

*Review article***Functional neuroanatomy and neuropathology of the human hypothalamus**

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**Abstract.** The human hypothalamus is involved in a wide range of functions in the developing, adult and aging subject and is responsible for a large number of symptoms of neuroendocrine, neurological and psychiatric diseases. In the present review some prominent hypothalamic nuclei are discussed in relation to normal development, sexual differentiation, aging and a number of neuropathological conditions.

The suprachiasmatic nucleus, the clock of the brain, shows seasonal and circadian variations in its vasopressin neurons. During normal aging, but even more so in Alzheimer's disease, the number of these neurons decreases. In homosexual men this nucleus is larger than in heterosexual men.

The difference between the sexually dimorphic nuclei of men and women arises between the ages of 2–4 to puberty. In adult men this nucleus is twice as large as in adult women. In the process of aging, a sex-dependent decrease in cell number occurs. The vasopressin and oxytocin cells of the supraoptic and paraventricular nucleus are present in adult numbers as early as mid-gestation. Lower oxytocin neuron numbers are found in Prader-Willi syndrome, AIDS and Parkinson's disease. Familial hypothalamic diabetes insipidus is based upon a point mutation in the vasopressin-neurophysin-glycopeptide gene.

Parvicellular corticotropin-releasing hormone-containing neurons in the paraventricular nucleus increase in number and are activated during the course of aging.

In post-menopausal women, the infundibular or arcuate nucleus contains hypertrophic neurons containing oestrogen receptors. These neurons may be involved in the initiation of menopausal flushes.

The nucleus tuberalis lateralis may be involved in feeding behaviour and metabolism. In Huntington's disease the majority of its neurons is lost; in Alzheimer's disease it shows very strong cytoskeletal alterations.

Tuberomammillary nucleus neurons contain, e.g., histamine or galanine, and project to the cortex. Strong cy-

toskeletal changes, as well as plaques and tangles are found in this nucleus in Alzheimer's disease.

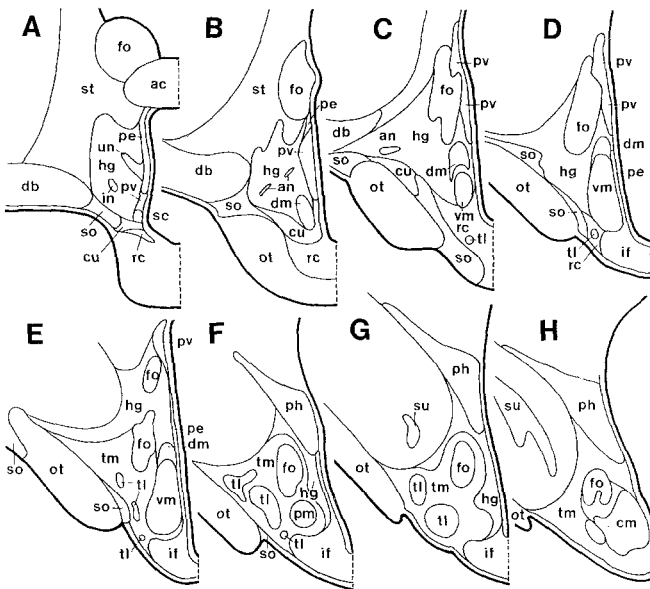
The various hypothalamic nuclei are probably involved in many functions and symptoms of which only a minority has been revealed.

**Key words:** Human hypothalamus – Development – Aging – Alzheimer's disease – Neuropathology

**Introduction**

The first to mention the hypothalamus as a distinct neuroanatomical entity was the Swiss anatomist Wilhelm His in 1893. One hundred years ago he proposed a subdivision of the brain on the basis of embryological development. The point of departure was the five brain-vesicles model described by Von Baer in 1828. Wilhelm His subdivided the second of these vesicles, the diencephalon, into three regions: epithalamus, thalamus and hypothalamus, which were arranged as longitudinal zones in superposition to one another (see Hofman and Swaab 1992a). The borders of the hypothalamus are situated *rostrally* to the lamina terminalis and *caudally* to the plane through the posterior commissure and the posterior edge of the mammillary body. The *dorsal* border is the hypothalamic sulcus, *ventrally* it includes the floor of the third ventricle, except for the infundibulum of the neurohypophysis. The *lateral* boundaries are situated rostrally to the internal capsule and basis pedunculi and more caudodorsally to the subthalamus (Nauta and Haymaker 1969). These borders are, however, equivocal (Braak and Braak 1992).

Most authors distinguish three regions (Fig. 1; Saper 1990), the first two of which we will discuss here: (1) the chiasmatic (preoptic) region (containing the supra-chiasmatic nucleus, the sexually dimorphic nucleus and the supraoptic and paraventricular nucleus); (2) the tuberal region (containing the ventromedial, dorsomedial and infundibular (arcuate) nucleus). Lateral structures



**Fig. 1A–H.** Chiasmatic and tuberal region of the hypothalamus in the human adult. The diagram shows the main landmarks and nuclear groups that are encountered as coronal sections and are traced antero-posteriorly (A–H). Each of the sections is spaced apart by 800  $\mu\text{m}$ ; *ac*, anterior commissure; *an*, accessory neurosecretory nucleus; *cm*, corpus mamillare; *cu*, cuneate nucleus; *db*, nucleus of the diagonal band; *dm*, dorsomedial nucleus; *fm*, fasciculus mamillo-thalamicus; *fo*, fornix; *hg*, hypothalamic gray; *if*, infundibular nucleus; *in*, intermediate nucleus; *oc*, optic chiasm; *ot*, optic tract; *pe*, periventricular nucleus; *ph*, posterior hypothalamic nucleus; *pm*, posteromedial nucleus; *pv*, paraventricular nucleus; *rc*, retrochiasmatic nucleus; *sc*, suprachiasmatic nucleus; *so*, supraoptic nucleus; *st*, nucleus of the stria terminalis; *su*, subthalamic nucleus; *th*, thalamus; *tl*, lateral tuberal nucleus; *tm*, tuberomammillary nucleus; *un*, uncinate nucleus; *vm*, ventromedial nucleus. From Braak and Braak (1992), with permission

are the lateral tuberal nucleus and the tuberomammillary nucleus), and (3) the mammillary complex. The chiasmatic region lies above the optic chiasm as well as anterior to it. It includes the walls of the preoptic recess. Its posterior border is defined by the magnocellular neurosecretory nuclei (Braak and Braak 1987). The cone-shaped tuberal region surrounds the infundibular recess and extends to the neurohypophysis, while the mammillary bodies dominate the mammillary region abutting the midbrain tegmentum (Saper 1990; Braak and Braak 1992).

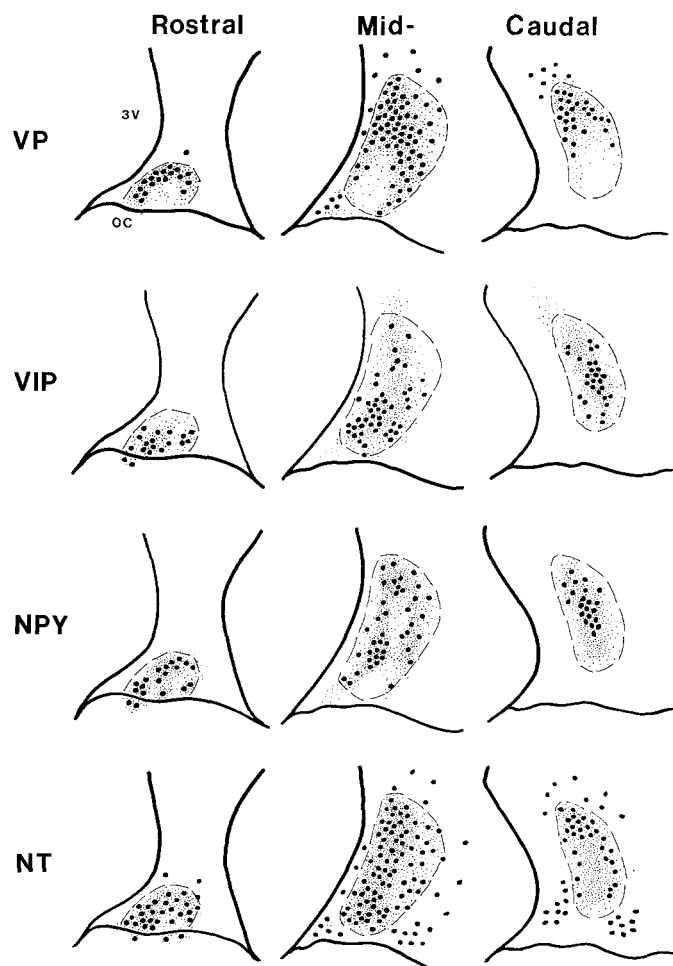
The human hypothalamus is involved in a wide range of functions in the developing, adult and aging subject, as well as in various diseases of different etiologies. Alterations in hypothalamic structures and functions are thought to be operative in diseases such as anorexia nervosa, bulimia, depression, 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. The hypothalamus is affected in neurodegenerative diseases and this might be the reason for particular symptoms, e.g. in Alzheimer's, Parkinson's, and Huntington's disease, and in multiple sclerosis. Moreover, this brain region is presumed to have altered as a result of endo-

crine effects on brain development in the adrenogenital syndrome, by hormones given during development (e.g. diethylstilbestrol (DES)), and in Turner's, Klinefelter's and Kallmann's syndrome (cf. Swaab et al. 1992a).

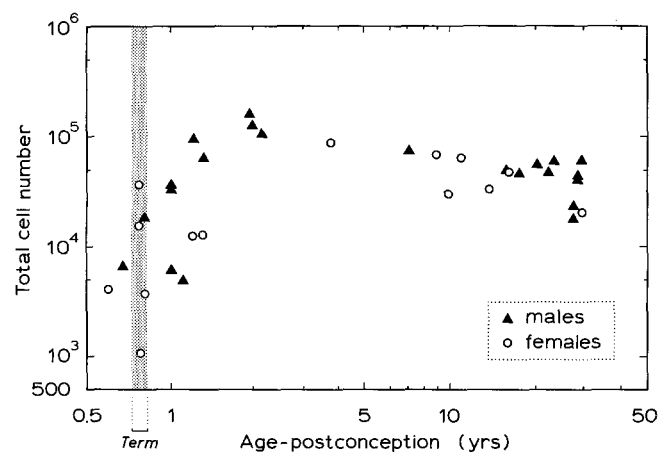
In spite of this impressive list, knowledge of normal development, sexual differentiation and aging of the human hypothalamus is of very recent date, and knowledge of its neuropathology is scanty (cf. Treip 1992). In the present review, recent data on a number of prominent hypothalamic nuclei are discussed in relation to normal development, sexual differentiation, aging and some neuropathological conditions.

### Suprachiasmatic nucleus

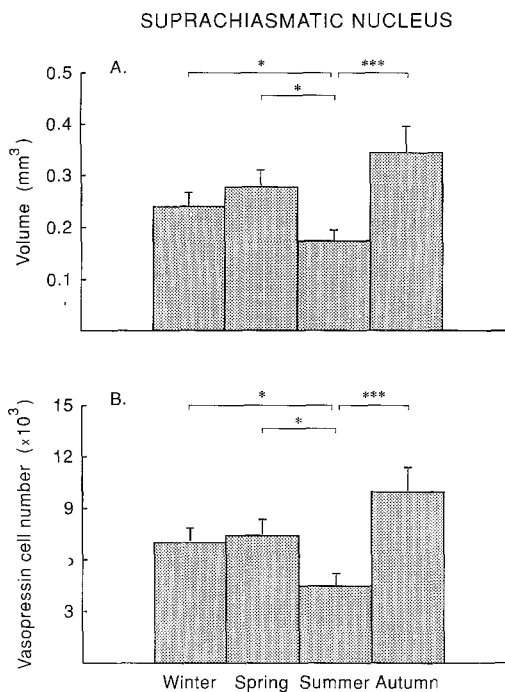
The suprachiasmatic nucleus (SCN) is a small structure (0.25 mm<sup>3</sup>) considered to be the major circadian pacemaker of the mammalian brain. It appears to coordinate hormonal and behavioural circadian rhythms (Rusak and Zucker 1979). In conventionally thionine-stained sections the human SCN cannot be recognized with certainty and therefore immunocytochemical labelling of the nucleus, e.g. with anti-vasopressin, is necessary (Swaab et al. 1990). The shape of the human SCN is sexually dimorphic, i.e. more elongated in women and more spherical in men, but the vasopressin cell number and volume are similar in both sexes (Swaab et al. 1985). Neurons that are immunoreactive for vasopressin, vasoactive intestinal polypeptide (VIP), neuropeptide-Y and neurotensin are present in the SCN in a particular anatomical organization (Fig. 2; Mai et al. 1991; Moore 1992). Typical for the human SCN, as compared to monkeys and other animals, are (1) the very large population of neurotensin cells and (2) the large population of NPY neurons obscuring a geniculohypothalamic tract – if such a tract is present in the human brain at all (Moore 1992). 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 to 2 years postnatally, after which they decrease gradually to some 50% of these numbers in adulthood (Swaab et al. 1990). Recent observations have revealed a marked seasonal variation in the volume and cell number of the human SCN in relation to the variations in photoperiod; values were twice as high in autumn as in summer (Fig. 4; Hofman and Swaab 1992b). Similar circadian fluctuations were observed in the SCN of young adults (Hofman and Swaab, unpublished results). A lesion in the suprachiasmatic region of the anterior hypothalamus, e.g. as the result of a tumour, indeed results in disturbed circadian rhythms in human beings (Schwartz et al. 1986; Cohen and Albers 1991). Totally blind people may show free-running temperature, cortisol and melatonin rhythms. In addition, they may suffer from sleep disturbances (Sack et al. 1992). These observations emphasize the importance of the light-dark cycle for synchronization and of the SCN for circadian rhythms in the human species.



**Fig. 2.** Diagrams showing the organization of the human SCN. The distribution of VP, VIP, NT and NPY neurons and fibres is shown at three levels, from rostral to caudal. From Moore (1992), with permission



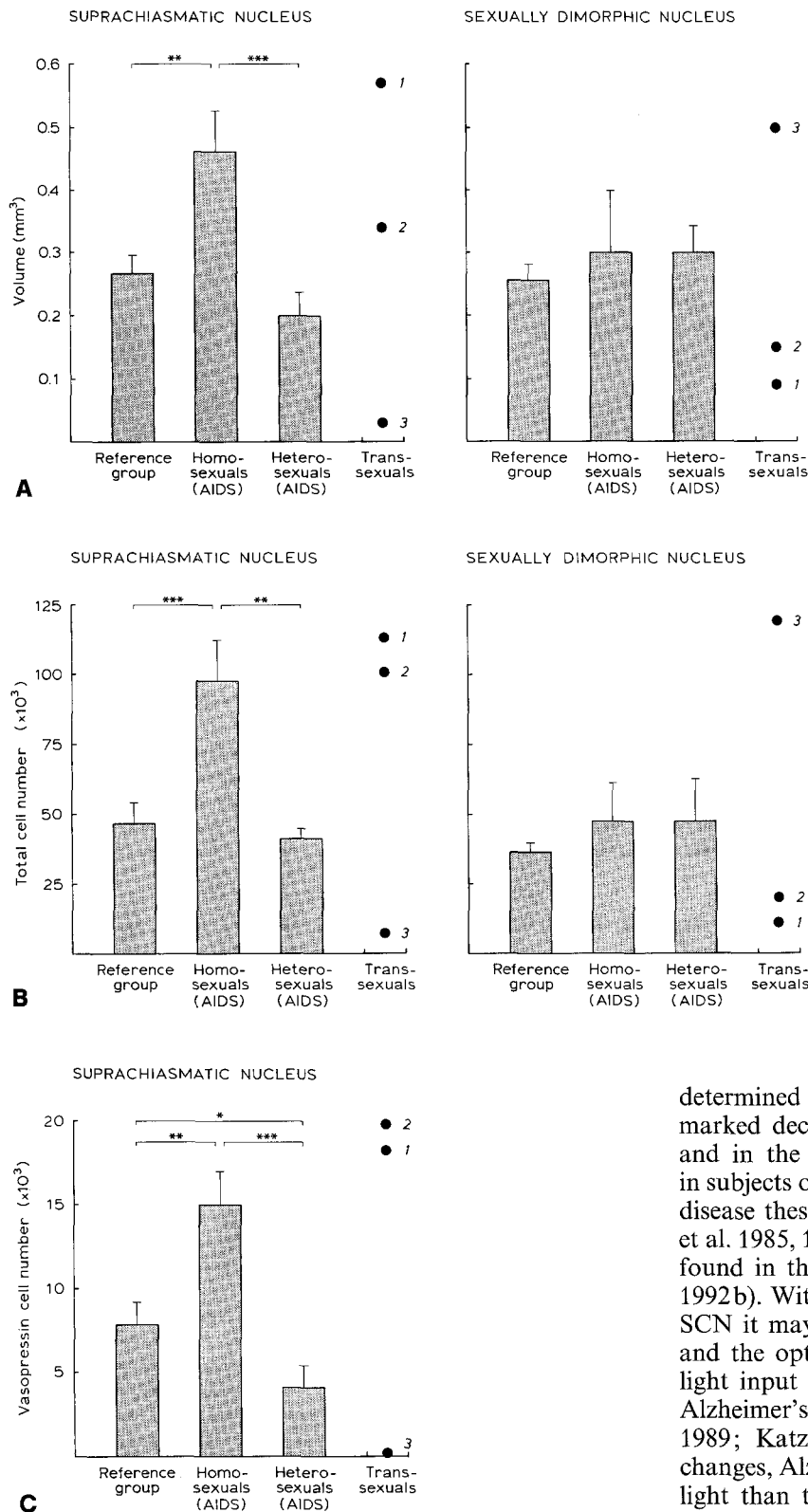
**Fig. 3.** Development of the human suprachiasmatic nucleus (SCN) of the hypothalamus. Log-log scale. The period at term (38–42 weeks of gestation) is indicated by the vertical bar. Note that total cell number is low at the moment of birth (21% of the cell number found in adulthood). There is no difference in the developmental course of the SCN in boys and girls. Cell numbers around 1 to 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



**Fig. 4A, B.** Seasonal variations in the volume (A) and the number of vasopressin immunoreactive neurons (B) of the suprachiasmatic nucleus (SCN). Subjects were grouped into four annual periods of equal length based on the time of death and a photoperiodic division of the year. Data are represented as means  $\pm$  SEM. In general, the SCN shows a striking seasonal variation, with low values in the summer and higher values in other periods of the year. (\*  $P < 0.05$ ; \*\*\*  $P < 0.001$ ; Kruskal-Wallis multiple comparisons test.) From Hofman and Swaab (1992b), with permission

Various circadian rhythms of the fetus disappear immediately after birth, but re-emerge in the neonate and continue to develop over a period of several weeks to months postnatally. Therefore it is generally believed that the fetal rhythms are predominantly driven by the mother (Honnebier et al. 1989). This idea was reinforced by the observation that postnatal development of various overt rhythms is paralleled by a strong increase in the number of vasopressin-expressing neurons in the SCN (Swaab et al. 1990). On the other hand, the fetal SCN itself already shows metabolic circadian changes in the squirrel monkey (Reppert 1992). Moreover, recent observations have shown that temperature rhythms are already present in some 50% of premature babies (Mirmiran and Kok 1991). In addition, melatonin receptors are apparent in the SCN area as early as the 18th week of gestation (Reppert 1992). We must, therefore, conclude that the fetal SCN, though immature, already shows endogenous circadian rhythms, and although most fetal rhythms are driven by the mother, some overt circadian rhythms, for example temperature rhythms, are present as early as the premature period.

Age-related changes in circadian rhythms have been reported in man as well as in other 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 (Prinz et al.



**Fig. 5.** A Volume of the human suprachiasmatic nucleus (SCN) and sexually dimorphic nucleus (SDN) as measured in four groups of adult subjects: (1) a male reference group ( $n=18$ ); (2) male homosexuals who died of AIDS ( $n=10$ ); (3) heterosexuals who died of AIDS ( $n=6$ ; 4 males and 2 females); and (4) three male to female transsexuals. The values indicate medians and the standard deviation of the median. The differences in the volume of the SCN between homosexuals and the subjects from both other groups are statistically significant (Kruskal-Wallis multiple comparison test, \*  $P<0.05$ ; \*\*  $P<0.01$ ; \*\*\*  $P<0.001$ ). Note that none of the parameters measured in the SDN showed significant differences among the three groups ( $P$  always  $>0.4$ ). B Total number of cells in the human SCN and SDN. The SCN in homosexual men contains 2.1 times as many cells as the SCN in the reference group of male subjects, and 2.4 times as many cells as the SCN in heterosexual AIDS patients. C The number of vasopressin neurons in the human SCN (the SDN does not contain vasopressin-producing cells). The SCN in homosexual men contains, on average, 1.9 times as many vasopressin-(VP)producing neurons as the reference group of male subjects and 3.6 times as many VP neurons as the SCN in heterosexual AIDS patients. In the right-hand column of each figure the individual values of three transsexual patients (T1–T3) are given. Note that 1 and 2 have a large SCN and a small SDN and that 3 has a small SCN and a large SDN. From Swaab et al. (1992a), with permission

1982; 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 mental decline (Fekete et al. 1985), as well as often leading to hospitalization of the elderly (Sanford 1975). For this reason the number of cells in the SCN was

determined during aging and in Alzheimer's disease. A marked decrease was found in SCN total cell number and in the number of vasopressin-expressing neurons in subjects of 80 to 100 years of age, while in Alzheimer's disease these changes were even more dramatic (Swaab et al. 1985, 1987). Cytoskeletal alterations have also been found in the SCN of Alzheimer patients (Swaab et al. 1992b). With respect to the degenerative changes of the SCN it may be important to note that both the retina and the optic nerve, which provide direct and indirect light input to the SCN, show degenerative changes in Alzheimer's disease (Hinton et al. 1986; Trick et al. 1989; Katz 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). Apparently 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. Preliminary observations (Okawa et al. 1991) showed that behavioural disorders such as wandering, agitation or delirium almost disappeared, and that sleep-wake rhythm disorders improved in Alz-

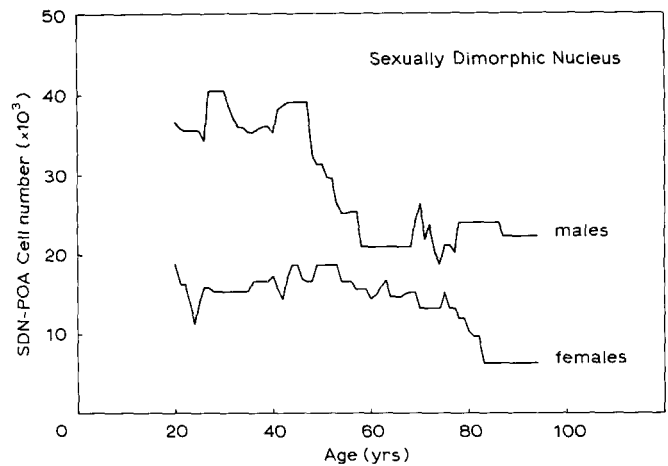
heimer patients following exposure to bright light for 2 h per morning. This indicates that stimulation of the SCN might have important therapeutical consequences.

Recent morphometric analysis of the SCN in 10 homosexual men revealed that the volume of this nucleus was 1.7 times as large as that of a reference group of 18 male subjects, and that it contained 2.1 times as many cells (Fig. 5; Swaab and Hofman 1990). It might be that the programmed postnatal cell death that usually occurs from 13 to 16 months after birth onwards is limited in homosexual men. In three male to female transsexuals some extreme values were observed in the SCN and SDN (Fig. 5). It is not yet clear what the functional implications of this finding might be, although there are various indications that the SCN is involved in aspects of sexual behaviour and reproduction (Swaab et al. 1987).

### Sexually dimorphic nucleus (intermediate nucleus, INAH-1)

The sexually dimorphic nucleus of the preoptic area (SDN) was first described in the rat brain by Gorski et al. (1978). Due to differences in perinatal steroid levels, the SDN in the male rat is three to eight times larger than in the female rat (Jacobson et al. 1980). On the basis of lesion experiments in rats it was found that the SDN seems to be involved in aspects of male sexual behaviour, i.e. mounting, intromission and ejaculation (Turkenburg et al. 1988; De Jonge et al. 1989). However, the effects of lesions on sexual behaviour are only slight, so it might well be that the major functions of the SDN are still unknown at present.

The SDN in the young adult human brain is twice as large in males ( $0.20 \text{ mm}^3$ ) as in females ( $0.10 \text{ mm}^3$ ) and contains twice as many cells (Swaab and Fliers 1985). The SDN is located between the supraoptic and paraventricular nucleus, at the same rostro-caudal level as the suprachiasmatic nucleus. The SDN is identical to the "intermediate nucleus" described by Braak and Braak (1987), and to the INAH-1 of Allen et al. 1989. In the human brain sexual dimorphism is not present at birth. At that moment, cell numbers are similar in boys and girls and the SDN contains no more than some 20% of the cell number found around 2 to 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 postnatally, 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, when they rapidly decrease. In females a second phase of marked cell loss sets in after the age of 70 (Fig. 6; Swaab and Hofman 1988; 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 (Vermeulen 1990). It is not clear whether the hormonal changes are the cause or effect of the observed cell loss in this nucleus. Cell numbers in the SDN of Alzheimer's



**Fig. 6.** Age-related changes in the total cell number of the sexually dimorphic nucleus of the preoptic area (SDN-POA) in the human hypothalamus. The general trend in the data is enhanced by using smoothed growth curves. Note that in males SDN-POA cell number steeply declines between the ages of 50 and 60 years, whereas in females a more gradual cell loss is observed around the age of 80 years. These curves demonstrate that the reduction in cell number in the human SDN-POA in senescence is a non-linear, sex-dependent process. From Hofman and Swaab (1989), with permission

disease patients were found to be within the normal range for age and sex (Swaab and Hofman 1988).

A prominent theory is that sexual orientation 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 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 of homosexual men who died of AIDS differed from that of the male reference groups in the same age range, nor 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 general formulation of Dörner's hypothesis that male homosexuals have "a female hypothalamus".

In Alzheimer's disease – not in controls – SDN neurons and dystrophic neurites are stained with cytoskeletal markers such as Alz-50, anti-tau, anti-paired helical filaments and anti-ubiquitin, in spite of the fact that there is no difference in SDN cell numbers between Alzheimer patients and controls (Swaab et al. 1992b).

### Supraoptic and paraventricular nucleus and accessory nuclei

The large 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. Vasopressin acts as anti-diuretic hormone on the kidney and, in women, oxytocin is involved in

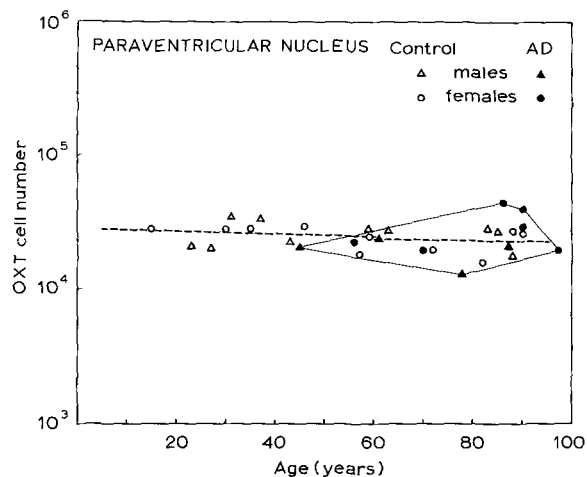


Fig. 7. Linear regression between OXT cell number in the PVN and age. Data of male and female control patients did not differ and were pooled. No statistically significant correlations were observed in either young or old control subjects. Values of male and female AD patients are delineated by a minimum convex polygon and were within the range of the controls. From Wierda et al. (1991), with permission

labour and lactation. Parvocellular vasopressin neurons of the PVN project into the brain and influence central processes (e.g. Fliers et al. 1986). Oxytocin has central effects, on e.g. food intake (see below), affiliation, maternal and reproductive behaviour (Carter 1992; Insel 1992). In males it might be involved in sexual arousal and ejaculation (Murphy et al. 1987). In addition to the neurohypophysial peptides, magnocellular oxytocin and vasopressin-containing cells of the SON and PVN co-express tyrosine hydroxylase, suggesting the possibility of dopamine production (Spencer et al. 1985; Panayotacopoulou and Swaab 1993). Clusters of magnocellular neurosecretory neurons containing oxytocin or vasopressin are also found in the hypothalamic gray in between these nuclei. These ectopic clusters, which tend to be arranged around blood vessels, are referred to as accessory nuclei (Dierickx and Vandesande 1977). The SON is subdivided in three parts. The largest part, the dorsolateral SON, has a volume of  $3 \text{ mm}^3$  (Goudsmit et al. 1990) and contains 53,000 neurons, 90% of which contain vasopressin and 10% oxytocin (Fliers et al. 1985). The dorsomedial and ventromedial SON together contain some 23,000 neurons. The entire SON thus contains 76,000 neurons (Morton 1961). The PVN has a volume of  $6 \text{ mm}^3$  (Goudsmit et al. 1990) and was estimated to consist of about 56,000 neurons (Morton 1961) of which some 25,000 contain oxytocin neurons and 21,000 express vasopressin (Wierda et al. 1991; J.S. Purba et al., submitted for publication; P.F. Van der Woude et al., in preparation). A recent study (A.M. Neijmeijer-Leloux, unpublished results) showed that the vasopressin and oxytocin cell number in the SON and PVN reaches adult level as early as the second half of gestation. The human SON and PVN thus seem to develop much earlier than the SCN and SDN.

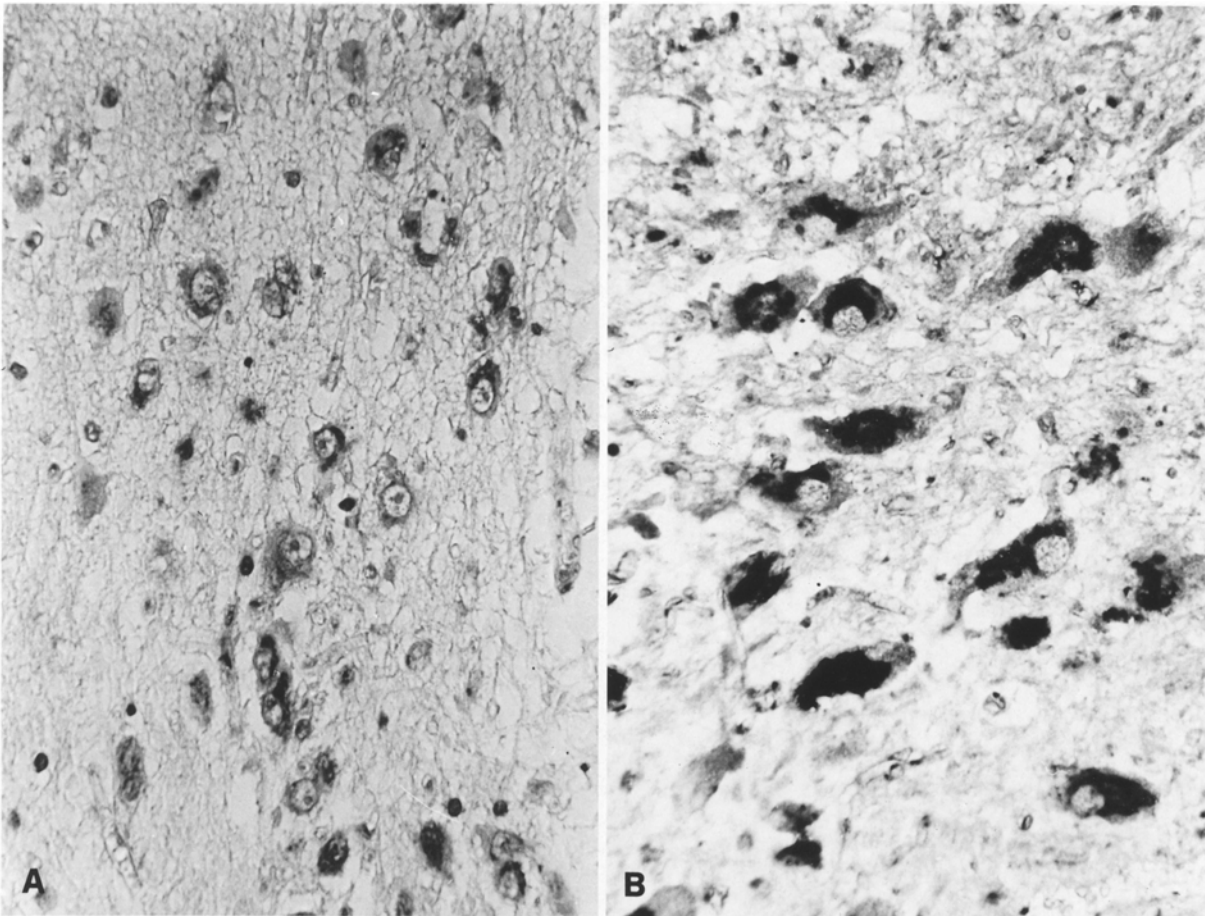
The neurons of the SON and PVN form a population of extremely stable cells in normal aging and in Alz-

heimer's disease; no loss in neurons or total cell number was observed (Fig. 7; Hofman et al. 1990; Goudsmit et al. 1990; Wierda et al. 1991; P.F. Van der Woude et al., in preparation). The observation that no cytoskeletal alterations were found in the SON in Alzheimer patients with several antibodies (Swaab et al. 1992b) is in accordance with this stability. Although in the PVN of Alzheimer patients some neuronal and dystrophic neurite staining can be observed with cytoskeletal antibodies (Swaab et al. 1992b), the cell number in the PVN remains unaltered. Various observations provide evidence for the hypothesis that activation of neurons interferes with the process of aging, and thus prolongs the life span of neurons or restores their function (Goudsmit et al. 1988b). 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 are activated in senescence as well, as can be judged from the increase in the size of the vasopressin-producing perikarya (Fliers et al. 1985), nucleoli (Hoogendijk et al. 1985) and Golgi apparatus (P.J. Lucassen et al., in preparation; Fig. 8), 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. 1988a). As appeared from animal experiments, this might be considered as a compensatory activation due to a loss of vasopressin receptors in the kidney during aging (Ravid et al. 1987).

However, there are also conditions that might lead to changes in the hypothalamo-neurohypophysial system. Recently, we observed a 50% reduction in the number of oxytocin-expressing PVN neurons in Prader-Willi syndrome, and a 40% and 20% reduction of these neurons in AIDS and Parkinson's disease respectively (J.S. Purba et al., submitted for publication). It remains to be determined what the functional implications of these changes are, e.g. in terms of autonomic regulation of eating behaviour and metabolism. It is of interest that so few oxytocin neurons were found in Prader-Willi syndrome (D.F. Swaab et al., unpublished observations), a condition characterized by an extreme obesity, while on the basis of animal experiments centrally projecting oxytocin neurons are thought to inhibit food intake (Olson et al. 1991).

In contrast to the SON, the PVN not only contains magnocellular vasopressin and oxytocin neurons, but also parvocellular ones that project to central brain regions (see above) or to the median eminence. Corticotropin-releasing hormone (CRH) neurons are examples of the latter type. In the human PVN they are not located in a well-defined subnucleus as they are in the rat, but are spread all over the PVN, except for the most rostral part where they are absent. Another property of CRH neurons in the PVN is that they may co-express vasopressin when activated. This occurs for instance in the process of aging (F.C. Raadsheer et al. 1993).

Moreover, the PVN contains a number of other peptide-containing neurons such as somatostatin; cells which are also found in the periventricular nucleus, in a ventral position to the PVN along the third ventricle.



**Fig. 8A, B.** Activation of the Golgi apparatus in SON and PVN neurons of the human hypothalamus as indicated by an increase in size and staining intensity of MG-160, a structural sialoglycoprotein of the medial cisternae. **A** Supraoptic neurons from a 29-year-

old control (#84186) and **B** from a 73-year-old control (#91-118). The antibody directed against MG-160 was kindly donated by Prof. Dr. N.K. Gonatas, School of Medicine, University of Pennsylvania, Philadelphia, USA

An interesting recent observation is that the density of LHRH-containing fibres in the PVN and periventricular nucleus dramatically decreased in cases of sudden infant death syndrome (Kopp et al. 1992).

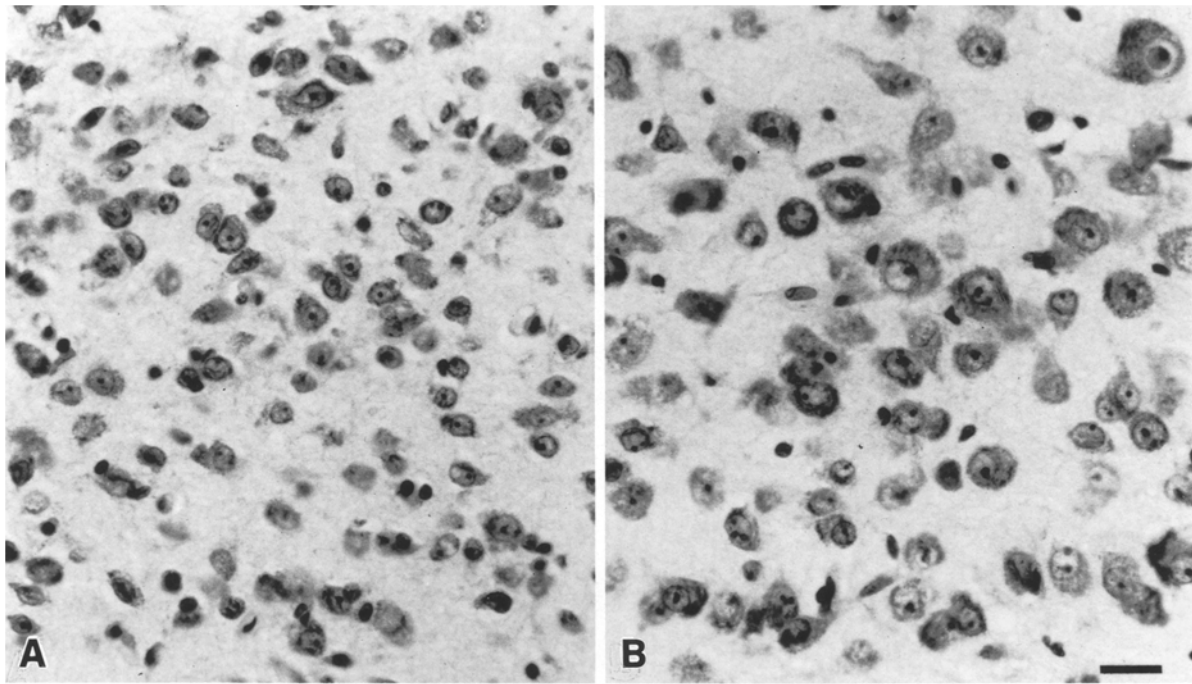
Familial hypothalamic diabetes insipidus is transmitted as an autosomal dominant gene. Affected individuals have low or undetectable levels of circulating vasopressin and suffer from polydipsia and polyuria, but they respond to substitution therapy with exogenous AVP or analogues. Urine production may amount to some 20 litres per day. Members of a Dutch family suffering from this disease appeared to have a point mutation in one allele of the affected family members, based upon a G to T transversion within the neurophysin encoding exon B (Bahnsen et al. 1992). In a Japanese diabetes insipidus family a G to A transition has been described in the same exon (Ito et al. 1991). Some of the few postmortem histological observations in other families with hereditary hypothalamic diabetes insipidus point to severe neuronal death in the SON and PVN in the case of familial hypothalamic diabetes insipidus (Braverman et al. 1965; Nagai et al. 1984; Bergeron et al. 1991) suggesting that

the mutated product might be toxic to the neurosecretory cell.

### The ventromedial and dorsomedial nucleus

The ventromedial nucleus (VMN) is supposed to play a role in various sexually dimorphic functions, i.e. feeding, aggression, sexual behaviour and gonadotropin secretion (Matsumoto and Arai 1983). In rats, the size of the VMN is sexually dimorphic. The nucleus is larger in males than in females, a difference determined in early neonatal development by sex hormones (Matsumoto and Arai 1983). There have as yet been no similar observations of the human VMN.

The pear-shaped VMN is a conspicuous structure of the tuberal region. The cell density is higher in the peripheral portions than in the centre of the nucleus. A narrow, cell-sparse zone surrounds the nucleus and facilitates its delineation from adjoining nuclear grays (Braak and Braak 1992). Study of the VMN shows that we should take the possibility of laterality into consideration when investigating the human hypothalamus. Both



**Fig. 9A, B.** Representative photomicrographs of cresyl violet-stained sections of the infundibular nucleus of pre-menopausal (A) and post-menopausal (B) women. The hypertrophied neurons are

distinguished not only by increased soma size, but also by larger nuclei, nucleoli and increased Nissl substance. Bar 20 µm for both photomicrographs. From Rance (1992), with permission

the VMN and the PVN contain a higher concentration of TRH, but not of LHRH, on the left-hand side (Borson-Chazot et al. 1986).

The ventromedial nucleus is interconnected with many neighbouring areas but also generates major projections to the magnocellular nuclei of the basal forebrain (Jones et al. 1976). These nuclei in turn send axons to virtually all parts of the cerebral cortex. It can be assumed, therefore, that the ventromedial nucleus influences higher cortical functions and behaviour via these pathways (Braak and Braak 1992). In this respect it is also interesting that the density of VMN neurons was clearly diminished in Down's syndrome subjects (Wisniewski and Bobinski 1991).

The dorsomedial nucleus (DMN) is poorly differentiated in the human brain and covers the anterior and superior poles of the ventromedial nucleus. Large numbers of cells which, according to their cytological features, belong to the hypothalamic gray, invade peripheral portions of the nucleus. The medium-sized nerve cells of the dorsomedial nucleus are markedly richer in lipofuscin deposits than those of the ventromedial nucleus (Braak and Braak 1992).

#### **Infundibular nucleus (arcuate nucleus)**

The horseshoe-shaped infundibular (or arcuate) nucleus surrounds the lateral and posterior entrance of the infundibulum. It contains, for instance, catecholamine-containing neurons (Spencer et al. 1985), somatostatin, neuropeptide Y and neurotensin (Saper 1990). In 1966 Sheehan and Kovacs described neuronal hypertrophy in a

subdivision of this nucleus in post-menopausal women and women suffering from postpartum hypopituitarism. Nucleolar size increase and multiplication confirm the activation of neurons in this area (Fig. 9; Ule et al. 1983; Rance 1992). This subdivision was named the *subventricular nucleus*, referring to its location; it is situated below and lateral to the third ventricle, and caudal to the tubero infundibular sulcus. Infundibular neuronal hypertrophy has also been described in chronically ill, hypogonadal men and in patients suffering from starvation and gonadal atrophy (Ule and Walter 1983; for review see Rance 1992). The hypertrophied neurons contained increased amounts of neurokinin B (NKB), substance P and oestrogen receptor transcripts. LHRH neurons are also found in this nucleus, but the hypertrophied neurons themselves do not contain this peptide. The NKB-containing neurons probably participate in the hypothalamic circuitry, which regulates oestrogen negative feedback on gonadotropin release in the human system by acting as an interneuron on the LHRH-containing cells. In addition, the NKB neurons may be involved in the initiation of menopausal flushes (Rance 1992). The LHRH-containing neurons that are normally present in the infundibular nucleus (Barry 1977) are absent in Kallman syndrome due to their failure to migrate from the olfactory placode to the brain (Schwanzel-Fukuda et al. 1989). In Down's syndrome a strong decrease in neuronal density and gliosis was observed in the arcuate nucleus (Wisniewski and Bobinski 1991). The authors consider that both this reduction in cell number and that in the VMH are related to the decreased growth hormone levels in this syndrome.

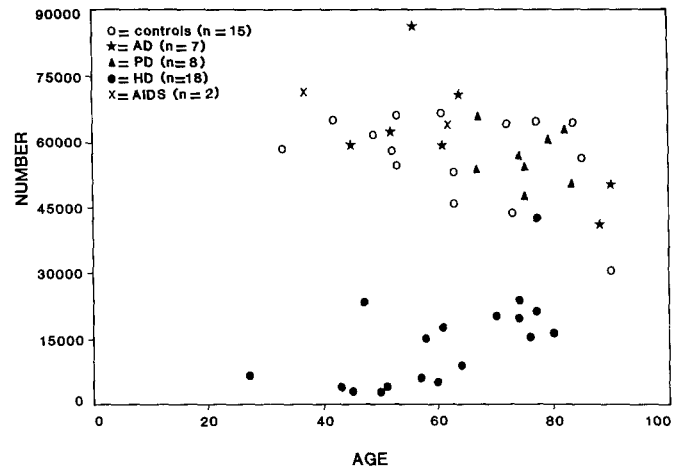




**Fig. 10.** Ventral aspect of the hypothalamus in an adult human brain showing the well-marked tubercles (indicated by arrows) produced by the nucleus tuberalis lateralis. From LeGros Clark (1938)

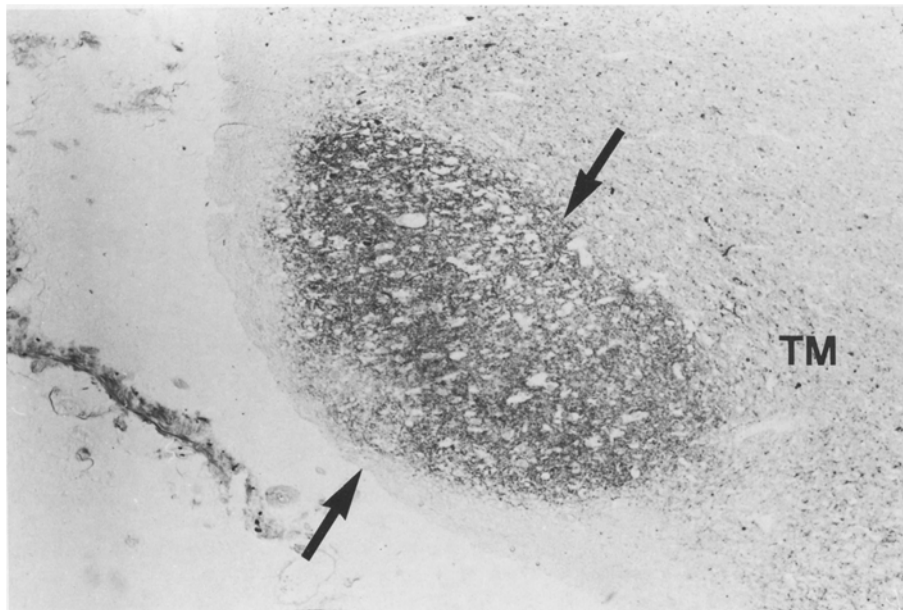
### Lateral tuberal nucleus

The lateral tuberal nucleus (nucleus tuberalis lateralis, NTL) can only be recognized in man and higher primates. Macroscopically, the presence of the NTL is revealed by the “lateral eminence on the ventral surface of the tuber cinerium” (Fig. 10; LeGros Clark 1938). The connections with other parts of the brain are as yet unknown, but receptors for corticotropin-releasing factor, somatostatin, muscarinic cholinergic receptors, benzodiazepin receptors and N-methyl-D-aspartate (NMDA) receptors have been localized in the NTL (Kremer 1992). In adulthood the NTL contains some 60,000 neurons, whereas in Huntington’s disease this number may be reduced to less than 10,000 (Fig. 11), and gliosis is found depending on the age at onset of the disease as well as the age at death (Kremer et al. 1990). Neuronal loss in the NTL may be a good estimator of severity of the disease and the NTL may be one of the brain structures that is primarily affected by the Huntington’s disease gene (Kremer 1992). It is presumed that this NTL vulnerability is related to the high density of NMDA receptors in this nucleus. 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 that in controls. The number of plaques in this nucleus was low, and they were exclusively of the amorphous type. Neurofibrillary tangles were rarely seen after conventional silver staining. Yet immunocytochem-



**Fig. 11.** Neuron number counts of the NTL in normal controls and neurological diseases. *AD*, Alzheimer’s disease; *PD*, Parkinson’s disease; *HD*, Huntington’s disease; *AIDS*, acquired immunodeficiency syndrome. Linear regression analysis of neuronal numbers vs age: for controls only ( $n=15$ ): neuron number =  $71,955 - (\text{age} \cdot 237.92)$ ,  $r = -0.38$ ,  $P = 0.15$ ; for the total group of controls, *AD*, *PD* and *AIDS* ( $n=32$ ): neuron number =  $79,126 - (\text{age} \cdot 315.19)$ ,  $r = -0.48$ ,  $P = 0.0053$ . From Kremer (1992), with permission

ical staining, using the monoclonal antibody Alz-50, showed such an abundant reactivity of both perikarya and dystrophic neurites that the NTL of Alzheimer’s disease patients could even be recognized by the naked eye (Kremer et al. 1991). Staining of Alzheimer hypothalami with tau-1, anti-paired helical filaments and anti-ubiquitin showed about the same density of NTL neurons but far less neuritic staining (Swaab et al. 1992b). The Alzheimer pattern of Alz-50 staining was also encountered in patients with Down’s syndrome (Kremer 1992). 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. Changes in Parkinson’s disease are less obvious: Lewy bodies appear in small quantities, the majority of them apparently lying outside a neuronal perikaryon. No neuronal loss is found (Kremer 1992). Lesions in the lateral hypothalamus of animals are known to be associated with weight loss. In Huntington’s and in Alzheimer’s disease, dementia goes together with severe weightloss in combination with normal or even increased food intake, as is the case in the condition described by Braak and Braak (1989) and H. Braak (personal communication). Because NTL pathology is, in different conditions, accompanied by cachexia, the NTL is thought to play a role in feeding behaviour and metabolism. Animal experiments that are necessary to reveal such a role can only be performed when we can establish the homology between the human NTL and a similar system, such as that of the rat. The observation (J.A.P. Van de Nes, unpublished results, Fig. 12) that prosomatostatin is a good marker of the NTL might be extremely helpful in this respect.



**Fig. 12.** Somatostatin staining of the NTL in the human hypothalamus. The subject was a 72-year-old female (#4725) who died of endocarditis lenta. The lateral tuberal nucleus can easily be recognized and delineated from the tubero-mamillary nucleus (TM) by means of the prosomatostatin antiserum S309. For information on the antiserum used, see Morrison et al. (1983). S309 was generously supplied by Dr. R. Benoit, Montreal, Canada. The bar represents 100  $\mu\text{m}$  (unpublished data of J.A.P. Van de Nes)

### Tuberomamillary nucleus

The tuberomamillary nucleus (TM) is formed by large, irregularly bordered, darkly staining neurons that surround the NTL, the fornix in its final descending course, and the mamillary body (Diepen 1962). Many of its neurons project extensively to the cortex (Saper 1985). For example, the major, if not the sole, histaminergic cortical innervation (Steinbusch and Mulder 1984; Watanabe et al. 1984; Panula et al. 1990; Airaksinen et al. 1991) originates from this group. For a long time now the TM has been known to be affected by Alzheimer's disease: the occurrence of tangles and deposition of plaques can be found in this nucleus (Ishii 1966; Ulfing and Braak 1984; Saper and German 1987; Simpson et al. 1988). We found numerous Alz-50 staining neurites in the TM of Alzheimer patients. Neuritic staining with other cytoskeletal antibodies had a markedly less distinct result than in NTL. In contrast to the NTL, the TM did show neurofibrillary tangles in Palmgren's silver impregnation (Swaab et al. 1992b). In the TM of Parkinson's disease patients, too, Lewy body formation has been observed (Sandyk et al. 1987). Morphometrics have only been applied to a few subjects and concern Galanin neurons. Their number did not change in Alzheimer's or Parkinson's disease (Chan-Palay and Jentsch 1992). No clear qualitative changes in the number of histamine neurons were observed between Alzheimer patients and controls (Chan-Palay and Jentsch 1992). Although the NTL is seriously affected in Huntington's disease (see above) the surrounding neurons of the TM are not affected in this condition. Interestingly, contrary to the NTL, the TM does not contain NMDA receptors.

### Summary and conclusions

Most authors distinguish three regions in the hypothalamus: (1) the chiasmatic (preoptic) region, (2) the tuberal

region and (3) the mamillary complex. The hypothalamus is involved in a wide range of functions in the developing, adult and aging subject, and alterations in various nuclei are observed in a great number of diseases and may be related to particular symptomatology. In the *chiasmatic region* the following nuclei have been discussed.

The SCN coordinates circadian and circannual rhythms. The human SCN can only be recognized reliably by means of immunocytochemistry, e.g. for vasopressin. The shape of this nucleus is sexually dimorphic. From 1 to 2 years postnatally until adulthood its vasopressin cell number decreases by 50%. A marked seasonal and circadian variation in the volume and vasopressin cell number of the SCN was observed in relation to the variation in photoperiod. During normal aging, the number of vasopressin neurons decreases. In Alzheimer's disease, the decrease in cell number is even more pronounced and cytoskeletal alterations are observed. This pathology might be the neural basis for the nightly restlessness observed in patients suffering from Alzheimer's disease, whereas degeneration of the visual system input to the SCN might contribute to these functional disturbances. It is exciting, therefore, to see that stimulation of the visual pathways by light therapy seems to improve the disturbances in behaviour in Alzheimer patients.

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 SDN (intermediate nucleus or INAH-1) is localized between the supraoptic and paraventricular nucleus. In adult men the SDN is twice as large as in adult women. In girls, the SDN shows a decreasing cell number during prepubertal development, leading to sexual dimorphism. During aging a decrease in cell number is found in both sexes. The latter change may be related

to a decrease in sexual activity and to changes in hormone levels. In Alzheimer's disease cytoskeletal changes are found in the SDN, but SDN cell numbers decrease at a rate similar to that in normal aging. Since the SDN in homo- and heterosexual men is similar in size and cell number, the hypothesis that homosexual men have a female hypothalamus is not supported.

The cells of the SON and PVN develop early in fetal life. Adult cell numbers are already present in mid-gestation. These cells produce vasopressin or oxytocin and co-express tyrosine hydroxylase. These nuclei are examples of neuron populations that seem to stay perfectly intact in aging and Alzheimer's disease. The cells do not show cytoskeletal changes in Alzheimer's disease. We suggest that this might be due to the activation of these neuroendocrine cells during the aging process. On the other hand, in other conditions the PVN may be affected, since the oxytocin neuron number is 50% lower in Prader-Willi syndrome, 40% lower in AIDS and 20% lower in Parkinson's disease.

Familial hypothalamic diabetes insipidus is an autosomal dominant disease based upon a point mutation in the vasopressin-neurophysin-glycopeptide gene. Neuronal death has been described in the SON and PVN in a few subjects with this condition. Parvicellular corticotropin-releasing hormone (CRH)-containing neurons are found throughout the PVN. CRH neurons are activated in the course of aging as shown by the increasing proportion of neurons that also contain vasopressin. LHRH innervation of the PVN is decreased in sudden infant death syndrome.

The *tuberal region* contains the ventromedial, dorso-medial and infundibular (or arcuate) nucleus. Part of the latter nucleus, the subventricular nucleus, contains hypertrophic neurons in postmenopausal women, in hypogonadal men, and in conditions such as starvation and postpartum hypopituitarism. The hypertrophied neurons contain neurokinin-B (NKB), substance-P and oestrogen receptors, and probably act on LHRH neurons as interneurons. The NKB neurons may also be involved in the initiation of menopausal flushes.

The NTL and TM are lateral structures of the tuberal region. The NTL might be involved in feeding behaviour and metabolism. In Huntington's disease most of the NTL neurons are lost. Although it does not show any decrease in neuronal numbers in Alzheimer's disease, a very strong Alz-50 staining is present in the NTL of Alzheimer patients. This is due to a dense network of dystrophic neurites and numerous staining 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 impending cell death. In Parkinson's disease only a few Lewy bodies are found, and no cell loss is observed in the NTL.

Tuberomammillary nucleus (TM) neurons project to the cortex and may contain histamine or galanin. Their number does not seem to diminish in Alzheimer's disease, although TM neurons show cytoskeletal alterations, plaques and tangles. In addition, Lewy bodies have been observed in the TM of Parkinson patients.

It can be concluded that the various hypothalamic nuclei are involved in a great number of functions and show clear and differential changes in development with respect to sex, menopause, aging and a number of neurological diseases. We suspect that only a small proportion of such changes has, at present, been revealed.

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