Melatonin stimulates dendritic maturation and complexity in rodents' hippocampus: implications for the treatment of neuropsychiatric diseases.

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Melatonin (MEL) is a small molecule with a molecular weight of 232 daltons. It is an indolamine secreted by the pineal gland during the dark phase of the photoperiod. Neuropsychiatric patients have memory and cognition loss associated with a decrease in the number of hilar cells and dendrite arborizations in the hippocampus. These abnormalities are related to MEL decreased nocturnal plasma levels. MEL acts as a neuroprotector due to its antioxidant properties, and it regulates cytoskeletal arrangements that play a crucial role in neuronal differentiation and development. Previously, it was demonstrated that MEL regenerates neurites in N1E-115 cells treated with okadaic acid. The indolamine also prevents cytoskeletal collapse caused by this compound and it increases neurite formation in these cells through protein kinase C (PKC) activation. PKC activated by MEL phosphorylates calmodulin (CaM), induces its translocation from the cytosol to the cytoskeleton where it activates CaM kinase II. This enzyme is a serine threonine kinase, and its stimulation phosphorylates the cytoskeletal associated proteins, MAP2 and STOP, to elicit dendrite formation and stabilization. In this work, we characterized dendrite formation elicited by MEL in hippocampal organotypic cultures and explored the participation of CaM kinase II in this process.

Dendrites were stained with a specific anti-MAP2 antibody and their architecture evaluated by the Sholl method. CaM kinase II participation was evaluated by using the specific kinase inhibitor KN-62. In the vehicle (VEH) incubated slices, two primary dendrites per cell were observed and their length, and thickness were 7.24 um and 1.41 um, respectively. Dendrite complexity was defined by the number of nodes, tips and total length. In the VEH incubated cells, these values were 2.3, 5.2, and 28.5 um, respectively. MEL increases primary (4.25/cell) and secondary (7.8/cell) dendrites optimally at 10-7M in hilar interneurons and mossy cells. Also, MEL increases thickness by 183.6% and length by 170.5% of primary dendrites. Dendrite complexity was also augmented by MEL (nodes=345.6%, tips=203.8%, total length=107.8%). KN-62 abolished the MEL effects on all parameters measured. Our results indicate that MEL stimulates dendritogenesis through CaM kinase II activation at physiological concentrations by augmenting dendrite formation, length and complexity of hilar cells. Data strongly suggest that MEL may modify neuronal cytoarchitecture by cytoskeletal rearrangements to produce modifications in hippocampal plasticity. Also, they support the idea that MEL can be useful in the treatment of neuropsychiatry diseases due to its neuroregenerative property.

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