Neuroendocrine Changes in Aging and Alzheimer's Disease

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Here in this well-concealed spot, almost to be covered with a thumbnail lies the very mainspring of primitive existence—vegetative, emotional, reproductive—on which with more or less success, man has come to superimpose a cortex of inhibitions.

— H. Cushing, 1929
(from Plum and Van Uiter, 1978)

Alterations in hypothalamic structures and functions are thought to be causal in diseases such as anorexia nervosa, 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 diseases and possibly in multiple sclerosis. Moreover, this brain region is presumed to be altered in adrenogenital syndrome, by hormones given during development (e.g., diethylstilbestrol (DES)), and in Turner's, Klinefelter's and Kallman's syndromes.

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 chapter, recent data on morphological alterations of several hypothalamic structures in normal aging and Alzheimer's disease are presented. The sexually dimorphic nucleus (SDN), the suprachiasmatic nucleus (SCN), the supraoptic nucleus (SON), the paraventricular nucleus (PVN), and the nucleus tuberalis lateralis (NTL) were selected in order to illustrate the variety in changes occurring in brain-endocrine interactions in the human hypothalamus.

lamus during these conditions. Alzheimer's disease can in many respects be considered as an advanced, accelerated form of aging.

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 rat, 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 (De Jonge et al., 1989; Turkenburg et al., 1988). 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. 1). The SDN is identical to the “intermediate nucleus” described by Braak and Braak (1987). Sexual dimorphism in the human brain is not present at birth (Fig. 1). 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 rapidly in a similar way in both sexes. A sex difference does not occur until about the fourth year postnatally, when cell numbers start to decrease in girls, whereas the cell numbers in the SDN remain stable until approximately 50 years of age in males (Swaab and Hofman, 1988). Cell numbers in the male SDN decrease sharply after this age and in females a second phase of marked cell loss sets in after the age of 80 (Fig. 1; Hofman and Swaab, 1989). The sharp decrease in cell numbers in this nucleus 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 so that this condition does not seem to affect the SDN in any specific way (Swaab and Hofman, 1988).

Nucleus Tuberalis Lateralis

The lateral tuberal nucleus (NTL) is present in man and higher primates. In adulthood it contains some 60000 neurons whereas in Huntington's disease this number may be reduced to about 10000 (Kremer et al., 1990)

Figure 1. 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 SCN is equally small in boys (Δ) and girls ($\circ$) 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 postnatally, 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 ($\square$) 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 (solid line) and females (dashed line), with $F_s[5,49] = 10.05$, $P < 0.001$, and $F_s[5,39] = 7.32$, $P < 0.001$, respectively). From: Swaab and Hofman, 1988 (with permission).

depending on the age at onset of the disease and age at death. Pathological changes in the NTL 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 NTL 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 NTL of Alzheimer's disease patients could even be recognized by the naked eye (Kremer et al., 1991). The NTL 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 are known to be associated with a catabolic state. In Huntington's and in Alzheimer's diseases 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 NTL pathology is accompanied by cachexia also in this condition (H. Braak, personal communication) the NTL is hypothesized to play a role in feeding behavior and metabolism.

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. 2). Subsequently, cell numbers rise to maximum values around 1–2 years postnatally, after which they decrease gradually to some 50% in adulthood (Swaab et al., 1990). Age-related changes in circadian rhythms have been reported in man as well as in nonhuman 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 (Mirmiran et al., 1988; Witting et al., 1990). In Alzheimer's disease the disruptions of the circadian rhythms are often so severe that they are even thought to contribute to the mental decline (Fekete 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.

Figure 2. 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 postnatally 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.

In the SCN of the aged rat, the total cell number remained unaltered, but the number of vasopressin- and vasopressin-intestinal-peptide (VIP)-expressing neurons in the SCN was significantly diminished (Chee et al., 1988; Roozendaal et al., 1987). 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).

Supraoptic and Paraventricular Nucleus

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. These neurons form a population of extremely stable cells. Neither in the course of normal aging nor in Alzheimer's disease patients were any significant loss in neurons or total cell number 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." 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 nucleoli (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., 1988) 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 number is so stable because they are extra-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.

Activation Restores Innervation

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 treated with testosterone for one month, the vasopressin innervation in the rat brain was restored. The vasopressin fiber system responding to the testosterone treatment

(Goudsmit et al., 1988) originates from the bed nucleus of the stria terminales (BST) and medial amygdala, where testosterone seems to stimulate vasopressin synthesis. 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 termination.

Summary and Conclusions

The human hypothalamus contains several nuclei manifesting a wide variety of changes in aging and Alzheimer's disease that might be related to a 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 cell numbers decrease at a similar rate as in normal aging (Swaab and Hofman, 1988).

The NTL 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 NTL of these patients that is based upon a dense network of dystrophic neurites and numerous stained perikarya. The NTL 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.

The SCN coordinates circadian rhythms. Its cell number decreases 50% from 1–2 years postnatally to adulthood and, subsequently, during normal aging. In Alzheimer's disease, the decrease in cell number is even more pronounced. This pathology might be the neural basis for the nightly restlessness observed in Alzheimer's disease, whereas alterations in the visual system (previously discussed) 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.

The cells of the SON and PVN 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 endocrine cells during the aging process, a hypothesis that will be tested in animal experiments. We have already shown that neurons also may be activated in very old rats, if the right stimulus (e.g., testosterone for the BST) is offered.

For several reasons, the hypothalamus offers a unique brain structure for the study of basic questions on the changes in aging and Alzheimer's disease, since (1) its nuclei can be delineated, which enables determination of changes in cell numbers, (2) the various hypothalamic nuclei show a wide range of variations in aging and Alzheimer's disease, and (3) it becomes increasingly possible to relate the cell number and neuropathological changes in the different nuclei to functional changes, either in terms of behavior or in endocrine changes. Such studies might establish the beginning of a neglected topic in neuropathology, namely, the neuropathology of the human hypothalamus.

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