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Defining the role of phosphomethylethanolamine N-methyltransferase from *Caenorhabditis elegans* in phosphocholine biosynthesis by biochemical and kinetic analysis.

[Palavalli LH](#), [Brendza KM](#), [Haakenson W](#), [Cahoon RE](#), [McLaird M](#), [Hicks LM](#), [McCarter JP](#), [Williams DJ](#), [Hresko MC](#), [Jez JM](#).

Donald Danforth Plant Science Center, 975 North Warson Road, St. Louis, Missouri 63132, USA.

In plants and *Plasmodium falciparum*, the synthesis of phosphatidylcholine requires the conversion of phosphoethanolamine to phosphocholine by phosphoethanolamine methyltransferase (PEAMT). This pathway differs from the metabolic route of phosphatidylcholine synthesis used in mammals and, on the basis of bioinformatics, was postulated to function in the nematode *Caenorhabditis elegans*. Here we describe the cloning and biochemical characterization of a PEAMT from *C. elegans* (gene, *pmt-2*; protein, PMT-2). Although similar in size to the PEAMT from plants, which contain two tandem methyltransferase domains, PMT-2 retains only the C-terminal methyltransferase domain. RNA-mediated interference experiments in *C. elegans* show that PMT-2 is essential for worm viability and that choline supplementation rescues the RNAi-generated phenotype. Unlike the plant and *Plasmodium* PEAMT, which catalyze all three methylations in the pathway, PMT-2 catalyzes only the last two steps in the pathway, i.e., the methylation of phosphomonomethylethanolamine (P-MME) to phosphodimethylethanolamine (P-DME) and of P-DME to phosphocholine. Analysis of initial velocity patterns suggests a random sequential kinetic mechanism for PMT-2. Product inhibition by S-adenosylhomocysteine was competitive versus S-adenosylmethionine and noncompetitive versus P-DME, consistent with formation of a dead-end complex. Inhibition by phosphocholine was competitive versus each substrate. Fluorescence titrations show that all substrates and products bind to the free enzyme. The biochemical data are consistent with a random sequential kinetic mechanism for PMT-2. This work provides a kinetic basis for additional studies on the reaction mechanism of PEAMT. Our results indicate that nematodes also use the PEAMT pathway for phosphatidylcholine biosynthesis. If the essential role of PMT-2 in *C. elegans* is conserved in parasitic nematodes of mammals and plants, then inhibition of the PEAMT pathway may be a viable approach for targeting these parasites with compounds of medicinal or agronomic value.

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