Abnormal adipocyte-derived hormones in Rett syndrome mirroring chronic oxidative stress and inflammation: effects of ω-3 PUFAs

Joussef Hayek [1], Silvia Leoncini [1,2], Cinzia Signorini [2], Thierry Durand [3], Jean-Marie Galano [3], Camille Oger [3], Jetty Chung-Yung Lee [4], Gloria Zollo [1,2], Alessio Cortelazzo [1,5], Roberto Guerranti [5], Lucia Ciccoli [2], Claudio De Felice [6]

[1] Child Neuropsychiatry Unit, University Hospital, Azienda Ospedaliera Universitaria Senese (AOUS), Policlinico "S.M. alle Scotte", Siena, Italy; [2] Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy; [3] Institut des Biomolecules Max Mousseron (IBMM), UMR 5247, CNRS/UM/ENSCM, Montpellier, France; [4] School of Biological Sciences, The University of Hong Kong, Hong Kong, China; [5] Department of Medical Biotechnologies, University of Siena, Siena, Italy; [6] Neonatal Intensive Care Unit, University Hospital, AOUS, Siena, Italy

Rett syndrome (RTT) is a severe progressive neurological disorder usually linked to two major X-linked gene mutations, i.e., methyl-CpG binding protein 2 gene (*MECP2*) and cyclin-dependent kinase-like 5 (*CDKL5*). MeCP2 may play a pivotal role in regulating energy metabolism in murine models of the disease, while elevated serum leptin levels in RTT patients and mouse models suggest an overall body metabolic imbalance (1,2).
In the present study, we evaluated circulating adipokines, macrophage-related cytokines (*i.e.*, TNF-α, IL-6, IL-8, IL-10, IL-12p70, TGF-β1, and RANTES), oxidative stress markers together with lipid profile and clinical examinations of *MeCP2*-RTT patients (*MeCP2*-RTT) (n=43) of *CDKL5*-RTT patients (*CDKL5*-RTT) (n=15), before and after polyunsaturated fatty acids (ω-3 PUFAs) supplementation.
Increased circulating levels of leptin ($p<0.001$), total and high-molecular weight (HMW-) - adiponectin ($p<0.001$ and $p<0.001$, respectively) were observed in untreated MECP2-RTT. The picture of leptin resistance were related to subclinical inflammation and macrophage-related cytokine dysregulation in *MECP2*-RTT. We observed, for the first time, hypoleptinemia ($p<0.001$) and hyperadiponectinemia ($p<0.001$) in *CDKL5*-RTT. This condition is related to a moderate inflammation status and different macrophage-related cytokine pattern when compared to *MECP2*-RTT. No relationships between circulating adipokines, BMI and lipid profile in RTT were evidenced. Omega-3 PUFAs were able to partially restore leptin resistance in *MECP2*-RTT although not influencing the hypoleptinemia state in *CDKL5*-RTT. In addition, ω-3 PUFAs partially counterbalanced cytokine changes, as well as aberrant redox homeostasis and inflammatory status.
Altered levels of adipocyte-derived hormones are a hallmark feature of RTT, although with different patterns linked to MECP2 and CDKL5 mutations.

References

1) Blardi P. et al. Clin Endocrinol 2009;70(5):706-9.
2) Torres-Andrade R. et al. Exp Physiol. 2014;99(9):1229-40.

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