Circadian system rhythm disorders in aging and Alzheimer's disease. Role of changes in melatonin, suprachiasmatic nucleus and corticosteroids

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The rhythmic fluctuations of bioperiodic functions allow the organism to adapt in phase to external periodic changes, such as the light/dark cycle and the seasons. The suprachiasmatic nucleus (SCN) and pineal gland are two major compounds of the human circadian time system. The SCN generates and co-ordinates biochemical, physiological, endocrine and behavioural circadian rhythms (Chapter 1). Vasopressin (AVP) is one of the major neuropeptides in the SCN and is involved in the amplification of the amplitude of circadian rhythms and in the synchronisation of the circadian rhythm of a light/dark cycle to the light entrainable oscillator. The pineal gland plays a major role as transducer of environmental light/dark information to the brain, and the secretory pattern of its hormone melatonin is related to the importance of light in human physiology and the control of biological rhythms. The production of melatonin is regulated by a polysynaptic innervation coming from the SCN. Melatonin receptors in the SCN provide a link for an SCN-pineal feedback circuit.

It is well known that the ability to adapt to environmental changes and stressful conditions decreases with aging. Sleep disruption, nightly restlessness and other circadian rhythm disturbances are frequently seen in aging people, glucocorticoid-treated patients and even more so in Alzheimer patients (AD). We hypothesised that decreased synthesis of AVP in the SCN, the reduction of melatonin levels in the pineal gland and increased corticosteroid levels that act on the SCN may be factors involved in the disorder of the biological timing mechanisms and in the pathogenesis of AD symptoms.

The studies in chapter 2 were carried out to determine whether melatonin production was affected in elderly people and AD patients. Melatonin levels were determined in the cerebrospinal fluid (CSF) of 85 patients with AD and in 82 age-matched controls. Ventricular postmortem CSF was collected during autopsy from clinically and neuropathologically well-defined AD patients and from control subjects without primary neurological or psychiatric disease. In old control subjects (over 80 years of age) CSF melatonin levels were half of those found in control subjects of 41-80 years of age. We did not find a diurnal rhythm in CSF melatonin levels in the control subjects. In AD patients the CSF melatonin levels were only one fifth of those found in control subjects. The melatonin level in AD patients expressing APOE-ε 3/4 was significantly higher than that in patients expressing ApoE-ε 4/4. Whether supplementation of melatonin may indeed improve behavioural disturbances in AD patients should be investigated.

Melatonin is a hormone that plays not only a major role in the regulation of circadian rhythms, but may also exert neuroprotective effects in aging and AD. These effects are attributed to its antioxidative and anti-β-amyloid toxicity actions as observed in vitro. For this reason we investigated (chapter 3) whether there was a relationship between
CSF melatonin levels and the neuropathological hallmarks in the brain of AD patients. Melatonin levels were determined in ventricular postmortem CSF of 66 definite AD and 11 transition AD patients and 44 controls. Braak staging and a modified Braak staging for cortex (MBSC) score of plaques, tangles and neuropil changes (the characteristic neuropathological hallmarks of AD) were used to evaluate the severity of AD neuropathology. We could demonstrate for the first time that cerebrospinal fluid melatonin levels of aged controls were negatively correlated with the neuropathological changes in the temporal cortex, where the AD process starts, and not in the frontal, parietal or occipital cortex. Those controls that did not have any neurofibrillary tangles or neuritic plaques had much higher melatonin levels (287.3±68pg/ml, 280.4±64pg/ml, respectively) than those controls who showed the earliest signs of AD pathology, i.e. a few neurofibrillary tangles and neuritic plaques (82.1±4pg/ml, 38.5±8pg/ml, respectively) in the temporal cortex. The decrease of cerebrospinal fluid melatonin levels thus seems to be a very early event in the development of AD that occurs even before the clinical symptoms show. The finding of a significant negative correlation between low melatonin levels and the earliest neuropathological changes in controls are of particular interest, because they may provide information about the very first stages of the disease that could so far not be monitored in any other way.

The possibility that a low melatonin level may be a marker for very early AD cannot easily be confirmed in lumbar puncture CSF, since only during the night measurable melatonin levels are expected. Therefore, it seems more attractive to study this question in plasma or saliva. As a first step toward this aim we measured saliva melatonin levels from 52 healthy volunteers divided into 4-different age groups (chapter 4). We found that an alteration of circadian rhythms of saliva melatonin occurred early in life, around 40 years of age. This shows that consistent alterations in the human circadian time system start already in middle-age, which agrees with various immunocytochemical data. A long-term follow-up of aged controls and their saliva melatonin levels up to the moment they develop the first cognitive complaints seems to be a realistic possibility for future research.

Several studies have revealed the presence of circadian rhythm disturbances in aging, AD and corticosteroid-exposed patients. In chapter 5, we investigated the possibility that these behavioral disturbances may have their basis in a decreased activity of the SCN. We found that the total amount of AVP mRNA in the SCN was three times lower in AD patients than in age- and clock-time-of-death-matched controls. The human SCN AVP mRNA-expressing neurons showed only a marked day-night difference in controls under 80 years. The amount of AVP mRNA was more than 3 times higher during the daytime than at night, whereas no clear diurnal rhythm of AVP mRNA in the SCN was observed in AD patients. There was no relationship between the amount of AVP mRNA in the SCN and age at onset of dementia, duration of AD or the neuropathological changes.
in the cerebral cortex. These findings suggest that a strongly decreased production of AVP in the SCN may be the neurobiological basis for behavioral rhythm disorders. It also explains the beneficial effects of light therapy on nightly restlessness in AD patients. Sleep impairment is one of the major side effects of glucocorticoid therapy. In addition, sleep disorders are observed during conditions involving increased levels of glucocorticoids, such as during aging and AD. The mechanism responsible for the circadian disorder during elevated levels of glucocorticoids is not understood, but an effect of these compounds on the SCN is presumed to be a major factor. In chapter 6, the amount of AVP mRNA expression in the SCN was investigated in 22 human subjects. The total amount of AVP mRNA expression in the SCN was reduced in glucocorticoid-exposed patients as compared with controls. No significant correlation was found between amount of AVP mRNA expression in controls or glucocorticoid-exposed group and the PMD or brain weight. The effect of glucocorticoids on the SCN is rapid and reversible. Our results show that the glucocorticoids have an inhibitory effect on the AVP mRNA expression in the human SCN, which may be a cause of the circadian rhythm disturbance as major side effects of glucocorticoid therapy, and in sleep disorders in aging and AD. We therefore hypothesise that, since the vasopressin effects from the SCN inhibit the hypothalamo-pituitary adrenal (HPA)-axis and corticosteroids inhibit the vasopressin production of SCN neurons, the vasopressin neurons of the SCN seem to be incorporated in the feedback system of the HPA-axis.

In Chapter 7 we investigated whether not only exogenous glucocorticoid exposure but also increased endogenous levels of glucocorticoids may affect circadian rhythms. Seven female students, screened for a variety of health and life style factors, were studied for 21 days by actigraphy before and during a period of stress. Academic examinations cause a significant increase in perceived stress scores. We demonstrated that the academic stress of an examination increases the fragmentation of circadian rest-activity rhythm and induces a disruption of the sleep-wake rhythm.

The present thesis suggests that degenerative changes of the SCN-pineal complex during aging and in AD may well be the neural substrate for the disrupted circadian rhythms reported in elderly subjects and AD patients. In addition, SCN function seems to be hampered by the increased glucocorticoid levels during these conditions. The surprisingly strong and early decrease of CSF melatonin levels during the occurrence of the very first AD change in the temporal cortex asks for future research on the level of the pineal in order to study the mechanism, and on the level of saliva melatonin in order to see whether this is a useful early marker of the AD process.