MOLECULAR BASIS
of
AGING

Edited by
Alvaro Macieira-Coelho, M.D., D.Sc., D.h.c.
Research Director
INSERM
Versailles, France
Chapter 18

AGE-RELATED CHANGES IN NEUROPEPTIDERIC NEURONS IN THE HUMAN HYPOTHALAMUS

Jiang-Ning Zhou and Dick F. Swaab

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I. INTRODUCTION

Since 72-year-old Brown-Séquard, more than one century ago, injected himself with testicular extracts and claimed remarkable physical and mental signs of rejuvenation, a close relationship between endocrine changes and aging has been supposed. Because of its central role in endocrine regulation, the hypothalamus has received the constant attention of gerontologists. Over the past decades there has been remarkable progress in the knowledge of hypothalamic neuropeptidergic systems in relation to aging, to which several technical developments have contributed. In the first place, the isolation and characterization of hypothalamic peptides have made subsequent immunocytochemical localization of neuropeptides possible in the human hypothalamus. It is now generally accepted that neuropeptides may either be released into the circulation as hormones, or act as neurotransmitters or neuromodulators when released from synapses, and may then influence central processes. In addition, many, if not all, hypothalamic peptides are colocalized with classical transmitters, e.g., acetylcholine, gamma-aminobutyric acid (GABA), or amines such as dopamine. Since the classical neurotransmitters show clear changes with aging, changes in the colocalizing neuropeptides may also be expected. Another reason to stress the importance of the hypothalamus for the aging process is that some hypothalamic systems themselves have been causally implicated in aging of the brain and in the life span. The present chapter tries to relate functional changes in aging with alterations in neuropeptidergic neurons of the human hypothalamus.

The hypothalamus is a complex, heterogeneous structure containing a number of nuclei which are often characterized by specific neuropeptides. Basically, there are two types of hypothalamic peptidergic neurons. The first one is the neuroendocrine type, which releases its peptide as a hormone into the general circulation in the neurohypophysis, e.g., vasopressin (AVP) and oxytocin (OXT), or into the portal circulation of the pituitary, e.g., AVP, luteinizing hormone-releasing hormone (LHRH), thyrotropin-releasing hormone (TRH), and corticotropin-releasing hormone (CRH). The second type of hypothalamic peptidergic neuron is the one that sends its axon into the brain where it terminates synaptically on
other neurons, acting as a neurotransmitter or neuromodulator. The same peptide may be present in both types of neurons, e.g., AVP is present in the hypothalamo-neurohypophysial-system (HNS) as a neurohormone and also in the suprachiasmatic nucleus as a neurotransmitter or neuromodulator.

II. SUPRACHIASMATIC NUCLEUS

The suprachiasmatic nucleus (SCN) is the major circadian pacemaker of the mammalian brain and coordinates hormonal and behavioral circadian rhythms. A relatively large number of neuropeptides have been identified in the human SCN. Neurons that are immunoreactive for vasopressin (AVP), vasoactive intestinal polypeptide (VIP), neuropeptide-Y (NPY), neurotensin (NT), and somatostatin (SOM) are present in the SCN in a characteristic anatomical orientation (Figure 1). Typical for the human SCN, as compared to monkeys and other animals, are the very large populations of NT and NPY neurons. Colocalization of different neuropeptides in the SCN has been found mainly in rat but also in human. For example, VIP-producing neurons in the SCN were shown to colocalize galanin, AVP, gastrin releasing peptide (GRP), or GABA.

Recent observations have revealed marked changes in the volume of AVP subpopulation and AVP cell number of the human SCN in relation to the season. In addition, a day-night fluctuation in the number of AVP expressing neurons in the SCN was found to be present, but only in young subjects, which suggests a diminution of circadian fluctuations of the SCN in human aging. Age-related changes in circadian rhythms have indeed been reported in man as well as in other species. Furthermore, a decrease in the number of AVP cells and total cell number was found in subjects aged 80 to 100, while these changes were even more pronounced in Alzheimer's disease patients than in controls (Figure 2).

A different pattern from that of the AVP neurons was found recently in the number of VIP expressing neurons of the human SCN during aging (Figure 3). The VIP cell number in the female SCN remained very stable during the life span. In males, however, the number of VIP neurons in the SCN reached its peak value in young males (10 to 40 years of age). Subsequently, a dramatic decrease in the number of VIP neurons in SCN was found in the middle-aged subjects (41 to 65 years of age). A significant reduction in the number of VIP expressing neurons was found in the old-age group (65 to 92 years of age). An age-dependent sex difference was observed in the SCN: males of 10 to 40 years of age had twice as many VIP neurons in the SCN as females. Due to the age-related fluctuations in VIP cell number in males, this sex difference was reversed in the middle-aged
group, the females having twice as many VIP neurons in the SCN. After 65 years, sex differences were no longer found (Figure 3).\textsuperscript{34,35} Since the SCN is the clock of the brain, the morphological sex differences may be related to sex differences that have been found in circadian control mechanisms of hamsters\textsuperscript{36} and humans.\textsuperscript{37} In addition, it has been found in rat that VIP expressing neurons from the SCN directly innervate LHRH neurons that are involved in reproductive functions.\textsuperscript{38} Although such a connection

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**Figure 1**

Diagram showing the organization of the human suprachiasmatic nucleus (SCN). The distribution of vasopressin (VP), vasoactive intestinal polypeptide (VIP), neurotensin (NT), and neuropeptide-Y (NPY) neurons and fibers is shown at three levels, from rostral to caudal. (From Moore, R. Y., Progress in Brain Research, Swaab, D. F., Hofman, M. A., Mirmiran, M., Ravid, R., and Van Leeuwen, F. W., Eds., Elsevier, Amsterdam, 1992. With permission.)
Figure 2
The number of vasopressin (AVP) immunoreactive neurons in the human SCN. The number of AVP neurons in the 81- to 100-year-old group decreased as compared to the 61- to 80-year-old subjects (p < 0.02). Data are represented as mean ± SEM. (From Swaab, P. F., Roozendaal, B., Ravid, R., Velis, D. N., Gooren, L., and Williams, R. S., Progress in Brain Research, Vol. 72, De Kloet, R. et al., Eds., Elsevier, Amsterdam, 1987. With permission.)

should be confirmed in the human hypothalamus, the sex difference in the number of VIP neurons in the SCN and the difference in the AVP subnucleus of the SCN according to sexual orientation also suggests a possible role of the biological clock in reproduction or sexual behavior.³⁹,⁴⁰ Females showed a very stable number of VIP neurons in the SCN with aging, whereas a decrease in the number of VIP neurons in the SCN was found in middle-aged males (Figure 3).³⁵ It is tempting to relate the changes in the peptidergic neurons of the SCN to functional changes, e.g., in circadian rhythmicity.

Although the number of AVP neurons in the SCN in 60- to 80-year-old subjects did not differ from the number found in young subjects,⁴¹ the circadian fluctuation in the number of AVP neurons in the human SCN diminished in subjects older than 50 years.³⁰ The number of AVP neurons
Figure 3
Lifespan changes in the number of vasoactive intestinal polypeptide (VIP) immunoreactive neurons in the human SCN. The blank bar indicates the males, the hatched bar indicates the females. The SCN of young males (10 to 40 years) contains twice as many neurons as that of young females ($p < 0.02$). This sex difference reverses in middle-aged subjects ($p < 0.02$). Since the number of VIP neurons decreased after 40 years, the cell number is significantly lower in elderly males than in young males ($p < 0.05$). (From Zhou, J. N., Hofman, M. A., and Swaab, D. F., *Neurobiol. Aging*, in press. With permission.)

did not decrease until after 80 years of age, suggesting that the circadian fluctuations in AVP neurons disappear earlier in the process of aging than the number of neurons expressing AVP.

The relation between VIP and changed circadian fluctuations is less clear. Circadian changes were found in plasma VIP levels in elderly males (74 to 85 years) and in subjects that were 10 years younger (65 to 75 years). However, these blood levels of VIP probably do not come from SCN neurons. The stability of VIP neurons, especially in the female SCN, might be related to some stable rhythms in normal human aging, such as the rhythmicity of temperature, prolactin, or cortisol. On the other hand, it has been proposed that the decreased AVP cell number might be the basis for circadian disturbances in aging and Alzheimer’s disease. Some observations suggest that a certain degree of plasticity remains present in the SCN neurons in aging. SCN neurons in old rats seem to continue to respond to increased input, since increased amounts of light improved and restored circadian rhythms in these animals. Such a nonpharmacological treatment of disturbances of the sleep-wake pattern may be of clinical importance, not only in aging but also in Alzheimer’s disease, where it may reduce nightly restlessness.
Other changes in peptidergic SCN neurons may also be present in aging. A dense plexus of substance P (SP) immunoreactive axons that overlaps the distribution of VIP expressing perikarya has recently been reported in the human SCN (Moore et al., personal communication, 1994). Interestingly, the number of SP neurons in the SCN of aged hamsters was increased three to four times compared with adult animals, day and night. However, observations on this peptidergic neuron population during the process of aging have not yet been performed in humans.

III. SEXUALLY DIMORPHIC NUCLEUS (INTERMEDIATE NUCLEUS, INAH-1)

The sexually dimorphic nucleus of the preoptic area (SDN) is identical to the intermediate nucleus as mentioned by Braak and Braak, and to the INAH-1 described by Allen et al. In girls, the SDN shows a decreasing cell number during prepubertal development, leading to sexual dimorphism. The SDN in the young adult human brain is twice as large in males as in females and contains twice as many cells. During aging, a decrease in cell number is found in both sexes. In males the cell number decreases strongly after 50 years of age, in females a second phase of cell loss appears after the age of 70 (Figure 4). The sharp decline in cell numbers in the SDN later in life might be related to the hormonal changes which accompany both male and female senescence and to the decrease in male sexual activity, although the causality of such a relationship has not yet been established. A good marker for the neuronal content of the majority of SDN neurons is not available at present. Only a few TRH neurons have so far been identified in this nucleus. Such TRH-positive neurons have also been identified in the rat.

IV. PARAVENTRICULAR AND SUPRAOPTIC NUCLEUS

The paraventricular (PVN) and supraoptic (SON) nucleus and their axons form the hypothalamo-neurohypophyseal-system (HNS). Immuno-cytological studies have established that in addition to oxytocin (OXT) and vasopressin (AVP), a large number of other neuropeptides are synthesized by neurons of the PVN and SON.

A. Vasopressin and Oxytocin

AVP and OXT are produced by the magnocellular neurosecretory system of the hypothalamic SON and PVN projecting to the neurohypo-
physiologic changes in the total number of the sexually dimorphic nucleus of the human hypothalamus. The general trend in the data is enhanced by using smoothed growth curves. Note that in males the SDN 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 in senescence is a nonlinear, sex-dependent process. (From Hofman, M. A. and Swaab, D. F., J. Anat., 164, 55, 1989. With permission.)

Figure 4

Age-related changes in the total cell number of the sexually dimorphic nucleus of the human hypothalamus. The general trend in the data is enhanced by using smoothed growth curves. Note that in males the SDN 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 in senescence is a nonlinear, sex-dependent process. (From Hofman, M. A. and Swaab, D. F., J. Anat., 164, 55, 1989. With permission.)

AVP acts as an antidiuretic hormone on the kidney and as a vasopressor on the blood vessels. OXT is involved in labor and lactation and in other reproductive processes. In addition to these functions, magnocellular OXT- and AVP-containing cells in the SON and PVN coexpress tyrosine hydroxylase, suggesting the possibility of dopamine production. AVP neurons of the PVN project into the brain, and animal experiments suggest that they may influence central processes such as certain aspects of memory. Peptides have been given as substitution therapy in disorders where a deficiency in these systems was presumed. However, clinical trials in which AVP or its analogs were administered to patients with Alzheimer's disease (AD) yielded inconsistent results. OXT also has central effects, e.g., on the inhibition of food intake and on maternal and reproductive behavior. In males, OXT might be involved in sexual arousal and ejaculation. In rodents, depending on the strain, either activation or deterioration of the HNS during aging has been reported. In contrast to the rodent data, nearly all human data point to an activation of the HNS with aging, especially of the vasopressinergic neurons. The mean profile area of AVP cells increased after the age of 80 years, suggesting an increased
peptide production from this age onwards.\textsuperscript{70} The OXT cells in these nuclei showed no such change.\textsuperscript{70} Neuronal hypertrophy has also been described in unidentified human SON and PVN neurons in aging.\textsuperscript{71} Although the correlation between cell size and peptide production is well established in adulthood, one might wonder whether this relationship would also persist in senescence. Since, for example, lipofuscin is known to accumulate in many types of aging nerve cells, this may theoretically cause an enlargement of cytoplasmic volume. Therefore, nucleolar size, which is a reliable parameter for neurosecretory activity, was also determined in the AVP and OXT cells in the same human material. A significantly increased nucleolar diameter was again found in AVP neurons of the SON and PVN in senescent subjects and not in the OXT cells.\textsuperscript{72}

These findings confirmed the idea that the previously observed increase in cell size was indeed due to enhanced neurosecretory activity. However, it could not be excluded from those data that the observed activation of neurosecretory AVP cells was a compensation for cell loss from the PVN or SON. Total cell number, and OXT and AVP cell numbers, have therefore also been determined in the PVN and SON. The results revealed that no significant differences in volume or total cell number were present in either the PVN or SON between young and old control subjects.\textsuperscript{73-75} Furthermore, a gradual increase in the number of AVP expressing neurons was even observed in the human PVN and SON with aging (Figure 5).\textsuperscript{76} These findings are in line with the increased cellular\textsuperscript{70} and nucleolar size\textsuperscript{72} that indicated increased AVP synthesis in this nucleus during aging. To further substantiate the hyperactivity of HNS neurons in aging, the size of the Golgi apparatus (GA) was determined in the human SON and PVN in a recent study. The GA, indeed, showed a clear increase in size and intensity with age in controls and Alzheimer patients (Figure 6).\textsuperscript{77} All these indications for activation of AVP are supported by the presence of a gradual increase in human plasma AVP levels during aging.\textsuperscript{4,78,79} In addition, an increase in AVP secretion upon osmotic stimulation was found in elderly subjects.\textsuperscript{80-84} Since the activation of AVP neurons in aging is probably due to loss of AVP receptors in the kidney,\textsuperscript{85,86} the observed activation of the HNS in senescence might be considered as a compensatory activation. This mechanism, however, must still be confirmed in humans.

The number of OXT expressing neurons in the PVN was found to remain constant during aging (Figure 7),\textsuperscript{87} which is in line with the absence of morphological signs of activation in these cells in senescence.\textsuperscript{70,72} The remarkable stability of the activated SON and PVN neurons in aging, and also in Alzheimer’s disease, supports our concept that activated neurons may be able to withstand the processes of aging or neurodegeneration better — a hypothesis that is paraphrased as “use it or lose it”.\textsuperscript{88}
B. Corticotropin-Releasing Hormone

Corticotropin-releasing hormone (CRH) immunoreactive neurons are restricted to the PVN in the human hypothalamus. As in rat, the CRH neurons of the human PVN are parvicellular. However, in the rat the CRH neurons are localized in a strictly defined subnucleus of the PVN, while they are spread throughout the entire PVN in humans, except for the most rostral part where they are absent. CRH plays a key role in the stress response of the hypothalamic-pituitary-adrenal (HPA) axis. CRH neurons appeared to be activated in aging as was shown by a number of parameters. In the first place, the number of CRH immunoreactive neurons in the human increases in the PVN (Figure 8). Another sign of activation of CRH neurons is an increase in the coexpression of AVP as appeared from animal experiments. Interestingly, an age-dependent increase in the colocalization of AVP was also found in the parvicellular CRH neurons in the human PVN with aging. Colocalization was especially noted in older control subjects (aged 43 to 91 years), whereas no colocalization was present in younger subjects (aged 23 to 37 years). In addition, an increase in cortisol with age was found in post-mortem cerebrospinal fluid.
Figure 6
Activation of the Golgi apparatus in supraoptic and paraventricular nucleus (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 cister-
nae. (A) Supraoptic neuron from a 29-year-old control, and (B) from a 73-year-old control. From Lucassen, P. J., Ravid, R., Gonatas, N. K., and Swaab, D. F., Brain Res., 632, 105, 1993. With permission.)

All these findings are in agreement with hormone measurements in the periphery, indicating an activation of the HPA-axis during aging. Moreover, resistance of cortisol secretion to dexamethasone suppression increases with age in controls. Hyperactivity of the HPA-axis is proposed to have severe long-term consequences, since increased levels of corticosteroids have been hypothesized to lead to irreversible hippocampal damage. The hippocampus normally inhibits CRH neurons and hippocampal lesions may, therefore, subsequently lead to more hyperactivity of CRH neurons. A positive feedback loop would then develop, leading to more CRH activation and more brain damage. Whether such a mechanism is indeed operative in the human brain in aging and AD remains, however, to be proven. There are also observations which do not agree with an activation of the HPA-axis in aging. Measurements of plasma adrenocorticotropic (ACTH) in 25 young and 28 elderly humans revealed no significant differences. Older people did not show significant change in ACTH response after having undergone major surgery. In addition, rhythms of ACTH and cortisol secretion showed no significant
change with age in healthy elderly subjects. Using frequent plasma sampling techniques, older subjects also had a normal circadian cortisol rhythm, although the cycle peaked at an earlier hour. These data indicate that the regulatory capacity of the HPA-axis function, though this function is only slightly elevated under basal conditions in elderly subjects, may be diminished. However, on the basis of the activation of CRH neurons we observed in the PVN, central effects of increased CRH activity should also be considered. Increased activity of CRH neurons that project into the brain may lead to symptoms of depression, since CRH when administered centrally in laboratory animals leads to signs and symptoms that are very similar to the symptoms of major depression. In addition, extremely activated CRH neurons were indeed observed in depressed patients.

C. Thyrotropin-Releasing Hormone (TRH)

The distribution of TRH neurons in the human hypothalamus has been studied only recently. The majority of TRH-containing neurons was
Figure 8
Linear regression between age and absolute CRH cell number in the PVN estimated by the dissector method (A) and the unfolding method (B). Filled circles and solid lines indicate control subjects; open circles and dashed lines indicate Alzheimer's disease patients. A significant correlation was found between age and absolute CRH cell number for control subjects with both the dissector and unfolding methods (respectively, $\rho = 0.66, p = 0.02$; $\rho = 0.62, p = 0.03$). (From Raadsheer, F. C., Oorschot, D. F., Verwer, R. W. H., Tilders, F. J. H., and Swaab, D. F., *J. Comp. Neurol.*, 339, 447, 1994. With permission.)
present in the PVN, especially in the dorsocaudal part of this nucleus. It is thought that these neurons project to the median eminence and regulate thyroid stimulating hormone (TSH) release. The TRH neurons in the PVN were mostly parvicellular, but a few magnocellular TRH-positive neurons were observed as well. The SON did not show any TRH immunoreactivity. High densities of TRH-positive fibers were seen, not only in the median eminence but also in other hypothalamic areas, e.g., in the PVN, ventromedial nucleus (VM), and in the perifornical area. The large number of TRH-containing fibers apparently terminating on neurons suggests important physiological functions of this neuropeptide as a neurotransmitter or neuromodulator in the human brain. Hypothalamic TRH levels and TRH secretion are reduced in old (24 to 28 months) rats.\textsuperscript{102,103} Up to now, no data are available concerning age-related TRH changes in the human hypothalamus. Increased basal TSH concentrations were reported in elderly people\textsuperscript{104} as well as in aged rats.\textsuperscript{105} These changes point to the possibility that hypothalamic TRH may be compensatorily increased in elderly subjects. It seems worthwhile, therefore, to study age-related changes of TRH in the human hypothalamus.

D. Other Peptides

The human PVN and SON contain a number of other peptidergic neurons such as prosomatostatin\textsuperscript{106} and LHRH.\textsuperscript{107} Recently, positive VIP neurons were found to be present in the PVN and SON.\textsuperscript{34,35} In humans, the VIP neurons are spread all over the PVN and are not localized in a particular subnucleus as was found in the rat.\textsuperscript{108} In addition, colocalization of galanin has been found in the human SON and PVN, mainly with AVP and less with OXT.\textsuperscript{25} This means that changes of galanin in the HNS can also be expected in aging.

V. INFUNDIBULAR (ARCUATE) NUCLEUS

The horseshoe-shaped infundibular (or arcuate) nucleus\textsuperscript{50} contains a large number of neurotransmitters and neuropeptides, e.g., catecholamine-containing neurons,\textsuperscript{61} somatostatin, neuropeptide Y, and neurotensin. Various neuroendocrine cell types that are involved in the hypothalomo-pituitary-gonadal (HPG) axis are located in this nucleus.

A. Luteinizing Hormone-Releasing Hormone (LHRH)

LHRH is less widely distributed in the brain than many other neuropeptides. LHRH-containing cell bodies are located predominantly in the
infundibular nucleus and preoptic area. LHRH-immunoreactive fibers project to the median eminence, septum, stria terminalis, ventral pallidum, dorsomedial thalamus, olfactory stria, and the anterior olfactory area of the human brain. Recently, a much wider distribution and greater number of LHRH neurons was found in the human hypothalamus using in situ hybridization. In this study, three subtypes of LHRH neurons were found as well as two types of small-sized neurons located primarily in the hypothalamus, suggesting that different functional subgroups of LHRH neurons exist in the human brain. The colocalization of delta sleep-inducing peptide (DSIP) and LHRH, as found in the arcuate nucleus of aged human subjects, suggests that DSIP may also play a physiological role in LHRH neurons.

The menopause represents a dramatic alteration in the function of the HPG axis in women. As a consequence of decreased levels of sex hormones, neuronal hypertrophy has been reported in the human infundibular nucleus in old men and postmenopausal women. The mean profile area of infundibular neurons from old men and postmenopausal women was significantly larger than that of young subjects (Figure 9). The density of hypertrophied neurons was also increased. Furthermore, the hypertrophied neurons contained increased amounts of neurokinin B, substance P,
and estrogen receptor mRNA, which indicated an increased neuronal activity as well.\textsuperscript{116,117} LHRH neurons are also found in this nucleus, but the hypertrophied neurons themselves do not contain this peptide. The neurokinin B-containing neurons are probably involved in the regulation of the HPG-axis and have been related to menopausal flushes.\textsuperscript{114} The sensitivity of LH to LHRH did not decrease in elderly males.\textsuperscript{118-120} On the other hand, a decreased sensitivity to sex steroid feedback was found in elderly (80 years) postmenopausal women as compared to younger postmenopausal women (55 years).\textsuperscript{121} No data on changes in the exact number of LHRH expressing neurons in relation to aging in the human hypothalamus are available at present.

B. Growth Hormone-Releasing Hormone (GHRH) and Somatostatin

In the rat the majority of GHRH-immunoreactive neurons are located in the arcuate nucleus.\textsuperscript{122,123} Together with the inhibiting somatostatin neurons that are situated in the periventricular nucleus,\textsuperscript{124} they regulate the secretion of growth hormone (GH), which is not only necessary for normal infant and childhood growth but also for the regulation of normal body composition and metabolism in adulthood.\textsuperscript{125} A current hypothesis states that a defective GH secretion may be one of the pacemakers of aging.\textsuperscript{126,127} In addition, Morimoto\textsuperscript{128} showed that the intensity of GHRH immunoreactivity in the median eminence of 20-month-old rats is markedly reduced in comparison with that of young rats. Interestingly, however, the number of immunoreactive neurons in the GHRH and somatostatin-containing neuronal perikarya in the hypothalamus in old colchicine-treated rats did not differ.\textsuperscript{128} These observations indicate that in old animals GHRH and somatostatin-containing neurons remain present and have the capacity to synthesize the respective peptides. However, either the production, transport rate, or release of GHRH should be changed in aging. Indeed, De Gennaro Colonna et al.\textsuperscript{129} reported a reduction in GHRH peptide and mRNA levels in the hypothalamus of (20-month) old male Sprague-Dawley rats. Both decreased somatostatin gene expression\textsuperscript{130,131} and increased somatostatin secretion have been reported in the rat.\textsuperscript{132} Endocrine studies indicate the presence of changes in GH regulation in human aging. In elderly people the response of GH to GHRH was shown to be significantly reduced.\textsuperscript{133,134} It has even been reported that GH responses to GHRH decline after 30 to 40 years in men and after menopause in women.\textsuperscript{135-137} Furthermore, the feedback effects of circulating GH on GHRH that are present in adult rats were not detectable in aged rats.\textsuperscript{129} Although it has been suggested that a decreased GHRH or increased somatostatinergic activity are the main events underlying the age-related
decline of GH secretion, no direct evidence is available about the changes of GHRH or somatostatin neurons in the human hypothalamus with aging.

VI. LATERAL TUBERAL NUCLEUS

The lateral tuberal nucleus (nucleus tuberalis lateralis, NTL) can only be recognized in man and higher primates. The only neuropeptide found so far that is characteristic for NTL neurons is somatostatin. In addition, some galanin and LHRH immunoreactive fibers have been found in the NTL. A dense innervation of prosomatostatin fibers, most probably derived from the NTL interneurons, were recently found in the NTL. Receptors for CRH, somatostatin, muscarinic cholinergic receptors, benzodiazepin receptors, and N-methyl-d-aspartate (NMDA) receptors have been localized in the NTL. In adulthood the NTL contains about 60,000 neurons. It has been shown that the number of NTL neurons may gradually decline with age. Although no significant correlation between NTL cell number and age was found, this may, however, be due to the small sample, especially in the oldest age group. No clear changes in the somatostatin immunoreactive neurons were observed in human NTL with aging.

VII. CONCLUSION

The main conclusion of the present review is that the aging process causes differential changes in the hypothalamus. Aging may start around middle-age in some peptidergic systems (e.g., the decreased number of VIP neurons in middle-aged males and the sharp decline of SDN neurons after 50 years). On the other hand, many more systems remain perfectly intact and are even activated (e.g., the unchanged number of VIP neurons in the female SCN and the increased number of CRH and AVP neurons of the PVN in the course of aging). The latter pattern argues against the idea that normal aging leads to a general decline in cellular functions, i.e., by "wear and tear".

Activation of some groups of nerve cells within the physiological range seems to lead to maintenance of neurons during aging. This "use it or lose it" hypothesis might explain why certain neurons degenerate in aging while others do not, and why recovery of various neuronal systems during aging can be obtained by restoration of the missing stimulus. The finding that some peptidergic neurons are activated during aging may have important functional consequences, e.g., the involvement of activated CRH neurons in the development of depression. In addition, the
presence of activated peptidergic neurons may have consequences for the treatment of elderly people with such peptides. When neuropeptides are given to elderly people, it should be taken into account that the release of many of them is already significantly increased.

Treatment of old and demented people with AVP and analogues was based upon the presumption that AVP levels in the brain were decreased, whereas it was shown later that the endogenous activity of AVP cells in the HNS was increased in old people. It can be concluded that the multitude of changes in the various hypothalamic nuclei may be the basis for many functional changes in aging, i.e., both endocrine and central alterations. We suspect, however, that only a small proportion of such changes has, at present, been revealed.

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