Possible cellular mechanism of Melatonin in Spinal Cord Injury: role of PPARα

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Spinal Cord Injury (SCI) is considered one of the most physically disabling and psychologically devastating conditions known to humans. SCI is defined as an injury resulting from an insult inflicted on the spinal cord that compromises, either completely or incompletely, its major functions (motor, sensory, autonomic, and reflex) that are in part due to the ensuing inflammatory response. Recently, we have reported that the pineal secretory product, melatonin, exerts important anti-inflammatory effects in an experimental model of SCI; however, no reports are available for its cellular mechanism. Previous studies have shown that melatonin have a function on the nuclear level binding receptors such us RXR, therefore, the aim of the present study was to investigate if Peroxisome proliferator-activated receptor (PPAR) alpha could play a role in the melatonin pathway in a mouse model of SCI. SCI was induced in PPARα KO and CD1 WT mice by the application of vascular clips (force of 24 g) to the dura after a four-level T5-T8 laminectomy. Melatonin (30mg/kg), or vehicle was intraperitoneally (IP) administered to the mice 1, 6 and 12 h after SCI and once daily thereafter for 10d to study the recovery of motor activity. Motor function [Basso Mouse Scale (BMS) of locomotion] improved gradually in the WT mice treated with Melatonin. However, PPARα KO melatonin treated mice didn't exhibit a recovery of motor function. Our result showed a considerably reducing of translocation of nuclear factor-kappa B (NF-κB) to the nucleus and its binding to DNA, thereby decreasing the upregulation of a variety of proinflammatory proteins like Mitogen-activated protein kinases (MAPK) (pP38, pJNK, pERK and pAKT) in WT mice treated with melatonin compared to PPARα KO where we found a notable inflammation analogous to SCI group. Melatonin treatment in PPARα KO mice in spinal cord tissue by histological examination has shown an increasing in lesion size and an improvement in neutrophilic infiltration compared to WT melatonin treated mice. In conclusion, we confirm the beneficial effect of melatonin in the SCI reducing neuroinflammation; in addition, we can hypothesize that melatonin anti-inflammatory action depends by PPAR α binding. These data add new information in the pharmacological research of SCI.