Recent advances in transport of water-soluble vitamins in organs of the digestive system: a focus on the colon and the pancreas

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Said HM. Recent advances in transport of water-soluble vitamins in organs of the digestive system: a focus on the colon and the pancreas. Am J Physiol Gastrointest Liver Physiol 305: G601–G610, 2013. First published August 29, 2013; doi:10.1152/ajpgi.00231.2013.—This review focuses on recent advances in our understanding of the mechanisms and regulation of water-soluble vitamin (WSV) transport in the large intestine and pancreas, two important organs of the digestive system that have only recently received their fair share of attention. WSV, a group of structurally unrelated compounds, are essential for normal cell function and development and, thus, for overall health and survival of the organism. Humans cannot synthesize WSV endogenously; rather, WSV are obtained from exogenous sources via intestinal absorption. The intestine is exposed to two sources of WSV: a dietary source and a bacterial source (i.e., WSV generated by the large intestinal microbiota). Contribution of the latter source to human nutrition/health has been a subject of debate and doubt, mostly based on the absence of specialized systems for efficient uptake of WSV in the large intestine. However, recent studies utilizing a variety of human and animal colon preparations clearly demonstrate that such systems do exist in the large intestine. This has provided strong support for the idea that the microbiota-generated WSV are of nutritional value to the host, and especially to the nutritional needs of the local colonocytes and their health. In the pancreas, WSV are essential for normal metabolic activities of all its cell types and for its exocrine and endocrine functions. Significant progress has also been made in understanding the mechanisms involved in the uptake of WSV and the effect of chronic alcohol exposure on the uptake processes.

colon; pancreas; transport; thiamine; riboflavin; niacin; pyridoxine; biotin; folate

THE WATER-SOLUBLE VITAMINS (WSV) are essential for normal human health and well-being because of their involvement in critical metabolic reactions that affect all aspects of cell function and survival. Deficiency of these micronutrients (which could be systemic or localized, i.e., tissue-specific) leads to a variety of clinical abnormalities (and, ultimately, death), while optimizing their body homeostasis improves health and prevents certain diseases. Humans cannot synthesize these micronutrients (except for some endogenous synthesis of niacin) and must obtain them from exogenous sources via intestinal absorption. The human intestine is exposed to two sources of WSV: a dietary source (which is mainly absorbed in the small intestine) and a bacterial source (in reference to the vitamins generated by the large intestinal microbiota). The first part of this review focuses on recent advances in our understanding of the mechanisms involved in the uptake of the microbiota-generated WSV, how these processes are regulated, and how they are affected by external factors. The second part of this review focuses on recent advances in the understanding of the mechanisms involved in the uptake of WSV by pancreatic exocrine (acinar) and endocrine (β) cells, their regulation, and the effect of chronic exposure to alcohol.

Production of WSV by Intestinal Microbiota and Their Absorption in the Large Intestine

Production of WSV by large intestinal microbiota. One of the most obvious advantages of the symbiosis between a host and its intestinal microorganisms is the supply of indispensable nutrients, such as vitamins, that are generated by the bacteria. Such a relationship between hosts and intestinal microbiota has been recognized for some time. The pioneering work of Cooper (22) in 1914 showing that pigeons with polyneuritis due to thiamine (vitamin B1) deficiency could be cured by feeding the animals an extract of fecal material was among the first to suggest that bacterial microflora synthesize WSV. Subsequent studies confirmed this suggestion by actual chemical identification of the vitamin in human and animal fecal material (1). The amount of WSV generated by intestinal microbiota varies depending on the type of diet consumed: it is larger following consumption of a diet that is rich in complex carbohydrates (fiber) than a diet that is rich in simple carbohydrates (e.g., sucrose) or meat (5, 19, 38, 55). The amounts of some of these vitamins (e.g., biotin and pyridoxine) found in the fecal material are similar to or greater than the amounts ingested in the

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diet (55). Knowledge about the bacterial species that produce the bulk of these valuable micronutrients has also been forthcoming in recent years, and it is now known that it is not necessary that the most abundant bacterial species produce the largest amount of WSV (2). We further know that the human intestinal microbial communities undergo selective pressure from the host and from other microbial competitors (2, 19, 25, 102) and that they are also influenced by external factors [e.g., use of antibiotics (25)]. An interesting recent discovery was the finding that the human gut microbiome is functionally clustered into three distinct enterotypes: enterotypes 1, 2, and 3 (2). While all the WSV biosynthetic pathways are represented in all these enterotypes, enterotype 1 (enriched in Bacteroides) was found to be especially overrepresented by enzymes involved in the biosynthetic pathway of the WSV biotin, as well as that of riboflavin (RF), pantothenic acid, and ascorbate, while enterotype 2 (enriched in Prevotella) was found to be overrepresented by enzymes involved in the biosynthetic pathways of thiamine, as well as folate (2). The identification of such functional differences among enterotypes in different human population groups may have nutritional and physiological consequences, but this requires further investigations.

**Absorption of WSV in the large intestine.** Absorption of WSV is the process by which WSV enters the body, and it is generally considered to be a prerequisite for its bioavailability. WSV is a water-soluble nutrient that is necessary for the absorption of thiamine, which is an essential vitamin for energy metabolism. WSV is absorbed primarily in the small intestine, with a smaller proportion being absorbed in the colon. WSV is absorbed through a process called passive diffusion, which is driven by the concentration gradient. The absorption of WSV is influenced by various factors, including the presence of other nutrients, the pH of the gut, and the bacterial composition of the gut.

**VITAMIN TRANSPORT IN THE LARGE INTESTINE AND THE PANCREAS**

Thiamine (vitamin B1) was the first member of the B-vitamin family to be discovered, and it is essential for the production of energy through anaerobic and aerobic pathways. The absorption of thiamine occurs in the epithelial cells of the colon, where it is transported across the membrane via a sodium-independent, pH-sensitive carrier-mediated mechanism. The carriers involved in this process are the human thiamine transporters, hTHTR-1 and hTHTR-2, which are expressed in the enterocytes of the colon. These transporters are responsible for the absorption of thiamine from the gut lumen into the bloodstream.

**Functional differences in the colon.** The absorption of thiamine in the colon is influenced by various factors, including the presence of other nutrients, the pH of the gut, and the bacterial composition of the gut. The absorption of thiamine is influenced by the pH of the gut, with the absorption being highest at a pH of 6.5. The absorption of thiamine is also influenced by the presence of other nutrients, such as folate and riboflavin, which are also absorbed in the colon. The absorption of thiamine is also influenced by the bacterial composition of the gut, with the absorption being highest in individuals with a healthy gut microbiome.

**Chronic alcoholism.** Chronic alcoholism can negatively impact the absorption of thiamine in the colon, as the absorption of thiamine is influenced by the pH of the gut, with the absorption being highest at a pH of 6.5. The absorption of thiamine is also influenced by the presence of other nutrients, such as folate and riboflavin, which are also absorbed in the colon. The absorption of thiamine is also influenced by the bacterial composition of the gut, with the absorption being highest in individuals with a healthy gut microbiome.

**Thiamine and Wernicke’s encephalopathy.** Thiamine deficiency is associated with Wernicke’s encephalopathy, a condition that is characterized by neurological and psychiatric symptoms. Wernicke’s encephalopathy is caused by a lack of thiamine, which is essential for the production of energy through anaerobic and aerobic pathways. Thiamine deficiency can be caused by a variety of factors, including chronic alcoholism, diabetes mellitus, and chronic bowel diseases.

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inhibition mediated by suppression of transcriptional activity of the SLC19A2 and SLC19A3 promoters.

**Absorption of Riboflavin.** RF, in the form of its metabolically active coenzyme flavin mononucleotide and flavin adenine dinucleotide, plays an important role in the transfer of electrons in biological oxidation-reduction reactions (e.g., carbohydrate, amino acid, and lipid metabolism, as well as conversion of folic acid and vitamin B6 to their active forms) (reviewed in Ref. 71). Systemic RF deficiency leads to a variety of clinical abnormalities that include degenerative changes in the nervous system and endocrine dysfunction; such deficiency occurs in patients with inflammatory bowel disease and chronic alcoholics, among others (reviewed in Ref. 71).

The normal microflora of the large intestine synthesizes considerable amounts of RF, and a significant portion of this RF exists in the free absorbable form (2, 39, 59). The amount of RF produced by the intestinal microbiota varies depending on the type of diet consumed: it is higher following ingestion of a vegetable-based diet than a meat-based diet (39). Previous studies have shown that the mammalian colonocytes are capable of absorbing RF (40, 83); recent investigations utilizing the human-derived colonic epithelial NCM460 cells showed the involvement of a highly efficient (apparent $K_m = 0.14 \mu M$) and specific carrier-mediated mechanism (Fig. 1) (75). Also, both of the recently cloned RF transporters (RFVT-1 and RFVT-3) are expressed in the large intestine (93, 105, 107), with expression and activity significantly higher for RFVT-3 than RFVT-1. These findings, together with the observation that knocking down RFVT-3 with gene-specific small interfering RNA (siRNA) leads to a severe inhibition of RF uptake by absorptive epithelia, suggest that this transporter plays a prominent role in RF uptake in the gut epithelia (93). Other studies used live-cell confocal imaging to show that the RFVT-1 protein is expressed mainly at the basolateral membrane domain of absorptive epithelia, while expression of RFVT-3 is exclusively confined to the apical membrane domain of these cells (90, 93) (Fig. 1).

Other studies have shown that the colonic RF uptake process is adaptively regulated by extracellular RF levels, with a significant and specific upregulation and downregulation of uptake in RF-deficient and -oversupplemented conditions, respectively (75). This adaptive regulation of colonic RF uptake was mediated via changes in the number (and/or activity) of the RF uptake carriers and involves transcriptional regulatory mechanism(s) (75). Finally, the colonic RF uptake process

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**Fig. 1.** Diagrammatic representation of transport systems that appear to be involved in absorption of microbiota-generated water-soluble vitamins (WSV). SMVT, sodium-dependent multivitamin transporter; RFC, reduced folate carrier; MDR-3, multidrug-resistance protein-3; PDZD11, PDZ-containing protein 11; RFVT-1, riboflavin transporter-1; RFVT-3, riboflavin transporter-3; THTR-1, thiamine transporter-1; THTR-2, thiamine transporter-2; TPP, thiamine pyrophosphate. Transporters for niacin, pyridoxine, and TPP have been functionally identified, but their molecular identity has not been determined. PDZD11 is an accessory protein that interacts with SMVT and affects its function and cell biology (65). Dashed lines separate the transporter(s) of a specific vitamin from that of other vitamins.
appears to also be under the regulation of an intracellular Ca\(^{2+}\)/calmodulin-mediated regulatory pathway (75).

The effect of chronic exposure to alcohol on colonic RF uptake has also been recently examined in a rat model, and a significant inhibition was observed (92). The mechanism(s) by which alcohol causes this inhibition of colonic RF uptake is not clear but could be similar to that observed in other intestinal absorptive epithelia (intestinal/renal), being mediated, at least in part, via transcriptional mechanism(s) (92).

**ABSORPTION OF NIACIN AND NICOTINIC ACID/NICOTINAMIDE.** Niacin (vitamin B\(_3\)) acts as a precursor for the synthesis of the coenzymes NAD and NADP, which participate in a variety of metabolic reactions that maintain cellular redox state. Recent studies have also suggested roles for niacin in maintaining normal intestinal homeostasis and reducing gut inflammation, in regulating the level of production of intestinal antimicrobial peptides, and in regulating the activity of the mammalian target of rapamycin signaling pathway (which is involved in cell proliferation, protein synthesis, and transcription) (37). Niacin deficiency leads to pellagra, a disease that is characterized by inflammation of mucous membranes, skin lesions, diarrhea, and dementia; it is of interest to also mention here that >90% of patients with pellagra develop colitis (79, 86), which demonstrates the important role of niacin in the maintenance of normal colonic health.

As with many other WSV, niacin is synthesized in a significant quantity by the large intestinal microbiota (20, 60); however, until recently, this source of the vitamin was assumed to be of little or no nutritional value because of the belief that the large intestine is incapable of absorbing the vitamin (Ref. 31 and references therein). Recent studies by Kumar et al. (47), however, directly tested the ability of mammalian colonicocytes to take up niacin and delineate the mechanism involved. Thus, using human colonic epithelial NCM460 cells, as well as native human colonic apical membrane vesicles obtained from organ donors and intact mouse colonic loops in vivo, Kumar et al. showed that uptake of nicotinic acid by colon cells is via an acidic pH-dependent (but not sodium-dependent), specific and high-affinity (apparent \(K_m = 2.50 \pm 0.80 \mu M\)) carrier-mediated process (Fig. 1) (47). This process is not affected by other bacterially produced monocarboxylic acids or by substrates of the human organic anion transporter-10 (i.e., urate and p-aminohippurate), a system that was believed to play a role in nicotinic acid uptake (6). Other studies have shown that the nicotinic acid uptake process is regulated by extracellular substrate availability and by intracellular protein tyrosine kinase- and Ca\(^{2+}\)/calmodulin-mediated regulatory pathways (47). The above findings, which establish the existence of a highly efficient carrier-mediated mechanism for niacin uptake by colonicocytes, support the concept that the bacterially synthesized niacin contributes to host niacin nutrition, and especially to the cellular nutrition and health of the local colonicocytes. Supporting the latter is the previous report of colitis in >90% of patients with pellagra (79), a disease caused by niacin deficiency. Also, niacin supplementation appears to alleviate the severe colitis in mice deficient in angiotensin I-converting enzyme 2 (37).

**ABSORPTION OF BIOTIN.** Biotin (vitamin B\(_7\), also known as vitamin H) acts as a cofactor for five carboxylases that play critical roles in fatty acid and amino acid metabolism and in gluconeogenesis; biotin also plays a role in regulating gene expression, normal immune function, and cell proliferation (reviewed in Ref. 6). Systemic biotin deficiency leads to growth retardation, neurological disorders, and dermatological abnormalities; also, biotin deficiency during pregnancy (at least in animals) causes embryonic growth retardation, congenital malformation, and death (reviewed in Ref. 6). Deficiency and suboptimal levels of biotin occur in a variety of conditions, including inflammatory bowel diseases, long-term parenteral nutrition, and chronic alcoholism (6).

The large intestinal microbiota synthesize considerable amounts of biotin [estimated to be similar to or greater than the amount taken in the diet (55)], and a significant portion of this biotin exists in the free (protein-unbound) form and, thus, is available for absorption (59). Recent studies that have classified the human gut microbiome into three functional enterotypes have reported that enterotype 1 is especially overrepresented in enzymes involved in the biotin biosynthetic pathway, implying a larger biotin generation in this group (2, 110). Human and animal colonicocytes can absorb biotin (16, 40, 83), and recent investigations have shown that this occurs via an efficient (apparent \(K_m = 19.70 \mu M\)) carrier-mediated mechanism (Fig. 1) (74). While this mechanism is specific for biotin and its close structural analogs (with a free carboxyl group), it also transports another WSV, namely, pantothenic acid (vitamin B\(_5\)), which plays a central role in energy-yielding metabolic reactions, as well as in fat and protein metabolism, and is also synthesized by the intestinal microbiota (74). It is for this reason that the transport system is referred to as the sodium-dependent multivitamin transporter (SMVT). The SMVT protein is a product of the SLC5A6 gene, and mRNA of this gene is expressed in mammalian small and large intestine. The SMVT protein is exclusively expressed at the apical membrane domain of polarized absorptive epithelia, as shown by immunological, functional, and live-cell confocal imaging studies (Fig. 1) (88). Other studies have described the existence of an accessory protein, PDZD11, in human colonic epithelial cells that interacts with the SMVT (at the COOH terminus of the transporter) and affects its function and cell biology (Fig. 1) (57). While another potential biotin transport system has been suggested in other tissues (108), the SMVT system appears to be the only system that operates in the mammalian gut. The latter conclusion is based on recent findings utilizing a gene-specific silencing (siRNA) approach in vitro (10) and a conditional (intestinal-specific) SMVT KO mouse model in vivo (34). In the latter studies, a complete inhibition of gut biotin (and pantothenic acid) uptake in SMVT KO mice was observed. Several interesting phenotypes were also observed in these SMVT KO animals (34): 1) two-thirds of the KO animals died prematurely prior to reaching the age of 2.5 mo due to acute peritonitis; 2) all the KO mice showed severe growth retardation and decreased bone density and length; and 3) all the KO animals showed severe histological abnormalities in the large intestine (chronic active inflammation and dysplasia), as well as the small intestine (shortened villi and dysplasia) (Fig. 2). While the mechanism(s) that mediates the distal gut inflammation is not clear, it is likely related to the role of biotin in maintaining normal innate and adaptive immune functions (55). An example of the latter is the important role of biotin in the activity of intestinal natural killer cells (62), which play an important role in maintaining normal intestinal epithelial homeostasis and in promoting the antipathogen response (62,
It is interesting to mention here that the activity of these cells (as well as the biotin level) is suppressed in patients with Crohn’s disease (4, 61, 62, 104).

The colonic biotin uptake process appears to be under the regulation of an intracellular PKC-mediated pathway (74). Other studies have shown that chronic alcohol exposure leads to a significant inhibition of colonic carrier-mediated biotin uptake (95). The mechanism through which chronic alcohol exposure causes inhibition of colonic biotin uptake is not clear but could be similar to that found in other intestinal epithelia mediated (at least in part) via a transcriptional mechanism(s) (95). Further studies are needed to confirm this suggestion.

**ABSORPTION OF FOLATE.** Vitamin B₂₉ (folate, a term that refers to all derivatives of folic acid) is required for the biosynthesis of pyrimidine and purine nucleotides (precursors of DNA and RNA, respectively); it also plays an important role in the metabolism of several amino acids, such as homocysteine. Thus an adequate supply of folate is necessary for normal cell function and growth/repair. Systemic deficiency and suboptimal levels of folate lead to a variety of clinical abnormalities, including megaloblastic anemia, growth retardation, and neural tube defects in the developing embryo. Such a deficiency is highly prevalent worldwide and occurs in different conditions, such as patients with chronic alcoholism, patients with intestinal diseases (e.g., celiac disease and tropical sprue), and patients with the genetic disorder hereditary folate malabsorption syndrome. Existence of a localized folate deficiency in tissues such as colonic mucosa has also been implied and suggested to play a role in the development of premalignant changes (23, 48).

The large intestinal microbiota synthesize folate in amounts that could approach or exceed the level in the diet (5, 23, 48), and the amount of this folate can be modulated by incorporation of fiber and prebiotics into the diet (5, 41, 44, 99). A number of studies have indicated that the microbiota-generated folate is of nutritional value to the host. For example, feeding animals a folate-deficient diet causes growth retardation and severe folate depletion only when sulfa drugs are added to the
diet (15, 43, 102). Other studies have shown that the introduction of radiolabeled p-aminobenzoic acid (a folate precursor) into the lumen of animal large intestine leads to the appearance of radiolabeled folate in different tissues (70).

The mechanism of folate uptake by human colonocytes has been delineated in studies using purified membrane vesicles isolated from the colon of organ donors and human-derived colonic epithelial NCM460 cells (28, 46). These studies showed that folate uptake by human colonocytes across the apical membrane domain is via an efficient (apparent $K_m = 8.20 \pm 2.40 \mu M$), specific, and pH-dependent carrier-mediated mechanism (Fig. 1). This mechanism is sensitive to the inhibitory effect of the anion transport inhibitors DIDS and SITS (28, 46). Exit of folate from the human colonocytes across the basolateral membrane has also been shown to involve a specific carrier-mediated mechanism (27). The reduced folate carrier (RFC) and the proton-coupled folate transporter (PCFT) are expressed in the colon, with higher expression of the former than the latter (52, 80, 109). This, combined with the fact that the colonic pH is more favorable for the function of RFC than PCFT, suggests that the former system plays a larger role in colonic folate uptake (Fig. 1). The colonic folate uptake process also appears to be under the regulation of an intracellular cAMP-mediated (through a mechanism independent of PKA) and a protein tyrosine kinase-mediated pathway (46).

Uptake of WSV by Pancreatic Cells

Uptake of thiamine. As mentioned above, thiamine is essential for normal metabolic functions of all cells, and low intracellular levels of the vitamin lead to impairment of energy metabolism, oxidative stress, and mitochondrial abnormalities. The pancreas contains high levels of thiamine (64), which it must obtain from its surrounding, as cells of this organ cannot synthesize the vitamin endogenously. Thiamine is important for the exocrine and endocrine functions of the pancreas (81). With regard to exocrine function of the pancreas, thiamine deficiency leads to a severe reduction of its content of digestive enzymes (81). As to endocrine function of the pancreas, deficiency of thiamine results in a marked impairment of insulin synthesis and secretion (66). Of relevance to the latter is the development of diabetes mellitus in patients with TRMA (51, 59), an autosomal recessive disorder caused by mutations of THTR-1 (26, 32, 43). These mutations produce impairment of cellular thiamine accumulation and development of localized thiamine deficiency in pancreatic β-cells (and other affected tissues). This in turn leads to derangements of cellular metabolism, cell stress, and apoptosis (59). In TRMA patients, supplementation with high doses of thiamine markedly improves the clinical symptoms of the disease, including a reduction or cessation of the need for exogenous insulin (51, 59).

The mechanism of thiamine uptake by pancreatic β-cells and islets, its regulation, and how clinically relevant mutations in THTR-1 found in patients with TRMA patients affect the physiology and cell biology of the system have been recently addressed using mouse-derived pancreatic β-TC-6 cells and freshly isolated primary mouse and human pancreatic islets (53). Results of these studies show that thiamine uptake is via a specific and pH (but not Na$^+$)-dependent carrier-mediated process that saturates in the nanomolar (apparent $K_m = 37.17 \pm 9.90 \mu M$) and micromolar (apparent $K_m = 3.26 \pm 0.86 \mu M$) ranges. Also, THTR-1 and THTR-2 are expressed in mouse and human pancreatic β-cells, with higher expression of the former than the latter (91). Other studies show that the thiamine uptake process of pancreatic β-cells is adaptively regulated by extracellular substrate level via, at least in part, a transcriptional mechanism(s) (53); also the process appears to be under the regulation of an intracellular Ca$^{2+}$/calmodulin- and protein tyrosine kinase-mediated pathway (53). Finally, clinical mutants of THTR-1 were found by live cell confocal imaging to result in mixed-expression phenotypes of this transporter in β-cells; however, all were functionally impaired (53).

The mechanism and regulation of thiamine uptake by pancreatic acinar cells have also been recently addressed using freshly isolated rodent primary and cultured pancreatic acinar cell lines (rat-derived AR42J and mouse-derived 266-6 pancreatic acinar cells) (91, 96). The results show the involvement of a specific carrier-mediated mechanism, in that THTR-1 and THTR-2 are expressed in these cells, although at a lower level than in pancreatic β-cells (91). The relative contribution of these transporters to total carrier-mediated pancreatic acinar thiamine uptake has also been addressed using a gene-specific (siRNA) silencing approach in vitro and Slc19a2 and Slc19a3 KO mice in vivo (91). Results of both approaches show that

Fig. 3. Carrier-mediated thiamine uptake by freshly isolated primary pancreatic acinar cells of Slc19a2 and Slc19a3 KO mice and their littermates. *$P < 0.01$. (From Ref. 91.)
while THTR-1 and THTR-2 are involved in thiamine uptake by pancreatic acinar cells, the former transporter plays a larger role than the latter (91).

Other studies have examined the effect of chronic alcohol feeding/exposure on thiamine uptake by rodent pancreatic acinar cells and reported significant inhibition compared with pair-fed controls (84, 96). Evidence that this effect is mediated at the level of transcription of the SLC19A2 and SLC19A3 genes was also obtained in studies using transgenic mice carrying the human SLC19A2 and SLC19A3 promoters and fed alcohol chronically and from studies with 266-6 cells transfected with the SLC19A2 and SLC19A3 promoters and chronically exposed to alcohol (84, 96). Chronic alcohol feeding also caused a significant inhibition of the level of expression of the thiamine-metabolizing enzymes thiamine phosphokinase and thiamine pyrophosphatase, which play important roles in regulating intracellular thiamine levels, as well as the level of expression of the mitochondrial membrane TPP transporter (a protein that transports cytoplasmic TPP into mitochondria) (96). The negative impact of chronic alcohol exposure on pancreatic acinar thiamine uptake and intracellular metabolism and compartmentalization may contribute to the deleterious effect of ethanol on pancreatic health by altering the resting state of the pancreas and reducing its defense mechanisms.

**Uptake of RF.** RF is essential for the normal metabolic activities of pancreatic β-cells; it also has the ability to reduce the level of free radicals and proinflammatory mediators, to which these cells are highly sensitive (14, 21). Pancreatic β-cells obtain RF from their surroundings, as they lack the ability to synthesize the vitamin. Recent studies used cultured pancreatic β-cells and freshly isolated primary mouse and human pancreatic islets to show that RF uptake by these preparations is via a specific and high-affinity (apparent K_m = 0.17 ± 0.02 μM) carrier-mediated mechanism (33). All three known mammalian RF transporters, i.e., RF transporters 1, 2, and 3 (RFVT-1, -3, and -2), are expressed in pancreatic β-cells/islets. However, expression of RFVT-1 predominates in mouse pancreatic β-cells/islets, while expression of RFVT-3 predominates in human pancreatic islets. The uptake process of RF by pancreatic β-cells/islets is adaptively regulated by extracellular substrate level via what appears to be a transcriptional mechanism(s); it also is under the regulation of an intracellular Ca^{2+}/calmodulin-mediated regulatory pathway.

**Uptake of folate.** As mentioned above, folate is essential for the biosynthesis of precursors of DNA and RNA, metabolism of several amino acids, and cellular methylation reactions. Thus an adequate supply of folate is necessary for normal cell function and growth of pancreatic cells. The pancreas maintains the second-highest level of folate after the liver (9, 106), and folate is essential for its normal exocrine function and health. Studies have shown that folate deficiency leads to a decrease in amylase secretion, appearance of immature secretory granules in pancreatic cells, and disappearance of secreted materials in the pancreatic duct, as well as disturbances in methyl metabolism (with a significant reduction of the ratio of S-adenosylmethionine to S-adenosylhomocysteine) (7–9). Other investigations have suggested that disturbance of the folate-dependent methyl group metabolism in the pancreas contributes to the pathogenesis of several pancreatic disorders (reviewed in Ref. 49) and that an inverse relationship exists between serum folate level and the risk of development of pancreatic cancer in humans (85).

Pancreatic acinar cells, like all other mammalian cells, cannot synthesize folate and, thus, must obtain the vitamin from the extracellular environment via transport across the cell membrane. Recent studies have delineated the mechanism of folate uptake by pancreatic acinar cells and show the involvement of a carrier-mediated mechanism at acidic and neutral/alkaline pH levels (73). The reduced folate carrier (RFC) and the proton-coupled folate transporter (PCFT) are expressed in pancreatic acinar cells, with higher expression of RFC than PCFT (73); the contribution of these systems to folate uptake by pancreatic acinar cells is not clear but most likely depends on the prevailing extracellular pH. The pancreatic folate uptake process is adaptively regulated by the prevailing extracellular folate level and also appears to be under the regulation of an intracellular cAMP/PKA-mediated pathway (73).

Finally, chronic feeding of alcohol to animals was found to lead to a significant inhibition of pancreatic acinar folate uptake and suppression of the level of expression of RFC and PCFT (73). These findings may contribute to the deleterious effects of chronic alcohol exposure on pancreatic health [i.e., acute and chronic pancreatitis (35)], which is multifactorial and involves a reduction of pancreatic defense mechanisms (35, 45, 50).

**Overall Summary and Future Directions**

This review summarizes recent findings of the existence of efficient, specific, and regulated carrier-mediated mechanisms for uptake of WSV in the large intestine. These findings support a role for the microbiota-generated WSV in host nutrition, and especially in the cellular nutrition of the local colonocytes. Further studies are needed to determine the exact contribution of this source of WSV to overall body vitamin homeostasis (level) under different conditions and the consequences of disrupting this source by external and internal factors on colonic health in humans.

The review also summarizes the recent finding of the mechanisms involved in the uptake of a few WSV by pancreatic cells and how common environmental factors affect these events. Further studies are needed to delineate the mechanisms of uptake of other WSV, how these events are regulated, and how disruption of these processes could contribute to the development of pancreatic diseases.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author.

**AUTHOR CONTRIBUTIONS**

H.M.S. is responsible for and design of the research; H.M.S. prepared the figures; H.M.S. drafted the manuscript; H.M.S. edited and revised the manuscript; H.M.S. approved the final version of the manuscript.

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