Melatonin drives beneficial Sirtuin 1 expression in leptin-deficient mice liver through MT1 receptor

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Melatonin (MEL) is a pleiotropic indoleamine produced by the pineal gland with a regulatory role of biorhythms, but acts also as powerful antioxidant and anti-inflammatory drug in metabolic diseases [1]. MEL, due to its lipophilic nature, is highly diffusible in any cellular site, comprising the nucleus where it regulates gene transcriptional activity. Nevertheless, its beneficial activity in the liver has been associated to membrane bound receptor 1 (MT1) that is involved also in pancreatic islets secretion. Sirtuin 1 (Sirt1) is an enzyme with NAD-dependent class III histone deacetylase activity, which maintains longevity and proper metabolism in mammalians. Different antioxidant compounds, like resveratrol, have been described as Sirt1 regulators but data on melatonin are still limited. So in the present study we extended to the liver the observations on beneficial melatonin role on kidneys of obese leptin-deficient (ob/ob) mice [2], by focusing on the distribution of Sirt1 and MT1 receptor in mice supplemented or not with MEL in drinking water at 100 mg/kg for 12 weeks. Retinol-binding protein-4 (RBP4), an adipokine involved in the control of insulin secretion, was also analysed as index of insulin resistance. Our immunohistochemical results demonstrated that in lean mice with or without MEL supply, nuclear Sirt1 signal was moderate and in ob/ob became scarce, whereas it was upregulated in all liver zones after MEL intake. MT1immunostaining was restricted to the pericentral zone 3 in lean groups, reduced in ob/ob but enhanced in ob/ob after MEL treatment. RBP4 expressed in every liver zone in ob/ob mice, was restricted to zone 3 after MEL treatment like in lean groups. These novel data suggest that the peculiar MT1 expression in the liver may rely with the Sirt1 protein expression in vivo. In summary, MEL by stimulating Sirt1 through its MT1 receptor is able to ameliorate metabolism, mitochondrial and endoplasmic reticular dysfunctions in obese liver.

References

Keywords
Melatonin; Melatonin receptor 1; Obesity; Sirtuin1; Liver.