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Melatonin limits adaptive ER stress and hepatosteatosis in leptin-deficient mice

Alessandra Stacchiotti[1], Antonio Lavazza [2], Lorena Giugno[1], Stefania Castrezzati[1], Rita Rezzani[1]

[1] Department Clinical and Experimental Sciences, Brescia University, 25123 Brescia, Italy
[2] Istituto Zooprofilattico Sperimentale della Lombardia ed Emilia-Romagna, 25124 Brescia, Italy

Non alcoholic fatty liver disease (NAFLD) impacts on about 30% of the population in industrialized countries, associated to the metabolic syndrome may be reversible or dramatically evolve into cirrhosis or hepatocellular cancer (Wree et al., 2011). Leptin-deficient homozygous mice (*ob*/*ob*) represent a well-known animal model to study obesity, associated with overweight, liver steatosis and insulin-resistance. Recently ER stress has been reported to contribute to hepatic steatosis and cell damage called lipoapoptosis (Flamment et al., 2010). Melatonin, the main pineal indoleamine, has been demonstrated to be useful to limit adipogenesis in many metabolic clinical conditions (de Luxan-Delgado et al., 2014). Therefore major aims of the present study were: 1.To localize ER stress, energy homeostasis and hypoxia markers in the liver of *ob*/*ob* mice receiving or not melatonin in drinking water at 100 mg/kg/day for 8 weeks; 2.To characterize hepatic steatosis and quantify macrosteatosis in different experimental groups. C57BL6 mice treated or not with melatonin were used as controls. Remarkably in *ob*/*ob* mice receiving melatonin, macrosteatosis, periportal GRP78 staining decreased while beta catenin became basolateral into hepatocytes. Furthermore melatonin limited nuclear CHOP staining, a recognized index of major sensitivity to apoptosis, but stimulated p62/SQSTM1 signal, involved in reducing lipogenesis. Moreover by TEM analysis, we visualized in *ob*/*ob* mice liver mitochondria that displayed more cristae and strict RER adhesion after melatonin intake. In conclusion, our morphological analysis suggests that melatonin might ameliorate NAFLD by anti-oxidative and ER stress modulatory abilities in obese mice.

References

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Keywords

Obesity, ER stress, Steatosis, Liver zonation, TEM.