Pathophysiology of spontaneous hypercalciuria in laboratory rats. Role of deranged vitamin D metabolism.

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Recent data suggest a causal role of deranged 1,25(OH)2D metabolism in the syndrome of idiopathic hypercalciuria. To test this hypothesis, we evaluated if vitamin D availability and/or increased serum 1,25(OH)2D were critical for the expression of hypercalciuria in laboratory rats. Ca balance, serum 25OHD3, and 1,25(OH)2D3 were studied in D-deprived (-D) and D-repleted (+D) male progeny (p) born to normocalciuric (NC) and spontaneously hypercalciuric (SH) rats. 7 of the 14 pSH and 2 of 21 pNC had SH, which was defined as urinary Ca greater than two standard deviations above the mean of values for control animals on days 5 and 6 of a low Ca +D diet (1.19 vs. 0.58 mg/d, P less than 0.001). Fasting serum Ca and 25OHD3 were similar to control. Serum 1,25(OH)2D3 was elevated in these nine SH rats (232 vs. 145 pg/ml, P less than 0.005). However, during vitamin D deprivation, their Ca excretion was also increased (1.53 vs. 0.45 mg/d, P less than 0.001), despite comparably reduced serum 1,25(OH)2D3 (102 vs. 106 pg/ml) and undetectable serum 25OHD3. Net intestinal Ca absorption on a low Ca diet was comparable during D repletion (-0.75 vs. -0.82 mg/d) or D deprivation (-0.80 vs. -2.15 mg/d), excluding primary hyperabsorption as the mediator of the hypercalciuria. Mild hypophosphatemia was present in SH on +D (5.8 vs. 6.9 mg/dl, […])

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Pathophysiology of Spontaneous Hypercalciuria in Laboratory Rats
Role of Deranged Vitamin D Metabolism

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Abstract

Recent data suggest a causal role of deranged 1,25(OH)2D metabolism in the syndrome of idiopathic hypercalciuria. To test this hypothesis, we evaluated if vitamin D availability and/or increased serum 1,25(OH)2D were critical for the expression of hypercalciuria in laboratory rats. Ca balance, serum 250HD3, and 1,25(OH)2D2 were studied in D-deprived (−D) and D-repleted (+D) male progeny (p) born to normocalciuric (NC) and spontaneously hypercalciuric (SH) rats. Of the 14 pSH and 2 of 21 pNC had SH, which was defined as urinary Ca greater than two standard deviations above the mean of values for control animals on days 5 and 6 of a low Ca +D diet (1.19 vs. 0.58 mg/d, P < 0.001). Fasting serum Ca and 250HD3 were similar to control. Serum 1,25(OH)2D2 was elevated in these nine SH rats (332 vs. 145 pg/ml, P < 0.005). However, during vitamin D deprivation, their Ca excretion was also increased (1.53 vs. 0.45 mg/d, P < 0.001), despite comparably reduced serum 1,25(OH)2D2 (102 vs. 106 pg/ml) and undetectable serum 250HD3. Net intestinal Ca absorption on a low Ca diet was comparable during D repletion (−0.75 vs. −0.82 mg/d) or D deprivation (−0.80 vs. −2.15 mg/d), excluding primary hyperabsorption as the mediator of the hypercalciuria. Mild hypophosphatemia was present in SH on +D (5.8 vs. 6.9 mg/dl, P < 0.005) and −D diets (6.2 vs. 7.9 mg/dl, P < 0.005), and was associated with higher rates of cyclic adenosine monophosphate excretion (32.8 vs. 26.9 and 48.5 vs. 41.0 nmol/mg creatinine, respectively).

Spontaneous hypercalciuria is therefore dissociable from increased Ca absorption, serum levels of 250HD3, or 1,25(OH)2D2. The data are most compatible with the hypothesis of a renal Ca leak which stimulates parathyroid hormone activity and increases serum 1,25(OH)2D2, if provided adequate 250HD3 as substrate.

Introduction

Despite recent insights into the syndrome of idiopathic hypercalciuria (IH)1 (1–28), it remains an unsettled issue as to whether IH results from a renal tubular leak, a primary enhancement of intestinal absorption of Ca, or a defect in the regulation of 1,25(OH)2D production. Thus, the renal leak theory is not supported by the frequent normal (5, 12, 15) or suppressed (4, 8, 10, 14, 19) parathyroid hormone levels. Urinary cAMP and fasting urine Ca to creatinine ratio (2, 19, 25) were elevated in only a minority of the IH patients (5, 8, 19). Likewise, a primary intestinal hyperabsorption could not explain urine Ca excretion in excess of net Ca absorption on a low Ca diet (10, 11, 27) or the increased renal Ca clearance rate after an overnight fast (5).

Recently, it was hypothesized that the primary defect may reside in the disordered regulation of 1,25(OH)2D production (1, 10, 14), as suggested by the absolutely or relatively elevated serum 1,25(OH)2D2 levels in these patients (4, 10, 13, 14, 21, 23, 25, 28). When Ca intake is adequate, hyperabsorption predominates, and is expressed essentially as absorptive hypercalciuria. When Ca intake is low, increased bone resorption produces a picture similar to renal hypercalciuria (29, 30) which is associated with negative Ca balance (30). Patients with immobilization and displaying resorptive hypercalciuria (31) are characterized by low to normal PTH and urinary cAMP, fasting hypercalciuria, and normal serum Ca, which is similar to many IH patients (5, 10, 11).

We reasoned that if the hypercalciuria is due to an increased serum 1,25(OH)2D2, it should be abolished if 1,25(OH)2D3 can be normalized by restricting its substrate, 250HD3. Vitamin D deprivation is only feasible in laboratory animals. Rats with spontaneous hypercalciuria (SH), recently described (32) and investigated by us (33), provide a useful model, since the hypercalciuria is inheritable (17, 24, 33) and it is associated with fasting normocalemia (33), proximal tubular dysfunctions (33), parathyroid hormone (PTH)-independent defects in the reabsorption of Ca (33) and PO4 (34), as well as normal response to thiazide (33) orthophosphate and PTH (35). The 7th generation normocalciuric (NC) and SH Wistar rats were therefore subject to the following studies to evaluate the role of deranged vitamin D metabolism.

Methods

Effects of vitamin D deprivation. Male progeny (p) born to the 7th generation NC (n = 21 from four crosses) and SH rats (n = 14 from three crosses) were weaned from their parents, placed in individual metabolic cages, and housed in special animal facilities devoid of sun or fluorescent light. They were fed a synthetic, vitamin D-deficient, Ca-deficient, and PO4-deficient metabolic diet (ICN, Cleveland, OH) supplemented to 1.8% Ca (with CaCO3) and to 0.8% P (with sodium PO4, 4:1 dibasic to monobasic forms). In brief, the diet was normal with respect to all minerals, vitamins, and nutrients except for the absence of vitamin D (D-deprived diet). The generous Ca supplement during the D-deprived phase was designed to prevent the development of secondary hyperparathyroidism (36, 37). After 5 wk of D-deficient

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1. Abbreviations used in this paper: IH, idiopathic hypercalciuria; NC, normocalciuric; p, progeny; PTH, parathyroid hormone; SH, spontaneously hypercalciuric.

diet, diet Ca and P were reduced to 0.5 and 0.6%, respectively, for 6 d, over the last 4 d of which urine was collected daily for Ca determination as previously described (38). Immediately thereafter, diet Ca was reduced to 0.007% (by analysis of six different batches of the same lot of food 0.006±0.0018%6) by deleting the CaCO₃ supplement, leaving P (0.6%) and vitamin D (absent) unchanged. Over the ensuing 6 d, urine (in acidified vials), stool, and food aliquots were collected daily to determine Ca excretion, absorption, and retention as previously detailed (38). At 7 p.m. on day 7, the animals were fasted with H₂O ad lib. The next morning, they were bled by retro-orbital puncture, as previously described (33, 38), for measurements of Ca, 25OHD₃, and 1,25(OH)₂D₃ as radioimmunoassay laboratory at 8 a.m. No food was given during the first period, for 18 h, or during the second period, for 8 d, after which the diet Ca was again deleted as P remained constant at 0.6%. For reasons that could only be attributed to lot differences, the Ca deficiency diet for this period was found by analysis of 10 separate batches to be 0.017±0.0025%6.

After an overnight 14-h fast, the animals were bled (3 ml each) as described previously (33, 38) for measurements of serum Ca, 25OHD₃, and 1,25(OH)₂D₃. Urine Ca was determined daily. Stool and food aliquots were digested for Ca analysis as previously described (38). Spontaneous hypercalciuria, defined as described, refers to Ca excretion 2SD above the mean of the normal on days 5 and 6 of the low Ca diet. The pelleted chow was necessary to prevent ingrown canine teeth that develops with the chronic exposure to the pulverized diet. During the 5th wk of the vitamin D repletion, urine was collected for two consecutive days, followed by full balance studies over an 8-d period, during which diet Ca was again deleted as P remained constant at 0.6%. For reasons that could only be attributed to lot differences, the Ca deficiency diet for this period was found by analysis of 10 separate batches to be 0.017±0.0025%6.

### Results

**Effects of vitamin D deprivation.** Immediately after bleeding, they were fed 4 d with a pellet form of regular rat chow (Ralston Purina Co., St. Louis, MO) that contained 5.6 IU of vitamin D₃, 1.2% Ca, and 0.8% P, before resuming for 4 wk the ICN pulverized synthetic diet containing 0.87% Ca and 0.60% P, now supplemented with 2.2 IU of vitamin D₃. The pelleted chow was necessary to prevent ingrown canine teeth that develops with the chronic exposure to the pulverized diet. During the 5th wk of the vitamin D repletion, urine was collected for two consecutive days, followed by full balance studies over an 8-d period, during which diet Ca was again deleted as P remained constant at 0.6%. For reasons that could only be attributed to lot differences, the Ca deficiency diet for this period was found by analysis of 10 separate batches to be 0.017±0.0025%6.

**Table I. Ca Excretion in Response to a Low Ca Diet in Progeny of NC and SH Rats**

<table>
<thead>
<tr>
<th>Diet Ca = 0.5%</th>
<th>Diet Ca = 0.007%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Vitamin D deprivation</td>
<td></td>
</tr>
<tr>
<td>pNC</td>
<td>2.6</td>
</tr>
<tr>
<td>(n = 21)</td>
<td>±0.1</td>
</tr>
<tr>
<td>F ratio = 186, P &lt; 0.00001*</td>
<td></td>
</tr>
<tr>
<td>pSH</td>
<td>5.8</td>
</tr>
<tr>
<td>(n = 14)</td>
<td>±1.1</td>
</tr>
</tbody>
</table>

**Diet Ca = 0.87%**

<table>
<thead>
<tr>
<th>Vitamin D depletion</th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>pNC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.41</td>
<td>1.02</td>
<td>0.97</td>
<td>0.73</td>
<td>0.66</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>(n = 21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>±0.21</td>
<td>±0.13</td>
<td>±0.13</td>
<td>±0.07</td>
<td>±0.08</td>
<td>±0.05</td>
<td></td>
</tr>
<tr>
<td>F ratio = 20.9, P &lt; 0.00001*</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>pSH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.25</td>
<td>1.35</td>
<td>1.47</td>
<td>1.13</td>
<td>0.98</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>(n = 12†)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>±0.37</td>
<td>±0.23</td>
<td>±0.21</td>
<td>±0.15</td>
<td>±0.12</td>
<td>±0.06</td>
<td></td>
</tr>
</tbody>
</table>

* P values denote statistical comparison between pNC and pSH for a given vitamin D status. † One rat was anorexic, and one rat died from bleeding after the D-deprived phase; both are excluded in Table I.

Calcitriol in Spontaneously Hypercalciuric Rats 421
Table II. Ca Metabolism in NC and SH Rats on a Low Ca Diet*

<table>
<thead>
<tr>
<th></th>
<th>Ingested Ca</th>
<th>Fecal Ca</th>
<th>Net Ca absorbed</th>
<th>Urine Ca</th>
<th>Retained Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/d</td>
<td>mg/d</td>
<td>mg/d</td>
<td>mg/d</td>
<td>mg/d</td>
</tr>
<tr>
<td>vitamin D deprivation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NC</td>
<td>0.93±0.04</td>
<td>3.03</td>
<td>-2.15±0.46</td>
<td>0.54±0.07</td>
<td>-2.70±0.48</td>
</tr>
<tr>
<td>(n=24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value‡</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.001 NS</td>
<td>NS</td>
</tr>
<tr>
<td>SH</td>
<td>1.12±0.05</td>
<td>1.93</td>
<td>-0.80±0.41</td>
<td>2.00±0.45</td>
<td>-2.83±0.80</td>
</tr>
<tr>
<td>(n=9)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>vitamin D repletion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NC</td>
<td>3.20±0.08</td>
<td>4.03</td>
<td>-0.82±0.47</td>
<td>0.70±0.04</td>
<td>-1.47±0.26</td>
</tr>
<tr>
<td>(n=24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value‡</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.001 NS</td>
<td>NS</td>
</tr>
<tr>
<td>SH</td>
<td>3.45±0.10</td>
<td>4.20</td>
<td>-0.75±0.81</td>
<td>1.38±0.11</td>
<td>-2.13±0.87</td>
</tr>
<tr>
<td>(n=9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean±SE. * Balance data from days 3–6 of the diet. ‡ P values refer to statistical comparison between NC and SH rats for a given vitamin D status.

during D deprivation (urine Ca = 0.95 mg/d), all the 23 NC rats remained normocalciuric, regardless of whether they were vitamin D deprived or repleted.

Effects of vitamin D deprivation on Ca absorption and retention (Table II). Fecal Ca elimination on the first 2 d of the low Ca diet, analyzed separately, reflected residual unab sorbed Ca that was ingested previously as part of the normal Ca diet. They were therefore excluded from consideration of true Ca absorption during the more steady state of the subsequent days. From days 3–6 of the low Ca, D-repleted diet, net Ca absorption was not different between the NC and SH rats (Table II). Hence, the increased Ca excretion in SH was not a consequence of increased gastrointestinal absorption. Furthermore, urine Ca in each of the nine SH rats exceeded the corresponding net Ca absorption, which argued against the intestine as the source of the extra excreted Ca.

During vitamin D deprivation, fecal Ca exceeded ingested Ca even beyond the 2nd d of the low Ca diet, so that net Ca absorption became negative in most animals. The apparent Ca secretion was not different between the SH and NC rats (Table II). The tendency for the absolute value to be greater for NC rats was due to four animals which secreted an average of 5.5–9 mg Ca/d. Over the range of net Ca absorption, which spanned from -4 to 1 mg/d, where SH and NC rats overlapped (i.e., excluding these four data points), analysis indicated that the hypercalciuria in SH was not due to less severe Ca malabsorption. This impression is supported by the absolute value of Ca excretion in each of the nine SH rats, which was far in excess of the individual value for both the ingested Ca and net Ca absorbed. These data therefore exclude primary hyperabsorption as the pathogenic mechanism for the SH.

Effects of D deprivation on serum 25(OH)D3 and 1,25(OH)2D3 in SH (Table III). Serum Ca after an overnight fast was not significantly different between the NC and SH rats during either vitamin D deprivation or repletion. The absence of a difference is probably due to three factors. First, as indicated by the balance data (Table II), Ca retention between the two groups differed by only 0.13 mg/d (−2.83 vs. −2.70) in D deprivation and by only 0.66 mg/d (−2.13 vs. −1.47) in D repletion. Over the course of 6 d of balance studies, the cumulative difference was therefore <1 and 4 mg, respectively. These were clearly too small a difference in retention to be reflected in the serum Ca between the NC and SH. Second, we did not have enough blood for ionized Ca (and necessarily simultaneous pH for proper interpretation) when the key variable of interest was the vitamin D metabolite. That would have been more sensitive and perhaps more revealing than the total serum Ca. Finally, in these intact animals, increased PTH secretion could have partially offset the tendency for the serum Ca to be reduced in the SH rats.

Serum PO4 was lower in the SH rats for both D-deprived and repleted phases. Coupled with our preliminary data suggesting increased renal PO4 excretion rates (34), and the increased cAMP excretion in the present male (Table III) and in previously published female SH rats (33), the hypophosphatemia is best interpreted as a reflection of renal PO4 wastage secondary to increased PTH activity.

Serum 25OH D3 measured in eight SH rats and eight NC rats was comparable after 5 wk of D-repleted diet. Serum 1,25(OH)2 D3 was, however, significantly increased in the SH rats (Table III), resembling human IH (4, 10, 13, 14, 21, 23, 25, 28). The elevated 1,25(OH)2 D3 could either be primary (and be responsible for the hypercalciuria) or secondary as a compensatory event to the hypercalciuria. Urinary cAMP excretion was increased (Table III), consistent with the notion of stimulated PTH activity and suggestive of a homeostatic linkage to the increased serum 1,25(OH)2 D3. These findings are therefore incompatible with resorptive hypercalciuria mediated by a vitamin D-independent mechanism, such as immobilization, since, in this disorder, the PTH-endocrine system should be suppressed (31).

During vitamin D deprivation, as expected, serum 25OH D3 was undetectable (<2 ng/ml), and was equally so in both SH and NC rats, confirming the status of substrate depletion in our preparation. More importantly, serum 1,25(OH)2 D3 measured in seven specimens pooled from SH rats and eight specimens pooled from NC rats was not longer different between SH and NC rats, since their values were comparably reduced (Table III). A similar range of 1,25(OH)2 D3 (92±16 pg/ml) was recently reported in young rats after 6 wk of vitamin D
deprivation but supplemented throughout with a high Ca diet (36). Since the SH rats, identified from screening by a D-repleted diet, had always been hypercalcemic even in D deprivation (Table III), the dissociation between increased Ca excretion and increased serum 1,25(OH)₂D₃ strongly argued against a cause-and-effect relationship between these two phenomena. Thus, the hypercalcemia was independent of not only 25OHD₃ availability, but also of serum 1,25(OH)₂D₃ levels, contrary to the predictions by the hypothesis of a disordered regulation of vitamin D metabolism. Cyclic AMP excretion was again increased in SH rats (Table III), a finding incompatible with resorptive hypercalcemia (31).

**Discussion**

Mounting evidence suggests that if IH is a pathogenetically homogeneous syndrome, it cannot be adequately explained by either a primary hyperabsorption or an intrinsic tubular transport defect. One recent hypothesis suggests a basic abnormality in the regulation of 1,25(OH)₂D₃ synthesis (1, 14). Anatomically, a single lesion in the proximal tubule of the kidney could theoretically account for not only the disordered 1,25(OH)₂D₃ production, but also the exaggerated excretion rates of a host of solutes (15) normally handled by the proximal tubule, like Na (5), and PO₄ (5, 14, 20, 22).

We therefore used the spontaneously hypercalcemic rats to test this hypothesis. The low Ca diet protocol (containing 1–4 mg/d) was employed to facilitate the identification of hypercalcemia (33) by reducing the inherent variability in Ca excretion (Table I), to minimize contamination of urine by food and feces and to mimic the Ca restricted condition under which previous observations implying disordered 1,25(OH)₂D₃ synthesis were made (10, 14, 25). Additionally, a low Ca diet would facilitate the unmasking of resorptive hypercalcemia by minimizing the influx of intestinal Ca without obscuring hyperabsorption, since from 1 to 4 mg of Ca was still ingested daily (Table II).

Based on the previous definition of SH (33–35), a total of 9 SH male rats were found. Four potential mechanisms could mediate the hypercalcemia: (1) hyperabsorption from intrinsic intestinal abnormalities; (2) increased bone resorption; (3) increased 1,25(OH)₂D₃, producing a hybrid of increased absorption and enhanced resorption; and (4) intrinsic tubular Ca leak. Compared with the NC rat fed the same vitamin D-replete diet, net Ca absorption in SH rats was normal, and comproably negative with Ca restriction (Table II), mitigating against the role of primary hyperabsorption.

Although superficially there appears to be no change in net Ca absorption with a change in the vitamin D status (Table II), the comparison was not meaningful because of the differences in age (6 wk) and protocol (the insertion of the 0.5% Ca diet between the high [1.8%] and low [0.007%] Ca diets for only the D-deprived phase). When diet Ca was adequate (0.5–0.87%), net Ca absorption was significantly increased by D repletion (53.6±5.3 vs. 14.4±4.9 mg/d in SH and 55.9±6.1 vs. 15±3.5 mg/d in NC rats). This increase was...
also evident in fractional terms (33.4±3.2 vs. 16.4±6.4% in SH and 34±1.4 vs. 17.6±4.0% in NC rats).

Despite the documented increase in serum 1,25(OH)2D3 in the D-repleted SH rats, Ca absorption was not significantly increased compared with the NC rats. These data, however, do not necessarily contradict each other, since the serum measurement was performed on day 7 of the low Ca diet after the balance studies. Based on the current concepts on resorptive hypercalciuria (31), PTH and cAMP should be suppressed by the increased serum 1,25(OH)2D3 in SH rats. The high serum 1,25(OH)2D3 and the increased urinary cAMP excretion (Table III) argue against the role of a primary increase in bone resorption. However, the increased serum 1,25(OH)2D3 was still compatible with a basic disturbance in 1,25(OH)2D3 production.

The hypercalciuria identified during vitamin D repletion was not abolished by vitamin D deprivation, at a time when serum 250HD3 was undetectable and serum 1,25(OH)2D3 levels were as low as the NC rats (Table III). Hence, SH is independent of vitamin D availability and serum 250HD3. More importantly, the dissociation between the increased Ca excretion and increased serum 1,25(OH)2D3 documented here offers no support for a pathogenetic role of this metabolite in the generation of the hypercalciuria.

The cumulative data in the rat are therefore best interpreted by the alternate hypothesis of a renal Ca leak (33). In this view, the tubular defect produces negative Ca balance, stimulates PTH, and elicits a compensatory increase in 1,25(OH)2D3 production. When substrate was restricted, 1,25(OH)2D3 was no longer elevated in SH rats, despite a similar setting of increased PTH activity, as reflected by cAMP excretion (Table III).

If SH in rats were pathophysiologically akin to idiopathic hypercalciuria in man, our findings would suggest that the increased serum 1,25(OH)2D3 in these patients is a homeostatic response secondary to the hypercalciuria. The response to thiazide, of at least the renal hypercalciuric patients, with correction of their high urine Ca, high serum 1,25(OH)2D3, and intestinal hyperabsorption (25), is perfectly compatible with this notion. It is interesting to note that 25(OH)D3 treatment of IH patients characterized by suppressible increases in serum PTH (22) did not aggravate their hypercalciuria. Similarly, high doses of cholecalciferol did not elicit a difference in the calciuric response between normal and hypercalciuric patients (27), as would be predicted if disordered control of 1,25(OH)2D3 production were the primary defect.

In summary, data from the SH rats suggest that their hypercalciuria is more likely the cause than the consequence of the increased serum 1,25(OH)2D3 levels. In vitro studies on the regulation of 1,25(OH)2D3 synthesis in these animals may potentially shed light on the genesis of the elevated serum concentration of this metabolite.

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