Methylation of Phosphatidylethanolamine is Required for Biogenesis and Stability of Triglyceride-rich Particles: Impaired Chylomicron Metabolism in PEMT-knock-out Mice

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The distribution of dietary lipids via intestinal chylomicrons (CM) and hepatic VLDL is fundamental for mammalian overall energy homeostasis. Both lipoproteins, CM and VLDL, contain triacylglycerols (TG) as major neutral core components, a monolayer envelope of phospholipids (PL), and either apolipoprotein-B-48 (CM), or B-100 (VLDL). Long-standing evidence suggests that de novo phosphatidylcholine (PC) synthesis is a prerequisite for VLDL secretion. The liver enzyme PE-N methyltransferase (PEMT), which produces specific PC subspecies by threefold methylation of PE, is fundamental for this process, since the absence of PEMT results in liver steatosis in PEMT-/--mice. Considering common mechanisms underlaying the assembly/secretion process of TG-rich lipoproteins, we investigated the intestinal CM metabolism in PEMT-/--mice. Adult PEMT-/--animals and PEMT+/+-(WT)-mice were fed either a high-fat (HF) or chow diet for 3 weeks. Using RT-PCR analyses, expression of PEMT transcripts was detected in RNA samples of WT-mice under HF conditions, and in a human model cell line for CM biosynthesis, Caco-2, in the presence of fatty acids. Oilred-O staining of frozen sections obtained from intestinal samples demonstrated overt neutral lipid accumulation in enterocytes of PEMT-/-, but not of WT animals. In line with this, in HF-PEMT-/--mice, but not in HF-WT-animals, immunostaining of intestinal thin sections revealed apical colocalizationof apoB with regions of neutral lipid abundance within enterocytes. HF-PEMT-/--, but not HF-WT-, enterocytes showed intense basolateral immunostaining for the lipid droplet cage protein, adipophilin/ADRP, indicating pronounced accumulation of cytosolic lipid droplets. Taken together, these data demonstrate for the first time HF-induced expression of PEMT in enterocytes. Our results emphasize a secretion defect for CM in the absence of PEMT resulting in a CM retention disease-like phenotype (similar to Anderson´s disease), and thus underscore a hitherto unrecognized role of PEMT for CM metabolism.