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Ageing of the Human Hypothalamus

Key Words

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Lateral tuberal nucleus

Abstract

The various hypothalamic nuclei show very different patterns of change in ageing. These patterns are a basis for changes in biological rhythms, hormones, autonomous functions or behavior. The suprachiasmatic nucleus (SCN) coordinates circadian and circannual rhythms. A marked seasonal and circadian variation in the vasopressin (AVP) cell number of the SCN was observed in relation to the variation in photoperiod. During normal ageing, the circadian variation and number of AVP-expressing neurons in the SCN decreases. The sexually dimorphic nucleus (SDN), intermediate nucleus or INAH-1 is localized between the supraoptic and paraventricular nucleus (PVN). In adult men the SDN is twice as large as in adult women. In girls, the SDN shows a first period of decreasing cell numbers during prepubertal development, leading to sexual dimorphism. During ageing a decrease in cell number is found in both sexes. The cells of the supraoptic nucleus and PVN produce AVP or oxytocin and coexpress tyrosine hydroxylase. These nuclei are examples of neuron populations that seem to stay perfectly intact in ageing. Parvocellular corticotropin-releasing-hormone (CRH)-containing neurons are found throughout the PVN. CRH neurons in the PVN are activated in the course of ageing, as indicated by their increase in number and AVP coexpression. Part of the infundibular (or arcuate) nucleus, the subventricular nucleus, contains hypertrophic neurons in postmenopausal women. The hypertrophied neurons contain neurokinin-B (NKB), substance P and estrogen receptors and probably act on LHRH neurons as interneurons. The NKB neurons may also be involved in the initiation of menopausal flushes. The nucleus tuberalis lateralis might be involved in feeding behavior and metabolism. It does not show any decrease in neuronal numbers in ageing. It is remarkable that the majority of the hypothalamic nuclei do not show signs of degeneration during ageing, but rather activation with the exception of the SDN and SCN.

Suprachiasmatic Nucleus

The suprachiasmatic nucleus (SCN) is a small structure (0.25 mm³) considered to be the major circadian pacemaker of the mammalian brain and coordinating

hormonal and behavioral circadian rhythms [1]. In conventionally thionine-stained sections the human SCN cannot be recognized with certainty and therefore immunocytochemical labelling of the nucleus, e.g. with antivasopressin, is necessary [2]. Neurons that are immunoreac-

tive for vasopressin (AVP), vasoactive intestinal polypeptide (VIP), neuropeptide Y (NPY) and neurotensin are present in the SCN in a particular anatomical organization [3, 4]. 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 [4]. The shape of the human SCN is sexually dimorphic, i.e. more elongated in women and more spherical in men, but the AVP cell number and volume are similar in both sexes [5]. Recent observations 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 [6]. Similar circadian fluctuations were only observed in the SCN of young adults [7]. A fragmentation of sleep-wake patterns occurs in senescence that is paralleled by a marked decrease in the number of AVP-expressing neurons in subjects of 80–100 years of age, while in Alzheimer's disease these changes were even more dramatic [5, 8]. The number of VIP-expressing neurons in the SCN of women did not show any age-related change as opposed to the neurons expressing AVP, whereas in men a complex pattern of changes with age of VIP-expressing neurons was observed. Between 10 and 30 years the SCN of men contained twice as many VIP neurons as that of women. A subsequent decrease in the number of VIP neurons in males was found between 40 and 60 years of age, which resulted in a smaller number of VIP neurons in men than in women. After 60 years of age no sex differences were found [9, Zhou et al., unpubl. data]. The sex differences in the human SCN might point to a role in sexual behavior or reproduction.

Sexually Dimorphic Nucleus (Intermediate Nucleus, INAH-1)

The sexually dimorphic nucleus (SDN) in the young adult human brain is twice as large in males (0.20 mm^3) as in females (0.10 mm^3) and contains twice as many cells [10]. The SDN is located between the supraoptic (SON) and paraventricular nucleus (PVN), at the same rostro-caudal level as the SCN. The SCN is identical to the 'intermediate nucleus' described by Braak and Braak [11], and to the INAH-1 of Allen et al. [12]. A sex difference does not occur until about the 4th year postnatally, when cell numbers start to decrease in girls, whereas in males the cell numbers in the SDN remain stable until approximate-

Fig. 1. Age-related changes in the total cell number of the SDN 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 age 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 nonlinear, sex-dependent process [from 14, with permission].

ly 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. 1) [13, 14]. 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 [14], and to the decrease in male sexual activity [15]. It is not clear whether the hormonal changes are cause or effect of the observed cell loss in this nucleus.

SON and PVN

The large neurosecretory cells of the SON and PVN produce the neuropeptides AVP and oxytocin (OXT) which are released into the blood circulation in the neurohypophysis. AVP acts as antidiuretic hormone on the kidney and, in women, OXT is involved in labor and lactation. Parvocellular neurons of the PVN project into the brain and influence central processes. OXT has central effects on, for example, food intake (see below), affiliation, maternal and reproductive behavior [16, 17]. In males OXT might be involved in sexual arousal and ejaculation [18]. In addition to the neurohypophysial pep-

tides, magnocellular OXT- and AVP-containing cells of the SON and PVN coexpress tyrosine hydroxylase, suggesting the possibility of dopamine production [19, 20]. The SON is subdivided into three parts. The largest part, the dorsolateral SON, has a volume of 3 mm³ [21] and contains 53,000 neurons, 90% of which contain AVP and 10% OXT [22]. The dorsomedial and ventromedial SON together contain some 23,000 neurons. The entire SON thus contains 76,000 neurons [23]. The PVN has a volume of 6 mm³ [21] and was estimated to consist of about 56,000 neurons [23] of which some 25,000 contain OXT neurons and 21,000 express AVP [24, 25, Van der Woude et al., unpubl. data]. The neurons of the SON and PVN form a population of extremely stable cells in ageing; no loss in neurons or total cell number was observed [21, 24–28, Van der Woude et al., unpubl. data]. Various observations provide evidence for the hypothesis that activation of neurons interferes with the process of ageing, and thus prolongs the life span of neurons or restores their function [29]. This hypothesis has been paraphrased as 'use it or lose it' [28]. 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 AVP-producing perikarya [22], nucleoli [29] and Golgi apparatus [30], and the enhanced AVP plasma levels [31]. As appeared from animal experiments this might be considered as a compensatory activation due to a loss of AVP receptors in the kidney during ageing [32].

In contrast to the SON, the PVN does not only contain magnocellular AVP and OXT neurons, but also parvocellular ones that project to central brain regions (see above) or to the median eminence. Examples of the latter type of neurons are the corticotropin-releasing hormone (CRH) neurons. 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 coexpress AVP when activated. This occurs, for example, in the process of ageing and might be causally related to symptoms of depression [33, 34]. The increasing number of VIP neurons we recently observed in the PVN [Zhou et al., unpubl. data] may be the cause of the increased prolactin levels in ageing, since VIP is a prolactin-releasing factor.

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The lateral tuberal nucleus (NTL) can only be recognized in man and higher primates. The connections with other parts of the brain are as yet unknown, but somatostatin [39], receptors for CRH, somatostatin, muscarinic cholinergic receptors, benzodiazepine receptors and N-methyl-D-aspartate (NMDA) receptors have been localized in the NTL [40]. In adulthood the NTL contains some 60,000 neurons, whereas in Huntington's disease this number may be reduced to less than 10,000, but in normal ageing there is no decrease in neuronal number [40]. Because, under different conditions, NTL pathology is accompanied by cachexia, the NTL is hypothesized to play a role in feeding behavior and metabolism.

Lateral Tuberal Nucleus

The horseshoe-shaped infundibular (or arcuate) nucleus surrounds the lateral and posterior entrance of the infundibulum. It contains, for example, catecholaminergic neurons [19], somatostatin, NPY and neurotensin [35]. In 1966 Sheehan and Kovacs [36] described neuronal hypertrophy in a subdivision of this nucleus, the subventricular nucleus, in postmenopausal women and women suffering from postpartum hypopituitarism. Nucleolar size increase and multiplication confirm the activation of neurons in this area [37, 38]. The hypertrophied neurons contain increased amounts of neurokinin B (NKB), substance P and estrogen 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 estrogen-negative feedback on gonadotropin release in humans by acting as an interneuron on the LHRH-containing cells. In addition, the NKB neurons may be involved in the initiation of menopausal flushes [38].

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