12). Exchange activity is also increased in metabolic acidosis (13). The effect of the thyroid hormone status of the rat on Na^+–H^+ exchange activity is examined in this communication.

METHODS AND MATERIALS

Animals. Euthyroid Sprague–Dawley male rats (250–300 g) were fed ad lib rat chow (Teklab Test Diet 83006) containing 20% protein, 0.7% calcium, and 0.5% phosphorus. Hypothyroid rats were given thiouracil added to the chow (3 g/kg of chow) and to the water (0.25 g/liter). Thyroid powder (recrystallized three times) from ICN Nutritional Biochemicals was added to the thiouracil-containing diet (0–3 g/kg of chow) to produce rats with different levels of serum T3 and T4. All rats were kept on the test diets for 3 wk. At sacrifice, aortic blood was collected. Serum concentrations of T3 and T4 were determined with Corning Medical T3 and T4 RIA kits. Standards were made by diluting T3 and T4 into rat serum collected 4 wk after thyroparathyroidectomy.

Brush Border Membrane Vesicles. Rat renal cortex brush border membrane vesicles were prepared as described (12, 14). In experiments in which Na^+ uptake was measured, the intravesicular medium was 150 mM KCl/25 mM 2-(*N*-morpholino)ethanesulfonic acid (Mes)/4 mM KOH, pH 5.5. In experiments in which H^+ flux was determined, the intravesicular medium was 150 mM sodium gluconate/10 mM Tris/16 mM Hepes, pH 7.5. In experiments in which the uptakes of phosphate, D-glucose, and L-proline were measured, the intravesicular medium was 300 mM mannitol/10 mM Tris/16 mM Hepes, pH 7.5.

Maltase, a brush border membrane enzyme marker (15), was enriched 15–17 times in specific activity in the membranes relative to the cortex homogenate. There was no relationship between the enrichment of the enzyme in the brush border membrane preparation and the thyroid status of the animal from which the membranes were obtained.

Transport Measurements. Uptakes of ^{22}Na, D-[^{3}H]glucose, L-[^{3}H]proline, and [^{32}P]phosphate were measured at 20°C by a Millipore filtration technique with 0.65-μm filters (12, 16). For Na^+ uptakes, 20 μl of the membrane vesicle suspension (170–350 μg of protein) was preincubated for 1 min at 20°C, and incubations were initiated by addition of 30 μl of uptake medium to give final concentrations of 142 mM KCl, 14.7 mM KOH, 10 mM Mes, 9 mM Hepes, and 1 mM NaCl (containing 0.1 to 0.2 μCi of $^{22}Na^+$; 1 Ci = 37 GBq), adjusted to pH 7.5. For glucose, proline, and phosphate uptakes, 10 μl of the membrane suspension (85–175 μg of protein) was preincubated at 20°C for 1 min, and incubations were initiated by

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addition of 40 μl of uptake medium containing final concentrations of 120 mM NaCl, 60 mM mannitol, 10 mM Tris, 16 mM Hepes, and 25 μM glucose, proline, or phosphate (0.1–0.2 μCi of D-[^{3}H]glucose, L-[^{3}H]proline, or [^{32}P]phosphate), adjusted to pH 7.5. All incubations were carried out in triplicate with fresh membranes.

The uptake of H^+ into membrane vesicles was measured by changes in absorbance of acridine orange (13). An Aminco DW-2 spectrophotometer was used in the dual-beam mode with 492 nm as the absorbing wavelength and 600 nm as the reference wavelength. Vesicles, loaded with sodium gluconate and 15 mM Hepes, adjusted to pH 7.5 with KOH, were diluted 100-fold into 150 mM tetramethylammonium gluconate/10 mM Tris/16 mM Hepes buffer, pH 7.5/20 μM acridine orange. Initially there was no pH gradient, but as intravesicular Na^+ was exchanged for extravesicular H^+, a pH gradient was generated via amiloride-sensitive Na^+–H^+ exchange. Extravesicular acridine orange, a weak base, was accumulated inside the vesicles resulting in a decrease in the extravesicular concentration (absorbance) of acridine orange.

The rate of pH gradient dissipation was measured by monitoring changes in fluorescence of 9-aminoacridine with time (12). Membrane vesicles, suspended with pH 5.5 buffer containing 0.5 mM 9-aminoacridine, were diluted 100-fold with 150 mM KCl/15 mM Hepes/7.8 mM KOH, adjusted to pH 7.5. As the pH gradient dissipated, the weak base 9-aminoacridine diffused from the intravesicular space to the extravesicular space, resulting in an increase of fluorescence.

RESULTS

Effect of Thyroid Hormone of Na^+ Uptake. Previous studies of Na^+–H^+ exchange in renal brush border membrane vesicles demonstrated that a transmembrane pH gradient induced a Na^+ gradient across the membrane; a transmembrane Na^+ gradient induced a pH gradient across the membrane; and amiloride inhibited both of these modes of Na^+–H^+ exchange by competitively inhibiting Na^+ uptake (9, 10). Na^+–H^+ exchange activity in renal vesicles was affected by the thyroid hormone status of the rats from which the membranes were derived (Fig. 1). With membrane vesicles from hyperthyroid rats (T3 = 15.0 ± 3.7 ng/ml, T4 = 65.8 ± 7.8 ng/ml), the initial (at 5 s) rate of 1 mM Na^+ uptake in the presence of a pH gradient [pH inside (pH_i) = 5.5; pH outside (pH_o) = 7.5] was 3.62 ± 0.70 nmol/mg of protein, a value significantly greater than 2.12 ± 0.26 nmol/mg of protein, the uptake found in vesicles from euthyroid rats (T4 = 0.9 ± 0.2 ng/ml, T4 = 10.5 ± 1.9 ng/ml). Na^+ uptake into vesicles isolated from hypothyroid rats (T3 = 0.2 ± 0.1 ng/ml, T4 = 0.4 ± 0.4 ng/ml) was significantly lower (0.90 ± 0.13 nmol/mg of protein), compared to the uptake into vesicles from euthyroid animals. Accumulations of Na^+ after 1 hr of incubation, at which time both Na^+ and H^+ gradients were dissipated, were the same in the three groups (hyperthyroid, 1.75 ± 0.31; euthyroid, 2.04 ± 0.03; and hypothyroid, 1.73 ± 0.42 nmol/mg of protein). This finding indicated that the average intravesicular volumes of vesicles isolated from hypo-, eu-, and hyperthyroid were comparable and were not altered by the thyroid status of the animal, suggesting that the differences in the initial rate of Na^+ uptake were not due to an alteration in vesicle size. When 1 mM amiloride was present in the uptake medium, Na^+ uptakes (5 s) were decreased to the same level in the three experimental conditions, 0.13 ± 0.03 nmol/mg of protein, indicating that thyroid status did not affect amiloride-insensitive Na^+ uptake. These observations were consistent with the hypothesis that thyroid hormone altered Na^+ uptake through Na^+–H^+ exchange in the brush border of the renal proximal tubule.

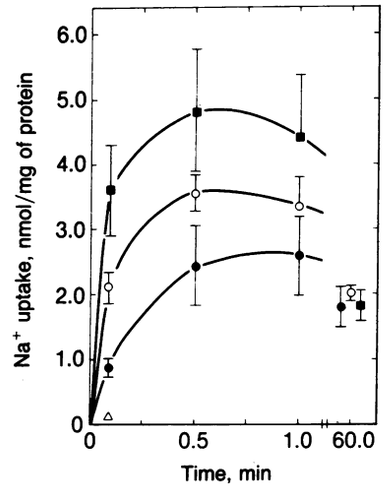

FIG. 1. Effect of thyroid hormones on brush border membrane Na^+–H^+ exchange activity. Na^+ (1 mM) uptake was measured in membrane vesicles from rats maintained on a normal diet (○), a diet containing thiouracil (●), and one containing thiouracil and thyroid extract (■). Uptake (at 5 s) in the presence of 1 mM amiloride in the medium was the same for all groups and is also shown (△). The initial pH gradient was pH_i = 5.5, pH_o = 7.5. Data represent the mean ± SEM of three experiments, each carried out in triplicate with different membrane preparations.

Because amiloride-sensitive, pH gradient-dependent Na^+ uptake was enhanced in vesicles from hyperthyroid rats, one would predict that Na^+-dependent H^+ flux would be greater in membrane vesicles from the hyperthyroid rats compared to those from hypothyroid animals. The results of an experiment, shown in Fig. 2, support this prediction. Initially in this experiment there was no transmembrane H^+ gradient (pH_i = pH_o = 7.5), but as intravesicular Na^+ exchanged with intravesicular H^+, a pH gradient developed. This was measured by monitoring the change in absorbance of acidine orange. The rate of pH gradient change was greater in vesicles from the hyperthyroid rat (serum T4 = 23.4 ng/ml) than in vesicles from the hypothyroid rat (serum T4 = 1.4

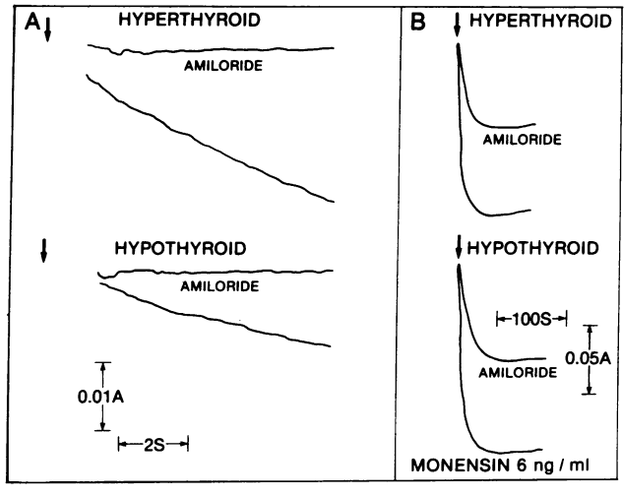

FIG. 2. Generation of a pH gradient in Na^+-loaded brush border membrane vesicles from hypothyroid and hyperthyroid rats. (*A*) Representative experiments showing traces in the absence and presence of 1 mM amiloride are illustrated. (*B*) Experiments repeated in the presence of monensin. Membrane protein concentrations were the same for all conditions.

ng/ml); when the experiments were repeated in the presence of 1 mM amiloride, there was no detectable change in acridine orange absorbance (Fig. 2A). These results were consistent with amiloride-sensitive Na^+–H^+ exchange being the predominant mechanism for vesicular acidification. The experiments were repeated in the presence of 25 μg of monensin, a Na^+–H^+ ionophore, per mg of protein (Fig. 2B). The maximum difference in absorbance was similar with membrane vesicles from hyperthyroid and hypothyroid rats, a finding consistent with the view that the intravesicular buffering capacity for the two treatment groups was the same. Recently, the quenching of the acridine orange fluorescence in the presence of amiloride has been reported (17). From Fig. 2B it could be seen that amiloride also decreased the absorbance change of acridine orange about 50% under these conditions. However, since absorbance differences could still be measured in the presence of amiloride (Fig. 2B), the amiloride inhibition of the pH gradient generation shown in Fig. 2A was not an artifact resulting from the complete interference by amiloride of acridine orange absorbance changes.

Relationship Between Na^+–H^+ Exchange Activity and Serum T4 and T3 Concentrations. In order to examine more closely the relationship between serum T3 and T4 concentrations and Na^+–H^+ exchange activity, rats were fed diets that contained thyroid extract between 0.01 and 3 g/kg of chow, in addition to thiouracil. Figs. 3 and 4 illustrate the correlation between the logarithm of serum T4 and T3 concentrations and Na^+ uptake. Rates of Na^+ uptake were normalized by dividing the amiloride-sensitive 5-s uptake by the 1-hr uptake. This method minimized the inherent experimental variation that was found when comparing experiments from different days and different membrane preparations. There was a high correlation ($r = 0.827$; $P < 0.001$) between the logarithm of serum T4 concentration and Na^+–H^+ exchange activity (Fig. 3). Normalized Na^+ uptake was also highly correlated with the logarithm of serum T3 concentration ($r = 0.711$; $P < 0.001$) (Fig. 4). The open datum points in both Fig. 3 and Fig. 4 represent individual experimental results from euthyroid rats that were on the same diet, without thyroid extract or thiouracil. Na^+–H^+ exchange activities in membrane vesicles from these animals were scattered near the regression line, consistent with the conclusion that treatment by thiouracil did not have nonspecific effects on the brush border membrane.

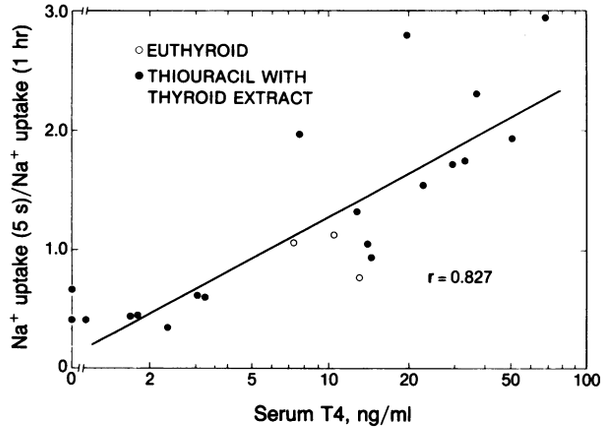

FIG. 3. Relationship between the logarithm of serum T4 concentration and Na^+–H^+ activity. Amiloride-sensitive Na^+ (1 mM) uptake (5 s) was normalized by dividing the uptake by the Na^+ uptake after 1 hr. Rats were fed the test diet containing thiouracil and 0–3.0 g of thyroid extract per kg of chow (●); euthyroid rats were fed the same diet without thiouracil and thyroid extract (○). The initial pH gradient was $pH_i = 5.5$, $pH_o = 7.5$.

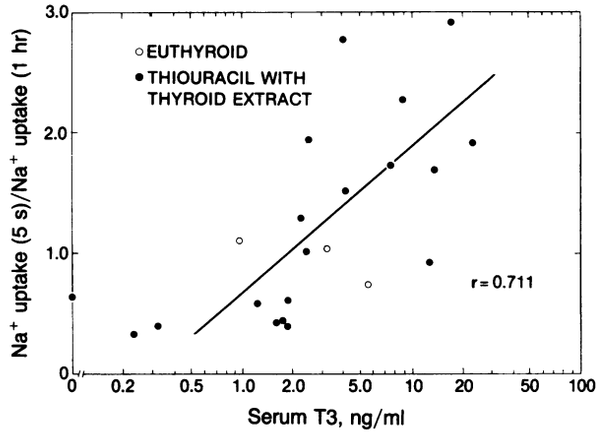

FIG. 4. Relationship between the logarithm of serum T3 concentration and Na^+–H^+ exchange activity. Experimental details are the same as described in Fig. 3.

Rate of pH Gradient Dissipation. Because it was feasible that the increased Na^+ uptake in membrane vesicles isolated from hyperthyroid rats resulted from a decrease in the rate of pH gradient dissipation rather than an increase in Na^+–H^+ exchange activity, the rates of pH gradient dissipation in the absence of Na^+ were measured in vesicles from rats having different concentrations of serum T3 and T4. Rates of passive pH gradient dissipation were measured by the changes in 9-aminoacridine fluorescence with time, from which the rate constant and $t_{1/2}$ were calculated (12, 13). In Fig. 5 the relationship between the logarithm of serum T4 concentration and $t_{1/2}$ is plotted. Vesicles isolated from hypothyroid rats had a higher $t_{1/2}$ than did vesicles from hyperthyroid rats. The correlation coefficient ($r = 0.704$, $P < 0.001$) and the slope of the regression ($b = -0.512$; $P < 0.001$) were highly significant. In data not illustrated, a similar significant relationship was found between the logarithm of serum T3 concentration and $t_{1/2}$ of pH gradient dissipation. Since the rate of pH gradient dissipation might be dependent upon a number

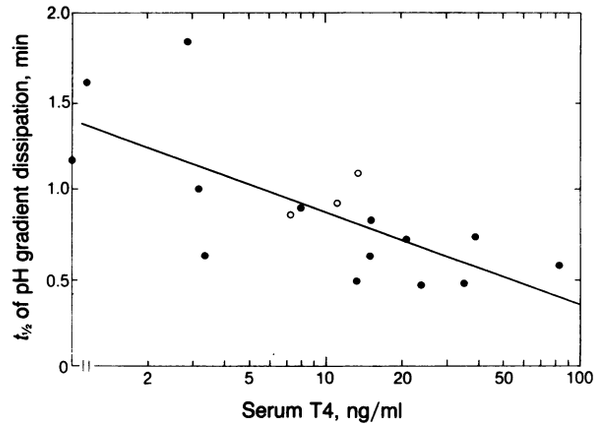

FIG. 5. Relationship between the logarithm of serum T3 concentration and the rate of passive dissipation of the pH gradient ($pH_i = 5.5$, $pH_o = 7.5$). Values of $t_{1/2}$ (min) were calculated from the rate of 9-aminoacridine fluorescence change in brush border vesicles isolated from rats on diets containing thiouracil and thyroid extract (0–3.0 g/kg of chow) (●), and on diets containing neither thiouracil nor thyroid extract (○). Brush border vesicles initially contained 150 mM KCl and 25 mM 2-(*N*-morpholino)ethanesulfonic acid/KOH (pH 5.5) and were diluted 100-fold into 150 mM KCl containing 15 mM Hepes/KOH (pH 7.5).

Table 1. Effect of thyroid hormones on phosphate, D-glucose, and L-proline uptakes into brush border membrane vesicles isolated from hypothyroid and hyperthyroid rats

Condition	Uptake, pmol/mg of protein		
	Phosphate	D-Glucose	L-Proline
Hyperthyroid*			
Na^+ dependent	334 ± 53	131 ± 9	192 ± 17
Na^+ independent	9 ± 3	3 ± 1	3 ± 1
Hypothyroid†			
Na^+ dependent	149 ± 37‡	133 ± 16	177 ± 9
Na^+ independent	8 ± 5	4 ± 1	2 ± 1

Initial rates (at 5 s) of uptake were measured in vesicles loaded with buffered mannitol, as described in the text. The uptake medium contained 25 μM substrate, either 150 mM NaCl (Na^+ dependent) or 150 mM KCl (Na^+ independent), and 15 mM Hepes/KOH, adjusted to pH 7.5.
*T4 = 17.3 ± 3.0 ng/ml.
†T4 = 0.3 ± 0.1 ng/ml.
‡$P < 0.05$.

of factors, the $t_{1/2}$ measured here might or might not reflect *in vivo* changes in passive H^+ permeability. Nevertheless, these findings clearly demonstrated that the relationship between serum T4 and T3 concentrations versus Na^+ uptake (Figs. 3 and 4) was not the consequence of change in the rate of pH gradient dissipation. In fact, the greater pH gradient dissipation rate measured in vesicles from hyperthyroid rats would tend to minimize the increase in Na^+ uptake.

Thyroid Hormones and Na^+-Dependent Uptakes of D-Glucose, L-Proline, and Phosphate. The brush border membranes contain a number of Na^+-dependent transport systems (18). To examine the specificity of the effect of thyroid hormones on Na^+–H^+ exchange, Na^+-dependent and -independent uptakes of D-glucose, L-proline, and phosphate were determined in membrane vesicles from hypothyroid (T4 = 0.3 ± 0.1 ng/ml) and hyperthyroid (T4 = 17.3 ± 3.0 ng/ml) rats. The initial rate (5 s) of Na-dependent phosphate uptake was significantly higher in the vesicles from hyperthyroid animals (Table 1). Na^+-dependent D-glucose and L-proline uptakes were not affected. Additionally, there were no apparent changes in passive (K^+ gradient) membrane permeability to D-glucose, L-proline, and phosphate since the thyroid status of the animal did not affect Na^+-independent rates of uptake. Consistent with the finding (Fig. 1) that the intravesicular volumes of the vesicles were not altered by a change in thyroid hormone status, the 90-min uptakes for the three substrates were the same irrespective of the treatment. The findings that the initial rates of Na^+-dependent D-glucose and L-proline uptakes were not affected by the thyroid state of the animal also argued against the possibility that the hormone altered the surface-to-volume ratio in the isolated vesicles. Serum phosphate concentrations were greater in the hyperthyroid rats compared to the hypothyroid rats—2.60 ± 0.09 mM versus 2.00 ± 0.22 mM, respectively. Because it was known that brush border membrane phosphate uptake was inversely related to serum phosphate levels (19, 20), the possibility that the increased rate of phosphate uptake in the hyperthyroid rat was attributable to an alteration in serum phosphate was precluded. Total serum Ca^{2+} was not significantly changed (2.53 ± 0.20 mM for hypothyroid rats versus 2.42 ± 0.10 for hyperthyroid rats), ruling out an effect of thyroid hormone on phosphate transport that was mediated by an alteration in serum Ca^{2+}.

DISCUSSION

The present study demonstrated that Na^+–H^+ exchange activity (i.e., amiloride-sensitive Na^+ and H^+ flux) in renal brush border membrane vesicles correlated with serum levels of T3 and T4. The membranes from hypothyroid rats had less Na^+–H^+ exchange activity, whereas membranes from hyperthyroid rats had greater activity, relative to preparations from euthyroid animals. The mechanism by which T3 and T4 regulate Na^+–H^+ exchange is not known. However, it was found that, when T3 or T4 (as high as 100 nM) was incubated with isolated brush border membranes for 45 min at 20°C, Na^+–H^+ exchange activity was not measurably altered (data not shown). Presumably the intact cell was necessary to demonstrate an effect of thyroid hormones on the Na^+/H^+ carrier. This contrasts with the interesting finding that thyroid hormone could directly stimulate Ca^{2+}-ATPase activity in human erythrocyte membranes (21). We also should point out that thyroid hormones have widespread effects on many renal functions—e.g., alterations in glomerular filtration rate and Na^+ load (1, 2, 4)—and any of these could be the signal for changes in brush border Na^+–H^+ exchange activity.

The T3- and T4-induced increase in Na^+ uptake may be attributable to changes in several membrane properties. One possibility is that the Na^+ leak through pathways other than Na^+–H^+ exchange is affected by thyroid hormone. Because Na^+ uptake, independent of the thyroid status of the animal, was the same in the presence of amiloride (Fig. 1), this alternative is precluded. A second possibility is that thyroid hormone alters the rate of pH gradient dissipation. In this case, the vesicles from hypothyroid rats would have the greatest rate of pH gradient dissipation, and vesicles from hyperthyroid rats would have the lowest rate. However, in the absence of Na^+, we found the opposite was true (Fig. 5)—i.e., vesicles from hypothyroid rats had the lowest rate and vesicles from hyperthyroid rats had the highest rate of pH gradient dissipation. These results, if they affected the initial rate of Na^+ would, in fact, limit the large differences that were observed. The third possibility, and the one we currently support, is that thyroid hormones induce a change in the activity of the Na^+–H^+ exchanger. Whether this alteration is a consequence of change in the K_m values, in the properties of the H^+ modifier site, in V_{max}, or in stoichiometry remains to be determined.

The present finding that thyroid hormones increased the uptake of Na^+ (in exchange for H^+) into the brush border membrane vesicle is concordant with the action of the hormones in enhancing renal Na^+ reabsorption (22, 23). Thus, the regulation by thyroid hormones of transtubular Na^+ flux has now been shown to be concomitant with modulation of the entry of Na^+ into the tubular cell across the luminal membrane, mediated by the exchange reaction, and with control of the pumping of Na^+ out of the cell across the basolateral membrane, mediated by the Na^+,K^+-ATPase (3). T3 is known to induce the synthesis of the Na^+ pump (5). Information is not available on how thyroid hormones increase exchanger activity. Further, it remains to be determined whether the effects of thyroid hormone on the two transport systems represent concerted actions, or if one precedes the other.

It was reported previously that the rate of isotonic fluid reabsorption in the proximal tubule of hypothyroid rats was decreased and that after treatment of the animals with T3, the rate could be mostly restored to the level found in euthyroid rats (24, 25). Because isotonic fluid reabsorption in the proximal tubule is dependent on the active reabsorptions of Na^+ and HCO_3^- (the latter via acid secretion) and the passive flux of Cl^- (26), it is tempting to speculate that the thyroid hormone regulation in proximal tubular Na^+–H^+ exchange, as demonstrated in the present communication, may provide an explanation, at least in part, for such changes in fluid reabsorption. In addition, a decreased flux of glycodiazine, which is handled by the kidney similarly to HCO_3^- (6), was found in the proximal tubule of hypothyroid rats (24). This

was restored to normal uptake after T3 treatment. These results are also consistent with thyroid hormone control of brush border membrane acid secretion, mediated by Na^+–H^+exchange, as reported in the present paper.

The present results indicate that the thyroid hormone status of the animal influences the Na^+-dependent uptake of phosphate by the renal brush border membrane vesicles. Membrane vesicles from hyperthyroid rats had increased initial rates of phosphate uptake. The Na^+-dependent uptakes of D-glucose and L-proline were not affected. These findings confirm and extend the recent report that membrane vesicles from animals injected with T4 had an enhanced rate of phosphate uptake (27) and that in hyperthyroidism there was an increased maximal tubular reabsorption of phosphate (28). Moreover, it was shown that the thyroid hormone induced changes in tubular transport of phosphate could not be explained by a change in plasma levels of parathyroid hormone, calcitonin, or phosphate, nor by an alteration in extracellular fluid volume (28). Instead, studies in our laboratory indicate that thyroid hormone acts directly on the renal cell in primary culture to increase Na^+-dependent phosphate uptake (unpublished data). Thus, the stimulation of brush border membrane vesicle phosphate uptake by thyroid hormone might account, at least in part, for the increase in proximal tubular phosphate reabsorption observed in the hyperthyroid animal.

The findings that thyroid hormones controlled the activities of the Na^+–H^+ exchanger and the Na^+/phosphate carrier is of interest because previous studies indicated that both transport systems were also regulated by glucocorticoids (12). However, whereas T4 or T3 increased Na^+–H^+ exchange and Na^+/phosphate uptake activities, dexamethasone enhanced exchange activity but decreased phosphate uptake. Preliminary experiments suggest that the actions of the hormones are independent, since dexamethasone could stimulate Na^+–H^+ exchange activity in hypothyroid rats with no measurable serum levels of T3 or T4. The multiple levels of regulation of the carriers and the pleiotropic responses to the hormones provide attractive models to examine the cellular and molecular mechanisms for endocrine control of transport processes.

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