STIMULATION OF THE CIRCADIAN TIMING SYSTEM IS EFFECTIVE IN THE TREATMENT OF SLEEP-WAKE RHYTHM DISTURBANCES IN AGING AND ALZHEIMER PATIENTS

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INTRODUCTION

Circadian rhythms, i.e. rhythms of approximately 24 hours, are present in many physiological and behavioral phenomena. Circadian rhythms are functional in the adaptation to the day-night differences in the environment. In aging, and even more so in Alzheimer's disease, the circadian rhythm in many behavioral and physiological variables is less prominent or even absent. A decrease in circadian modulation has amongst others been observed in hormone levels, temperature, electroencephalographic (EEG) activity, alertness and sleep (Van Someren et al., 1993). Elderly start napping during the day and often complain of disturbed sleep during the night. In Alzheimer's disease, this fragmentation of the sleep-wake pattern is even more pronounced, and may even closely resemble the pattern that is found after lesions of the suprachiasmatic nucleus (SCN) in animal studies.

This hypothalamic structure is the biological clock of the brain, and is of critical importance in the circadian modulation of behavior and physiology. In aging, and even more so in Alzheimer's disease, a marked reduction of vasopressin-expressing neurons is found in the SCN (Swaab et al., 1985). The combined anatomical, physiological and behavioral findings suggest that a dysfunctional clock may underlie the sleep-wake pattern fragmentation. Therefore, based on the 'Use it or lose it' concept (Swaab, 1991), we have tried a number of strategies presumed to stimulate the circadian timing system in order to promote the activity and preservation of neurons of in the circadian timing system, and thereby enhance the functionality of the clock. The 'Use it or lose it' concept hypothesizes that a high level of activity may protect neurons from degeneration and even to some extent restore their functionality, just like muscle atrophy occurs after disuse and muscle restoration after activation. Increased input to the circadian timing system can, amongst others, be effected by means of bright environmental light, peripheral nerve stimulation and increased levels of physical activity.
Figure 1.
Schematic overview of the inputs to the suprachiasmatic nucleus, and their interactions, that may be relevant for the concept of SCN-stimulation. For reasons of clarity, temperature input is only shown for the SCN, whereas thermosensitivity has in fact been demonstrated in the pineal, SCN, septum, raphe nuclei, locus coeruleus and somatosensory afferents. Inputs are in outlined font, structures in bold, tracts in normal font and neurotransmitters and hormones in italics. Abbreviations: 5-HT=5-hydroxytryptamine (serotonin); DR=dorsal raphe nucleus; GABA=gamma amino-butyric acid; GHT=geniculohypothalamic tract; Glu=glutamate; IGL=intergeniculate leafllet; LC=locus coeruleus; MR=median raphe nucleus; NA=noradrenalin; NPY=neuropeptide Y; RGC=retinal ganglion cells; RGT=retinogeniculate tract; RHT=retinohypothalamic tract; SCN=suprachiasmatic nucleus; SHT=spinohypothalamic tract.
ANIMAL STUDIES

Our studies in aged rats have demonstrated improvement of both functional and anatomical signs of degeneration of the circadian timing system after prolonged environmental stimulation. Witting et al. (1993) demonstrated that the decreased amplitude in the circadian distribution of sleep and wakefulness, as is present in old rats, could be restored to the level of young rats by means of increasing the intensity of daytime environmental light. Lucassen et al. (1995) demonstrated that such increased light input counteracted the age-related decrease in the number of vaso-pressin-expressing neurons in the rat suprachiasmatic nucleus.

HUMAN STUDIES: HEALTHY AND DEMENTED ELDERLY

In human, we have used the rest-activity rhythm as a marker of the functionality of the circadian timing system, because this variable can easily be assessed using actigraphy. An actigraph is a small wrist-worn solid state recorder that continuously assesses the activity level, resulting in a time-series from which the strength of the circadian rhythm can be calculated.

In a correlational study, we first investigated which constitutional and environmental factors were related to the severity of rhythm disturbances in Alzheimer patients. Regression analyses showed the most severe rest-activity rhythm disturbances in patients with a sedentary rather than physically active life style, and in patients exposed to low levels of environmental light (Van Someren et al., 1996).

Consequently, we investigated the effect of additional bright light on rest-activity rhythm disturbances in demented patients. Additional bright light improved the coupling of rest-activity rhythms to stable environmental clues (so called Zeitgebers) in patients with relatively intact vision, but not in patients with severely compromised sight (partial blindness, cataract) (Van Someren et al., 1997a). An example is given in figure 2.

The effect of additional physical activity was investigated in healthy elderly subjects, since fitness training appeared unfeasible in most demented subjects. Fitness training improved the fragmentation of periods of rest and activity that has been found both during normal aging and, more pronounced, after SCN-lesions (Van Someren et al., 1997b).

Whereas the effect of light and activity on the circadian timing system is well documented, the possible effect of somatosensory input to the SCN has only recently been suggested by our group (Van Someren et al., in press). In rats and squirrel monkeys, it has been demonstrated that the SCN is innervated by direct spinohypothalamic projections conveying somatosensory information (Cliffer et al., 1991; Newman et al., 1996). We have therefore investigated whether additional somatosensory input (by means of transcutaneous electrical nerve stimulation, or TENS) would provide an alternative means for the activation of SCN neurons. In early-stage demented elderly, repeated TENS was indeed found to improve the coupling of rest-activity rhythms to Zeitgebers, whereas placebo-treatment was ineffective (Van Someren et al., in press).
Figure 2.
Raw activity data (left panels) of a patient with Alzheimer's disease assessed three times for five days: before (upper left panel), during (middle left panel) and after (lower left panel) light treatment. The right panels show double plots of the average 24-hour activity level (solid line) and one standard deviation above this level (dashed line). Note the decreased variability and the smoother average during light treatment.

CONCLUSION

The anatomical and functional findings from the reported studies confirm the previous notion that the SCN is a structure in which plasticity is highly preserved throughout the life span (Rutishauser and Landmesser, 1996) and even in dementia. In addition to the clinical relevance of manipulating circadian rhythms, the SCN therefore appears to be a suitable structure for the study of the "use it or lose it" concept (Swaab, 1991).
REFERENCES


