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Review

Folate and thiamine transporters mediated by facilitative carriers (SLC19A1-3 and SLC46A1) and folate receptors ☆

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ABSTRACT

The reduced folate carrier (RFC, SLC19A1), thiamine transporter-1 (ThTr1, SLC19A2) and thiamine transporter-2 (ThTr2, SLC19A3) evolved from the same family of solute carriers. SLC19A1 transports folates but not thiamine. SLC19A2 and SLC19A3 transport thiamine but not folates. SLC19A1 and SLC19A2 deliver their substrates to systemic tissues; SLC19A3 mediates intestinal thiamine absorption. The proton-coupled folate transporter (PCFT, SLC46A1) is the mechanism by which folates are absorbed across the apical-brush-border membrane of the proximal small intestine. Two folate receptors (FOLR1 and FOLR2) mediate folate transport across epithelia by an endocytic process. Folate transporters are routes of delivery of drugs for the treatment of cancer and inflammatory diseases. There are autosomal recessive disorders associated with mutations in genes encoded for SLC46A1 (hereditary folate malabsorption), FOLR1 (cerebral folate deficiency), SLC19A2 (thiamine-responsive megaloblastic anemia), and SLC19A3 (biotin-responsive basal ganglia disease).

Contents

Abbreviations: RFC, reduced folate carrier; PCFT, proton-coupled folate transporter; ThTr1, thiamine transporter-1; ThTr2, thiamine transporter-2; FOLR1, folate receptor 1 or FRα; FOLR2, folate receptor 2 or FRβ; CSF, cerebrospinal fluid; HFM, hereditary folate malabsorption; TRMA, thiamine-responsive megaloblastic anemia.

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1. Introduction

The folates and thiamine are members of the B family of vitamins. Both are metabolized to active forms that are poor export substrates and accumulate in cells where they sustain key metabolic reactions. Folates carry a negative charge, and thiamine a positive charge, at physiological pH (Fig. 1A). Each is transported into cells by a specific member of the SLC19 family of solute carriers with a high degree of structural specificity (Table 1). SLC19A1, the reduced folate carrier (RFC), transports folates but not thiamine; SLC19A2 (thiamine transporter 1- ThTr1) and SLC19A3 (thiamine transporter 2-ThTr2) transport thiamine but not folates. These transporters function optimally at physiological pH and are the major routes of delivery of folates and thiamine to systemic tissues. Intestinal absorption of folates is mediated by another member of the solute carrier family, SLC46A1 (Table 2), the proton-coupled folate transporter (PCFT), also required for folate transport across the blood:choroid plexus:cerebrospinal fluid barrier. Folates are also transported by an endocytic mechanism mediated by two folate membrane receptors, FOLR1 and FOLR2. SLC19A1-3 are members of the 2A.48 subfamily of the Saier "transporter classification system" (http://www.tcdp.org/), while SLC46A1 is not classified in this system. The physiological roles of SLC19A2, SLC46A1, FOLR1, and to some extent SLC19A2 have been established by the autosomal recessive inherited disorders caused by loss-of-function mutations in these genes. Folate transporters also play an important role in the delivery of folate analogs to neoplastic and inflammatory cells for the treatment of cancer and inflammatory/autoimmune diseases, respectively. The recent development of diagnostic and therapeutic agents linked to folic acid, transported into malignant and immune cells via folate receptor mediated endocytosis, is a novel approach to the selective delivery of drugs to these tissues. Much of what has been learned about the mechanisms of folate transport has come from studies focused on folate analogues, in particular, methotrexate and, more recently, pemetrexed. Membrane transport of folates has been the subject of several recent reviews (Matherly et al., 2007; Matherly and Goldman, 2003; Zhao et al., 2009a, 2011)

2. The biological roles of folates and thiamine

The major physiological folate is 5-methyltetrahydrofolate (Fig. 1A). This is the predominant dietary form of folate, the folate absorbed in the intestine, the form in blood and delivered to mammalian tissues. The carbon at the N- 5 position is donated to homocysteine in the synthesis of methionine, yielding tetrahydrofolate to which up to eight glutamate residues are added to the γ-carboxy of the glutamic acid moiety to form a series of polyglutamate derivatives. These are the preferred substrates for folate-requiring enzymes. These congeners are retained within cells, because they are poor substrates for folate transporters, where they acquire a carbon from formate or serine to form 10-formyltetrahydrofolate or 5,10 methylene-tetrahydrofolate, required for the synthesis of purines and thymidylate, respectively, and ultimately the synthesis of DNA and RNA (Fig. 1B) (Stokstad, 1990). Several of these reactions are inhibited by antifolates. For instance, of the agents currently in clinical use, methotrexate and pralatrexate inhibit the enzyme dihydrofolate reductase to suppress regeneration of tetrahydrofolate from dihydrofolate formed during the synthesis of thymidylate. This results in tetrahydrofolate depletion and cessation of tetrahydrofolate-cofactor-requiring reactions. Pemetrexed and raltitrexed, in their polyglutamate forms, inhibit formation of thymidylate by inhibiting the enzyme thymidylate synthase (Goldman et al., 2010). Higher pemetrexed polyglutamates also inhibit an enzyme required for *de novo* purine synthesis, 5-aminoimidazole-4-carboxamide ribonucleotide transformylase, resulting in the build-up of ZMP with cells, activation of AMP kinase, and inhibition of mTOR (Rothbart et al., 2010).

Thiamine plays an entirely different role in cellular metabolism. Following its uptake into cells, thiamine is converted to thiamine pyrophosphate (TPP) by thiamine pyrophosphokinase (Fig. 2). Thiamine pyrophosphate is a coenzyme required for several key enzymes involved in energy production from carbohydrate and amino acid metabolism. Enzymes that require thiamine pyrophosphate include: pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, and transketolase (Frank et al., 2007). Like other phosphorylated derivatives of a variety of metabolites required for biosynthetic reactions and energy metabolism, these congeners are also retained and accumulate within cells.