CHAPTER 62

The human hypothalamus in development, sexual differentiation, aging and Alzheimer’s disease

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Introduction

The human hypothalamus is involved in a wide range of functions in the developing, adult and aging subject, as well as in various diseases of different etiologies. Alterations in hypothalamic structures and functions are thought to be operative in diseases such as anorexia nervosa, bulimia, depression, Cushing’s disease, diabetes insipidus, Prader-Willi syndrome, polycystic ovaries syndrome and the malignant neuroleptic syndrome as well as in disturbances in sleep and temperature regulation. In addition, the hypothalamus is affected in neurodegenerative diseases and might be responsible for particular symptoms, e.g., in Alzheimer’s, Parkinson’s and Huntington’s disease and possibly in multiple sclerosis. Moreover, this brain region is presumed to have altered in adenogenital syndrome, by hormones given during development (e.g., diethylstilbestrol (DES)), and in Turner’s, Klinefelter’s and Kallman’s syndrome.

In spite of this impressive list, knowledge on the normal development, sexual differentiation and aging of the human hypothalamus is hardly available. Data on how the pathophysiology of the conditions mentioned above is reflected in the morphology of the human hypothalamus are essentially nonexistent. In the present paper, recent data on morphological alterations of several hypothalamic structures in normal development, sexual differentiation, aging and Alzheimer’s disease are reported. The sexually dimorphic nucleus (SDN), the suprachiasmatic nucleus (SCN), the suprachiasmatic nucleus (SON), the paraventricular nucleus (PVN) and the lateral tuberal nucleus (LTN) (Fig. 1) have so far been studied with respect to the changes occurring in brain-endocrine interactions in the human hypothalamus during these conditions. Alzheimer’s disease can in many respects be considered as an advanced, accelerated form of aging. During both conditions, activated neurons seem to have a better chance for survival.

Sexually dimorphic nucleus

The sexually dimorphic nucleus of the preoptic area (SDN) was first described in the rat brain by Gorski et al. (1978). The SDN in the male rat is 3–8 times larger than in the female, due to differences in perinatal steroid levels (Jacobson et al., 1980). The SDN is involved in aspects of male sexual behavior (i.e., mounting, intromission and ejaculation). Mounting behavior is not only affected by SDN lesions in male rats, but also in female rats (Turkenburg et al., 1988; De Jonge et al., 1989).

The SDN in the young adult human brain is twice as large in males as in females and contains twice as many cells (Swaab and Fliers, 1985; Fig. 2). The SDN is identical to the “intermediate nucleus” described by Braak and Braak (1987). Sexual dimor-
phism in the human brain is not present at birth (Fig. 2). At that moment, the SDN contains only some 20% of the cell number found around 2 - 4 years of age. From birth up to this age, cell numbers increase equally rapidly in both sexes. However, a sex difference does not occur until about the fourth year post-natally, when cell numbers start to decrease in girls, whereas in males the cell numbers in the SDN remain stable until approximately 50 years of age (Swaab and Hofman, 1988). After this age, cell numbers in the male SDN decrease sharply. In females a second phase of marked cell loss sets in after the age of 70 (Hofman and Swaab, 1989). The sharp decrease in cell numbers in the SDN later in life might be related to the dramatic hormonal changes which accompany both male and female senescence (Hofman and Swaab, 1989), and to the decrease in male sexual activity. It is not clear whether the hormonal changes would be cause or effect of the observed cell loss in this nucleus. Cell numbers in the SDN of Alzheimer's disease patients were found to be within the normal range for age and sex (Swaab and Hofman, 1988).

A prominent theory on sexual orientation is that it develops as a result of an interaction between the developing brain and sex hormones (Gladue et al., 1984; Dörner, 1988). According to Dörner's hypothesis, male homosexuals would have a female differentiation of the hypothalamus. This theory was not supported by our data on the SDN in homosexual men. Neither the SDN volume, nor the cell number in the hypothalamus of homosexual men who died from AIDS differed from that of the male reference groups in the same age range, nor
Suprachiasmatic nucleus

The suprachiasmatic nucleus (SCN) is considered to be the major circadian pacemaker of the mammalian brain, coordinating hormonal and behavioral circadian rhythms (Rusak and Zucker, 1979). At birth the SCN contains some 13% of the vasopressin expressing neurons and 20% of the total cell number found in adulthood (Fig. 3). Subsequently, cell numbers rise to maximum values around 1 – 2 years post-natally after which they decrease gradually to some 50% in adulthood (Swaab et al., 1990). Recent observations (Hofman and Swaab, unpublished results) have revealed a marked seasonal variation in the volume and cell number of the human SCN in relation to the variations in photoperiod.

Age-related changes in circadian rhythms have been reported in man as well as in non-human species (Van Gool and Mirmiran, 1986). A fragmentation of sleep–wake patterns occurs in senescence, a phenomenon that is even more pronounced in Alzheimer’s disease (Witting et al., 1990). In Alzheimer’s disease the disruptions of the

from that of heterosexuals also suffering from AIDS (Swaab and Hofman, 1988, 1990). The fact that no difference in SDN cell number was observed between homo- and heterosexual men who had died of AIDS refutes the global formulation of Dörner’s hypothesis that male homosexuals have “a female hypothalamus”.

Fig. 2. Development and sexual differentiation of the human sexually dimorphic nucleus (SDN) of the preoptic area of the hypothalamus. Log-log scale. Note that at the moment of birth the SDN is equally small in boys (△) and girls (○) and contains only about 22% of the cell number found at 2 – 4 years of age. The SDN cell number of a female neonate with a pituitary aplasia (A) is fully within the range of other neonates. Cell numbers reach a peak value around 2 – 4 years post-natally, after which a sexual differentiation occurs in the SDN due to a decrease in cell number in the SDN of women, whereas the cell number in men remains approximately unchanged up to the age of 50. Note that in men the reduction in cell number in senescence is less dramatic. The largest discrepancy in cell number between men and women is found around 30 years and in people older than 80, whereas the sexual dimorphism in the SDN cell number is least around the age of 60. The SDN cell number in homosexual men (■) does not differ from that in the male reference group. The cell number of the SCN of two male-to-female transsexuals (T) is within the female range, whereas the SDN of a woman with a Prader-Willi syndrome (P) is small. The curves are quintic polynomial functions fitted to the original data for males (drawn line) and females (dashed line), with F_5 (5,49) = 10.05, P < 0.001, and F_5 (5,39) = 7.32, P < 0.001, respectively. (From Swaab and Hofman, 1988, with permission.)

Fig. 3. Development of the human suprachiasmatic nucleus (SCN) of the hypothalamus. Log-log scale. The period at term (38 – 42 weeks of gestation) is indicated by the vertical bar. Note that total cell number is low at the moment of birth (21% of the cell number found in adulthood). There is no difference in the developmental course of the SCN in boys and girls. Cell numbers around 1 – 1.5 years post-natally are more than twice the adult cell numbers. After these high levels a decrease to adult total cell number is found. (From Swaab et al., 1990, with permission.)
circadian rhythms are often so severe that they are even thought to contribute to the mental decline (Fetke et al., 1985). In addition, sleep disturbances often lead to hospital admission of the elderly (Sanford, 1975). Total SCN cell numbers and numbers of vasopressin expressing neurons were, therefore, determined during aging and in Alzheimer’s disease. A marked decrease was found in SCN cell number in subjects of 80–100 years of age, while in Alzheimer’s disease these changes were even more dramatic (Swaab et al., 1985, 1987). In this respect it is important to note that both the retina and the optic nerve which provide direct and indirect input to the SCN show degenerative changes in Alzheimer’s disease (Hinton et al., 1986; Katz et al., 1989; Trick et al., 1989). In addition to degenerative changes, Alzheimer patients are generally exposed to less light than their age-matched controls (Campbell et al., 1988). As a result, both the input of the visual system to the SCN and the SCN itself seem to be seriously affected in Alzheimer’s disease. The contribution of each of these components to circadian disturbances has yet to be investigated.

In the SCN of the aged rat, total cell number remained unaltered, but the number of vasopressin and vasoactive intestinal peptide (VIP) expressing neurons in the SCN was significantly diminished (Roozendaal et al., 1987; Chee et al., 1988). These changes may be related to the diminished amplitude of circadian rhythms observed in aged rats (Van Gool and Mirmiran, 1983). Recent observations (Witting et al., in preparation) showed that by increasing the environmental light intensity, the circadian amplitude of sleep/wakefulness in old rats can be brought up to the level of young animals. This finding fits with the idea that activation might restore neuronal functions in aging (see below).

Recent morphometric analysis of the SCN revealed that the volume of this nucleus in 10 homosexual men was 1.7 times as large as that of a reference group of 18 male subjects and contained 2.1 times as many cells (Swaab and Hofman, 1990). It might be that the programmed post-natal cell death, usually occurring 13 – 16 months after birth, is limited in homosexual men. The observation that a similarly enlarged SCN was present in a woman with Prader-Willi syndrome, a congenital luteinizing hormone-releasing hormone deficiency in which sex hormones are very low (Swaab et al., 1987), suggests that the interaction with sex hormones in some stage of development might be essential for the programmed SCN cell death.

**Supraoptic and paraventricular nuclei**

The neurosecretory cells of the hypothalamic supraoptic and paraventricular nucleus (SON and PVN) produce the neuropeptides vasopressin and oxytocin which are released into the blood circulation in the neurohypophysis. A recent study (A.M. Neijmeijer-Leloux (unpublished results) showed that the vasopressin and oxytocin cell numbers in the SON and PVN are already at the adult level in the second half of gestation. The SON and PVN seem thus to develop much earlier than the SCN and SDN.

The neurons of the SON and PVN form a population of extremely stable cells. Neither in the course of normal aging nor in Alzheimer’s disease patients could any significant loss in neurons or total cell number be observed (Goudsmit et al., 1990). Various recent observations provide evidence for the hypothesis that activation of neurons may interfere with the process of aging, and thus prolong the life span of neurons or restore their function. This hypothesis is paraphrased as “use it or lose it” (Swaab, 1991). The SON and PVN neurons are not only metabolically highly active throughout life, but they are even additionally activated in senescence as can be judged from the increase in the size of the vasopressin containing perikarya (Fliers et al., 1985) and nucleioli (Hoogendijk et al., 1985), and the enhanced plasma levels of vasopressin (Frolkis et al., 1982) and neurophysins (Legros et al., 1980). Similar activation of vasopressin neurons was observed in the aged rat (Fliers and Swaab, 1983; Goudsmit et al., 1988b) and is probably due to a loss of vasopressin receptors in the kidney during aging (Ravid et al., 1987). The hypothesis that the neurosecretory cell numbers are so stable because
they are additionally activated needs to be tested experimentally, e.g., by long-term inhibition of these neurons during aging, in which case neuronal degeneration is expected to occur.

An example of activation restoring a peptide system during aging was recently observed in the rat. Vasopressin innervation in the senescent male rat brain is particularly decreased in those regions where the fiber density in young adult males was shown to be dependent upon plasma levels of sex steroids (Fliers et al., 1985). Plasma testosterone levels and testicular weight decrease progressively with age in the rat (Ravid et al., 1987). However, when old rats were supplemented with testosterone for 1 month, the vasopressin innervation in the rat brain was restored (Goudsmit et al., 1988a). The vasopressin fiber system responding to the testosterone treatment originates from the bed nucleus of the stria terminalis (BST) and medial amygdala, where testosterone stimulates vasopressin synthesis, as determined by in situ hybridization (Miller et al., 1989). In castrated male rats, in which axonal transport was blocked by means of colchicine, testosterone increased the number of BST neurons expressing vasopressin (Van Leeuwen et al., 1985). Moreover, vasopressin-producing neurons in the BST and amygdala were shown to contain steroid hormone receptors (Axelson and Van Leeuwen, 1990). Thus, the increased vasopressin staining in aged animals following testosterone treatment demonstrates how activation of the synthetic activity of peptidergic neurons (i.e., BST neurons) may reverse the age-related changes in their terminals.

**Lateral tuberal nucleus**

The lateral tuberal nucleus (LTN) is present in man and higher primates. In adulthood it contains some 60,000 neurons whereas in Huntington’s disease this number may be reduced to less than 10,000 (Kremer et al., 1990) depending on the age at onset of the disease and age at death. Pathological changes in the LTN have also been described in depression (Horn et al., 1988), Kallman’s syndrome (Kovacs and Sheehan, 1982) and dementia with intracranial argyrophilic grains and silver-staining coiled bodies, containing straight filaments (Braak and Braak, 1989). In Alzheimer’s disease, the number of LTN neurons did not differ from controls. The number of plaques in this nucleus was low, and they were exclusively of the amorphous type. Neurofibrillary tangles were rare in conventional silver stainings. Yet, immunocytochemical staining using the monoclonal antibody Alz-50 showed such an abundant reactivity of both perikarya and neurites that the LTN of Alzheimer’s disease patients could even be recognized by the naked eye (Kremer et al., 1991). The LTN seems to represent a brain area in which Alzheimer’s disease affects the neurons in a limited way, without further progress to the classical changes of silver-staining of tangles and neuronal loss. Lesions in the lateral hypothalamus of animals are known to be associated with weight loss. In Huntington’s and in Alzheimer’s disease, dementia is combined with severe weight loss associated with normal or even increased food intake, as is the case in the condition described by Braak and Braak (1989). Because LTN pathology is accompanied by cachexia (H. Braak, personal communication) the LTN is hypothesized to play a role in feeding behavior and metabolism.

**Conclusions**

The human hypothalamus contains several nuclei manifesting a wide variety of changes in aging and Alzheimer’s disease that might be related to particular symptomatology.

In the first place, the SDN shows a decreased cell number during prepubertal development leading to sexual dimorphism and, subsequently, a decrease in cell number in both sexes during normal aging. The latter change is possibly related to a decrease in sexual activity and changes in hormone levels. In Alzheimer’s disease, SDN cell numbers decrease at a similar rate as in normal aging. Since the SDN in homo- and heterosexual men is similar in size and cell number, the idea that homosexual men have a female hypothalamus is not supported.
The SCN coordinates circadian and circannual rhythms. Its cell number decreases to 50% from 1–2 years post-natally to adulthood and, subsequently, during normal aging. A marked seasonal variation in the volume and cell number of the SCN was observed in relation to the variation in photoperiod. In Alzheimer’s disease, the decrease in cell number is very pronounced. This pathology might be the neural basis for the nightly restlessness observed in Alzheimer’s disease, whereas alterations in the visual system (see before) might contribute to these functional disturbances. It seems worthwhile, therefore, to try and see whether stimulation of the visual pathways by light therapy might increase the amplitude of the circadian rhythms in Alzheimer patients in a similar way as it does in the aged rat.

Recently, we found that the SCN in homosexual men is about twice as large as that of a reference group. The functional meaning of this observation is not yet clear.

The cells of the SON and PVN develop early. Adult cell numbers are already present halfway gestation. These nuclei are examples of neuron populations that seem to stay perfectly intact in aging and Alzheimer’s disease. We hypothesize that this might be due to the activation of these neuroendocrine cells during the aging process, a hypothesis that will be tested in animal experiments. We have already shown that neurons may be activated also in very old rats, if the right stimulus (e.g., testosterone for the BST) is offered.

The LTN might be involved in feeding behavior and metabolism. It does not show any decrease in neuronal numbers in Alzheimer’s disease. Yet, a very strong Alz-50 staining is present in the LTN of these patients which is based upon a dense network of dystrophic neurites and numerous staining perikarya. The LTN in Alzheimer’s disease patients seems, therefore, to be in an early phase of the disease process. In addition, we may conclude that Alz-50 is not simply a marker for cell death.

In general, the data are consistent with the notion that Alzheimer’s disease can, in many aspects, be considered as an accelerated form of aging, during which activated neurons have a better chance for survival.

It is hoped that these morphometrical studies of the hypothalamic nuclei might provide a basis for more insight into the involvement of the different systems of the human hypothalamus in health and disease.

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