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Melatonin synthesis in the human pineal gland

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The mammalian pineal organ is a peripheral oscillator, depending on afferent information from the so-called master clock in the suprachiasmatic nuclei of the hypothalamus. One of the best studied outputs of the pineal gland is the small and hydrophobic molecule melatonin. In all vertebrates, melatonin is synthesized rhythmically with high levels at night, signalling the body the duration of the dark period. Changes or disruptions of melatonin rhythms in humans are related to a number of pathophysiological disorders, like Alzheimer's disease, seasonal affective disorder or the Smith-Magenis-Syndrome. To use melatonin in preventive or curative interferences with the human circadian system, a complete understanding of the generation of the rhythmic melatonin signal in the human pineal gland is essential.

Melatonin biosynthesis is best studied in the rodent pineal gland, where the activity of the penultimate and rate-limiting enzyme, the arylalkylamine N-acetyltransferase (AA-NAT), is regulated on the transcriptional level, whereas the regulatory role of the ultimate enzymatic step, achieved by the hydroxyindole O-methyltransferase (HIOMT), is still under debate. In rodents, Aa-nat mRNA is about 100-fold elevated during the night in response to adrenergic stimulation of the cAMP-signalling pathway, with AA-NAT protein levels closely following this dynamics. In contrast, in all ungulates studied so far (cow, sheep), a post-transcriptional regulation of the AA-NAT is central to determine rhythmic melatonin synthesis. AA-NAT mRNA levels are constantly elevated, and lead to a constitutive up-regulation of AA-NAT protein, which is, however, rapidly degraded via proteasomal proteolysis during the day. AA-NAT proteolysis is only terminated upon the nocturnal increase in cAMP levels.

Similar to ungulates, a post-transcriptional control of this enzyme seems evident in the pineal gland of the primate *Macaca mulatta*.

Studies on the molecular basis of melatonin synthesis in the human being are sparse and almost exclusively based on phenomenological data, derived from non-invasive investigations. Yet the molecular mechanisms underlying the generation of the hormonal message of darkness can currently only be deciphered using autoptic material. We therefore analyzed in human post-mortem pineal tissue Aa-nat and Hiomt mRNA levels, AA-NAT and HIOMT enzyme activity, and melatonin levels for the first time simultaneously within tissue samples of the same specimen. Here presented data show the feasibility of this approach. Our results depict a clear diurnal rhythm in AA-NAT activity and melatonin content, despite constant values for Aa-nat and Hiomt mRNA, and for HIOMT activity. Notably, the here elevated AA-NAT activity during the dusk period does not correspond to a simultaneous elevation in melatonin content. It is currently unclear whether this finding may suggest a more important role of the ultimate enzyme in melatonin synthesis, the HIOMT, for rate-limiting the melatonin rhythm, as reported recently for the rodent pineal gland.

Thus, our data support for the first time experimentally that post-transcriptional mechanisms are responsible for the generation of rhythmic melatonin synthesis in the human pineal gland.