Methyl donor deficiency impairs fatty acid oxidation through PGC-1α hypomethylation and decreased ER-α, ERR-α, and HNF-4α in the rat liver

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Résumé en anglais	BACKGROUND & AIMS: Folate and cobalamin are methyl donors needed for the synthesis of methionine, which is the precursor of S-adenosylmethionine, the substrate of methylation in epigenetic, and epigenomic pathways. Methyl donor deficiency produces liver steatosis and predisposes to metabolic syndrome. Whether impaired fatty acid oxidation contributes to this steatosis remains unknown.METHODS: We evaluated the consequences of methyl donor deficient diet in liver of pups from dams subjected to deficiency during gestation and lactation. RESULTS: The deprived rats had microvesicular steatosis, with increased triglycerides, decreased methionine synthase activity, S-adenosylmethionine, and S-adenosylmethionine/S-adenosylhomocysteine ratio. We observed no change in apoptosis markers, oxidant and reticulum stresses, and carnityl-palmitoyl transferase 1 activity, and a decreased expression of SREBP-1c. Impaired beta-oxidation of fatty acids and carnitine deficit were the predominant changes, with decreased free and total carnitines, increased C14:1/C16 acylcarnitine ratio, decrease of oxidation rate of palmitoyl-CoA and palmitoyl-L-carnitine and decrease of expression of novel organic cation transporter 1, acylCoA-dehydrogenase and trifunctional enzyme subunit alpha and decreased activity of complexes I and II. These changes were related to lower protein expression of ER-α, ERR-α and HNF-4α, and hypomethylation of PGC-1α co-activator that reduced its binding with PPAR-α, ERR-α, and HNF-4α. CONCLUSIONS: The liver steatosis resulted predominantly from hypomethylation of PGC1-α, decreased binding with its partners and subsequent impaired mitochondrial fatty acid oxidation. This link between methyl donor deficiency and epigenomic deregulations of energy metabolism opens new insights into the pathogenesis of fatty liver disease, in particular, in relation to the fetal programming hypothesis.
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