Intestinal Absorption of Water-Soluble Vitamins (44007)

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Abstract. **Vitamin utility is a scientific/medical topic that appears to be pursued as ardently by the lay public as by scientists and medical practitioners. A group of epidemiologists evaluates the effects on health of vitamin intake in the natural diet and by supplementation. The role in ocular disease, cancer of the breast or colon, and cardiovascular disease are a few of the concerns. The results and recommendations concerning dietary vitamin intake will likely continue to change. However, the processes by which dietary vitamins are delivered from intestinal chyme to the blood are more certain. The concept of homeostasis might apply to various of the vitamins as it does to minerals, water, etc. This review will discuss some common methods used to study vitamin absorption and the proposed mechanisms of absorption, and will conclude with a section about dietary regulation.** [P.S.E.B.M. 1996, Vol 212]

Methods Used to Study Vitamin Absorption

The processes of vitamin uptake into intestinal absorptive cells and delivery to the circulation have been under consideration for decades. Although the intent of investigators to understand the processes has remained the same, the methodology available for investigation continues to evolve. Advances have been on two fronts: (i) intestinal absorption is now evaluated at the level of cell membrane transporters and intracellular enzymes, and (ii) techniques for quantifying vitamins and their metabolites have improved notably.

Early methods for evaluating intestinal absorption of nutrients were most helpful in evaluating which dietary components were absorbed and which were rejected by the body. Most of the studies were conducted *in vivo*. In humans, double or triple lumen tubes were placed through the mouth with the distal ends reaching different positions of the intestine. A solution with known composition (e.g., of a vitamin) was infused through the proximal tube, and samples were taken from the distal position. When a nonabsorbable dye was used to mark volume changes in luminal content, the extent of vitamin absorption could be calculated. With other models, samples could also be taken from the blood to determine the extent of vitamin metabolism.

Intact intestinal preparations *in vitro* have allowed considerably more insight into cellular mechanisms underlying vitamin absorption. Strips of small intestine mounted in lucite chambers allowed six to eight defined areas of mucosal surface to be exposed to a particular vitamin, with control of substrate concentration, presence of metabolic inhibitors, etc. Isolated cells from intestinal mucosa have been useful for evaluating short-term properties of vitamin absorption and metabolism. A recent advance has been to use monolayers of intestinal epithelial cells in culture. This allows the best opportunity to evaluate vitamin transport and metabolism in a known and identified intestinal cell type. A notable limitation of such cell lines is

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that many have different metabolic characteristics from normal cells.

Progress in distinguishing between transport and metabolism of vitamins has been made with the use of tissue disrupted by mechanical, ultrasonic, osmotic, or freezing stress. Two components most useful for evaluation have been the cell membranes and the cytoplasm. Membranes obtained specifically from the brush border or the basolateral cell surface are processed into small spheres or vesicles. These can be constructed to have at the initial time of evaluation an internal composition that resembles the intracellular electrolyte composition of an enterocyte. The outside solution typically resembles the electrolyte composition of mammalian extracellular fluid. Either solution can be altered to observe the effect on substrate transport. Brush border vesicles characterize substrate uptake, whereas basolateral vesicles are a good model of exit from the enterocyte toward the circulation. The trans-membrane electrical potential can be manipulated with the combination of ionic gradients and changes in membrane permeability brought about by ionophores. With this preparation, the properties of vitamin transport without complications of simultaneous metabolism can be determined. A limiting feature of this is that the density of vitamin transporters in the cell membrane is a small fraction of what occurs for many sugar and amino acid transporters. A second factor is that because there is no cell membrane Na-K ATPase functioning, the transmembrane ionic gradient established by the conditions of preparation is temporary: it is typically eliminated by diffusion within 1–2 min. Thus, in the case of vitamins, the amount transported during the 20-sec. period of greatest ionic gradient might not be sufficient to establish accumulation against a concentration gradient; Thus, the "overshoot" phenomenon is difficult to demonstrate. This limitation is clearly one reason that we have less detailed information about intestinal transport of vitamins than is available for nutrients that have a higher density of transporters.

A second opportunity in working with disrupted cells is in evaluating the properties of vitamin metabolism separate from membrane transport. The cell homogenate is typically centrifuged to participate membranous matter. The supernatant is fractionated with ammonium sulfate to remove a great amount of nonfunctional protein and achieve a modest degree of enzyme purification. The resulting crude preparation can be used or additional steps of enzyme isolation and purification may be used. Those who investigate the intestine are fortunate in having much more tissue available from one animal than, for instance, those who study the corneal epithelium or some small component of the brain.

In a brief review of a rather broad topic such as vitamin absorption, specific details about each substrate must be deemphasized in favor of a more generalized format that each vitamin can fit into. This paper will cover water-soluble vitamins exclusive of folate and cobalamin (vitamin B_{12}), both of which were covered at length in Johnson's extensive text on gastrointestinal function (1). A summary of this material appears in Table I.

Table I. Properties of Vitamin Absorption in Small Intestine

Vitamin	MW	Species	Site of absorption	Process involved	Appt. K_m	Other properties
L-ascorbic acid	176	Human	Ileum	Active transport	0.3 m*M*	1
		Guinea pig	Ileum	Active transport	0.2 m*M*	1,6
Dehydro-L-ascorbic acid	174	Guinea pig	Ileum	Facilitated transport and intracellular reduction	0.1 m*M*	4,5
Biotin	244	Hamster, rat, squirrel, mouse, human	Proximal	Facilitated transport (or active transport?)	1–10 μ*M*	1,5
Folic acid (pteroylglutamic acid)	441	Rat	Jejunum	Facilitated transport	6 μ*M*	
		Rabbit	Jejunum	Folate-OH^- exchange	0.2 μ*M*	
Inositol	180	Hamster	Small bowel	Active transport	0.1 m*M*	1
		Chicken	Small bowel	Facilitated transport	0.1 m*M*	1
Nicotinic acid	123	Rat	Jejunum	Nonionic diffusion	None	5
Nicotinamide	122	Chicken	Proximal	Intracellular metabolism	None shown	4
Pantothenic acid	219	Rat, chicken	Small bowel	Active transport	17 μ*M*	1
Riboflavin	376	Human	Proximal	Facilitated transport	0.4 μ*M*	2
		Rat	Proximal	Facilitated transport	0.3 μ*M*	1,3,6
Thiamine	337	Rat	Proximal	Active transport	0.3 μ*M*	1,3,5
		Rat	Basolateral membranes	Primary active transport	1.3 μ*M*	
Vitamin B_6	206	Rat, hamster, human	Proximal	Intracellular metabolism	—	3,4

Note. MW, molecular weight; 1, Na^+ dependent; 2, bile salt dependent; 3, phosphorylated; 4, metabolized other than by phosphorylation; 5, electroneutral process; 6, electrogenic process.

Ascorbic Acid

Intestinal uptake and metabolism of ascorbic acid, and its oxidized metabolite dehydro-L-ascorbic acid (DHAA), have been studied extensively. Guinea pigs are a useful model because they resemble primates in lacking the ability to synthesize ascorbic acid from glucose and therefore require it in the diet. Intact segments of either guinea pig and human intestine demonstrated that ascorbic acid is taken up against a concentration gradient by a process dependent on intact metabolic energy (2, 3). Studies on the entry step of ascorbic acid from luminal content into the absorptive cell (enterocyte) demonstrated a saturable mechanism that was highly dependent on the presence of Na^+ (4). The properties of ascorbic acid transport across the brush border membrane were further evaluated in membrane vesicles (Fig. 1) (5). When a Na^+ gradient existed across the membrane from outside to inside, ascorbic acid uptake occurred with a peak at ~1 min that was approximately twice the equilibrium value reached at 5–10 min of incubation. These findings were consistent with the classic Na^+ gradient–dependent concept of substrate accumulation (secondary active transport) introduced by Crane (6).

Movement of ascorbic acid from the enterocyte toward the circulation is an energetically favorable step brought about by the high intracellular ascorbic acid concentration and the intracellular electrical negativity (35–50 mV) relative to the serosal surface. Studies with basolateral membrane vesicles indicated that this step is saturable. Although a process of facilitated diffusion is suggested, additional experimental evidence would be helpful.

The proportion of total vitamin C in food that is present in the oxidized form depends on the length and conditions of storage. The body would seem to benefit from absorbing dietary DHAA, providing there is a convenient way to reduce it to the useful molecule. Intestinal cellular mechanisms exist to conserve dietary DHAA. One is a carrier mediated transport mechanism at the brush border membrane that serves to bring DHAA into the enterocyte (Fig. 2). The second is a cytosolic enzyme that uses glutathione (and NADPH?) to reduce the compound to ascorbic acid.

One additional transporter for vitamin C has been identified in the enterocyte. This exists at the basolateral cell surface and appears to be specific for DHAA. The utility of this is speculative, but it might serve to regulate the whole-body redox state of vitamin C. The emerging concept is that ascorbic acid becomes oxidized in the body as a consequence of its several known functions, including one antioxidant function. In this, ascorbic acid scavenges various reactive oxygen species that would otherwise have the potential to react with sensitive cellular components and result in tissue damage or disease (7). The metabolite, DHAA, can be brought back to the useful, reduced state by being transported from blood to cell, and is then acted on by the same enzyme that is active in handling dietary DHAA.

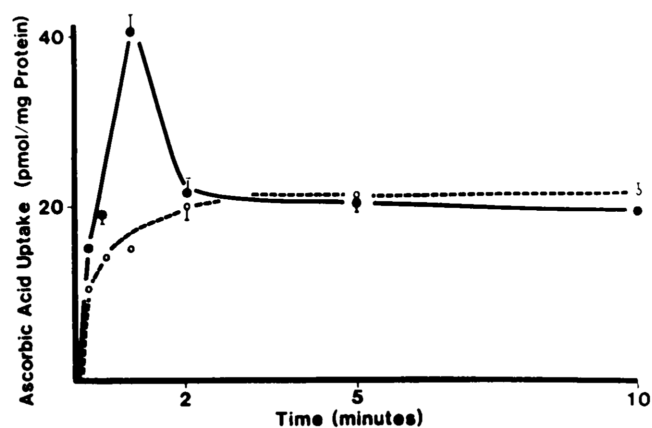

Figure 1. Time course of ascorbic acid uptake into guinea pig ileal brush-border membrane vesicles. Vesicles were preequilibrated in 300 m*M* mannitol and 20 m*M* HEPES-Tris (pH 7.0). Incubation was at 20°C in a medium containing 65 μ*M* L-[^{14}C]ascorbic acid, 100 m*M* mannitol, 20 m*M* HEPES-Tris (pH 7.0), and either 100 m*M* NaCl (●) or 100 mM KCl (○); eight observations. HEPES, *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid; Tris, tris(hydroxymethyl)aminomethane. (Reproduced with permission from Am J Physiol **250:**G461–G468, 1986.)

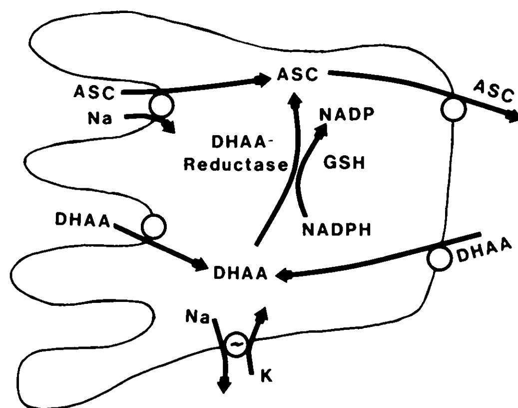

Figure 2. Model of known events in intestinal absorption of reduced and oxidized forms of vitamin C in animals that require L-ascorbic acid (ASC); model may also apply to events in renal reabsorption of filtered L-ascorbic acid both in animal species that require dietary L-ascorbic acid and in those that synthesize it. L-Ascorbic acid is taken up across the brush-border membrane against a concentration gradient coupled with Na^+ diffusion down an electrochemical potential gradient entering the cell. L-Ascorbic acid leaves the transport cell by a carrier-mediated process at the basolateral membrane, perhaps in exchange for interstitial dehydroascorbic acid (DHAA). Dehydroascorbic acid from either the lumen or interstitium enters the cell by facilitated diffusion and is enzymatically reduced. (Reproduced with permission from Am J Physiol **254:**G824–G828, 1988.)

Biotin

As for ascorbic acid, the choice of animal species for studying biotin absorption is important. In both rats and humans the total excretion of biotin is significantly greater than dietary intake. The significance of this is not known, in that biotin synthesis is thought to occur by microorganisms in the colon and the major site of the vitamin's absorption is the proximal or middle small intestine in both humans (8) and rat (9). This was due to a greater V_{max} of uptake, indicating that the density of transport carriers decreases distally. With use of the everted jejunal sac technique, biotin transport at low substrate concentrations was inhibited by the presence of structural analogs, was Na^+ dependent, energy dependent, and temperature dependent, and proceeded against a transmucosal concentration gradient. With use of thin-layer chromatography for analysis of ^3H-label reaching the serosal fluid, it was determined that little or no metabolic alteration of biotin occurs during transport. In brush border membrane vesicles of jejunum, transport of biotin by a carrier-mediated process was calculated by subtracting uptake in the presence of a choline gradient from the total uptake (i.e., values determined in the presence of an inwardly directed Na^+ gradient (Fig. 3) (10). Transport of the anionic biotin was not affected by imposing an electrically positive intravesicular potential, suggesting that biotin transport is an electroneutral process. In basolateral membrane vesicles derived from human jejunum, transport of biotin was independent of a transmembrane Na^+ gradient and saturable with a transporter having higher affinity for the substrate than the system at the brush border (11). Two recent reports have made use of a human intestinal epithelial cell line (CACO-2) to further characterize transepithelial transport of biotin as a Na^+-dependent process that relies on cellular metabolic energy, is saturable, and has other characteristics of a carrier-mediated process (12, 13).

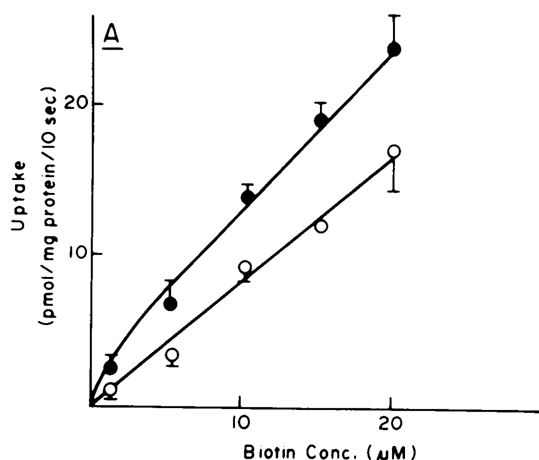

Figure 3. Transport of biotin in jejunal BBMV as a function of concentration in the presence of a Na^+ and a choline gradient. (A) Jejunal BBMV were preloaded with 280 m*M* mannitol and 20 m*M* HEPES-Tris (pH 7.4). Incubation was performed for 20 s at 37°C in an incubation buffer of 100 m*M* NaCl (●) or choline chloride (○), 80 m*M* mannitol and 20 m*M* Mes-Tris (pH 6.0) and different concentrations of biotin. Each point represents the mean ± SEM of three experiments. (Reproduced with permission from Biochim Biophys Acta **945:**195–201, 1988.)

Nicotinic Acid and Nicotinamide

Several animal species have been used in the evaluation of intestinal handling of the niacin vitamers, nicotinic acid and nicotinamide. A one-pass perfusion system was used to study absorption of nicotinic acid and nicotinamide (14). The amide form was absorbed more rapidly into the vascular perfusate than the acid. The uptake curve was nearly linear with dose for nicotinamide at all doses evaluated (up to 1.6 mmole administered) and for nicotinic acid up to ~0.16 mmole. This suggested to the authors that the uptake process is nonsaturable and probably the result of simple diffusion. In short-term studies the amide was absorbed rapidly with little hydrolysis to nicotinic acid (15). The primary form reaching the vascular perfusate when the acid form was administered *via* the lumen was the unchanged substrate.

A different result derives from more recent longer-term (60-minute) studies (16). Of [^3H]nicotinic acid placed in ligated loops of proximal rat jejunum, >90% of the label recovered from the gut walls was in the amide form. *In vitro* studies also revealed that conversion was rapid: >40% conversion after 10 min. Analysis of the serosal fluid indicated that only nicotinic acid and nicotinamide were present. The authors favored the interpretation that rapid conversion of nicotinic acid might represent metabolic trapping of a radio-labeled form that does not rapidly cross the brush border membrane. This results in maintenance of a substrate gradient that promotes additional uptake of nicotinic acid.

The mechanism of nicotinic acid uptake into enterocytes was evaluated on isolated strips of rat jejunum (17). It was considered that penetration of this vitamin might be a function of the amount of the nonionic, diffusible form, which is determined by the "virtual pH" at the mucosal surface. Measurements have been made with microelectrode pH electrodes by several investigators with the conclusion that thin layer of fluid adjacent the brush border membrane is acidic relative to the luminal bulk content. The extent of nicotinic acid uptake was found to have a close correlation with the proportion present in the nonionic form; the acidic microenvironment increases the proportion of nonionic nicotinic acid and thereby enhances absorption. The authors noted that their conclusion contrasted with the suggestion from studies on everted sacs of rat small intestine (18); Elbert et al. (17) suggested that the kinetic data in the earlier paper

are not decisive and could be compatible with uptake by either simple diffusion or by a carrier-mediated process.

In isolated cells and isolated segments of chick intestine *in situ,* nicotinamide uptake and metabolism were evaluated at a physiological concentration of 11 μM (19). ^{14}C-nicotinamide was taken up and rapidly metabolized to NAD by isolated cells. Data collected with isolated loops *in vivo* agreed with *in vitro* findings. There is no indication that nicotinamide is taken into cells against an electrochemical gradient.

Pantothenic Acid

Although examples of human pantothenic deficiency have been documented (20), a deficiency is normally seen only during severe malnutrition. Cats, rats (21), and fish (22) are most easily brought to a state of clinical deficiency. In small rainbow trout, a deficiency was apparent after 16 days on a pantothenic acid-deficient diet. A much longer time was required in larger fish.

Enzymatic hydrolysis in the intestinal lumen releases pantothenic acid from coenzyme Q (23). Absorption of pantothenate did not have an obvious saturable component when evaluated in the millimolar concentration range. However, when reevaluated in rat or chick intestine *in vitro* at concentrations in the more physiological range (0.9–20 μM), evidence of a saturable process was evident (24). Over an incubation period of 30–40 min, pantothenic acid accumulated in absorptive cells of rat and chick intestine to values as great as 10-fold that in the bathing medium. This accumulation was not observed in tissue incubated in buffer with choline or K^+ substituted for Na^+. Metabolic conversion of the vitamin was minimal in tissue of both species. Dependence of pantothenic acid transport on intact cellular metabolic energy supplies was demonstrated in isolated chick epithelial cells. Accumulation of the substrate occurred under control conditions; samples exposed to cyanide ceased to take up the vitamin, and moved closer to equilibration with the bathing medium pantothenic acid concentration (Fig. 4).

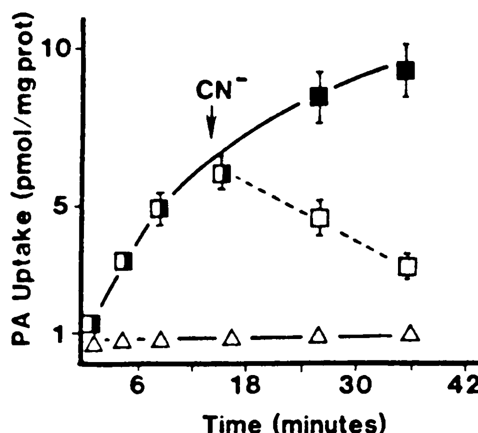

Figure 4. Properties of pantothenic acid (PA) uptake and release in isolated intestinal epithelial cells of chicken. *Data points* are mean ± SEM of four determinations. [^{3}H]PA was present at 0.9 μM. NaCN was present where indicated at 2.5 mM. ■, Control; □, cells exposed to cyanide after 14 min of control conditions; △, cells exposed to NaCN for 10 min prior to [^{3}H]PA addition and during uptake. (Reproduced with permission from Am J Physiol **250:**G155–G160, 1986.)

Riboflavin

The primary site of riboflavin absorption was demonstrated in early studies to be the small intestine, and the maximum absorbable single dose was 18 mg (25). The initial step in processing of dietary riboflavin is dephosphorylation of flavin-mononucleotide (FMN). Sequential processes of FMN and flavin-adenine-dinucleotide hydrolysis are followed by absorption of the free vitamin.

Preparations of rabbit brush border membrane vesicles were used to eliminate the intracellular metabolism that normally occurs during riboflavin absorption (26). Uptake of riboflavin over time was independent of the bathing solution Na^+ concentration, and there was no accumulation of the substrate in the vesicular space exceeding the bath solution. When riboflavin uptake was examined as a function of concentration, the initial rate of jejunal uptake had an apparent K_m of 7.24 ± 1.06 and a V_{max} of 24.3 ± 1.5 pmol/mg protein/5 sec. Nonlabeled riboflavin and the presence of chemically related compounds inhibited the rate of uptake. However, membrane transport inhibitors (e.g., furosemide) were without effect on uptake. Studies with anion substitution and valinomycin K^+-induced intravesicular electrical potentials had no effect on riboflavin uptake. These results indicate participation of a carrier-mediated process that is Na^+ independent and electroneutral. In a human-derived cultured intestinal epithelial cell line (Caco-2) riboflavin uptake was also found to be saturable and independent of Na^+ (27). It occurs without metabolic alteration of the substrate.

Studies from another laboratory (28) confirm that uptake of riboflavin into rat small intestinal brush border vesicles has a saturable component. A carrier-mediated process is also indicated by countertransport experiments in which the presence of nonlabeled riboflavin brought about movement of ^{3}H-riboflavin against a concentration gradient (Fig. 5). The implication of this type of study is that a specific carrier exists in the brush border membrane that recognizes riboflavin and can use a concentration gradient of the nonlabeled molecule to drive the radiolabeled form across the vesicle membrane. Specific binding of riboflavin could be the first step of a specific entry mechanism in absorptive cells.

Studies on other rat intestinal brush border mem-

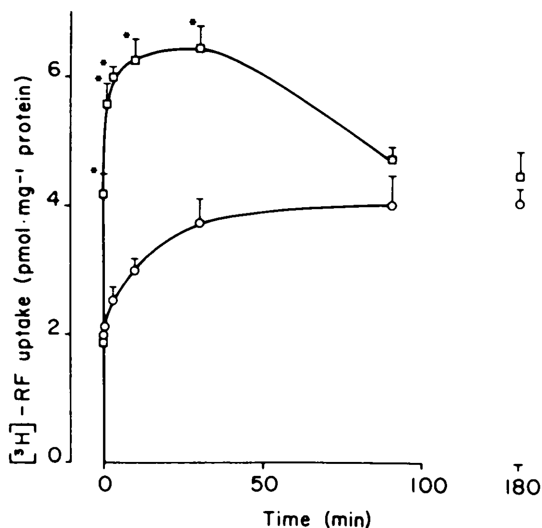

Figure 5. Countertransport of riboflavin at equilibrium in rat small intestinal brush border membrane vesicles. Vesicles were preincubated at 25°C for 30 min in a medium containing (m*M*): 280 D-mannitol, 2 $MgSO_4$, 10 TRIS-HEPES (pH 7.5), and 12.5 μM unlabeled riboflavin (■); in the same medium without unlabeled riboflavin (control) (○). Vesicles were 11-fold diluted and incubated in a medium containing (m*M*): 280 D-mannitol, 2 $MgSO_4$, 100 NaCl, 10 TRIS-HEPES, pH 7.5, and 0.25 μM [^{3}H]-riboflavin ([^{3}H]-RF). Symbols represent means ± SEM of triplicate determinations for each of three different preparations. When not shown, SEM were within symbol area. * $P < 0.001$ *vs* control (Student's *t* test). (Reproduced with permission from J Membr Biol **135**:217–223, 1993.)

brane vesicles displayed riboflavin transport (29) with properties different from those described above for rabbit and rat intestine. Carrier mediated transport was Na^+ dependent and brought about a distinct overshoot phenomenon. The K_m of transport was notably lower than in (26). Here, the use of K^+ diffusion potentials indicated an electrogenic process. The differences between laboratories are difficult to reconcile.

Riboflavin movement from the enterocyte toward the circulation has received less research attention than the brush border uptake process. The former was recently studied in basolateral membrane vesicles made from rabbit small intestine (30). The initial rate of uptake was saturable with a K_m ~5 μM, but showed no preference for Na^+ or K^+. Nonlabeled riboflavin or the presence of structural analogs caused significant inhibition. Trans-stimulation of riboflavin efflux from preloaded vesicles by nonlabeled riboflavin was also demonstrated. K^+ diffusion potentials were without effect. These results suggest a specific carrier system for transport across the basolateral cell membrane.

Thiamin

The results of studies from several laboratories (31–33) indicate that there is active transport of thiamin toward the circulation when the vitamin is present at a low (physiologic) concentration. Free thiamin in the intestinal lumen is derived from hydrolysis of dietary phosphoesters. Although guinea pig intestine evaluated *in vitro* did not show evidence of a specific transport mechanism for thiamin (34), uptake and transmural flux in rat intestine were saturable functions of the vitamin concentration. Also, the property of countertransport brought about by everted rings of intestine also indicate the occurrence of carrier-mediated transport.

Free thiamin accumulated in rat intestinal mucosa to a concentration greater than 2-fold higher than in the bathing medium (35). Considering that thiamin is a monovalent cation at physiological pH and that the intracellular electrical potential of the enterocyte is ~40 mV negative with respect to the luminal surface, sufficient electrical driving force exists to explain the modest accumulation observed. Intracellular phosphorylation serves to keep the intracellular concentration of free thiamin low, promoting additional uptake of the vitamin.

If thiamin uptake from intestinal lumen into absorptive cells is attributed to simple diffusion, then a process elsewhere in the enterocyte must account for the mucosa-to-serosa net flux mentioned above. Rindi and co-workers (36) recently evaluated thiamin movement across the basolateral cell membrane of rat small intestine. With [^{3}H]thiamin present at a low concentration (1 μM) outside of basolateral membrane vesicles, and Na^+, Mg^{++}, and ATP present, vesicles showed a transient accumulation of vitamin or "overshoot" at 30–60 sec. This was not seen when ATP was absent or when NaCl was replaced by KCl. Also, brush border vesicles did not bring about an overshoot. This convincing study suggests that thiamin is transported out of the absorptive cell coupled directly to hydrolysis of ATP; this represents a novel form of primary active transport.

Vitamin B_6

The biologically active component of vitamin B_6 is pyridoxal phosphate; this functions as a cofactor in several enzymatic conversions of amino acids. Structurally related components include the phosphorylated and nonphosphorylated forms of pyridoxine, pyridoxyl and pyridoxamine. Hydrolysis of the phosphorylated forms occurs in the small intestinal lumen (37, 38). Uptake of pyridoxal phosphate is saturable and a function of intraluminal alkaline phosphatase.

Unlike several of the other water-soluble vitamins, absorption of vitamin B_6 does not demonstrate net transepithelial transport or accumulation intracellularly in the free form (39). Uptake into both guinea pig and rat intestine *in vitro* indicated uptake occurs by simple diffusion. In prolonged studies on perfused intestine *in vivo* (40) or on everted rings *in vitro* (41) saturation of vitamin B_6 entry into intestinal mucosa was observed, but this does not necessarily suggest

facilitated membrane transport. Rather, intracellular metabolism of pyridoxine might lead to compartmentation of the vitamin after its uptake into the mucosa (42).

Regulation of vitamin absorption

Three studies have provided evidence that dietary vitamin intake has feedback regulatory control of future vitamin absorptive capacity. Ascorbic acid supplementation in guinea pigs resulted in a ~50% decrease in the rate of vitamin C absorption after 14 or 28 days (43, 44). Also, regulation of riboflavin absorption was evident in rats fed high levels of that vitamin. There is a demonstration that intracellular cAMP regulates enterocyte riboflavin uptake through an effect of protein kinase A on the activity of membrane transporters (45). Although vitamin B_6 status of the rat is regulated homeostatically, this did not appear to be through a variation in intestinal absorption (46). Also, Stein and Diamond (47) did not detect that dietary levels of pantothenic acid have a regulatory role on absorption of the vitamin.

The possibility must be considered that intake of one vitamin at a high dose might result in downregulation of intestinal absorption of the vitamin. This could have consequences in the health of individuals who have wide variations in their diets. For instance, consider the circulating level of a vitamin taken by an alcoholic individual whose diet is notably deficient, other than for supplements brought by his sister. The man recognizes that his diet is inadequate and, takes 3–4 g of ascorbic acid daily, which keeps his circulating level clearly elevated. His sister is not highly dependable, however, and fails to visit her brother on some occasions. Thus, it's likely that when on a high dose of a particular vitamin, the man's vitamin absorption mechanism will be downregulated. If his source of vitamins is abruptly discontinued at that point, he would be left with poor capacity for absorption and also a dietary deficiency at the same time. Thus, the man's circulating level of the vitamin would go through wide swings, rather than maintaining the presumed ideal of constancy. The interesting aspects of ontogenetic development of nutrient metabolism in the intestine are being developed (48, 49), but are not sufficiently defined for review.

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