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Absorption and blood/cellular transport of folate and cobalamin: pharmacokinetic and physiological considerations

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Abstract

The systems involving folate and cobalamin have several features in common: 1) their dietary forms require luminal digestion for absorption; 2) intestinal bacteria in the upper intestine synthesize and utilize both vitamins, creating possible competition for the nutrients; 3) there is one major intestinal brush border protein essential for absorption; 4) both are subject to extensive entero-hepatic circulation. Finally, human mutations have confirmed the role of specific transporters and receptors in these processes. There are other features, however, that distinguish the metabolism of these vitamins: 1) upper intestinal bacteria tend to produce folate, while cobalamin (cbl) utilization is more common; 2) cbl absorption requires a luminal binding protein, but folate does not; 3) folate absorption can occur throughout the small bowel, but the cbl receptor, cubilin, is restricted to the distal half of the small bowel; 4) movement into cells uses transporters, exchangers, and symporters, whereas cbl is transferred by receptor-mediated endocytosis; 5) folate is carried in the blood mostly in red blood cells, whereas cbl is carried on specific binding-proteins; 6) folate can enter cells via multiple systems, but cbl uptake into all tissues use the transcobalamin receptor (TC-R), with the asialoglycoprotein receptor (ASGP-R) present in hepatocytes for uptake of haptocorrin-cbl (HC-cbl) complexes. In summary, the systems for absorption and distribution of folate and cobalamin are complex. These complexities help to explain the variable clinical responses after oral administration of the vitamins, especially when provided as supplements.

Keywords

folate; cobalamin; vitamin B12; transport; pharmacokinetics

1.0 Introduction

The bioavailability of folate and cobalamin is complex, both for body stores and especially for target tissues. At the same time, unique mechanisms exist for uptake and excretion from intestinal mucosa. Both vitamins undergo enterohepatic circulation (EHC), improving the

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time for maintaining body stores, but increasing risk during malabsorption. These complexities suggest that understanding the effects of vitamin supplementation can be improved using pharmacokinetic and physiological principles [1,2]. Although there are both rapidly and slowly equilibrating compartments in the body, both folate and cobalamin are distributed to those tissues in which the endogenous pools appear to turn over rapidly. Thus, clearance data will reflect mostly replacement of the rapidly turning over compartments of the vitamins. However, there is an endogenous content of the vitamin in all solid tissues, but rather little is known regarding intracellular concentrations of folate or cobalamin (and their metabolites) or residence time in target tissues. Moreover, unique mechanisms exist for uptake and secretion from somatic cells. With all of these complexities, the lack of consistent prediction for clinical effects of vitamin supplementation is therefore not surprising.

In addition, there are features of gastrointestinal physiology that can modify PK parameters. When gastric emptying is delayed from medication or underlying disease, Cmax can be delayed. When intestinal motility is increased, transit time is shortened, and the area under the curve (AUC) can be decreased, if small bowel residence time is decreased. Any alteration in bile secretion will alter the number of times that the plasma pool of the vitamin is subjected to EHC is changed, with consequences to the retention of the supplemented vitamin. The absorption of both vitamins is relatively limited to one section of the small intestine; the transporter for folate (PCFT) is restricted to the upper half of the small intestine, and the receptor for the intrinsic factor (IF)-cobalamin (cbl) complex is limited to the distal small intestine. Thus, if the intestine is compromised by surgery or rapid transit, absorption can be altered. Moreover, such altered absorption would be magnified by the EHC. The intestinal microbiota either produce (folate) or consume (cobalamin) each vitamin, thus competing for absorption or transporters with vitamin supplements. Finally, changes in splanchnic flow with disease can modify absorption of either vitamin. Moreover, folate undergoes first pass metabolism by the liver to a more active form, improving the early availability of active vitamin.

2.0 Pharmacokinetics

The rapidly equilibrating tissues include plasma, red cells, liver, and kidney, while slowly equilibrating tissues include adipose tissue, muscle, bone, and brain. Compartmental analysis after intravenous dosing can identify rapidly equilibrating tissues (rbc for folate, hepatocytes for folate and cobalamin), and slower equilibrating tissues (e.g. fat soluble vitamins in adipose tissue). Slow redistribution from these latter tissues can lead to a long measured terminal half-life. First pass metabolism can modify the PK of drug supplements. For some vitamins the hepatic extraction ratio is low, <1, e.g. for cobalamin or vitamin C, whereas for others hepatic extraction ratio is >1, e.g. vitamin D [3]. Folate undergoes extensive first pass metabolism in the intestine (Greiner 4). Both folate and cobalamin undergo EHC, a useful mechanism for retaining nutrients, especially if hepatic extraction is not excessive, but the EHC can lead to major losses from the body during conditions of suboptimal absorption [1].

2.1 Folate pharmacokinetics

Folate body stores are small relative to daily need, so folate deficiency occurs frequently in the absence of supplementation. Folic acid (pteroylglutamic acid) occurs largely as polyglutamates in food, and must be hydrolyzed to the monoglutamate form for absorption, a reaction mediated by folate conjugase on the brush border of enterocytes in the proximal small intestine [4]. Many of the dietary forms of folic acid are substituted and reduced, but synthetic folate available for supplementation is neither substituted nor reduced, as that form is very stable. Synthetic folate is more 1.7 times more available when added to food, but the range of folate bioavailability from the diet is 44–80%, a wide variability. The diets of adults in the USA and Canada contain 262-2807 dietary folate equivalents with mean intakes of ~700 μg/day. Absorption of the monoglutamate form occurs in part by a saturable transport process with an acidic pH optimum via the proton-coupled folate transporter (PCFT, *SLC46A1*) that is expressed widely, including on the brush border membrane of the proximal intestine and renal tubule. PCFT is active only at pH 5–6, as in the microenvironment of those membranes [5]. The Km for this system is 1–3 μM. In addition, there is an apparently unsaturable pathway that is active when luminal concentrations of folate exceed 5–10 μM [6]. This dual system is responsible for part of the variation in bioavailability at the extreme levels of folate intake.

Reduced folates and the oxidized form, folic acid, are absorbed similarly in vivo, although differences have been demonstrated using in vitro preparations [7]. Methyltetrahydrofolate is absorbed rapidly unchanged, but other forms are converted by the intestinal mucosa [4]. Some vitamin escapes reduction in the enterocyte and is delivered to the liver to be metabolized. When folinic acid (5-formyltetrahydrofolate) is given orally, the absolute bioavailability is only 4%, yet most of the plasma metabolite is the 5-methyl-THF form, indicating extensive first pass metabolism by the intestine [8]. The 5-methyl-THF continues to accumulate in plasma over 2–3 h after oral administration, and much more than after intravenous folinic acid, confirming that the intestine is the organ most responsible for adding the methyl group and reducing the vitamin. Folic acid is the non-methylated and oxidized form used for supplements in tablets and foods, but it is less of a substrate for hepatic dihydrofolate reductase than are the dietary forms of the vitamin, and thus is utilized less efficiently than natural forms of the vitamin that are usually in the tetrahydro- form. Perhaps as a result of these differences in metabolism, folic acid supplements appear to be more bioavailable than dietary folates in many foods [9].

Once absorbed, the monoglutamate folic acid is converted to the polyglutamate form in tissues. A kinetic model in women demonstrated fast- and slow-turnover nonsaturable pools, as well as a saturable slow-turnover pool [10]. This recycling with conversion and catabolism accounts for 2–6 times the total folate pool in the body [11]. Mean residence time in tissues for the polyglutamate form is long, 199–212 d at various doses, whereas the monoglutamate form in transition has a tissue half-life of only half a day [8,9]. These models also predict a considerable biliary component contributing to the fecal content of folate. Because of these complex kinetics, the steady state level of plasma folate does not occur until 6–10 days after daily administration of radiolabeled folate [12]. The metabolism of various forms of folate varies, and that may alter the kinetics of absorption of the parent

compound. For example, folic acid metabolites accumulate more slowly and last longer than metabolites from folinic acid (5-formyl-tetrahydrofolic acid) [13]. Pregnancy may alter the time to reach equilibrium with supplements, reaching a plateau at 8 weeks [14].

The relative effect of low doses of supplemental folate (<200 μg/day) is dose related, but the maximum effect (on homocysteine levels) is reached by 400 μg/day [15]. Folate deficiency can also alter the partition of folate between body tissues [11]. In healthy young male volunteers steady-state concentrations of serum folate were not achieved until 6 weeks at a dose of 200 μg, and at 12–14 weeks after a dose of 400 μg, but the data in support of these delays in reaching a plateau were not included in the article [16]. Although dietary polyglutamate-folate must be converted to the monoglutamate form prior to absorption, the polymorphism C1561T that reduces absorption does not alter folate bioavailability in vivo as assessed by serum folate [17]. These data show that supplemental folate does not reach steady-state levels for a considerable time (2–14 weeks), depending upon a number of factors that may influence the size of the body pools.

2.2 Cobalamin pharmacokinetics

Dietary cobalamin (cbl) ranges from 5–15 μg/day bound to enzymes that must be released by gastric proteases, bound to salivary haptocorrin(HC), and then transferred from haptorrin to intrinsic factor (IF) by the action of pancreatic proteases [18,19]. The EHC of cbl has been estimated at 5–10 μg/day, due to secretion of HC-cbl into bile with reformation of the IF-cbl complex in the intestinal lumen. The IF-cbl complex is taken up by receptor-mediated endocytosis in the distal half of the human small intestine [20,21]. The IF-cbl receptor (cubilin) co-localizes with intestinal alkaline phosphatase on the intracellular membranes surrounding post-prandial triglyceride droplets, but a role for cubilin in fat absorption has not yet been defined [22]. In the enterocyte cbl is released from IF by the action of lysosomal cathepsin L [23]. These complex physiological actions lead to a considerable delay in the Cmax (7 h) of orally administered cbl, and a prolonged terminal half-life of ~25 h [24]. Altering the initial absorption of cyano-cbl with an absorption enhancer (sodium N-[8-(2-hydroxybenzoyl)amine]caprylate) markedly shortens Tmax to 0.5 h, but has no effect on subsequent cbl metabolism and terminal half-life [25]. Cobalamin is released from the enterocyte attached to transcobalamin (TC), the protein that delivers the vitamin to all body tissues. TC also mediates the uptake of the TC-cbl complex from urine, a process that involves the TC receptor on the brush border of renal tubular cells. A large proportion of cbl in plasma is bound also to HC, the cbl binding protein secreted from white blood cells. The HC-cbl complex is taken up by the liver via the asialoglycoprotein receptor, and secreted into bile. The HC-cbl complex in the proximal intestine is subject to the same release and transfer of cobalamin as occurs with dietary cbl, and forms the basis for the EHC of cobalamin [26].

3.0 Folate and cobalamin metabolism by intestinal microbiota

Folate absorption from the intestine must compete with folate produced by or metabolized by microorganisms in the upper small intestine. There are strains of bacteria that produce both high level and low level of folate [27]. Many specis encode complete pathways for

chorismate, a precursor for folate biosynthesis, but only a few contain the complete pathway. Para-aminobenzoic acid (pABA) is synthesized from chorismate as a branch point in folate biosynthesis. Folate synthesis then occurs via a condensation reaction between 6-hydroxymethyl-7,8 dihydroopterin pyrophosphate and pABA using dihydrofolate synthase. Whether folate production or utilization by bacteria predominates in the upper intestine may determine the efficacy of folate absorption. In addition, considerable folate (46% of a 400 μg dose) can be absorbed when delivered to the colon [28]. Thus, folate produced from bacteria might be captured all along the length of the intestine.

In contrast to folate, no complete pathways of biotin, pyridoxine, menaquinone, or cobalamin are present in bifidobacterium genomes. This genus is one of the most common of the facultative anaerobes present in human small intestine. Cobalamin is produced only by bacteria, mostly anaerobes, so cbl production in the upper gut is not at all common. At least 30 genes are involved in the de novo biosynthesis of the vitamin (in reality a pseudovitamin in bifidobacterium) in *L. reuteri*. Most other strains of bifidobacterium do not support complete or even partial biosynthesis [27]. Thus, bacterial overgrowth in the upper gut produces competition for dietary and EHC cbl. Most intestinal bacteria contain multiple vitamin B12 transporters, not specific for cobalamin, the form that is required by mammals [29]. Thus, the utilization of cbl in the upper gut is complicated by competition for uptake between dietary and EHC cobalamin and other corrinoids, such as cobinamide.

4.0 Folate transporters

The reduced folate carrier (RFC) is present on the plasma membrane of many cells, but is not active at the acid pH (~5.5–6.0) of the microclimate adjacent to the intestinal brush border. Most monoglutamate folic acid absorption is mediated by the proton-coupled folate transporter (PCFT), linked with the sodium/hydrogen exchanger, NHE [30]. The folate analog, methotrexate, is a substrate for RFC in the enterocyte, but is less well transported by PCFT than folic acid. On the other hand, folic acid is transported only at acid pH but not at the neutral pH at which RFC is active [3']. Folate leaves the basolateral membrane via multi-drug resistance protein, subtype 3 (MRP3) [30]. The EHC of folic acid is mediated by uptake into hepatocytes via the organic anion transporting peptides OATP1B1 and OATP1B1, and also perhaps by MRP3 and MRP4, and by release into bile on the basolateral side of hepatocytes by MRP2 and by the breast cancer resistance protein, BRCP [31,32].

Folate uptake into and out of cells is mediated by different transporters [30]. RFC (solute carrier family SLC19A1) is responsible for uptake into most cells, as well as that of thiamine. This transporter releases folate from cells as well, but other members of the family, SLC19A2 and SLC19A3 export thiamine but not folate. RFC uses the organic phosphate gradient to drive uphill transport into cells. Folate receptors (FR) also mediate cellular uptake of monoglutamate folates, but they are attached to the membrane by a glycosylphosphatidylinositol (GPI) anchor and mediate folate uptake by endocytosis [30]. Folate release from cells is mediated by many transporters, including PCFT, multi-drug resistance proteins (MRPs), and the breast cancer resistance protein (BCRP). The low density lipoprotein receptor-related protein 2 (LRP2) also mediates folate uptake in the developing neural tube in mice [33].

The role of some of these various folate transporters has been verified by the loss of function demonstrated by mutations of various human genes. PCFT mutations are linked to hereditary folate malabsorption, whereas mutations in RFC are linked to methotrexate resistance, and SLC19A2 and A3 are linked to thiamine-responsive anemia and biotin-responsive basal ganglia disease, respectively [32]. Loss of function of FR1 leads to the syndrome of cerebral folate deficiency, and decreased renal clearance of folate. FR1 also contributes to colonic absorption in the colon. Mutations in FR2 are embryonic lethal in mice, but have been found in hepatic cancer and hematological malignant cells. The function of this transporter is still to be completely defined.

5.0 Cobalamin binding proteins and receptors

Three binding proteins (IF, HC, and TC) mediate cobalamin uptake into cells of the adult mammal via three receptors (IF-cbl R/cubilin, asialoglycoprotein R, and TC-R) [34]. As in the case for folate transporters, the functions of many of these proteins and receptors have been verified by mutations in human genes [19]. Amnionless (AMN) is the protein that binds cubilin to the membrane. Mutations that lead to cbl malabsorption in Imerslund-Grasbeck syndrome (IGS) are found in exons 1-28 of cubilin (the AMN binding region), exons 5-8 (the IF-cbl binding region), and exons 20 and 22 that produce the proteinuria found in IGS. Mutations have been found throughout the AMN and IF exons, leading to cbl malabsorption.

During development, provision of cobalamin is crucial, but cubilin is expressed at very low levels in the yolk sac and the early developing fetus [35]. In the human yolk sac both cubilin and megalin/gp330 (a 660 kDa transmembrane protein) are expressed in the endodermal layer, and cubilin but not megalin increases during gestation [36]. These data suggest that megalin binding promotes the absorption of the cubilin-cbl complex. Available intrinsic factor (IF) is very low in the fetus and its circulation, although it has been detected in human amniotic fluid at 13 weeks of gestation [37]. Thus, a role for cubilin-mediated endocytosis in fetal health cannot be ruled out. In support of this possibility is the persistence of megalin-cublin endocytosis in the adult renal tubule, where it mediates uptake of transferrin, another cubilin ligand [38,39]. Another receptor that may mediate cbl uptake during early development is the transcobalamin receptor (TC-R). This receptor is found on apical membranes of human intestinal enterocytes, and of differentiated Caco-2 cells [40]. In culture the apical membrane receptor can bind ~15% of the capacity of the basolateral TC-cbl complex. Moreover, apically bound TC-cbl is transcytosed, in contrast with basolateral TC-cbl that is retained in the cell. In further studies with Caco-2 cells the TC-R appears to migrate from the basolateral to the apical membrane, forming complexes with megalin during transcytosis [41]. These data show that during early development alternative cbl uptake systems are in place to provide this essential vitamin to growing tissues.

Once cbl is taken into cells via the TC-R, it is released from TC (or IF) by lysosomal enzymes. After the TC-cbl complex is taken up by lysosomes and the cbl released, cbl is transported to the cytoplasm via the LMBD1 protein, perhaps in coordination with binding to CblC [42]. The role of LMBD1 in mediating cbl release from lysosomes has been confirmed by its deficiency in cblF disease, and an additional inborn error of vitamin B12

metabolism has been found to have mutations in ABCD4, and ABC transporter [43]. However, not all transcellular release of cbl requires lysosomes. Multi-drug resistance protein 1 (MRP-1) mediates the ATP-dependent transfer of cbl across vesicular membranes, yet MRP-1 knockout mice show no signs of cbl deficiency [44]. Thus, at least two mechanisms of cbl exit from cells exist, one using IF-TC transfer in lysosomes, and the other bypassing the acid vesicles and using MRP-1. The cytosolic cbl is then subject to extensive metabolism by a series of proteins, and mutations in these proteins lead to a variety of disorders, cbl A through cblG. CblC is the key intracellular protein that converts cobalt-carbon bonds (adenosyl-, cyano-, and hydroxyl-) by hemolytic and heterolytic cleavage to Cbl2+, which is then partitioned to either the MeCbl pathway in the cytoplasm, or to the AdoCbl pathway in the mitochondrion [45]. Mutations in either CblC or CblD (that binds CblC) can lead to impaired AdoCbl or MeCbl synthesis. Mutations have been found in the proteins CblA to CblG, affecting either or both synthetic pathway that are essential for activity of the two mammalian cbl-dependent enzymes, methionine synthase and methylmalonyl-CoA mutase [46].

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Abbreviations

cbl	cobalamin
IF	gastric intrinsic factor
HC	haptocorrin
TC	transcobalamin
TC-R	transcobalamin receptor
AMN	amnionless
EHC	entero-hepatic circulation
PCFT	proton-coupled folate transporter
THF	tetrahydrofolate
RFC	reduced folate carrier
NHE	sodium/hydrogen exchanger
MRP	multi-drug resistance protein
FR	folate receptor
IGS	Imerslund-Grasbeck syndrome
ASGP-R	asialoglycoprotein receptor

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