

Methyl donor deficiency induces cardiomyopathy through altered methylation/acetylation of PGC-1 α by PRMT1 and SIRT1

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Cardiomyopathies occur by mechanisms that involve inherited and acquired metabolic disorders. Both folate and vitamin B12 deficiencies are associated with left ventricular dysfunction, but mechanisms that underlie these associations are not known. However, folate and vitamin B12 are methyl donors needed for the synthesis of S-adenosylmethionine, the substrate required for the activation by methylation of regulators of energy metabolism. We investigated the consequences of a diet lacking methyl donors in the myocardium of weaning rats from dams subjected to deficiency during gestation and lactation. Positron emission tomography (PET), microscope and metabolic examinations evidenced a myocardium hypertrophy, with cardiomyocyte enlargement, disturbed mitochondrial alignment, lipid droplets, decreased respiratory activity of complexes I and II and decreased S-adenosylmethionine:S-adenosylhomocysteine ratio. The increased concentrations of triglycerides and acylcarnitines were consistent with a deficit in fatty acid oxidation. These changes were explained by imbalanced acetylation/methylation of PGC-1 α , through decreased expression of SIRT1 and PRMT1 and decreased S-adenosylmethionine:S-adenosylhomocysteine ratio, and by decreased expression of PPAR α and ERR α . The main changes of the myocardium proteomic study were observed for proteins regulated by PGC-1 α , PPARs and ERR α . These proteins, namely trifunctional enzyme subunit α -complex, short chain acylCoA dehydrogenase, acylCoA thioesterase 2, fatty acid binding protein-3, NADH dehydrogenase (ubiquinone) flavoprotein 2, NADH dehydrogenase (ubiquinone) 1 α -subunit 10 and Hspd1 protein, are involved in fatty acid oxidation and mitochondrial respiration. In conclusion, the methyl donor deficiency produces detrimental effects on fatty acid oxidation and energy metabolism of myocardium through imbalanced methylation/acetylation of PGC-1 α and decreased expression of PPAR α and ERR α . These data are of pathogenetic relevance to perinatal cardiomyopathies. Copyright © 2011 Pathological Society of Great Britain and Ireland. Published by John Wiley & Sons, Ltd.

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