Circadian Rhythm-Related Behavior Disturbances and Structural Hypothalamic Changes in Alzheimer’s Disease

Witte J. G. Hoogendijk, Eus J. W. van Someren, Majid Mirmiran, Michel A. Hofman, Paul J. Lucassen, Jiang-Ning Zhou, and Dick F. Swaab

Age-related changes in circadian rhythm (e.g., fragmented sleep-wake patterns) occur in many older persons but are particularly pronounced in patients with Alzheimer’s disease. In these patients, disruptions of circadian rhythms can be severe enough to increase mental decline, agitation during the day, and restlessness at night. Moreover, patients whose nocturnal restlessness disrupts the sleep of the caregiver are more likely to be institutionalized than those who have cognitive impairment alone.

In a nursing home, poor light conditions exacerbate circadian rhythm disturbances. Institutionalized patients with Alzheimer’s disease generally are exposed to less environmental light during the day than their age-matched controls, because they participate in few outdoor activities and watch television in dimly lit rooms. Furthermore, patients sleep in rooms where the corridor lights are kept on during the night. The degenerative changes in the retina and optic nerve associated with Alzheimer’s disease also decrease patients’ exposure to light. All these factors can affect the synchronization of the brain’s biologic clock to 24-hour environmental cues.

Sleep disturbances in patients with Alzheimer’s disease have been treated with hypnotic medications, but these drugs have limited therapeutic efficacy and may decrease daytime alertness. Another treatment strategy—exposure to bright light—is effective. The exact mechanism of action of light therapy has only recently become better understood.

From The Netherlands Institute for Brain Research (W. J. G. Hoogendijk, MD; E. J. W. van Someren, MSc; M. Mirmiran, PhD; M. A. Hofman, PhD; P. J. Lucassen, PhD; J.-N. Zhou, MD; and D. F. Swaab, MD, PhD) and the Valerius Clinic, Department of Psychiatry, Research Institute Neurosciences Free University (W. J. G. Hoogendijk, MD), Graduate School Neurosciences Amsterdam, Amsterdam, The Netherlands.
FUNCTION-STRUCTURE RELATIONSHIPS

Correlating function (e.g., behavior) with a particular brain structure or correlating dysfunction (e.g., behavioral disturbance) with the pathology of that structure is difficult because many structures and circuits usually are involved. The hypothalamus, however, has several unique properties that make it suitable for studying function-structure relationships.

The hypothalamus contains, in addition to conventional neurons, neuroendocrine cells whose activity can be monitored by measuring plasma levels of hormones secreted by these cells. These nuclei can be easily delineated, allowing researchers to measure increases or decreases in the number of these cells. In patients with Alzheimer’s disease, the different hypothalamic nuclei are not affected to the same degree, and some are not affected at all. In addition, the neurotransmitter, neuromodulator, and neurohormonal content of many hypothalamic nuclei, as well as their specific functions, have been described. For example, we know that the magnocellular vasopressin neurons of the supraoptic and paraventricular nucleus are involved in antidiuresis, the oxytocin neurons are involved in reproduction and satiety, and the corticotropin-releasing neurons of the paraventricular nucleus play an important role in the stress response and mood. The suprachiasmatic nucleus (SCN), also known as the biologic clock, is involved in regulating circadian and circannual rhythms. A lesion in the suprachiasmatic region of the anterior hypothalamus (e.g., as the result of a tumor) disturbs circadian rhythms in human beings.

The human SCN is a small structure located on top of the optic chiasm (see Figure 1) that cannot be recognized with certainty in conventional 6- to 10-μm thionine-stained paraffin sections. To identify this structure, immunocytochemical labeling of the nucleus with antivasopressin or antivasoactive intestinal polypeptide is necessary.

The SCN generates biologic rhythms corresponding to an approximately 24-hour period. In a process called entraining, this endogenous SCN rhythm normally is synchronized to the 24-hour environmental light-dark cycle. Entraining occurs through a direct neuronal pathway from the retina to the SCN; this was shown by staining degenerating neurons in patients with optic nerve damage. The retinohypothalamic tract is the principal pathway mediating the entraining effects of light on the SCN. Persons who are completely blind often lack the entraining effects of light and may show free-running temperature, cortisol, and melatonin rhythms. They also may suffer from sleep disturbances. Observations in patients with a tumor in the SCN region and those in blind people emphasize the importance of the light-dark cycle for synchronizing the circadian activity of the SCN.

The hypothesis that the SCN is the biologic clock of the brain has been confirmed in several animal models. In rats, circadian rhythmicity is maintained when different parts of the optic system (e.g., the optic cortex) are severed. Only after enucleation of both eyes do the rhythms become free running, and a lesion directly in the SCN itself causes complete arrhythmicity. Furthermore, when
Figure 1. Location of structures in the human hypothalamus. Panel A is a more anterior view than Panel B. Bnst-Dspm = darkly staining posteromedial component of the bed nucleus of the stria terminalis; Inah 1-4 = interstitial nucleus of the anterior hypothalamus 1-4; Pvn = paraventricular nucleus; Scn = suprachiasmatic nucleus; Sdn = sexually dimorphic nucleus of the preoptic area; Son = supraoptic nucleus. Reprinted with permission from Swaab & Hofman (1995). Trends in Neuroscience, 18, 264-270.

fetal SCN tissue of one animal is transplanted into an animal with an SCN lesion, rhythmicity is restored. When SCN tissue is isolated in vitro, neuronal firing and vasopressin release maintain their circadian rhythmicity. These results indicate that a function-structure relationship exists for circadian rhythms and the SCN.

DYSFUNCTION-PATHOLOGIC STRUCTURE RELATIONSHIPS

Several studies have addressed the occurrence of circadian rhythm disturbances in aging and Alzheimer’s disease. One of the characteristics of Alzheimer’s disease is an increase in nocturnal wakefulness after the patient initially falls asleep. In older persons, in general, the number of spontaneous daytime naps increases, but patients with Alzheimer’s disease spend even more time napping during the day than their age-matched controls (see Figure 2).

These sleep disturbances are related to changes in the SCN. In persons aged 80 to 100 years, the number of vasopressin-expressing neurons in the SCN decreases substantially; in patients with Alzheimer’s disease, these changes occur at an earlier age and are even more pronounced (see Figure 3).

Circadian and circannual fluctuations in vasopressin-expressing neurons in the SCN decrease with age. The marked diurnal oscillation in the number of
Figure 2. Raw data of rest and activity recorded over several days. The top and middle data are from 41-year-old and 78-year-old healthy control subjects, with rest (low bars) during the night and activity (high bars) during the day; the bottom data are from a 79-year-old patient with Alzheimer's disease. Note the frequent naps and nighttime activity in Alzheimer's disease. Reprinted with permission from Mirmiran et al. (1988). Journal of Neuroscience Methods, 25, 209-214.

vasopressin-expressing neurons in the SCN of young subjects (i.e., low numbers of vasopressin-expressing neurons at night and peak levels during early morning) is not seen in persons older than age 50. In young persons, the number of vasopressin-expressing neurons is low in summer and peaks in autumn; in
Figure 3. Number of vasopressin-expressing cells in healthy control subjects aged 0 to 100 years and patients with Alzheimer’s disease (AD) (mean age, 79 years). Vertical lines denote standard error of the mean. Note the low values in the AD group and the 81- to 100-year-old group; these values were significantly different from those for the groups aged 0-20 and 40-80 (Student-Newton-Keuls multiple range test: p < .05). The overall effect of age on vasopressin-expressing cells was also significant (analysis of variance: p = .026). Reprinted with permission from Swaab et al. (1985). Brain Research, 342, 37-44.

persons aged 50 and older, this annual cycle is disrupted and less pronounced. These findings indicate that a dysfunction-pathologic structure relationship appears to exist for sleep disturbances and a decreased number of vasopressin-expressing neurons in the SCN in older persons and patients with Alzheimer’s disease.

The authors currently are studying other dysfunction-pathologic structure relationships in the hypothalamus. They recently found a strong activation of neurons expressing corticotropin-releasing hormone in the paraventricular nucleus of depressed patients. They also are trying to confirm the putative role of corticotropin-releasing hormone in depression in patients with Alzheimer’s disease. To do so, the authors are studying the paraventricular corticotropin-releasing hormone-expressing neurons of 50 patients with Alzheimer’s disease, who have been longitudinally tested for behavioral disturbances (e.g., observable signs of depression).
Figure 4. Number of vasopressin (AVP)- and vasoactive intestinal polypeptide (VIP)-expressing cells in the suprachiasmatic nucleus of rats of different ages after housing under low (hatched bars) or high (white bars) light intensity. Bars show the mean ± standard error of the mean. Note that the number of AVP-expressing cells in the old group after high light treatment does not differ significantly from that for the young and middle-aged groups. *p < .05, compared with young and middle-aged rats housed under low light intensity. Reprinted from Lucassen et al. (1995). Brain Research, 693, 261-266 (Figure 2).
TREATMENT OF CIRCADIAN RHYTHM DISTURBANCES

Rest-activity disturbances in elderly persons and patients with Alzheimer's disease are influenced by daytime activity and exposure to light. Sleep-wake variables also are highly correlated with cognitive measures.

The relationship between sleep-wake disturbances and exposure to light suggests that light therapy is a viable method of treating this problem. Indeed, improvement was seen in Alzheimer's disease patients with behavioral disorders, such as wandering or agitation, and those with sleep-wake disturbances who were exposed to extra amounts of light. Exposure of older rats to bright light appears not only to reverse age-related alterations in circadian sleep-wake rhythm disturbances but also prevents age-related decreases in the number of vasopressin-expressing neurons in the SCN (see Figure 4). Thus, the therapeutic effects of light therapy on the dysfunction may be explained by its effects on the pathologic structure.

CONCLUSION

Owing to several unique properties, the hypothalamus provides a model for studying function-structure and dysfunction-pathologic structure relationships. Studies of these relationships may help explain and predict the effect of therapeutic interventions. One result of such studies has been the use of light therapy to alleviate circadian rhythm-related behavioral disturbances in patients with Alzheimer's disease. The use of light therapy in humans arose from observations in rats that age-related decreases in vasopressin-expressing neurons in the SCN could be prevented by exposure to bright light. Future research into dysfunction-pathologic structure relationships may have important therapeutic consequences for older persons and those with Alzheimer's disease.

SUGGESTED READING


Offprints. Requests for offprints should be directed to Witte J.G. Hoogendijk, MD, The Netherlands Institute for Brain Research, Meibergdreef 33, 1005 AZ Amsterdam ZO, The Netherlands.