MELATONIN PROTECTS FROM THE LONG-TERM MORPHOLOGICAL AND FUNCTIONAL CONSEQUENCES OF A NEONATAL HYPOXIC-ISCHEMIC BRAIN INJURY IN RATS

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Background: Perinatal brain damage is a major cause of acute mortality and chronic neurologic morbidity in infants and children. Among the main factors responsible for brain injury, inflammation, hypoxia-ischemia and formation of free radicals (FR) appear to play key roles. Melatonin (Mel) is an endogenously produced indolamine formed in higher amount in adult than in neonates which shows potent FR scavenger as well as indirect antioxidant activity.
Aim: To examine whether Mel provides significant protection against brain damage and to evaluate its long-term consequences in a neonatal model of hypoxia-ischemia.
Methods: On postnatal-day 7, newborn rats were subjected after anaesthesia to permanent legation of the right common carotid artery (ischemia) followed to 2.5h hypoxia after 3h (hypoxia-ischemia, HI). The neuroprotective effect of Mel was evaluated by histology 7 days after HI, or when rats reached adulthood using behavioral (T-maze and Morris maze) and histological analyses.
Results: A clear trend toward reduction of brain damage was observed when three doses of 5 mg/kg Mel were administered 5 min before ischemia, 30 min before hypoxia, and 5 min after hypoxia, respectively. A significant protective effect was found when a higher dose of Mel (15 mg/kg) was given immediately after the HI procedure and repeated 24h and 48h later. Injury reduction was associated with decreased inflammatory cell recruitment. Mel administration did not effect body weight at adulthood, but significantly improved behavioural asymmetry in the T-maze (% choices ipsilateral to the damage side: Control, 53±2.53; HI, 66.10±2.53; HI-Mel, 57.7±3.46; Control vs HI, $P>0.05$; Control vs HI-Mel, NS) and learning abilities in the Morris maze (n° of sessions to reach the criterion: Control, 6±0.90; HI, 21.6±2.89; HI-Mel, 11.5±3.02; Control vs HI, $P<0.05$; Control vs HI-Mel, NS). Consistently, brain injury was significantly attenuated in the Mel group.
Conclusions: Mel is neuroprotective not only before brain insult but also after the onset of HI-induced brain damage. Moreover Mel significantly improves functional and histological outcomes suggesting that Mel could represent a potentially safe approach to perinatal brain damage in humans.