Neurohypophysial peptides in the human hypothalamus in relation to development, sexual differentiation, aging and disease

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**Summary**

The two neuronal systems that contain neurohypophysial peptides in the hypothalamus, i.e., (i) the supraoptic and paraventricular nucleus and (ii) the suprachiasmatic nucleus, show quite different patterns of changes in the human in relation to development, aging and disease.

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**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. In addition, magnocellular oxytocin and vasopressin containing cells of the SON and PVN are co-expressing tyrosine hydroxylase, suggesting the possibility of dopamine production [1].

The SON has a volume of 3 mm$^3$ [2] and contains some 76,000 neurons [3]. The PVN has a volume of 6 mm$^3$ [4] and was estimated to consist of about 56,000 neurons of which some 25,000 contain oxytocin and 21,000 vasopressin [5,4]. A recent study (A.M. Neijmeijer-Leloux, unpublished results) showed that the vasopressin and oxytocin cell number in the SON and PVN is at adult level as early as the second half of gestation. The SON and PVN thus seem to develop much earlier than the SCN [6].

The neurons of the SON and PVN form a population of extremely stable cells in normal aging and in Alzheimer's disease; no loss in neurons or total cell number was observed [2,4,5]. The observation that no cytoskeletal alterations were found in Alzheimer patients with several antibodies in the SON [7] is in accordance with this stability. However, in the PVN of Alzheimer patients some neuronal and dys-
trophic neurite staining is observed with cytoskeletal antibodies [7]. Various 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’ [8]. The SON and PVN neurons are not only metabolically highly active throughout life, but are extra activated in the course of aging as well, as can be judged from the increase in the size of the vasopressin containing perikarya [9], nucleoli [10] and Golgi apparatus (Lucassen et al., unpublished observation), and the enhanced plasma levels of vasopressin [11]. Similar activation of vasopressin neurons was observed in the aged rat [12,13] and is probably due to a loss of vasopressin receptors in the kidney during aging [14].

Recently, we observed a 50% reduction in the number of oxytocin expressing PVN neurons in Prader-Willi syndrome, a 40% reduction in AIDS and a 20% reduction in Parkinson’s disease (Purba et al., unpublished results). It remains to be determined what the functional implications of these changes are, e.g., in terms of autonomic regulation eating behavior and metabolism. Concerning the finding of decreased numbers of oxytocin neurons in Prader-Willi syndrome, characterized by enormous obesitas, it is interesting that centrally projecting oxytocin pathways are thought to inhibit food intake [15].

In contrast to the SON, the PVN does not only contain magnocellular vasopressin and oxytocin neurons, but also parvicellular ones that project to central brain regions 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 localized in a well-defined subnucleus as they are in the rat, but are spread all over the PVN, except for the most rostral part. Another property of CRH neurons in the PVN is that they co-express vasopressin when activated. This occurs in increasing numbers of CRH neurons in the process of aging, suggesting an activation of the hypothalamo-pituitary-adrenal axis (Raadsheer et al., unpublished results).

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 l 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 [16]. In a Japanese diabetes insipidus family a G to A transition has been described in the same exon [17]. 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 case of familial hypothalamic diabetes insipidus [18–20]. This situation is quite different from that in the Brattleboro rat, where the mutant neurons seem to remain intact.

Suprachiasmatic nucleus

The suprachiasmatic nucleus (SCN) is a small structure (0.25 mm³) that is considered to be the major circadian pacemaker of the mammalian brain, coordinating hormonal and behavioral circadian rhythms [21]. In conventionally thionine-stained sections the human SCN cannot be recognized with certainty. For this purpose immunocytochemical labelling of the nucleus is necessary [6]. The shape of the human SCN is sexually dimorphic, i.e., more elongated in women and more spherical in men, but the cell number and volume are similar in both sexes [22]. Neurons that are immunoreactive for vasopressin, VIP, neuropeptide-Y and neurotensin are present in the SCN in a particular anatomical organization [23,24]. 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
geneticulo-hypothalamic tract – if such a tract is present in the human brain at all [24]. At birth the SCN contains some 13% of the vasopressin-expressing neurons and 20% of the total cell number found in adulthood. Subsequently, cell numbers rise to maximum values around 1–2 years postnatally, after which they decrease gradually to some 50% of these numbers in adulthood [6]. 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 the autumn as in the summer [25]. Similar circadian fluctuations were observed in the SCN of young adults (Hofman and Swaab, unpublished results).

Since fetal circadian rhythms are generally not observed during the immediate postnatal period and develop gradually – over several weeks to months postnatally [26], it is generally believed that the fetal rhythms are predominantly driven by the mother. The postnatal development of various overt rhythms is paralleled by a strong increase in the number of vasopressin-expressing neurons [6]. On the other hand, based upon observations in squirrel monkeys [27] and the presence of temperature rhythms in some 50% of the premature [28] the human fetus may already be capable of expressing endogenous circadian rhythmicity. In addition, melatonin receptors are apparent in the SCN area as early as the 18th week of gestation [27].

Age-related changes in circadian rhythms have been reported in man as well as in non-human species. A fragmentation of sleep-wake patterns occurs in senescence, a phenomenon that is even more pronounced in Alzheimer’s disease [29]. 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, as well as often leading to hospital admission of the elderly. For this reason, the total SCN cell numbers and numbers of vasopressin expressing neurons were 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 [22,30]. 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. In addition to degenerative changes, Alzheimer patients are generally exposed to less light than their age-matched controls. As a result, both the input of the visual system to the SCN and the SCN itself [7] 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 Japanese observations showed that behavioral disturbances diminish in Alzheimer patients after exposure to bright light for 2 h per morning.

Recent morphometric analysis of the SCN revealed in ten homosexual men that the volume of this nucleus was 1.7-fold as large as that of a reference group of 18 male subjects, and that it contained 2.1-fold as many cells [31]. It might be that the programmed postnatal cell death, usually occurring from 13–16 months after birth onwards, is limited in homosexual men. 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 behavior and reproduction [30].

Concluding, it is clear that in the various stages of life the various vasopressin and oxytocin neurons of the human hypothalamus execute different functions. In addition, these systems seem to be involved in a number of disease processes in a differential way. This means that such neuropeptide systems in the human hypothalamus should be studied by procedures allowing microscopical resolution, chemical characterization and a good estimation of their numbers and activity stage in the various conditions.

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References


