THE SILENT INFORMATION REGULATOR 1 (SIRT1) IS A KEY PLAYER IN NEUROPROTECTIVE EFFECTS OF MELATONIN IN PERINATAL BRAIN INJURY

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Increasing evidence indicates that melatonin possesses protective effects toward different kinds of injuries. In our lab we found that melatonin is effective in reducing brain injury and its long-term consequences after both hypoxia-ischemia (HI) and LPS-induced brain inflammation. In both kinds of injury, melatonin preserved the expression of SIRT1, a nicotinamide adenine dinucleotide (NAD+)-dependent deacetylase involved in the epigenetic regulation of important regulatory genes. We recently studied the early modulation of SIRT1 and its downstream targets after HI and melatonin treatment. Necrotic cell death, assessed by propidium iodide injection, was observed 1 h after HI in the ischemic side of the brain. Melatonin, administered 5 min after the ischemic insult, significantly reduced necrotic cell death in the ischemic area. In parallel, we found a reduced activation of the early phases of intrinsic apoptosis. These effects were concomitant to increased expression of SIRT1, reduced expression and acetylation of p53, and increased autophagy activation. Glial cells activation was also significantly reduced by melatonin. Interestingly, however, reactive glial cells did not express SIRT1.

Our results give further insight on the role that SIRT1 plays in the neuroprotective effect of melatonin. In the light of the increasing evidence of a role of SIRT1 in neuronal progenitor cells (NPCs) differentiation, we suggest that the different expression of SIRT1 in neurons and glial cells found after melatonin in the damaged side of the brain might contribute to differentiate NPCs toward a neuronal phenotype. This effect could be particular relevant for damaging events occurring during development because this is a period of intensive differentiation of NPCs.