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Research Article

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Calcium and Sodium Transport and Vitamin D Metabolism in the Spontaneously Hypertensive Rat

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Abstract. Serum ionized calcium levels are lower and immunoreactive parathyroid hormone levels are higher in the spontaneously hypertensive (SH) rat than in the normotensive Wistar-Kyoto (WKy) control. We postulated that there is either a defect in the regulation of vitamin D metabolism by parathyroid hormone or that the gut target organ for vitamin D in the SH rat is unresponsive. To test these hypotheses we measured serum concentrations of vitamin D metabolites and intestinal transport of calcium and sodium. Compared with that of WKy controls, in vitro calcium transport by duodenal sacs of the SH rat was decreased ($P < 0.001$) at 5 wk, before the development of hypertension, and at 12 wk, after hypertension was well established. When measured in vivo in the most proximal 20 cm of small intestine, maximum velocity (V_{\max}) for calcium transport was decreased ($P < 0.05$) and net absorption of sodium and water was increased ($P < 0.05$) in SH rats as compared with WKy rats. V_{\max} for calcium transport was also decreased ($P < 0.05$) in the most distal 20 cm of small intestine of SH rats, but net sodium and water transport were the same in SH and WKy rats. At 12 wk, serum concentration of 1,25-dihydroxycholecalciferol [$1,25-(\text{OH})_2\text{D}_3$] was the same in both SH and WKy groups, but its precursor, 25-hydroxycholecalciferol, was increased ($P < 0.05$) in the SH rat. We conclude that in the SH rat: (a) the concentration of $1,25-(\text{OH})_2\text{D}_3$ is inappro-

priately low in relation to the elevated immunoreactive parathyroid hormone and the depressed calcium absorption, suggesting a defect in the regulation of vitamin D metabolism; and (b) the depressed calcium absorption, in the setting of normal concentrations of [$1,25-(\text{OH})_2\text{D}_3$], demonstrates unresponsiveness of the gut to vitamin D and may explain in part the low serum ionized calcium found in earlier studies. The presence of these abnormalities before we found a significant difference in blood pressure suggests that they may be causal, not secondary, to the hypertension.

Introduction

Evidence from many sources suggests that calcium has a role in hypertension. Dietary calcium intake is lower in patients with hypertension than in normotensive individuals (1, 2). In epidemiologic studies, low dietary calcium has been associated with hypertension (3, 4). Low calcium intake increases blood pressure in Wistar-Kyoto (WKy)¹ rats (5), which are controls for the spontaneously hypertensive (SH) rats developed from this strain. High calcium intake lowers blood pressure in SH (6–8) and in WKy rats (6).

Total serum calcium is similar in patients with essential hypertension and normotensive controls, but serum ionized calcium is decreased in hypertensive patients (9). This is also true of SH rats as compared with WKy rats: under comparable feeding conditions, serum ionized calcium is lower in SH than in WKy rats (7, 10, 11). Serum immunoreactive parathyroid hormone is elevated in patients with essential hypertension (12) and in SH rats (7). These findings suggest abnormalities in calcium homeostasis in hypertension; parathyroid hormone apparently increases appropriately in response to decreased ionized calcium

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1. Abbreviations used in this paper: $1,25-(\text{OH})_2\text{D}_3$, 1,25-dihydroxycholecalciferol; $24,25-(\text{OH})_2\text{D}_3$, 24,25-dihydroxycholecalciferol; $25-\text{OH}-\text{D}_3$, 25-hydroxycholecalciferol; S/M, serosal-to-mucosal; SH, spontaneously hypertensive; WKy, Wistar-Kyoto.

in serum but fails to correct the decreased serum calcium concentration. Therefore, if the parathyroid response is adequate, either the regulation of formation of 1,25-dihydroxycholecalciferol [1,25-(OH)₂D₃] by parathyroid hormone is defective, or calcium absorption by the alimentary tract target organ is relatively unresponsive to 1,25-(OH)₂D₃. In addition, SH rats older than 17 wk develop hypercalciuria, which is consistent with a defect in calcium transport by the renal tubule (7). To examine possible defects in the animal model, we measured vitamin D metabolites in serum and calcium absorption by the small intestine in SH rats and normotensive WKy controls.

Methods

Animals. Weanling male rats that weighed at least 35 g (mean body weights at 23 d: WKy = 57 g and SH = 53 g) were obtained from the SH-WKy breeder colonies of The University of Iowa Cardiovascular Center (Iowa City, IA). Groups of animals from weekly litters were housed individually in metabolic cages and weighed weekly. Animals were fed Purina Chow 5012 (1.01% calcium, 0.74% phosphorous, 0.21% magnesium, 3.3 IU vitamin D per g; Ralston Purina Co., St. Louis, MO) ad lib and allocated randomly for calcium transport measurements or drawing of blood. Food intake of ad lib-fed, 12-wk-old SH rats was slightly greater than that of WKy rats. To evaluate the effect of this difference in food intake on 1,25-(OH)₂D₃ in one set of studies, SH rats were divided into two groups when they began to eat more. One SH group was pair-fed to the mean intake of WKy animals, and the other SH group was fed ad lib. In this experiment all animals were used for measuring vitamin D metabolites in serum. Animals were exsanguinated from the aorta to measure serum concentrations of calcium and magnesium by atomic absorption, phosphorous (13), and vitamin D metabolites by the method of Horst et al. (14). Blood pressure was measured with an electrospigmomanometer (model AMS6; IITC, Inc., Landing, NJ) and recorded (model R511 dynograph; Beckman Instruments Inc., Fullerton, CA) at weekly intervals beginning at 6 wk.

Transport studies. Calcium transport was measured in vitro at 5 and 12 wk using everted duodenal sacs as previously described (15) and a 0.4 mM calcium chloride solution that contained tracer ⁴⁵Ca (15 μ Ci/liter; 34 mCi/mg, New England Nuclear, Boston, MA), 151 mM sodium chloride, 20 mM glucose, and 4 mM NaHPO₄, adjusted to pH 7.2. The segment of small intestine (8 cm in 5-wk-old animals and 10 cm in 12-wk-old animals) immediately distal to the pylorus was used. The bile duct was ligated, the segment was stripped from the mesentery, everted, and tied at one end. In the 5-wk-old animals, the serosal side of the sac was filled with 0.5 ml (0.75 ml in 12 wk animals) of the solution described above. Methods for incubation, measurement of water movement, and analysis of calcium and ⁴⁵Ca has been described previously (15). Calcium transport is expressed as ⁴⁵Ca concentration ratios of serosal-to-mucosal (S/M) media and as net calcium transport into the serosal medium.

Calcium transport was measured in vivo at 12 wk by in situ luminal perfusion of proximal and distal segments of small intestine (16). 20-cm-long segments of the most proximal small intestine just distal to the pylorus, and of the most distal small intestine just proximal to the cecum, were cannulated. An isotonic saline solution (12 ml) that contained various concentrations of calcium, tracer ⁴⁵Ca, and phenol red (5 mg/100 ml) was recirculated with a peristaltic pump from a reservoir through each segment at 2 ml/min for 2 h. After 2 h the luminal contents were drained into the reservoir, the perfused segments were excised, and

their length and weight were measured. Calcium and ⁴⁵Ca were analyzed as above, and phenol red was analyzed colorimetrically (17). After correction for net water movement, net calcium absorption was calculated from initial and final calcium concentration, and flux of calcium out of the lumen into the animal (influx) was calculated from ⁴⁵Ca data as previously described (16). Data were analyzed statistically by the *t* test.

Results

In preliminary studies we measured food intake of groups of 5-wk-old SH and WKy rats of the same initial weight. Food intake was slightly greater in SH rats, and they grew more rapidly than WKy rats from 5 to 12 wk. Food intake per gram body weight was the same for both groups. To assess the effect of the difference in food intake (15% greater in SH), we pair-fed half of the SH rats with the WKy group and fed the remainder ad lib for two more weeks. Serum 1,25-(OH)₂D₃ did not differ significantly among groups: WKy, 53 \pm 7; SH ad-lib fed, 44 \pm 6; SH pair-fed, 33 \pm 3 pg/ml, mean \pm SE. We concluded that the small difference in calcium intake between SH and WKy rats fed ad lib had no significant effect on 1,25-(OH)₂D₃. In all other experiments animals were fed ad lib, conforming with most previous studies.

Body weight and the weight and length of intestinal segments of animals used in transport studies are shown in Table I. In vitro transport was examined at 5 and 12 wk and in vivo studies were done at 12 wk. At 5 wk, body weight and segment length were the same in WKy and SH animals. Duodenal weights, however, were greater in SH rats at 5 and 12 wk. Mean values for body and segment weight for 12-wk old animals were also greater in SH animals, but the difference was not always significant. Segment lengths did not differ significantly. Segment thickness (weight/length; data not shown) was also calculated; mean thickness was greater in SH rats for both segments, but the increase was significant only for the proximal segment (*P* < 0.025). All proximal segments were thicker than distal segments (*P* < 0.05).

Table II shows systolic blood pressure of a group of 55 representative animals during these studies. After 7 wk, blood pressure became significantly greater in SH than in WKy rats.

Fig. 1 shows data from in vitro calcium transport studies of S/M concentration ratios of ⁴⁵Ca developed by everted sacs of duodenum of 5- and 12-wk-old animals after 60 min of incubation. The younger animals developed significantly greater concentration ratios than the older animals (*P* < 0.05), and at both 5 and 12 wk the concentration ratio was lower in the SH group (*P* < 0.001). At 12 wk the S/M gradient for SH animals was small (1.4), but greater than unity. Net calcium transport into the serosal medium per unit weight of mucosa of duodenal sacs showed the same pattern as ⁴⁵Ca concentration ratios of Fig. 1: decreased transport in the SH animals (*P* < 0.001) at both 5 and 12 wk and lower values in older rats (*P* < 0.05).

Results of in vivo studies are shown in Figs. 2–5. Fig. 2 shows, for proximal small intestine of 12-wk-old SH and WKy rats, the relationship between calcium influx and luminal con-

Table I. Body Weight and Weight and Length of Intestinal Segments of Rats Used in Transport Studies (Mean±SE)

| Group (<i>n</i>) | [Ca ⁺⁺]* | Body weight | Segments studied | | | |
|--------------------|----------------------|---------------------|------------------|------------------------|------------------------|---------------|
| | | | Length† | | Wet weight | |
| | | | cm | | mg | |
| | | | <u>Duodenum</u> | <u>Duodenum</u> | | |
| In vitro studies | | | | | | |
| 5-wk-old animals | | | | | | |
| WKy (8) | 0.4 | 105±4 | 8 | 601±16 | | |
| SH (9) | 0.4 | 114±4 | 8 | 692±15 | | |
| 12-wk-old animals | | | | | | |
| WKy (8) | 0.4 | 279±6 | 10 | 831±17 | | |
| SH (11) | 0.4 | 314±6 | 10 | 1,008±31 | | |
| In vivo studies§ | | | <u>Proximal</u> | <u>Distal</u> | <u>Proximal</u> | <u>Distal</u> |
| WKy (6) | 0 | 293±8 | 21.2±1.1 | 20.4±1.5 | 1,193±73 | 1,218±176 |
| SH (6) | 0 | 320±3 | 20.5±1.0 | 23.1±1.5 | 1,397±56 | 1,338±83 |
| WKy (6) | 0.6 | 284±10 | 20.9±1.2 | 17.4±0.6 | 1,177±87 | 1,070±89 |
| SH (6) | 0.6 | 322±4 | 23.3±1.0 | 22.1±2.0 | 1,592±57 | 1,431±128 |
| WKy (8) | 2.0 | 288±7 | 20.0±0.9 | 22.2±1.4 | 1,211±64 | 1,434±138 |
| SH (8) | 2.0 | 309±7 | 21.1±0.9 | 22.6±1.5 | 1,476±51 | 1,471±115 |
| WKy (7) | 3.4 | 293±7 | 22.1±1.3 | 18.9±1.7 | 1,165±60 | 1,010±97 |
| SH (10) | 3.4 | 324±6 | 21.5±0.6 | 19.0±1.8 | 1,290±61 | 1,106±130 |
| WKy (7) | 6.8 | 281±10 | 19.1±1.0 | 18.9±1.9 | 1,070±51 | 950±72 |
| SH (7) | 6.8 | 299±6 | 21.1±1.3 | 20.9±1.8 | 1,422±92 | 1,375±146 |

* [Ca⁺⁺] is initial calcium concentration of the solution used in the transport study. † Segment length measured at the time of preparation of sac. For in vivo studies, segment lengths were measured at the end of the absorption study. § All in vivo studies were performed at 12 wk.

^{||} SH > WKy, *P* < 0.01.

centration of calcium over the range of 0–6.8 mM. Influx rate increases steeply at low concentrations and flattens at high concentrations, approaching a limiting value. This is consistent with a saturable mediated process that follows Michaelis-Menten kinetics. Data were analyzed by the method of Lineweaver and Burk (18) and K_t ² and maximum velocity (V_{max}) were calculated (Table III). The curves shown in Fig. 2 were calculated with these constants. The calculated curves closely fit the experimental points. Constants calculated by the Eadie-Hofstee plot (19) were

2. K_t is used for transport kinetics and is analogous to K_m , used for enzyme kinetics.

similar. K_t values for proximal segment calcium transport in WKy and SH rats did not differ, but V_{max} was significantly decreased in SH rats. The decrease in V_{max} is consistent with the significantly lower calcium influx in SH at each concentration point (Fig. 3).

Fig. 3 shows a similar plot of calcium influx for distal small intestine of SH and WKy rats. Data were analyzed as described above for the proximal segment and showed K_t to be the same in both SH and WKy rats but V_{max} to be significantly lower in SH rats (Table III). At all concentrations, mean influx was lower in SH than in WKy rats, but the differences were not significant.

Figs. 4 and 5 show the net calcium absorption data corre-

Table II. Blood Pressure

| Group | Age (weeks) | | | | | | |
|----------------------------|---------------|-------|-------|--------|--------|--------|--------|
| | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| | Torr. mean±SE | | | | | | |
| WKy | 100±10 | 122±4 | 124±5 | 135±6 | 134±8 | 135±9 | 134±8 |
| SH | 127±6 | 143±4 | 163±2 | 167±4 | 176±4 | 176±4 | 188±7 |
| WKy vs. SH, <i>P</i> value | >0.05 | >0.05 | <0.01 | <0.001 | <0.001 | <0.001 | <0.001 |

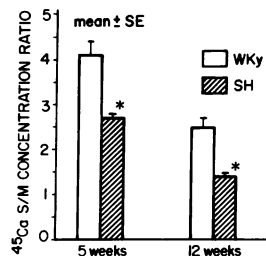


Figure 1. In vitro studies. S/M concentration ratios of ^{45}Ca developed at 1 h by everted duodenal sacs of WKy and SH rats at 5 and 12 wk of age. The younger animals developed a significantly greater concentration ratio ($P < 0.05$) than the older animals. The ratio for SH animals was lower than for WKy rats at corresponding time intervals ($P < 0.001$). WKy animals are normotensive. SH animals are normotensive at 5 wk and hypertensive at 12 wk. *WKy and SH data differ significantly.

sponding to data from the influx studies plotted in Figs. 2 and 3. Over the entire concentration range, mean net absorption in the proximal segment is lower ($P < 0.01$) in SH than in WKy rats (Fig. 4). The slightly lower mean net absorption data in the distal segment of SH rats do not differ significantly from WKy data (Fig. 5). Calcium efflux, calculated as the difference between influx (Figs. 2 and 3) and net absorption (Figs. 4 and 5) data, was independent of luminal calcium concentration and did not differ in WKy and SH groups.

Net sodium and water absorption during calcium absorption studies are shown in Fig. 6. In the proximal segment, mean net sodium and water absorption were greater in SH than in WKy rats. There was no difference in the distal segment between SH and WKy groups.

Serum concentration of vitamin D metabolites, total serum calcium, magnesium, and inorganic phosphorus at 12 wk are shown in Table IV. Data are from a separate group of ad libed animals and show no significant difference between WKy and SH rats for 1,25-(OH) $_2\text{D}_3$ and 24,25-dihydroxycholecal-

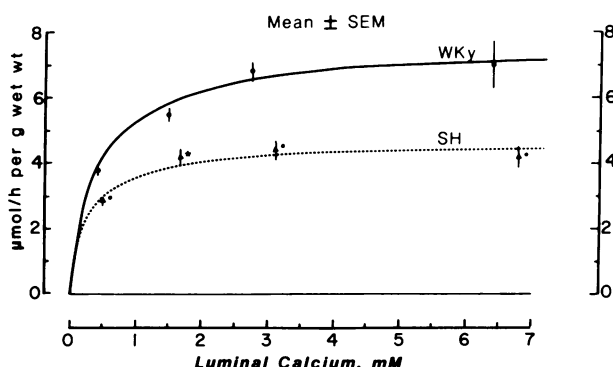


Figure 2. In vivo studies. Proximal small intestine of 12-wk-old WKy and SH rats: relationship between calcium influx and luminal calcium concentration. Data points follow Michaelis-Menten kinetics. Analysis by method of Lineweaver and Burk (18) shows K_t to be the same in WKy and SH rats, but V_{\max} to be decreased in SH ($P < 0.05$) (Table III). Curves were calculated from K_t and V_{\max} values and fit experimental data points closely. *WKy and SH data differ significantly.

Table III. Kinetic Constants (Mean \pm SEM)

| | Proximal | | Distal | |
|---------------------|-----------------|-----------------------|-----------------|-----------------------|
| | WKy | SH | WKy | SH |
| Influx data | | | | |
| K_t (mM) | 0.47 ± 0.10 | 0.27 ± 0.10 | 0.13 ± 0.04 | 0.14 ± 0.06 |
| V_{\max} * | 7.6 ± 0.4 | $4.6 \pm 0.3^\dagger$ | 3.0 ± 0.1 | $2.5 \pm 0.1^\dagger$ |
| Net absorption data | | | | |
| K_t (mM) | 0.78 ± 0.56 | 0.56 ± 0.54 | 1.3 ± 0.5 | 1.1 ± 1.0 |
| V_{\max} | 07.1 ± 1.4 | 3.8 ± 1.0 | 2.8 ± 0.6 | 1.9 ± 0.8 |

* Micromoles per hour per gram wet weight segment. † SH less than WKy, $P < 0.05$.

ciferol [24,25-(OH) $_2\text{D}_3$]. Concentration of 25-hydroxycholecalciferol (25-OH-D $_3$) is more than one and one-half times greater in SH than in WKy rats. Although mean values for serum calcium and inorganic phosphorus were slightly lower, and for magnesium slightly higher, in SH rats, differences were not significant.

Discussion

These studies demonstrate defects in intestinal calcium transport and vitamin D metabolism in SH as compared with WKy rats. The ability to develop a transmucosal calcium concentration gradient in vitro was decreased in the proximal small intestine, and V_{\max} for in vivo calcium transport was decreased in both the proximal and distal small intestine of SH rats. Despite the defect in calcium transport, sodium and water transport were increased in the proximal small intestine of SH rats. Thus, there is no generalized depression of transport in SH rats. Because, based on in vitro studies, the defect in calcium transport is present before a significant difference in blood pressure, it is not secondary to the elevated blood pressure and could be a

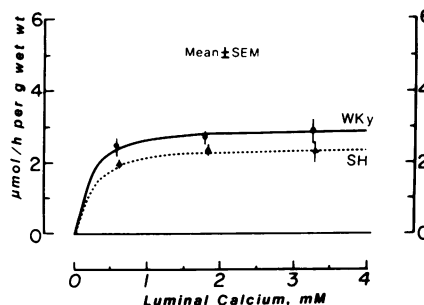


Figure 3. In vivo studies. Distal small intestine of 12-wk-old WKy and SH rats: relationship between calcium influx and luminal calcium concentration. Analysis of transport data as for the proximal segment (Fig. 2) showed K_t to be the same in SH and WKy rats, but V_{\max} to be lower in SH ($P < 0.05$) (Table III).

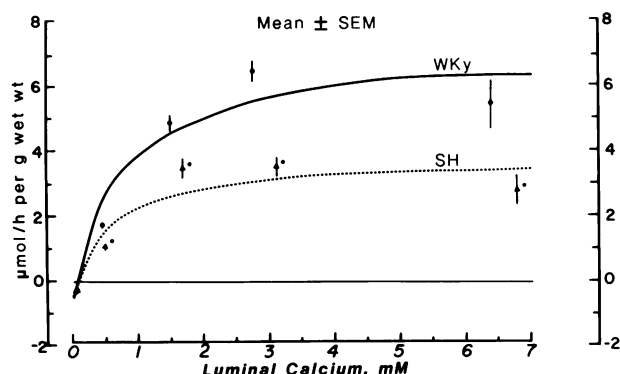


Figure 4. In vivo studies. Proximal small intestine of 12-wk-old WKy and SH rats: relationship between net calcium absorption and luminal calcium concentration. Transport data were analyzed as in Fig. 2. K_t was the same in SH and WKy rats, V_{max} was lower in SH rats, but not significantly (Table III). Over the entire concentration range, mean net absorption in the proximal segment is lower in SH than in WKy rats (* $P < 0.01$).

contributing factor in the development of hypertension. The defect in calcium transport and the development of hypertension in the SH rat may also be genetically linked but causally unrelated, and the calcium transport defect may appear at an earlier age than does the elevation in blood pressure.

Vitamin D deficiency produces a defect in Ca^{2+} transport that has the same characteristics that appear in the SH rat. The vitamin D-depleted rat studied in vitro using everted duodenal sacs has a decreased capacity to develop an S/M concentration gradient for calcium (20–23). In vivo, vitamin D depletion in the rat decreases net absorption of Ca^{2+} by decreasing flux out of the lumen (23) but does not affect flux into the lumen, whether measured directly (24) or indirectly (23) as in the present study. However, this defect in calcium transport occurs in the setting of the same serum concentration of $1,25-(OH)_2D_3$ in SH and WKy animals. Thus, the defect may be the result of resistance of the small intestine of SH rats to vitamin D action.

Evidence for vitamin D resistance in the 12-wk-old SH rat

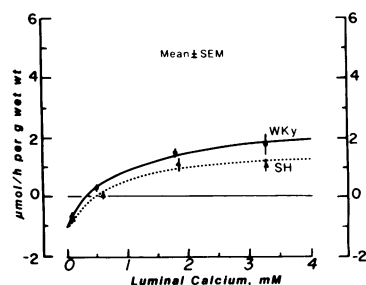


Figure 5. In vivo studies. Distal small intestine of 12-wk-old WKy and SH rats: relationship between net calcium absorption and luminal calcium concentration. Transport data were analyzed as in Fig. 2, and showed no difference between WKy and SH rats. The slightly lower mean net calcium absorption in

the distal segment of SH rats is not significantly different from that of WKy animals.

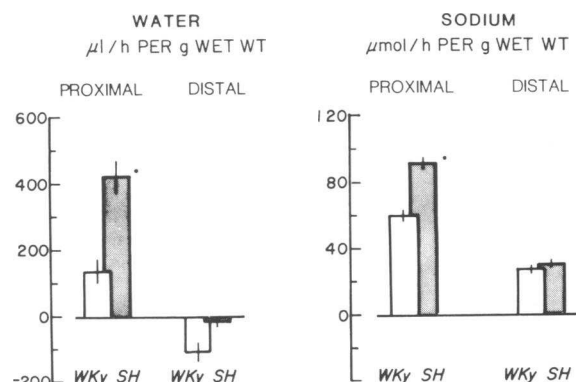


Figure 6. In vivo studies. Proximal and distal small intestine of 12-wk-old WKy and SH rats: net flux (mean ± SEM) of water (left) and sodium (right) during net absorption of calcium (combined data from all studies: WKy, $n = 34$; SH, $n = 37$). Transport of water and sodium in the proximal segments was greater in SH animals (* $P < 0.05$), but did not differ in the distal segment.

is provided by an earlier study (25). Pharmacologic doses of $1,25-(OH)_2D_3$ (30 ng for in vitro sac studies and 100 ng for in vivo perfusion studies) failed to increase duodenal calcium transport above the basal level in the SH rat, although the WKy rat responded. This dose of $1,25-(OH)_2D_3$ is 3 to 11 times that required to produce a maximum in vitro transport response. Further studies are required to determine if the small intestine is vitamin D resistant or if there is an intrinsic defect in the transport process for calcium.

Vitamin D resistance can be examined by measuring mucosal vitamin D receptors, but if these are normal, a post-receptor defect may be present. Vitamin D acts at the brush border to control calcium entry as well as on the calcium extrusion process at the basolateral cell membrane, and it may be involved in the transit of intracellular calcium from the brush border to the basolateral cell membrane through vitamin D-dependent in-

Table IV. Serum Concentrations of Vitamin D Metabolites, Total Calcium, Magnesium, and Inorganic Phosphorus in Ad Lib-Fed SH and WKy Rats at 12 Wk (Mean ± SE)

| Substance | WKy | SH |
|----------------------------------|----------------|------------------|
| Number of animals | 13 | 22 |
| $1,25-(OH)_2D_3$ (pg/ml) | 62 ± 5 | 71 ± 5 |
| $25-OH-D_3$ (ng/ml) | 23.9 ± 0.5 | $38.5 \pm 0.6^*$ |
| $24,25-(OH)_2D_3$ (ng/ml) | 2.8 ± 0.4 | 2.3 ± 0.3 |
| Calcium (μM) | 2504 ± 31 | 2444 ± 18 |
| Magnesium (μM) | 897 ± 1 | 946 ± 16 |
| Inorganic phosphorus (mg/100 ml) | 7.3 ± 0.2 | 6.5 ± 0.3 |

* WKy > SH, $P < 0.05$.

testinal calcium binding protein. Because of these multiple actions of vitamin D, distinguishing a primary calcium transport defect from one secondary to vitamin D resistance will be difficult.

The kidney may also be involved in this transport defect. Although urinary calcium excretion is similar in young SH and WKy rats, for example, at 12 wk of age (7) and at 11–17 wk of age (26), urinary calcium excretion is greater in SH than in WKy rats from week 17 onward and by 43 wks is almost four times greater in the SH rat (7). Elevated renal calcium excretion could contribute to the decreased serum ionized calcium in the older animals. Although not demonstrable by measurement of urine calcium in young animals, a genetic defect similar to that which we found in the enterocyte may be present in the renal tubule cell, which is also a target for $1,25\text{-(OH)}_2\text{D}_3$.

Earlier studies have shown that concentrations of ionized calcium in serum is reduced (7, 10, 11) and that parathyroid hormone is higher in SH than in WKy rats (7). In this context, the finding of the same concentration of $1,25\text{-(OH)}_2\text{D}_3$ in serum of both groups is paradoxical: SH rats are not responding to the stimulus to increase $1,25\text{-(OH)}_2\text{D}_3$. This is most consistent with a defect in regulation of $1,25\text{-(OH)}_2\text{D}_3$ production, especially in the context of elevated 25-OH-D_3 in SH rats. To define the nature of the abnormality in vitamin D metabolism, further study will be needed.

Our calcium transport studies agree with earlier data in the rat that show a higher rate of calcium absorption in proximal than in distal small intestine (27–29). A previous study examined duodenal calcium transport in SH and WKy rats at 5 and 12 wk using everted sacs and in vivo perfusion (25). SH and WKy rats developed the same S/M concentration ratios at 5 wk, but at 12 wk the ratio was greater in SH than in WKy rats. The absolute values for S/M ratios of 2.5 at 5 wk were low for both SH and WKy rats, considering that incubation was for 90 min (rather than 60 min, as in this study); and that the gradient was developed using 0.25 mM calcium, so that less calcium would have to be transferred per unit increase in gradient than for the 0.4 mM calcium used in this study. The S/M concentration ratio developed by 12-wk-old WKy rats was lower than that developed by 5-wk-old WKy and SH rats. SH rats did not show a decline in concentration ratio at 12 wk as compared with 5 wk. Thus, the age-related decline in S/M ratio was present for WKy, but not for SH, rats. In vivo duodenal calcium transport studies at 12 wk confirmed in vitro studies: transport of 1 mM calcium measured as ^{45}Ca was greater in the SH than in the WKy rat. As mentioned previously, these studies also demonstrated responsiveness of WKy but not of SH rats to pharmacologic doses of $1,25\text{-(OH)}_2\text{D}_3$.

Our findings may be important in relation to hypertension in SH rats. Calcium malabsorption by the small intestine could cause calcium depletion and may explain in part the low ionized calcium in serum of SH rats. However, the large intestine also absorbs calcium (30) and may be important in calcium homeostasis. In contrast to influx studies, calcium efflux was the same in SH and WKy rats. Since we have not examined calcium

transport by the large intestine in SH and WKy rats, no conclusions can be made about calcium balance. Previous studies have shown that increased dietary calcium lowers blood pressure in SH rats (6, 7) and in WKy rats (6), and that low dietary calcium increases blood pressure in WKy rats (5). Calcium malabsorption that causes calcium depletion could therefore contribute to the development of hypertension. Studies of humans also suggest a decreased calcium intake for patients with essential hypertension (1). Patients with essential hypertension, like the SH rat, show decreased ionized calcium (9) and elevated parathyroid hormone (12) compared with normotensive controls. Thus, our findings may be relevant to essential hypertension.

Our findings of altered membrane transport of calcium and sodium by the enterocyte of the SH rat agree with the behavior of several other types of cells. The erythrocyte of the SH rat shows increased sodium and potassium permeability (31) and decreased binding of calcium to the inner membrane surface (32). The adipocyte of the SH rat shows decreased calcium binding to the membrane (33), an increased intracellular calcium pool (34), and decreased membrane fluidity (35). Calcium binding to subcellular fractions of the aortic wall (36) and aortic smooth muscle (37) is also decreased. Increased net sodium efflux (38), sodium-potassium turnover (39), and $\text{Na}^+\text{K}^+\text{-ATPase}$ activity (40) has been demonstrated for arterial wall and smooth muscle of the SH rat. Thus, in general, in cells from the SH rat, cell-membrane permeability to sodium is increased in association with elevated $\text{Na}^+\text{K}^+\text{-ATPase}$ activity. Two current mechanisms for calcium regulation of smooth muscle relaxation and contraction have recently been reviewed (41). The complexity of the calcium cycle precludes defining a relationship between our findings and those reviewed above to the state of tension in arterial smooth muscle.

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