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EPITHELIAL TRANSPORT OF WATER-SOLUBLE VITAMINS

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INTRODUCTION

Epithelial transport of the water-soluble vitamins has received increased attention in recent years. Processes such as intestinal absorption and renal reabsorption are critical for nutrient utilization and conservation, particularly

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for the micronutrients, which often occur at limiting concentrations in the diet. Bioavailability is, fundamentally, the net result of a series of nutrient transport phenomena. In addition, alterations in cellular (5) and subcellular (organelle) (49) uptake of nutrients may lead to nutrient deficiency that is clinically significant and, potentially, to toxicity.

The transport mechanisms described to date for water-soluble vitamins typically have relatively high affinity but low capacity. This characteristic has hampered their identification and particularly their isolation from mammalian epithelia. In contrast, transport elements for the monosaccharides and amino acids are typically more abundant in cells and have apparent K_t and V_{max} values that are at least two to three orders of magnitude higher than those estimated for the water-soluble vitamins.

The epithelia most extensively studied are those of the intestine and the kidney, which are readily accessible to experimental manipulation. Although the body of literature on transport of the water-soluble vitamins is considerable, our understanding is far from complete. Transport mechanisms apparently differ for the various water-soluble vitamins, which are, to be sure, chemically and biochemically heterogeneous. In addition, for a given vitamin, transport mechanisms may differ among epithelia. Finally, multiple routes of uptake may exist for a given vitamin. The comparative physiology of water-soluble vitamin transport is largely unexplored, although some species differences have been noted (15, 109). Developmental aspects of the transport systems are of increasing interest.

This review discusses mechanistic studies, published during the past 15 years, of water-soluble vitamin transport by mammalian kidney and intestine. We focus upon seven of these vitamins—thiamin, riboflavin, niacin, pyridoxine, pantothenate, biotin, and folate—because recent extensive reviews are available for vitamins B_{12} (17, 43, 95) and C (75). The sections that follow consider historical aspects, conceptual issues, and methodology, as well as uptake, metabolism, and cellular disposition. Several excellent reviews on these and related topics have been published (5, 15, 21, 33, 41, 43, 47, 49, 50, 52, 53, 71–79, 95, 96, 117, 118).

HISTORICAL PERSPECTIVE

For many of the micronutrients, particularly the water-soluble vitamins, early uptake studies were stymied by analytic and other technical problems. For example, (*a*) the vitamins are characteristically present in biologic systems at very low concentrations (10^{-7} to 10^{-9} M); (*b*) they are often in multiple biochemical forms (e.g. the six vitaminic forms of vitamin B_6 and its phosphates); and/or (*c*) they are often associated with proteins (e.g. the flavoproteins). In addition, tissue viability is a major concern in studies using in vitro preparations, a point discussed below.

The first systematic experimental studies of water-soluble vitamin absorption were reported by Turner & Hughes in 1962 (113, 114). These investigators expected to demonstrate active transport processes for the vitamins similar to those described in the 1950s for the monosaccharides and amino acids. They relied, however, on standard techniques, particularly on relatively insensitive microbiologic assays, to detect small changes in vitamin concentration that occurred during long (1-hr) incubations of rat intestinal tissue. Turner & Hughes also used relatively high concentrations of the vitamins, 10 to 100 μM.

Because they were unable to demonstrate active vitamin transport under their experimental conditions, Turner & Hughes concluded that passive diffusion (a much less interesting mechanism to physiologists) accounted for intestinal absorption of nicotinic acid, pantothenic acid, biotin, folic acid, and vitamin B_{12} (113, 114). This interpretation was adopted uncritically and found its way into the textbooks, where it reappeared regularly for more than a decade.

Diffusion of the water-soluble vitamins seems teleologically unlikely, given their low concentration in foodstuffs and in animal tissues and their efficient conservation by the body under most other circumstances. It also seems physiologically unlikely, given the molecular size (molecular weights ranging from 123 to 1357) and state of ionization at physiologic pH (pK_a values of pH 4–9) of this heterogeneous class of relatively polar compounds.

Together, the advent of radioactively labeled vitamins of high specific activity, the development of improved physiologic techniques, and the realization that clinical vitamin deficiency could occur even with an apparently adequate dietary intake set the stage for a new era of research on intestinal vitamin transport. This work was reviewed ably by Matthews in 1974 (52). Until the 1980s, water-soluble vitamin research involving the kidney was primarily concerned with the development of urinary vitamin and metabolite profiles as an approach to probing nutrient metabolism and nutritional status.

CONCEPTUAL ISSUES

Cells in epithelial tissues are characterized by their polarity; the luminal (apical) and basolateral surfaces encounter biochemical environments that may be quite different. In contrast, single cells such as leukocytes encounter a uniform extracellular compartment, the plasma. Nutrient uptake and secretion can occur at both the luminal and the basolateral membranes, and for a given nutrient, the transport properties of the two membranes may be quite different. In general, absorption is assumed to involve transcellular movement of the transported species. In intact tissue, however, paracellular (intercellular) and other pathways are also available, particularly in "leaky" epithelia such as the small intestine and renal proximal tubule. The multiple potential routes of

uptake and secretion complicate the design and interpretation of transport studies, because the possible fates of the vitamin include uptake; metabolism before, during, and/or after transport; intracellular accumulation; and efflux or secretion.

METHODOLOGY

In early transport studies of the water-soluble vitamins, the conditions under which experiments were conducted were often unphysiologic. In some studies, vitamin concentrations were in the mM range, although the intestine, for example, probably encounters only vitamin concentrations that are at or below the plasma level under most circumstances (19). Additional relevant variables include pH (the pH of intestinal contents tends to be slightly acidic) (22, 64, 94), osmolarity, composition of the test solution (40, 66, 67, 121), provision of oxygen and metabolic substrates, and temperature of the test solution. Vitamin transport can also be affected by the presence of alcohol (8, 92), other drugs (90a, 120, 122), disease (91, 115), nutrient deficiency (16, 37, 59, 116), and developmental stage (51, 81, 83, 88). In addition, the water-soluble vitamins and their metabolites can affect the epithelial uptake of other substances (28, 40, 46, 111).

Sensitive methods of detection are crucial, to rule out molecular modification of the radiolabeled compound and to detect vitamin uptake with maximum reliability. Differentiating vitamin transport from vitamin metabolism often proves difficult (see below).

Experimental approaches to water-soluble vitamin transport include studies with intact tissue, isolated or cultured cell preparations, and membrane preparations. The interpretation of studies with intact tissue, which can be conducted in vivo or in vitro, is complicated by the presence of multiple cell types and routes of uptake. Also, the control and manipulation of all potentially relevant variables, such as ion concentrations, can be difficult. When cell preparations are used, major concerns include heterogeneity of cell populations, the loss of cell polarity, the possibility of simultaneous luminal and basolateral uptake and/or release, and cell viability. Cell culture systems appear to offer significant advantages on all of these points, compared with freshly isolated cells (50). With subcellular membrane preparations, the focus becomes the initial events of uptake (47). The major concern is that this approach is artifactual, although such studies may be useful in elucidating the role of binding/carrier proteins in vitamin transport.

MECHANISM OF UPTAKE

Tables 1 and 2 summarize the recent literature on transport of water-soluble vitamins by mammalian intestine and kidney. Most of these studies were

TABLE 1 Literature review: uptake of water-soluble vitamins by mammalian intestine

Vitamin	Experimental Approach		
	Intact Tissue	Enterocytes	Membranes
Thiamin (71)[a,b]	24[c], 37, 38[d], 39, 48, 68, 71, 110[d], 116	—	31[e]
Riboflavin (53)	20, 45, 83, 84, 115	32[c]	1
Niacin (33)	22, 27, 34, 35, 80		3
Pyridoxine (41, 53)	14, 54, 55–65, 66[d], 67, 93[f], 112	—	119
Pantothenate	23, 101	—	—
Biotin	4[g], 11, 12, 18, 86	25[g], 26	89[d], 90[d]
Folate (79, 96)	8[h], 51, 85, 99, 121	7[i]	7[i], 70[j], 82[d], 83, 87, 91, 94[k], 100
Vitamin B_{12} (17, 43, 95)	—	—	—
Ascorbic acid (75)	-		-

[a] Numbers indicate reference citations (see *Literature Cited*).
[b] Numbers in parentheses indicate review articles (see *Literature Cited*).
[c] Unless indicated otherwise, the source of intestinal tissue was the rat.
[d] Human.
[e] Guinea pig.
[f] Mouse.
[g] Hamster.
[h] Primate.
[i] Goat.
[j] Pig.
[k] Rabbit.

conducted with tissue from experimental animals. Studies on water-soluble vitamin transport by choroid plexus (102, 103, 105–108) are not discussed in further detail here. The major stages of epithelial transport are: initial uptake at the luminal membrane, intracellular disposition (including metabolism), and basolateral release. Examples in which the contribution of these processes have been elucidated are discussed below.

Initial Uptake

The initial events of vitamin uptake have been elucidated primarily through studies with membrane vesicles. Recent insights into the mechanisms of folate uptake by intestine and kidney are summarized below.

Studies with preparations of intact intestinal tissue demonstrated that folate uptake can occur by saturable and nonsaturable mechanisms (79, 96).

TABLE 2 Literature review: uptake of water-soluble vitamins by mammalian kidney

Vitamin	Experimental Approach		
	Intact tissue	Cells	Membranes
Thiamin	—	—	—
Riboflavin (53)[a,b]	104[c]	9	—
Niacin (33)	—	13[c]	40[c]
Pyridoxine (41, 53)	30[d]	10	—
Pantothenate	44	—	2[c]
Biotin	—	—	69[c]
Folate	97, 98	42[e]	6
Vitamin B_{12}	—	—	—
Ascorbic acid (75)	—	—	—

[a] Numbers indicate reference citations (see *Literature Cited*).
[b] Numbers in parentheses indicate review articles (see *Literature Cited*).
[c] Rabbit tissue.
[d] Unless indicated otherwise, the source of renal tissue was the rat.
[e] Monkey.

The saturable mechanism is significantly affected by luminal pH, is energy-dependent, and can accommodate some structural analogs and folate derivatives. Membrane vesicle studies have confirmed the pH and concentration dependence and the competition by structural analogs observed with intact tissue. Interestingly, pH affects both saturable and nonsaturable components of transport, probably by anion (folate/hydroxyl ion) exchange as well as by an effect on the affinity of the (putative) folate carrier, which has yet to be isolated.

Because dietary forms of folate are typically conjugated, luminal digestion to the monoglutamyl forms precedes membrane uptake and appears to be rate limiting (79, 96). This is true for most of the water-soluble vitamins, which are present in animal and plant tissues largely in the coenzyme forms (1, 27, 29). For some of these vitamins, hydrolysis and uptake may be coupled (1, 27, 29, 30, 34, 35, 54, 58, 61, 62, 64, 65). The subsequent intracellular disposition of absorbed folate includes reduction and methylation. Some absorbed folate may be retained intracellularly, in association with folate-dependent enzymes and/or binding proteins.

In contrast, the mechanism of renal reabsorption of folate appears to be receptor-mediated endocytosis; it involves recognition of folate in the glomerular filtrate by the folate-binding protein present in the luminal membrane of the proximal tubular epithelium. This mechanism is consistent with the kinetics and substrate specificity observed in urinary clearance and microinfusion studies (97, 98). Similar high-affinity folate-binding proteins have been

isolated from many tissues (115a); the folate-binding protein in milk may enhance folate bioavailability in suckling animals (51, 85).

In intestine and kidney, initial uptake of the water-soluble vitamins generally occurs by a mechanism that is saturable at physiologic concentrations of the vitamin, while at higher concentrations, the relationship between vitamin concentration and uptake is linear. For most of these vitamins, uptake is characterized by structural specificity; for many, sodium-dependence has been reported. These and other data suggest that vitamin uptake largely occurs by means of carrier-mediated (facilitated) processes.

Role of Vitamin Metabolism

Kinase-mediated metabolic trapping is a plausible mechanism to account for the cellular uptake and accumulation of thiamin, riboflavin, pyridoxine, and pantothenate. Because uptake and phosphorylation may be coupled, special experimental approaches (e.g. analog and inhibitor studies) can be used to establish the relative role of phosphorylation in the overall uptake process (118).

In rat proximal tubular cells (9, 10), the transport of both riboflavin and pyridoxine is saturable and demonstrates substrate selectivity. Following uptake, riboflavin and pyridoxine are readily converted to their phosphorylated forms; after a 30-min incubation, nearly 90% of newly absorbed pyridoxine has been metabolized (10). However, for both riboflavin and pyridoxine, although initial uptake by renal cells appears to be dissociated from phosphorylation, cellular accumulation is a function of kinase activity and, hence, of metabolic trapping (9, 10, 53).

Membrane studies that define the initial events of uptake provide important complementary data. For example, pyridoxine uptake by renal brush-border membranes demonstrates sodium dependence (E. R. Smith, D. B. McCormick, unpublished data), a result that is consistent with studies using intact proximal tubular cells (10).

Recent analytic developments, particularly in high-performance liquid chromatography, should now permit more complete examination of the intracellular metabolism of all of these vitamins. Such information may be very significant in understanding their subsequent disposition.

Cellular Disposition

Very little is known about the cellular disposition of the water-soluble vitamins following uptake. The possibilities include (*a*) luminal and basolateral release, perhaps coupled with binding proteins or other species; (*b*) metabolic trapping or other metabolism and association with cellular binding proteins or enzymes; and (*c*) intracellular transport into organelles such as mitochondria (49). Cultured cells, subcellular fractionations, and membrane vesicle studies

provide promising approaches for determining the traffic patterns and fate of newly absorbed water-soluble vitamins. Clearly, under most circumstances, the vitamins are conserved and made available to the general circulation, so that the net flux is transcellular. However, vitamin disposition may be affected to some extent by the cellular content of the vitamin (42, 68) and of the enzymes for which the vitamin is a cofactor; the cellular concentration, in turn, may be related to dietary composition and/or physiologic state.

CONCLUSION

Table 3 summarizes current understanding of the likely mechanisms of intestinal and renal uptake of the water-soluble vitamins. There are some intriguing similarities and differences, but an obvious major challenge for the 1990s is to fill in the gaps. Saturable uptake mechanisms apparently exist for

TABLE 3 Likely mechanisms of luminal uptake of water-soluble vitamins by mammalian intestine and kidney

	Epithelium	
Vitamin	Intestine	Kidney
Thiamin	a, b, c, d, e, f	
Riboflavin	a, b, c, d, f	a, b, c, d, e
Niacin	a, b, c, f, g	—
Pyridoxine	b, e	a, b, c, d, e
Pantothenate	a, b, c, f	a, c, d
Biotin	a, b, c, f	a, c, d
Folate	a, b, d, f, g	a, d, g, h
Vitamin B_{12}	a, b, d, h	—
Ascorbic Acid	a, b, c, d, f, i	a, c, f, i

[a] Saturable uptake.
[b] Nonsaturable uptake.
[c] Sodium dependent.
[d] Competition by structural analogs.
[e] Metabolic trapping, kinase mediated.
[f] Requires metabolic energy.
[g] pH dependent.
[h] Receptor-mediated uptake.
[i] Species specificity.

most of the vitamins, although documenting such a mechanism for the intestinal uptake of pyridoxine has been difficult. For most, additional routes of entry are available, especially at higher vitamin concentrations. Isolation and purification of the transport elements should permit biochemical resolution of these mechanistic observations. Dietary and other means of modulating vitamin-transport activity (21) represent an emerging research area that may also lead to therapeutic applications.

That so little is known about the physiology of intestinal absorption and renal reabsorption of the water-soluble vitamins may seem surprising. The bioavailability of nutrients present has long been a fundamental assumption of feeding studies, the standard experimental paradigm of nutrition research (36). Nutrient uptake is obviously essential for all cells. Nutrient uptake by the epithelia is particularly significant, however, because one function of these "altruistic" tissues is to protect the organism against nutrient deficiency and probably toxicity. In addition nutritional requirements are directly related to the efficacy with which the nutrients are conserved.

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