Molecular mechanisms involved in the adaptive regulation of human intestinal biotin uptake: a study of the hSMVT system

Jack C. Reidling, Svetlana M. Nabokina, and Hamid M. Said
Veterans Affairs Medical Center, Long Beach; and University of California College of Medicine, Irvine, California

Submitted 20 July 2006; accepted in final form 29 August 2006

Reidling JC, Nabokina SM, Said HM. Molecular mechanisms involved in the adaptive regulation of human intestinal biotin uptake: a study of the hSMVT system. Am J Physiol Gastrointest Liver Physiol 292: G275–G281, 2007. First published September 7, 2006; doi:10.1152/ajpgi.00327.2006.—Biotin, a water-soluble micronutrient, is vital for cellular functions, including growth and development. The human intestine utilizes the human sodium-dependent multivitamin transporter (hSMVT) for biotin uptake. Evidence exists showing that the intestinal biotin uptake process is adaptively regulated during biotin deficiency. Nothing, however, is known about molecular mechanisms involved during this adaptive regulation. This study compared two human-derived intestinal epithelial cell lines (HuTu-80 and Caco-2) during biotin-deficient or biotin-sufficient states and with an approach that assessed carrier-mediated biotin uptake, hSMVT protein and RNA levels, RNA stability, and hSMVT promoter activity. The results showed that during biotin deficiency, a significant and specific upregulation in carrier-mediated biotin uptake occurred in both human intestinal epithelial cell lines and that this increase was associated with an induction in protein and mRNA levels of hSMVT. The increase in mRNA levels was not due to an increase in RNA stability but was associated with an increase in activity of the hSMVT promoter in transfected human intestinal cells. Using promoter deletion constructs and mutational analysis in transiently transfected HuTu-80 and Caco-2 cells, a biotin deficiency-responsive region was mapped to a 103-bp area within the hSMVT promoter that contains gut-enriched Kruppel-like factor (GKLF) sites that confer the response to biotin deficiency. These results confirm that human intestinal biotin uptake is adaptively regulated and provide novel evidence demonstrating that the upregulation is not mediated via changes in hSMVT RNA stability but rather is due to transcriptional regulatory mechanisms that likely involve GKLF sites in the hSMVT promoter.

intestinal biotin absorption; mechanism of adaptive regulation; human sodium-dependent multivitamin transporter

THE ESSENTIAL MICRONUTRIENT BIOTIN operates as a coenzyme for five carboxylases catalyzing essential steps in fatty acid biosynthesis, gluconeogenesis, and catabolism of several branched-chain amino acids and odd-chain fatty acids (3, 43). Neurological disorders, growth retardation, and dermal abnormalities have been reported during severe biotin deficiency (3, 4, 39). In humans, biotin deficiency and suboptimal levels have been described during pregnancy (20), in patients on long-term therapy with anticonvulsant agents (15, 16), in a substantial numbers of alcoholics (5, 11), in patients with inflammatory bowel diseases (2, 41), and in infants with seborrheic dermatitis and Leiner’s disease (19, 21). Delineating the mechanisms involved in maintaining and regulating biotin levels is of considerable physiological and nutritional importance, perhaps assisting in the designing of valuable tactics to optimize biotin body homeostasis during conditions of biotin deficiency and suboptimal levels.

Biotin is not synthesized by humans or other mammals and must be obtained from exogenous sources. Dietary food sources high in biotin include organ meat (the liver and kidney), egg yolk, green leafy vegetables, and cow’s milk. Lean meat, cereals, and fruits are poor sources of biotin (7). Humans absorb dietary biotin in the small intestine; however, a bacterial supply produced by the normal microflora of the large intestine may also contribute to overall biotin body levels (47). Dietary biotin not only exists in a free form but also a protein-bound form (17) that is digested by gastrointestinal proteases and peptidases to biocytin (N-biotinyl-L-lysine) and biotin-containing short peptides and is eventually converted to free biotin by the action of biotinidase (17, 39, 46). The mechanism of uptake of free biotin in the small and large intestine has been studied using a variety of intestinal preparations (for reviews, see Refs. 28 and 39 and the references therein) and has been shown to occur via a Na⁺ gradient-dependent, carrier-mediated mechanism functionally located only at the apical membrane domain of polarized intestinal epithelial cells (26, 30, 33–37).

Due to the fact that two other functionally unrelated nutrients, the water-soluble vitamin pantothenic acid and the metabolically important antioxidant lipoate (27, 34, 43), share the biotin transport system, the transporter has been named the sodium-dependent multivitamin transport system (SMVT) system. The SMVT system has been cloned from multiple species including the rat, rabbit, human, and, more recently, mouse [see Refs. 6, 23, and 23 and unpublished observations from our laboratory (GenBank Accession No. AY572835)] with the cDNAs sharing significant identity at both the nucleotide and predicted amino acid levels. Based on hydrophobicity, each of these proteins is predicted to have 12 transmembrane domains with both the amino- and carboxy-terminals being on the cytoplasmic side of the membrane and multiple potential N-glycosylation sites. In the human and mouse, SMVT is expressed in the small and large intestine (although at different levels) (2, 35), which corroborates the observations on the existence of a functional Na⁺-dependent, carrier-mediated biotin uptake system in both regions of the gut.

A study (1) from our laboratory has determined the contribution of the human (h)SMVT system toward overall carrier-mediated biotin uptake in human intestinal epithelial cells using specific small interfering RNA (siRNA) as an approach for gene silencing of the hSMVT gene, with the results showing

Address for reprint requests and other correspondence: H. M. Said, Veterans Affairs Medical Center-151, 5901 E. 7th St., Long Beach, CA 90822 (e-mail: hmsaid@uci.edu).

http://www.ajpgi.org

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

http://www.ajpgi.org

G275
hSMVT to be the main (if not the only) biotin uptake system in the human intestine. In additional investigations (10, 25), we cloned the human 5′-regulatory region of the hSMVT gene and determined the minimal regions for basal promoter activity in intestinal epithelial cell lines (NCM460, Caco-2, and HuTu-80), identifying gut-enriched Kruppel-like factor (GKLF) and activator protein (AP)-2 as factors that interact with and contribute to promoter activity in vitro as well as determining in vivo promoter activity.

Intestinal transport of a variety of other nutrients is regulated by substrate availability (12, 14, 26, 31, 38), and this type of adaptive regulation in transport is substrate, cell, and transporter specific in nature. As examples, dietary deficiencies of folate and riboflavin lead to an upregulation in their intestinal uptake, whereas a decrease in dietary levels of glucose and amino acids leads to a downregulation in their intestinal uptake (12, 14, 26, 31, 38). In addition, while the intestinal absorption of phosphate is adaptively upregulated during dietary phosphate deficiency in the intestine, no such adaptive regulation occurs in the pulmonary epithelia (40). Furthermore, a study (24) from our laboratory has demonstrated that the intestinal thiamin uptake process is adaptively upregulated during dietary thiamin deficiency and that the upregulation is mediated via transcriptional regulatory mechanism(s) involving thiamin transporter (THTR)-2 but not THTR-1 (24). With regards to biotin, studies from our laboratory using rat intestinal brush-border membrane vesicles (32) and cultured human intestinal epithelial cells (18) have shown that the intestinal biotin uptake process is adaptively regulated during biotin deficiency. Nothing, however, is known about the molecular mechanism(s) involved in this adaptive regulation.

Our objectives in this investigation were to first confirm the effect of biotin deficiency on human intestinal biotin uptake and then to determine the molecular mechanism(s) involved in this adaptive regulation. We chose to apply an approach utilizing human-derived intestinal epithelial cells (HuTu-80 and Caco-2) grown in biotin-deficient medium compared with cells grown in biotin-sufficient medium. The comparison of two human intestinal epithelial cell lines supports that our findings are similar to the intestinal situation and not a cell line-specific phenomenon. The results of our investigation confirm that the human intestinal biotin uptake process is adaptively upregulated, in a specific manner, during biotin deficiency and that this upregulation appears to occur via an increase in hSMVT protein and mRNA levels that are ultimately mediated not by changes in RNA stability but rather by transcriptional regulatory mechanism(s) involving GKLF sites in the hSMVT promoter.

**MATERIALS AND METHODS**

**Materials.** [1H]biotin and [3H]thiamin (specific activity: >30Ci/mmol, radioactive purity: >98%) were purchased from American Radiolabeled Chemical (St. Louis, MO). All chemicals and reagents used in this study were of analytical/molecular biology grade and were purchased from commercial sources.

**Cell culture and uptake experiments.** Human-derived intestinal epithelial Caco-2 cells (passage 20, American Type Culture Collection (ATCC), Manassas, VA; these cells were derived from colorectal adenocarcinoma obtained from a 72-yr-old Caucasian male) and HuTu-80 cells (passage 20, ATCC; these cells were derived from duodenum adenocarcinoma obtained from a 53-yr-old Caucasian male) were grown in DMEM supplemented with 10% (vol/vol) FBS, glutamine (0.29 g/l), sodium bicarbonate (2.2 g/l), penicillin (100,000 U/l), and streptomycin (10 mg/l) in 75-cm² plastic flasks at 37°C in a 5% CO₂-95% air atmosphere with media changes every 2–3 days. Cells were plated at a density of 2 × 10⁶ cells/well onto 12-well plates. For experiments of biotin deficiency, a growth medium lacking biotin was used (DMEM from GIBCO-BRL, Grand Island, NY) and the FBS (10%) added was made biotin deficient by a preincubation with avidin-agarose (Sigma, St. Louis, MO). This method, described previously (9), takes advantage of the fact that each avidin molecule binds four biotin molecules. Briefly, a 2-ml suspension of avidin-agarose containing 1.5 mg avidin was combined with 50 ml of FBS for 1 h with gentle mixing at room temperature. The biotin-avidin-agarose complex was then removed by centrifugation at 450 g, and the FBS was decanted into a new container. To create a biotin-deficient state, cells were incubated in this medium for 4 days with fresh changes of medium daily. Uptake experiments were performed (between passages 23 and 36) on postconfluent (5 days after cells were seeded, 3 days after cells reached confluence) monolayers of Caco-2 or HuTu-80 cells. Uptake was measured at 37°C in Krebs-Ringer buffer (containing (in mM) 133 NaCl, 4.93 KCl, 1.23 MgSO₄, 0.85 CaCl₂, 5 glucose, 5 thiamine, 10 HEPES, and 10 MES; pH 7.4). Labeled and unlabeled biotin or thiamin were added to the incubation medium at the onset of incubation, and uptake was examined during the initial linear period. The reaction was terminated by the addition of 2 ml of ice-cold buffer followed by immediate aspiration. Cells were then rinsed twice with ice-cold buffer, digested with 1 ml of 1 N NaOH, neutralized with HCl, and then measured for radioactive content using a scintillation counter. The protein content of cell digests was measured in parallel wells using a Bio-Rad DC Protein Assay kit (Bio-Rad, Richmond, VA).

**Transfection and reporter gene assay.** The hSMVT promoter- luciferase reporter constructs utilized in this study were generated previously (25). Caco-2 or HuTu-80 cells at <80% confluence in 12-well plates were cotransfected using Lipofectamine 2000 reagent (Life Technologies, Rockville, MD) according to the manufacturer’s instructions with 2 µg of each construct and 100 ng of control plasmid Renilla luciferase-thymidine kinase (pRL-TK) (Promega, Madison, WI). Cells were lysed with passive lysis buffer (supplied in the assay system), and Renilla-normalized firefly luciferase activity was determined using the Dual Luciferase Assay system (Promega). Data are presented as means ± SE of at least three independent experiments and given as fold expression over the pGL3-Basic promoter empty vector set, which was arbitrarily set at 1.

**Quantitative real-time PCR and Western blot analysis.** Quantitative real-time PCR (qPCR) was performed using a Bio-Rad iCycler (Hercules, CA) and a Qiagen Quantitect SYBR green PCR kit (Valencia, CA). RNA from intestinal cells was isolated using TRIzol (Invitrogen, Carlsbad, CA) according to the manufacturer’s procedures. RNA was DNase treated, and first-strand cDNA was made from 5 µg of the isolated total RNA primed with oligo-dT using an Invitrogen Superscript synthesis system. A dilution series of the RT products (1, 1/10, and 1/100) was then used in the subsequent qPCR. Primers used in the qPCR were specific for hSMVT (forward: 5′-TGTCTACCCTTCCCCATCATGGA-3′; and reverse: 5′-TAGAGCCCAGATTGGGAGAGA-3′) or human β-actin (forward: 5′-GACCGGCTCCTCTTGTGA-3′; and reverse: 5′-TAGAGAGGGCCACAC3′). The qPCR consisted of a 15-s 95°C melt followed by 40 cycles of 95°C melt for 30 s, 58°C annealing for 30 s, and 72°C extension and data collection for 1 min. Melt curve analysis with plasmid DNA was performed for the generation of standard curves, and negative controls without reverse transcriptase were used with every reaction. To compare the relative relationship between hSMVT levels in biotin-deficient and control cell lines, we utilized a calculation method provided by the iCycler manufacturer (Bio-Rad) as described previously (24). Western blot analysis was performed as previously described (25) using antibodies designed to be specific for
hSMVT protein (Sigma-Genosys, The Woodlands, TX). Densities of specific bands were determined (as unitless measurements) using the UN-SCAN-IT gel automated digitizing system (version 3.1, Silk Scientific).

**RNA stability assay.** A RNA decay rate assay (i.e., RNA stability assay) was performed as previously described (13). HuTu-80 or Caco-2 cells were maintained in control or biotin-deficient growth medium and then analyzed for RNA stability by the addition of actinomycin D (1 μM, Sigma) to the growth medium followed by an isolation of total RNA using TRIZol (Invitrogen) and the manufacturer’s procedures at specific time points of 1, 18, 20, 24, 40, and 46 h. RNA was then reverse transcribed with oligo-dT, and qPCR analysis was performed with specific primers to either hSMVT, human (h)THTR-1, or β-actin using the conditions and primers described above. The primers used for hTHTR-1 were forward 5'-AGCCAGACCGTCTCCTTGTAGTA-3' and reverse 5'-TAGAGAGGGCCACACCAC-3'.

**Statistical analysis.** Transport data presented in this study are the results of three separate experiments and are expressed as means ± SE (in pmol·mg protein⁻¹·10⁻³·s⁻¹). Western blot analysis, qPCR, and luciferase assays were all performed on at least three separate occasions. Differences between the means of control and biotin-deficient cells for various outcome parameters were tested for significance using Student’s t-test with the critical value of probability (P value) chosen as 0.05. Uptake of biotin and thiamin by the carrier-mediated system was determined by subtracting the uptake by passive diffusion (determined from the slope of the line between uptake at a high pharmacological concentration of 1 mM and the point of origin) from the total uptake.

**RESULTS**

**Effect of biotin deficiency on biotin uptake and hSMVT expression in human intestinal HuTu-80 and Caco-2 epithelial cells.** We examined and compared the effect of maintaining the human-derived intestinal epithelial cell lines HuTu-80 and Caco-2 in biotin-deficient or biotin-sufficient growth medium for 4 days on biotin uptake and on the levels of hSMVT protein and mRNA. A significant (P < 0.01) upregulation in [³H]biotin (9 nM) uptake was found in cells grown under biotin-deficient conditions compared with those grown under control conditions (Fig. 1A); however, no increase in the uptake of unrelated thiamin (15 nM) was observed (thiamin uptake of 0.16 ± 0.01 and 0.17 ± 0.009 pmol·mg protein⁻¹·3·min⁻¹ in HuTu-80 cells and 0.13 ± 0.002 and 0.14 ± 0.003 pmol·mg protein⁻¹·3·min⁻¹ in Caco-2 cells maintained in biotin-deficient and control growth media, respectively). These findings further confirmed that carrier-mediated intestinal biotin uptake is adaptively upregulated at the functional level during biotin deficiency and suggests that the regulation is specific in nature.

It was determined that the upregulation in biotin uptake during biotin deficiency was associated with an increase in hSMVT protein and mRNA levels as indicated by Western blot analysis and by qPCR, respectively (Fig. 1, B and C). Our findings indicated that the increase in biotin uptake is mediated via an increase in the level of hSMVT protein that is, in turn, mediated by an increase in mRNA levels and suggests the possibility that the mechanism of the observed RNA induction involves RNA stability and/or transcriptional regulatory mechanisms.

**Effect of biotin deficiency on hSMVT RNA stability in human intestinal epithelial cells.** To determine if changes in RNA stability caused the observed increase in intestinal hSMVT mRNA levels during biotin deficiency, we performed a RNA decay rate assay (i.e., RNA stability assay) (13). In these experiments, we added the transcriptional inhibitor actinomycin D (1 μM) after incubating HuTu-80 or Caco-2 cells in biotin-deficient growth medium followed by examination of the hSMVT RNA decay rate using qPCR. The results showed no difference in the decay rate of hSMVT RNA between cells maintained in biotin-deficient media and those maintained in control growth media (Fig. 2). The decay rate of RNA of unrelated hTHTR-1 and β-actin (used as controls) was also not affected by biotin deficiency. These findings point to the possible involvement of transcriptional regulatory mecha-

---

Fig. 1. A: initial rate of carrier-mediated biotin uptake by HuTu-80 and Caco-2 cells maintained in biotin-deficient and control growth media. Cells were incubated for uptake experiments at 37°C in Krebs-Ringer buffer (pH 7.4). [³H]biotin (9 nM) was added to the incubation medium at the onset of incubation. Uptake was measured after a 3-min incubation (i.e., initial rate; unpublished data). Data are means ± SE of 3–5 separate uptake determinations. B: expression of human sodium-dependent multivitamin transporter (hSMVT) protein in HuTu-80 and Caco-2 cells grown under biotin-deficient and control conditions. Western blot analysis was performed using 150 μg protein from the membranous fraction of HuTu-80 or Caco-2 cells. The blot was probed with polyclonal antibodies directed against a specific peptide of hSMVT and detected using the ECL system. C: effect of biotin deficiency on the level of hSMVT RNA expression. Real-time PCR was performed using gene-specific primers, and total RNA was isolated from control or biotin-deficient HuTu-80 or Caco-2 cells. Data are from 3 different experiments and expressed relative to β-actin as means ± SE and presented as the relative expression over control cells, which was set at 1. *Statistically significant (P < 0.01).
nism(s) in causing the adaptive regulation in intestinal biotin uptake during biotin deficiency.

Effect of biotin deficiency on activity of the full-length hSMVT promoter P1P2 and on the individual promoters P1 and P2 transiently expressed in HuTu-80 and Caco-2 intestinal epithelial cells. A previous study (10) has shown that the hSMVT gene has two potential transcriptional initiation sites included within a full-length promoter (P1P2) that contains two distinct promoters: promoter 1 (P1) and promoter 2 (P2). To directly test the possibility that transcriptional regulation plays a role in adaptive regulation during biotin deficiency, we examined the activity of the hSMVT promoters P1P2, P1, and P2 in HuTu-80 and Caco-2 cells maintained in biotin-deficient and control growth media. The results showed that the activity of both the full-length and individual promoters to be significantly higher in cells maintained under biotin-deficient conditions compared with those maintained under control conditions in both cell lines (Fig. 3). These findings clearly showed the involvement of transcriptional regulatory mechanism(s) in the regulation of human intestinal biotin uptake during biotin deficiency.

Determination of a biotin-responsive region in the hSMVT P1 promoter. Given that P1 is the more predominant promoter compared with P2 in intestinal epithelial cells, we set out to identify a biotin-responsive region in the hSMVT P1 promoter. The promoter activities of deletion constructs in biotin-deficient and biotin-sufficient HuTu-80 and Caco-2 cells were utilized. The results (Fig. 4) showed that a biotin-responsive region was encoded in a 103-bp sequence (see Fig. 5 for sequence) in the P1 promoter. This was based on the observation that progressive deletions of the hSMVT P1 promoter were not associated with a disappearance of the biotin-responsive effect until the deletion reached a 130-bp construct; thus, this fragment did not contain the responsive region and suggested that the previous sequence, i.e., the 103-bp region before this deletion, did contain a responsive region. Interestingly, the identified biotin-responsive region contained cis-regulatory elements, GKL and AP-2 sites, that are important for the basal activity of the promoter (25). We therefore next examined the role of these sites in mediating the biotin deficiency effect on promoter activity in HuTu-80 and Caco-2 cells.

Role of specific cis-regulatory elements in the biotin-responsive region of the hSMVT P1 promoter in mediating the effect of deficiency. As stated above, the biotin-responsive region of the hSMVT P1 promoter contains GKL and AP-2 binding sites that are important for the basal activity of this promoter (25). In this study, we investigated the possible role of these sites in mediating the biotin deficiency effect on the activity of the hSMVT promoter. This was achieved by examining how the biotin-dependent response in promoter activity reacts to mutations in the sites by using previously generated mutant constructs (25) transiently transfected into Caco-2 cells. The results showed that mutating GKL sites in the hSMVT P1 promoter led to a marked abatement of the biotin-dependent responses.
response (Fig. 5). On the other hand, mutation of an AP-2 site located in the biotin-dependent response region failed to affect the biotin-dependent response on the hSMVT promoter activity. These findings suggested a critical and specific role for GKLF sites in mediating the biotin-dependent response on the hSMVT P1 promoter. Similar results were obtained using HuTu-80 cells (data not shown).

DISCUSSION

Our intentions in this study were to first confirm that adaptive regulation occurs in the human intestinal biotin uptake process during biotin deficiency and then determine the molecular mechanism(s) involved in this regulation. Given that the human intestine expresses the hSMVT transporter and that it accounts for most (if not all) carrier-mediated biotin uptake in intestinal epithelial cells (1), we focused our attention on this system. The experiments utilized two different human intestinal epithelial cell lines (HuTu-80 and Caco-2) to examine if any observed effect(s) was related to cell line-dependent characteristics and also to support intestinal specificity.

Our results confirmed that biotin deficiency leads to a specific and significant upregulation in human intestinal epithelial cell carrier-mediated biotin uptake that was associated with an increase in the protein and mRNA levels of hSMVT. The increase in hSMVT mRNA levels suggested that RNA stability of the hSMVT message and/or transcriptional regulatory mechanisms of the hSMVT gene are involved in mediating the upregulatory events. To test these possibilities, we first examined the stability of hSMVT mRNA. We found that the hSMVT mRNA decay rate was parallel in biotin-deficient compared with biotin-sufficient human intestinal cells, suggesting that RNA stability was not a factor in the observed upregulatory event associated with the adaptive regulation.

Next, to test if transcriptional regulatory mechanisms of the hSMVT gene were involved in mediating the upregulatory events, we took advantage of the availability, in our laboratory, of hSMVT promoter-luciferase constructs. Experiments using these constructs showed that biotin deficiency was associated with an increase in the activity of the hSMVT full-length promoter P1P2 as well as the two distinct promoters P1 and P2 and supported the notion that transcriptional mechanism(s) may be involved in the regulation of the intestinal biotin absorption process.

To elaborate on the finding that transcriptional mechanisms are involved in the biotin-deficient response, we mapped a biotin-responsive region in promoter P1 using Caco-2 cells. Cells were transiently transfected with the hSMVT promoter P1 233-bp luciferase construct mutated at the activator protein (AP)-2 or gut-enriched Kruppel-like factor (GKLF) sites located in the biotin-responsive region (shown above) and then maintained in biotin-deficient or control growth media for 4 days. The cell lysate was isolated and assayed for firefly luciferase activity. Luciferase activity was normalized relative to the activity of simultaneously expressed Renilla luciferase. Results are expressed relative to the pGL3-Basic vector, which was set at 1, and represent means ± SE of at least 3 independent experiments. *Statistically significant (P < 0.01).
basal promoter activity but, in addition, contained cis-regulatory elements that bound the factors GKLF and AP-2. This information allowed us to focus on these factor-binding sites in our further analysis of the promoter’s role in the biotin-deficient response. We found that mutation of GKLF sites caused attenuation of the biotin-deficient response but mutation of an AP-2 site had no such effect, providing evidence that GKLF may participate in increasing promoter activity in response to biotin deficiency. GKLF (also known as KLF-4) plays a critical role in mammalian gut development, growth, and differentiation (44, 48); therefore, it is not surprising that this factor may be involved in the gut response to nutrient levels.

The observations of adaptive regulation in biotin uptake and hSMVT expression in intestinal epithelial cells during biotin deficiency observed in this investigation are in line with our previous findings of an increase in the V_{\text{max}} (i.e., apparent number) of biotin carriers (18, 32). Our findings in the present study, however, are in contrast to observations on biotin transport regulation using two other human tissues. In human liver HepG2 cells, biotin deficiency caused a decrease in biotin uptake and decreased levels of hSMVT (22); in leukocytes isolated from individuals made marginally biotin deficient, decreased levels of hSMVT mRNA were also found (42). Taken together, these results support the idea that the biotin-deficient effect is cell type specific and may be similar to phosphate regulation, where the intestinal absorption of phosphate is adaptively upregulated during dietary phosphate deficiency in the intestine yet no such adaptive regulation occurs in the pulmonary epithelia (40).

In conclusion, the results of this study confirm that biotin uptake by human intestinal epithelial cells is adaptively regulated during biotin deficiency and show that transcriptional mechanisms via GKLF may be involved in this regulation.

GRANTS

This study was supported by grants from the Department of Veterans Affairs and by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Grants DK-56061 and DK-58057. J. C. Reidling was supported by NIDDK Award DK-73032.

REFERENCES


