Discriminating between melatonin signaling at the cell surface and neuronal mitochondria

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Video Abstract

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Abstract

The physiological effects of melatonin are far reaching, from acting as an neuroprotective agent to regulating circadian rhythms and sleep cycles. An imbalance of this hormone has even been linked to neurodegenerative diseases such as Parkinson's, Alzheimer's, and Huntington's. The precise molecular mechanism by which melatonin exerts these effects, however, remains a mystery. To shed light on this process, a team of researchers has developed a melatonin-like compound that is unable to penetrate the cell membrane and binds only to cell-surface receptors. Melatonin's physiological effects on the brain are controlled by the lock-and-key-like properties of this hormone and its receptors. When melatonin binds to its corresponding receptor, a biochemical signal is sent into the cell. But recent data suggests that this interaction may also occur inside the cell, itself. Specifically, on mitochondria within brain cells. Verifying the existence of these intracellular receptors and discriminating between signaling events at these different sites would provide important insights into the therapeutic effects of melatonin. But the hormone's ability to freely travel through the cell makes this challenging. To remedy this, a team of researchers from France and the US designed and synthesized a series of melatonin-like compounds with different chemical properties. While tracking the precise whereabouts of a hormone in a cell is exceedingly difficult, the research team was able to use florescent tags to do just that. These efforts paid off – one of the synthetic hormones, ICOA-13, was unable to penetrate the cell membrane and was found to activate receptors exclusively outside the cell. This cell-impermeable compound allowed the researchers to differentiate, for the first time, the biochemical signals at the cell surface from those on neuronal mitochondria. As researchers continue to understand the physiological effects of melatonin and its role in human health, this new molecular tool will be vital for the design of new drugs and treatment strategies for numerous neurodegenerative diseases.