

## AGE AND CIRCADIAN RHYTHMS

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The Suprachiasmatic Nucleus (SCN) is considered to be an endogenous "clock" of the mammalian brain, which coordinates hormonal and behavioral circadian rhythms. Age-related changes in biological circadian rhythms have been reported in man as well as other species. The increase both in time spent in wakefulness during the night, and in daytime naps can be characterized as a disruption of circadian sleep/wake rhythms in senescence. Since this phenomenon is even more prominent in Alzheimer's disease patients than in age-matched controls (Prinz et al., 1982), the study of the SCN in relation to age and Alzheimer's disease is of particular interest. However, the very existence of this nucleus in the human brain was questioned until recently, because of difficulties in visualizing it by means of conventional histological staining techniques (see Lydic et al., 1980). Immunocytochemical staining with antibodies against vasopressin (VP) has turned out to be a good marker for the human SCN (Dierickx & Vandesande, 1977), similar to what had been found earlier in the rat (Swaab et al., 1975). In the human material, ±16% of the total SCN cell number could be stained with anti-VP, irrespective of age, sex or dementia. VP cells and fibres were visible throughout the SCN (Swaab et al., 1985). This has enabled us to apply morphometric techniques in order to follow age-related changes in volume and cell number of the human SCN.

### human SCN

A marked decrease in SCN volume, VP cell number and total SCN cell number was found in 80-100 year-old patients as compared with the younger age groups. Corresponding SCN changes in Alzheimer's disease patients were even more pronounced than those observed during normal aging (Swaab, et al., 1985). From partial lesions in the SCN of the rat it is clear that the size of the SCN is crucial for expression of its pacemaker properties (Pickard & Turek, 1983; Van den Pol & Powley, 1979). The observed decrease in SCN volume and cell number in senescence and, even more pronounced, in Alzheimer's disease suggests, therefore, a causal relationship between age-related changes in the SCN and disturbances of circadian rhythmicity, such as sleep/wake patterns. However, alterations in the SCN occur at a later age than the changes in circadian rhythms. Thus, the observed cell loss seems to be a late correlate of functional changes appearing much earlier. In relation to the cognitive disturbances in aging and Alzheimer's disease, it might be of interest that a circadian organization of performance efficiency exists, in animals as well as in men. Disruption of the circadian rhythm due to degeneration in the SCN might consequently also have its implications on cognitive functions (see Van Gool and Mirmiran, 1986).

### rat SCN

Abnormal temporal organization of sleep, in combination with quantitative changes in various sleep parameters, in particular a reduction in the percentage of REM sleep, have also been found in aged Wistar and in Brown-Norway rats (van Gool and Mirmiran,

1983). However, so far no structural changes were found in the rat SCN in senescence (Peng et al., 1980). In old Brown-Norway rats we found indeed an unaltered total cell number in the SCN of senescent rats. However, a decrease was observed in the number of neurons stained with anti-VP in the SCN (Roozendaal et al., in prep.). Since replacement of the VP neuron following degeneration in the aging brain in patients by administration of the peptide or transplantation entails so many theoretical, practical and ethical problems, non-pharmacological therapies deserve more attention than has hitherto been given to them. One therapy that seems to have special promise in aging research is the use of sensorily "enriched" environments.

#### enriched environment

We recently applied the enriched environment on senile rats. The changes in sleep/wake patterns found in aged rats in standard conditions (Van Gool and Mirmiran, 1983) are opposite to those induced by an enriched environment in young ones, e.g., in respect to the increased amount of REM sleep found in the latter condition (Mirmiran et al., 1982). In order to determine whether or not such a response to the environment is still possible at an advanced age, 25-month old rats were placed in 'enriched environment' cages, outfitted daily with a new arrangement of objects such as ladders, boxes and tubes. The sleep pattern of the old "enriched" rats came to resemble in certain respects that of young "standard" rats; in particular, the age-related REM sleep reduction was no longer present after enrichment rearing (Van Gool & Mirmiran, 1984). This 'therapeutic' effect of the environment on sleep was, however, not accompanied by a

## References

- Dierickx, K., and Vandesande, F., Immunocytochemical localization of the vasopressinergic and the oxytocinergic neurons in the human hypothalamus, *Cell Tiss. Res.*, 184, 15-27, 1977.
- Lydic, R., Schoene, W.C., Czeisler, C.A., and Moore-Ede, M.C., Suprachiasmatic region of the human hypothalamus: homolog to the primate circadian pacemaker? *Sleep* 2, 355-361, 1980.
- Mirmiran, M., Van der Dungen, H. and Uylings, H.B.M., Sleep patterns during rearing under different environmental conditions in juvenile rats. *Brain Res.*, 233, 387-398, 1982.
- Peng, M.T., Jiang, M.J. and Hsu, H.K., Changes in running-wheel activity, eating and drinking and their day/night distributions throughout the life span of the rat. *J. Geront.*, 35, 339-347, 1980.
- Pickard, G.E. and Turek, F.W., The suprachiasmatic nuclei: two circadian clocks? *Brain Res.*, 268, 201-210, 1983.
- Prinz, P.N., Vitaliano, P.P., Vitiello, M.V., Bokan, J., Raskind, M., Perskind, E., and Gerber, C., Sleep, EEG and mental function changes in senile dementia of the Alzheimer's type, *Neurobiol. Aging* 3, 361-370, 1982.
- Swaab, D.F., Pool, C.W., and Nijvelt, F., Immunofluorescence of vasopressin and oxytocin in the rat hypothalamo-neurohypophyseal system, *J. Neural Transm.*, 36, 195-215, 1975.
- Swaab, D.F., Fliers, E. and Partiman, T.S., The suprachiasmatic nucleus of the human brain in relation to sex, age and senile dementia, *Brain Res.*, 342, 37-44, 1985.
- Van den Pol, A.N. and Powley, T., A fine-grained anatomical analysis of the role of the rat suprachiasmatic nucleus in

circadian rhythms of feeding and drinking. *Brain Res.*, 160, 307-326, 1979.

Van Gool, W.A.. and Mirmiran, M., Age-related changes in the sleep pattern of male adult rats. *Brain Res.* 279, 394-398, 1983.

Van Gool, W.A.. and Mirmiran, M., Experience in an enriched environment alleviates active sleep reduction in old rats. Abstract to the 7th ESRS Congress, Munich, 1984.

Van Gool, W.A. and Mirmiran, M., Aging and circadian rhythms. In: D.F. Swaab, E. Fliers, M. Mirmiran, W.A. Van Gool and F. Van Haaren, *Aging of the Brain and Senile Dementia*, Progress in Brain Research, Elsevier, Amsterdam, 1986, in press.