New melatonin-based neurogenic compounds and their in vivo efficacy for the treatment of nervous system diseases

CSIC and UAM have discovered a new family of melatonin agonists (MT₁ / MT₂) that show potent neurogenic effects both in vitro and in vivo experiments. These compounds also modulate serotonin receptors (5-HT₁A), show interesting antioxidant properties, and are able to cross the blood-brain barrier. Therefore, these compounds are particularly useful for developing auto-repair therapies from neural stem cells in the CNS. In addition, their powerful antioxidant actions and their 5-HT₁A modulation make them excellent candidates as drugs for the treatment of diseases of the nervous system related to stroke, neurodegeneration, depression, psychiatric and cognitive disorders.

Pharmaceutical companies interested in a patent licence are sought for.

Promote neurogenesis in vivo: neuronal differentiation and maturation

Neurogenesis, defined as the generation of new neurons to replace damaged ones, is a promising approach in the treatment of neurodegenerative and psychiatric diseases, including major depression. The compounds of the present invention are melatonin analogs but metabolically more stable that modulate melatonin receptors (MT₁ and MT₂), showing binding values in the nanomolar range (190 – 1.0 nM) with EC₅₀ values (half maximal efficacy concentration) between 1.0 μM and 3.0 nM. Besides, they give inhibition values of 94% (in HEK-293 transfected cells at 10 μM) and 38% of response in comparison with serotonin, used as reference, for 5-HT₁A receptor that is considered as one of the biological targets in neurogenesis. In addition, these melatonin analogs are potent antioxidants, up to two-fold more than trolox, the aromatic part of vitamin E responsible for radical capturing.

In in vitro experiments using stem cells from subventricular zone (SVZ) of adult rats, these compounds promote early neurogenesis (Tuj1, green) and neural maturation (MAP2, red), better than melatonin itself. Wild-type mice were treated with an intraperitoneally injection of a melatonin agonist once daily for 7 days and hippocampus sections were analyzed with BrdU (green, cell proliferation) and NeuN (red, mature neurons). Tested compound increases the neural differentiation and maturation of progenitor cells, without significantly affecting the proliferation rate. Thus, these melatonin-based compounds are capable of regenerating damaged neuronal populations in vivo without causing the appearance of tumors.

Main applications and advantages

- Small heterocyclic compounds with in vivo neurogenic actions that repair neuron damage in stroke, neurodegenerative and psychiatric diseases, including depression.
- Modulate serotonin and melatonin receptors, are potent antioxidants and CNS-permeable.
- Compounds promote differentiation of neural stem cells and maturation into neurons in in vitro and in vivo experiments, without increasing the normal proliferation rate.

Patent Status
PCT patent application filed

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