Circadian clock genes oscillate in the human pineal gland and are desynchronized in Alzheimer's disease

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Circadian disturbances, such as nightly restlessness, are major clinical problems in Alzheimer's disease (AD). The deterioration of the neurons in the biological clock, the suprachiasmatic nucleus (SCN), and a dysfunction of the pineal gland are supposed to be responsible. Circadian clock genes and melatonin production oscillate in the rodent pineal gland under the sympathetic control originating from the SCN through noradrenalin acting on b_1-adrenergic receptor (b_1-ADR) of pinealocytes. We hypothesized that clock genes may also be rhythmically expressed in the human pineal gland and affected during the AD process. Here we studied circadian clock genes, b_1-ADR expression and melatonin levels in the postmortem human pineal gland of 24 aged controls (Braak stage 0), 22 cognitively intact subjects with the earliest AD changes (Braak stage I-II), and 22 late stage AD patients (Braak stage VI). In controls, *hBmal1* was rhythmically expressed, with a trough during the day, while *hCry1* displayed a peak at night. *hPer1* and b_1-ADR mRNA were positively correlated with two peaks at the light-dark transition periods. *hClock* was not rhythmically expressed in controls. In both the earliest and late stages of AD, clock gene expression was arrhythmic, as were the b_1-ADR mRNA and melatonin levels. Moreover, the positive correlation between *hPer1* and b_1-ADR mRNA had disappeared. We conclude that circadian clock genes oscillate in the human pineal gland, but are desynchronized already in the earliest stages of AD. Our data also suggest that a dysregulation from the SCN is most probably responsible for the pineal changes in AD.

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