CHAPTER 6.1

The human hypothalamo-neurohypophysial system in health and disease

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The present paper reviews the changes observed in the human supraoptic (SON) and paraventricular (PVN) nuclei,

and their projections to the neurohypophysis, median eminence and to other brain areas in health and disease.

The supraoptic (SON) and paraventricular (PVN) nuclei (SON, PVN)

One of my anatomist friends who has made notable contributions to our knowledge of the anterior lobe hormones has challenged me to produce any corresponding clinical or experimental evidence of posterior lobe activity. To this challenge, this and the succeeding papers are a partial answer.

H. Cushing, 1932, p. 60

The hypothalamo-neurohypophysial system

The supraoptic (SON) and paraventricular (PVN) nuclei (Fig. 1) and their axons running to the neurohypophysis form the hypothalamo-neurohypophysial system (HNS) that represents the classical example of a neuroendocrine system. The SON and PVN are supplied with unusually rich capillary beds. The density of this capillary bed would decrease with age in the PVN, but not in the SON (Abernethy et al., 1993). The decrease in the PVN is, however, rather unexpected and needs confirmation, as a stability was found in the number of

oxytocin neurons in aging (Wierda et al., 1991) and even an activation of corticotrophin-releasing hormone (CRH) and vasopressin neurons (Raadsheer et al., 1994a,b; Van der Woude et al., 1995). In order to establish the proportion of SON and PVN cells that project to the neurohypophysis, Morton (1961) determined neuronal numbers in these nuclei for a period of 12–45 months following hypophysectomy, an operation performed in those days as a palliative measure in the treatment of hormone-dependent metastatic mammary carcinoma (see also below). After hypophysectomy there was an average loss of neurons from both the SON and PVN of over 80%. From this observation it was concluded that most neurons of the SON and PVN project to the neurohypophysis. Since the apparent lack of retrograde changes in the accessory SON cells, the islands between the SON and PVN, it seems likely that their axons project more proximally to the stalk of the pituitary (Morton, 1961). Following hypophysectomy or transection of the stalk it took until about a year after the operation for the stump of the stalk to be innervated again throughout (Daniel and Prichard, 1972).

The SON is subdivided in three parts. The largest part, the dorsolateral SON (Fig. 1), has a volume of 3 mm³ (Goudsmit et al., 1990) and contains 53 000 neurons, 90% of which contain vasopressin and 10% oxytocin, mainly in its dorsal part (Fliers et al., 1985; Fig. 2). Indeed, J. Purba (unpublished data) counted 49 240 vasopressin and 5460 oxyto-

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Fig. 1. Thionine (left) and anti-vasopressin (right) stained section through the chiasmatic or preoptic region of the hypothalamus. OC, optic chiasm; OVL, organum vasculosum lamina terminalis; PVN, paraventricular nucleus; SCN, suprachiasmatic nucleus; SDN, sexually dimorphic nucleus of the preoptic area (intermediate nucleus); SON, dorsolateral part of the supraoptic nucleus; III, third ventricle. Scale bar, 1 mm.

cin neurons in this part of the SON. The dorsomedial and ventromedial SON together contain some 23 000 neurons (Morton, 1961). According to Dierickx and Vandesande (1977) 85% of the neurons of the medial part of the SON contain vasopressin and 15% oxytocin. The entire SON thus contains some 76 000 neurons on one side (Morton, 1961). The PVN has a volume of 6 mm³ (Goudsmit et al.,

1990) and was estimated to consist of about 56 000 neurons (Morton, 1961) of which some 25 000 contain oxytocin and 21 000 express vasopressin (Wierda et al., 1991; Purba et al., 1993; Van der Woude et al., 1995). The estimate of the exact neuron numbers in the SON and PVN depends, however, strongly on the methods used (Harding et al., 1995).

Fig. 2. Consecutive sections of a 49-year-old female control stained for vasopressin and oxytocin. (A) Dorsolateral supraoptic nucleus (SON) stained with an antiglycopeptide (Boris Y-2) against the vasopressin precursor and (B) oxytocin staining (O-1-V, purified). Note that the relatively small oxytocin cell population is clearly separated from the vasopressin cell population. Asterisk indicates a blood vessel that is present in both consecutive sections: OC, optic chiasm. Scale bar, 100 μ m (from Evans et al., 1996, with permission).

Neurosecretion

In the 1940s practically everybody vigorously, or even viciously, rejected the concept of neurosecretion.

(Bertha Scharrer, personal communication).

For a long time it was believed that the neurohypophysis made a product and that this function was regulated by the innervating nerves. In 1908, P.T. Herring first described the 'peculiar hyaline bodies' seen in sections of the neurohypophysis and expressed the belief that they represented the secretory product of the epithelial investment of the posterior lobe known as the pars intermedia. The globules appeared to find their way toward the tuber cinereum and 'in favorable histological preparations could be seen passing between the bodies of the ependymal cells to enter the infundibular

cavity' (Cushing, 1932; p. 59). A famous case report tells of a man who, in 1910, received a gunshot wound, resulting in a polyuria of 97 liters a day and sexual dystrophy. At autopsy the bullet was found to be lodged in the sella-turcica and to have destroyed the infundibular process and posterior lobe (Vonderahe, 1940; Brooks, 1988). Although such observations revealed the antidiuretic function of the neurohypophysis, the concept of 'neurosecretion' in vertebrates as found in the large neurons of the human supraoptic and paraventricular nucleus, was not proposed until 1939, by the Scharrers (Scharrer and Scharrer, 1940; Brooks, 1988; Meites, 1992). According to the critics of those days, this concept was based on 'nothing more than signs of pathological processes, postmortem changes or fixation artifacts'. In the 1940s 'practically everybody vigorously or even viciously' rejected the concept that a neuron

could have a glandular function (B. Scharrer). This initially highly charged reception of the neurosecretion concept was followed by acceptance only when Bargmann (1949) demonstrated the same Gomori-positive material in the neurohypophysis and in the neurons of the SON and PVN and concluded that the axons from the SON and PVN transport material to the neurohypophysis. He called the aggregate of fibers 'the neurosecretory pathway'.

Seeking a new method for revealing neurosecretory material, he (Bargmann) placed sections from a dog's brain into acid-permanganate-chrome-alum-hematoxylin, according to Gomori's method... and was astonished at what he found (instead of shouting Eureka, Bargmann, waving the cigar that was always in his hand exclaimed (magna voce): 'Donnerwetter!'), the cells of the supraoptic and paraventricular nuclei and the fibers extending into the infundibulum and reaching the posterior lobe had selectively taken on a blue hue! ... When, everafter, in papers dealing with hypothalamic neurosecretion 'Gomori-positive' and 'Gomori-negative' results were cited, Gomori would comment in conversation that he found the terms distasteful but amusing. 'Right now' he once said before lunch to a fellow-Hungarian, Jacob Furth: 'I feel Gomori-negative'

(Anderson and Haymaker, 1974).

In 1955, Dr. Vigeaud received the Nobel Prize for the elucidation of vasopressin and oxytocin and the synthesis of vasopressin. The nonapeptides vasopressin and oxytocin are synthesized as part of a large precursor that includes a neurophysin for both peptides and a c-terminal glycoprotein for vasopressin. The vasopressin and oxytocin precursor genes are only separated by 12 Kb in the human genome. The genes are located on the distal short arm of chromosome 20 (Schmale et al., 1993). When the neurophysins were discovered by Asher et al. they were recognized as the inactive fragments of the precursor with a higher molecular weight and were thought to act as carriers for vasopressin and oxytocin. The role of neurophysins is at present also considered in the light of the knowledge on mutations in the neurophysin part, causing diabetes insipidus. Any disruption of the structure

and thus of the three-dimensional conformation of neurophysins by mutations may cause a decline in the binding and activity of endopeptidases responsible for the cleavage of vasopressin. Mutations in the neurophysins may also produce a change in the polymerization of neurophysins and salt bridges, with the result that there may be, e.g. an accelerated aspecific enzymatic degradation of the hormone revealing the clinical symptomatology. So rather than being a mere inactive part of the precursor, neurophysins are now considered as an essential system for carrying and protecting the non-peptides (Legros and Geenen, 1996). This concept is supported by observations on a Dutch family with hereditary hypothalamic diabetes insipidus, based upon a single G to T transversion in the neurophysin-encoding exon B (Bahnsen et al., 1992). When this mutant DNA was stably expressed in a mouse pituitary cell line, the mutant precursor was synthesized but processing and secretion were dramatically reduced and the protein did not seem to reach the trans-Golgi network (Olias et al., 1996). Other studies on reversal mutant AVP genes showed accumulation of mutant AVP precursors in the endoplasmic reticulum and reduced viability of the cell lines (Ito et al., 1997; see below).

Vasopressin and oxytocin: Production and release

Vasopressin is synthesized in the SON and PVN (Dierickx and Vandesande, 1979), suprachiasmatic nucleus (SCN; Swaab et al., 1985), diagonal band of Broca (DBB), nucleus basalis of Meynert (NBM) (Ulfig et al., 1990), and bed nucleus of the stria terminalis (BST) (Fliers et al., 1986; Mai et al., 1993), and oxytocin in the PVN and the dISON (Dierickx and Vandesande, 1979) (Figs. 1–3). Vasopressin and oxytocin are produced in different neurons (Dierickx and Vandesande, 1979; Hoogendijk et al., 1985). The observation in rat that under extreme forms of stimulation the neurons may produce both peptides (Mezey and Kiss, 1991) has not been followed up in humans yet. A rostro-caudal gradient in the ratio between vasopressin and oxytocin neurons is present in the PVN. Whereas the ratio of vasopressin: oxytocin cells remained 80% from rostral to caudal over a

Fig. 3. Vasopressin pathways in the human brain. Question marks indicate that at present no site of origin or termination is known. (A) Amygdala; AM, anteromedial subnucleus of the basal nucleus; BST, bed nucleus of the stria terminalis; DBB, diagonal band of Broca; DMV, dorsal motor nucleus of the nervus vagus; LC, locus coeruleus; NSM, nucleus septalis medialis; NTS, nucleus of the solitary tract; PBN, parabrachial nucleus; PVN, paraventricular nucleus; SCN, suprachiasmatic nucleus; SN, substantia nigra; SON, supraoptic nucleus (scheme from E.J. van Zwieten).

distance of 1.5 mm in the dlSON. In the PVN this ratio starts below 20% rostrally, goes up to 60% in the caudal half, after which the ratio decreases again (Swaab et al., 1987b). Recently Mai et al. (1993) pointed to an additional oxytocin containing cell group dorsolateral to the fornix which they refer to as the paraforminal cell group. It is not clear why this cell group should not be considered as part of the PVN. 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 generally referred to as 'accessory nuclei'. They contain more oxytocinergic neurons than vasopressinergic ones (Dierickx and Vandesande, 1977). However, in the older literature, Feremutsch (1948) called the scattered cells and islands of neurosecretory cells between the SON and PVN 'intermediate nucleus'. This is a confusing term, since Brockhaus (1942) originally used the same name for the sexually dimorphic nucleus

of the preoptic area (SDN-POA) (Braak and Braak, 1992). Because male subjects have higher vasopressin plasma levels than females (Van London et al., 1997; Asplund and Åberg, 1991), sex differences in the hypothalamo-neurohypophysial system were expected to be present. And indeed we recently found an increased activity of vasopressin neurons in the dISON of young males as compared to young females (unpublished data).

Neuroendocrine functions and factors affecting vasopressin and oxytocin release

Vasopressin and oxytocin released into the blood circulation act as neurohormones. In humans, 90% of the circulating vasopressin bound to platelets (Preibisz et al., 1983; Bichet et al., 1986; Nussey et al., 1986; Van der Post et al., 1994) and a patient with autoimmune thrombocytopenia (D.F.S., unpublished data) had indeed low total vasopressin levels in the platelet fraction. Vasopressin acts as an anti-diuretic hormone on the kidney and regulates freewater clearance by V2-type vasopressin receptors coupled to aquaporins (Knepper, 1994). In spite of the suggestions of Cushing (1932) that there would be no clinical or experimental evidence in those days of posterior lobe function (see citation at the beginning of this chapter), endocrine effects on the kidney and uterus had already been known for years. In 1913 Von den Velden and Farini already described the antidiuretic effect of posterior pituitary extracts in patients suffering from diabetes insipidus and in 1909 Blair-Bell reported the oxytocin effects of posterior pituitary extracts in labor.

The hypothalamus integrates signals from osmoreceptors that are probably localized in the organum vasculosum lamina terminalis and stretch receptors of the vascular tree. Predominant stimuli for thirst and vasopressin release in human are osmolality of the extracellular fluid and hypovolemia. Suppression of thirst sensation and decreased vasopressin secretion are probably mediated by stimulation of oropharyngeal receptors and/or distension of the stomach. In this way, plasma osmolality is regulated within narrow boundaries of 2–3 mosmol/kg (Jenkins, 1991). Osmotic stimuli cause a release of vasopressin (Kirkland et al., 1984; Helderman et al., 1978; Phillips et al.,

1984; Robertson and Rowe, 1980). Moreover, orthostasis, smoking and nicotine cause vasopressin release (Rowe et al., 1980) and alcohol inhibits vasopressin release in young subjects (Helderman et al., 1978). Chronic alcohol consumption causes a loss of vasopressin neurons (Harding et al., 1996). Morphine gives a release of vasopressin, whereas naloxon is without effect on basal vasopressin levels in man (Van Wimersma Greidanus and Grossman, 1991). In urine, vasopressin shows a nocturnal increase in levels. In enuretics, however, this normal diurnal rhythm is absent (Rittig et al., 1989; see below). Plasma vasopressin is reported to be lower during menstruation than at ovulation (Forsling et al., 1981). In addition, vasopressin release is inhibited by glucocorticoids and stimulated in case of adrenal insufficiency (Ahmed et al., 1967; Erkut et al., 1998).

In women, oxytocin is involved in labor and lactation. During normal delivery, stretching of the lower birth canal is thought to trigger the neurohormonal 'Ferguson' reflex, leading to rapid secretion of oxytocin by the pituitary gland, which results in strong expulsive contractions. The Ferguson reflex is blocked by epidural analgesia (Goodfellow et al., 1983), while alcohol, too, inhibits oxytocin release during labor (Thornton et al., 1992). A significant increase in oxytocin blood levels is found at the onset of full cervical dilatation and crowning of the fetal head, but this increase does not occur following a lumbar epidural block. This explains why, following epidurals, more forceps deliveries are required. Indeed, oxytocin treatment during the second stage of labor with epidural analgesia reduces the need for forceps (Goodfellow et al., 1983). Since a competitive analogue of oxytocin inhibits contractions in uncomplicated preterm labor (Turnbull, 1987; Åkerlund et al., 1987) oxytocin might be involved in the initiation of preterm labor. It should be noted though that more recent research shows that a marked increase of oxytocin blood levels occurs only in a minority of the patients with a normal delivery. Progress of labor was not found to be related to an increase in oxytocin blood levels in that study either, which does not support a role for oxytocin during spontaneous at-term labor (Thornton et al., 1992). However, changes in oxytocin and

vasopressin (V_1) receptors could also modify uterine activity. Such receptors are present in pregnant human myometrium and decidua (Ivanisevic et al., 1989). Only oxytocin (not vasopressin) receptors are thought to increase during pregnancy in the human uterus (Tence et al., 1990). In fact, uterine oxytocin receptors peak in early labor (Maggi et al., 1990), suggesting a role in parturition. As shown by the presence of oxytocin mRNA in human amnion, chorion, and decidua, oxytocin is also produced in these tissues, while oxytocin gene expression increased 3–4 fold around the time of onset of labor. The possible role of this extrahypothalamic oxytocin in the onset and course of labor that would not be reflected in increased blood levels is, however, not yet established (Chibbar et al., 1993). The putative role of fetal vasopressin and oxytocin in parturition is discussed below.

Neurotransmitters and neuromodulators

... and evidence will be presented to show that posterior-lobe extracts are far more potent when injected into the cerebral ventricles than by any other means of administration.

(Harvey Cushing, 1932, p. 21)

Commercially available posterior lobe extract ('obstetrical pituitrin') which Cushing, 1932, p. 59 injected into the ventricle in 38 instances in 24 subjects convalescing from operations for pituitary adenoma, appeared to have a pronounced stimulatory effect, essentially parasympathetic in character, and, apparently, central in origin (Fig. 4). Since intramuscularly injected pituitrin had an opposite effect, and no central effects were noted when the hypothalamus was affected by hydrocephaly or by a tumor, Cushing indeed had solid evidence to propose a central action (i.e. on the hypothalamus) of neurohypophysial extracts. These impressive observations passed into oblivion, perhaps because the scientific community chose to put every effort into refuting the 'neurosecretion' concept proposed by Scharrer and Scharrer (1940). The initially highly charged reception of the neurosecretion concept was followed by acceptance

only when Bargmann (1949) demonstrated the same Gomori-positive material in the neurohypophysis and in the neurons of the SON and PVN. In the concept of neurosecretion, the proposition of Barry (1954) concerning the existence of Gomori-positive endings outside the hypothalamus ('synapses neurosécrétoires') could not be properly appreciated and was, therefore, eventually forgotten, which is likely to have been expedited by the fact that his articles were in French.

When De Wied (1965) showed that posterior lobectomy in the rat resulted in an accelerated extinction of conditioned shuttlebox avoidance response, and, later on, that this behavioral deficiency could be alleviated by peripherally adminis-

Fig. 4. Showing the vaso-dilatator and sudorific effects, sparing the bone flap of the recent operation, of 2.5 mg of pilocarpine injected into the cerebral ventricles: an intraventricular injection of one ml of pituitrin in susceptible persons gives an equally marked response (Cushing, 1932, p. 58).

tered vasopressin (De Wied and Bohus, 1966), it was also only natural that these effects were explained on the basis of the release of neurohypophysial hormones into the bloodstream, which in turn would transport the peptides back to the brain. However, a number of observations have made it extremely unlikely that the vascular route or the cerebrospinal fluid (CSF), would be a major channel for the central actions of neurohypophysial hormones (Swaab, 1982; Swaab et al., 1987a; Kruisbrink et al., 1987). In the meantime, moreover, immunocytochemical observations had revealed yet another site of production for vasopressin, the suprachiasmatic nucleus (SCN) (Swaab et al., 1975). Immunocytochemistry subsequently led to the rediscovery of extensive extrahypothalamic pathways terminating in structures ranging from the olfactory bulb to the spinal cord (Swanson, 1977; Buijs et al., 1978; Sofroniew and Weindl, 1978). The main sources of these vasopressinergic and oxytocinergic pathways were thought to be the SCN and the PVN, although the SON could not be excluded altogether as an additional site of origin. Later, however, colchicine treatment has revealed vasopressin-containing neurons in the rat bed nucleus of the stria terminalis (BST), amygdala, dorsomedial hypothalamic nucleus, locus coeruleus, and septum (Caffé and Van Leeuwen, 1983; Van Leeuwen and Caffé, 1983). Previously, the putative source of the fiber projections had been established only by tracing immunocytochemically stained fibers in serial sections. However, this method proved to be unreliable because, when vasopressin projections from the SCN were checked by lesioning this nucleus, it turned out not to be the source, e.g., of the lateral septum VP innervation, but other proposed target regions of the SCN, viz., the dorsomedial nucleus of the hypothalamus and the organum vasculosum of the lamina terminalis, were confirmed (Hoorneman and Buijs, 1982). Ultrastructural immunocytochemical observations in rat have shown that extrahypothalamic peptidergic fibers terminate synaptically on other neurons (Buijs and Swaab, 1979).

In the human brain vasopressin and oxytocin fibers probably originating in the PVN, project, e.g. to the nucleus basalis of Meynert (NBM), the diagonal band of Broca (DBB), septum, BST,

locus coeruleus, the parabrachial nucleus, the nucleus of the solitary tract, the dorsal motor nucleus of the nervus vagus, substantia nigra, dorsal raphe nucleus and spinal cord (e.g. Fliers et al., 1986; Sofroniew, 1980; Unger and Lange, 1991; Fodor et al., 1992; Van Zwieten et al., 1994, 1996; Fig. 3). In addition, vasopressin-containing fibers innervate the fissures of the chorioid plexus in rat (Brownfield and Kozlowski, 1977), while the chorioid plexus of the human brain was found to contain vasopressin binding sites. In Alzheimer's disease a 2-fold increase in vasopressin binding sites was found in this structure (Korting et al., 1995). Vasopressin is thought to play a role in the choroid plexus with respect to ion and water transport and to reduce CSF production (Nilsson et al., 1992). An extension to the extrahypothalamic neurohypophysis containing fiber distribution in the human brain was given by Mai et al. (1993), but without a distinction of the fibers being vasopressinergic or oxytocinergic.

In the human PVN it is not possible to determine with certainty which neurons that express oxytocin or vasopressin are of a neuroendocrine nature and project to the neurohypophysis and which oxytocin neurons project to the brain where they act as neurotransmitter or neuromodulator. In the first place, unlike that of the rat, in the human PVN the cells cannot be subdivided into a part containing only magnocellular elements projecting to the neurohypophysis and one containing only parvocellular elements projecting to the brain stem, because there is a continuous distribution from small to large oxytocin and vasopressin neurons in the human PVN. Moreover, in contrast to the rat, neither type of oxytocin or vasopressin neuron of the human PVN is localized in a particular subnucleus of the PVN. This is also the case with corticotrophin-releasing hormone (CRH) neurons (Swaab et al., 1995; Raadsheer et al., 1993). The absence of an arrangement of the PVN into subnuclei is certainly not restricted to humans. It has also been observed in the cow, the cat and the guinea pig (Swaab et al., 1995).

The central vasopressinergic fibers may be involved in blood pressure and temperature regulation, regulation of osmolality and corticosteroid secretion and influence cognitive functions, aggres-

sion, social attachment and paternal behavior (Legros et al., 1980; De Wied and Van Ree, 1982; Buijs et al., 1983; Fliers et al., 1986; Legros and Ansseau, 1992; Holsboer et al., 1992; Insel, 1997). In contrast, oxytocin would give rise to sedation and lowering of blood pressure. Oxytocin levels rise after non-noxious stimulation such as touch, light exposure and high temperature. Oxytocin is held responsible for the antistress effects that occur during lactation and oxytocin has central effects on food intake as well (Uvnäs-Moberg, 1997). Oxytocin neurons are considered to be the putative satiety neurons for eating behavior. Our observations in Prader-Willi patients, who have an insatiable hunger and extreme obesity, support this idea, as a 42% decrease in oxytocin-expressing neurons in the PVN was found in this disorder (Figs. 5 and 6; Swaab et al., 1995). Increased oxytocinergic activity in depression may be related to eating disorders (Purba et al., 1996) and increased

vasopressin levels to suicidal behavior (Inder et al., 1997). Alterations in PVN function have been proposed in schizophrenia too, on the basis of the highly decreased numbers of neurophysin-containing neurons that were found in the PVN of schizophrenic patients. No differences were found in the SON of schizophrenic patients, however (Mai et al., 1993), but it is not known if and how the PVN changes may contribute to the symptomatology of the disorder. In Parkinson's disease the number of oxytocin-expressing neurons in the hypothalamus is decreased (Purba et al., 1994).

Oxytocin, vasopressin and sexual behavior

Oxytocin is thought to be involved in affiliation, including pair bonding in monogamous animals (Insel, 1997) and maternal and reproductive behavior (Carter, 1992; Insel, 1992; Anderson-Hunt and Dennerstein, 1995). The synapses between vaso-

Fig. 5. Characteristic pattern of obesity in a patient with Prader-Willi syndrome (from Kaplan et al., 1991, with permission).

Prader-Willi Syndrome

Fig. 6. Number of oxytocin-expressing (left panel) and vasopressin-expressing (right panel) neurons in the PVN of 27 controls and five Prader-Willi syndrome (PWS) patients. Note that the oxytocin neuron number of these patients is about half of that of the controls (left), which is not the case for vasopressin (right) (from Swaab et al., 1995, with permission).

pressin neurons of the SON and neuroendocrine LHRH neurons as observed in monkey suggest a coordinated role of vasopressin and gonadotropin secretion. In men, oxytocin might be involved in sexual arousal and ejaculation (Murphy et al., 1987) and in both men and women oxytocin induces contractions of smooth muscle cells and may thus facilitate transport of eggs and sperm (Carmichael et al., 1994). In female animals, oxytocin was found to facilitate estrus, sexual arousal, receptivity and other mating behaviors, including lordosis. An as yet unconfirmed case report has described a woman who began to take a contraceptive pill containing progesterone only. She experienced accentuated physiological and psychological sexual arousal after she had co-incidentally used a prescribed synthetic oxytocin spray for 'let-down' of breast milk (Anderson-Hunt, 1994; Anderson-Hunt and Dennerstein, 1995). In agreement with this case report, oxytocin levels are known to rise during sexual arousal and peak during orgasm in both women and men. In multiorgasmic subjects

oxytocin peaks immediately prior to and during terminative orgasm, i.e. the oxytocin peak coincides with sexual saturation. The intensity of orgasmic contractions, but not their duration, correlated positively with increases in oxytocin levels. Naloxon decreases the level of pleasure at orgasm and blocks the periorgasmic rise of oxytocin levels (Murphy et al., 1990; Carmichael et al., 1994). Animal experiments show a mechanism of interaction between sex hormones and oxytocin by initiating the production of receptors for this peptide (Anderson-Hunt and Dennerstein, 1995). Indeed, oxytocin levels are significantly higher in women on oral contraceptives and oxytocin levels recorded during the menstrual week are significantly lower than during the rest of the period (Uvnäs-Moberg et al., 1989). The plasma concentration of vasopressin during the menstrual cycle is doubled on days 16–18 as compared to day 1 (Forsling et al., 1981). In the non-pregnant human uterus oxytocin and vasopressin receptors of the V_1 subtype are present (Guillon et al., 1987). Vasopressin may have a

role in stimulating uterine contractions. In this respect it is of interest that women with primary dysmenorrhea, who have an increased uterine activity and a decreased blood flow in the uterus have increased plasma levels of vasopressin (Åkerlund et al., 1979).

The fetal SON, PVN and birth

Fetal neurohypophysis and birth

... since the abnormal process of birth frequently produces no effect, difficult birth in itself in certain cases is merely a symptom of deeper effects that influenced the development of the fetus.

Sigmund Freud, 1897

Not only maternal but also fetal neurohypophysial hormones play an active role in the birth process. Fetal oxytocin was proposed to initiate parturition (Schrieffer et al., 1982) or accelerate the course of labor (Swaab et al., 1977; Boer et al., 1980). Fetal vasopressin levels in umbilical cord blood are much higher following normal delivery than at any other stage of life (Chard et al., 1971; Oosterbaan and Swaab, 1989). Fetal vasopressin is one of the hormones that plays a role in the adaptation of the fetus to the stress of labor, for example by redistribution of the fetal blood flow with a marked reduction in the flow to gastrointestinal and peripheral circulations and an increase in the flow to essential organs such as the brain, the pituitary, the heart and the adrenals (Iwamoto et al., 1979; Pohjavuori and Fyhrquist, 1980). The neurons producing these neuropeptides are already present early in fetal life. Using neurophysin staining that did not distinguish between oxytocin or vasopressin neurons, Mai et al. (1997) detected staining SON neurons from 10 weeks of gestation onwards, roughly coinciding with the arrival of the optic tract fibers. Vasopressin and oxytocin have been found as early as 11 and 14 weeks of gestational age respectively (Fellmann et al., 1979; Burford and Robinson, 1982). Neurophysin was demonstrable at 13 weeks of gestation in the accessory nuclei and at 14 weeks of gestation in the PVN.

Vasopressin-neurophysin was detected from 18 weeks of gestation onwards, and vasopressin-mRNA from 21 weeks of gestation in the SON, PVN and accessory nuclei (Murayama et al., 1993). An increase in vasopressin and oxytocin levels in the pituitary and the brain during the development of the fetus has been described by a number of researchers (Skowsky and Fisher, 1977; Schubert et al., 1981; Burford and Robinson, 1982; Khan-Dawood and Dawood, 1984).

Most cells of the magnocellular system seemed to derive from the region of the hypothalamic sulcus and migrate laterally and ventrally before expressing neurophysin at their site of settling. The cells possibly migrate along epidermal growth factor receptor positive radial glial cells that extend from the hypothalamic sulcus into the lateral hypothalamus. A dense catecholaminergic network of fibers is already present in the PVN of a 3- to 4-month-old fetus (Nobin and Björklund, 1973).

Because premature children are more sensitive to the stress of birth, we determined the number of oxytocin or vasopressin-expressing neurons in the human fetal hypothalamo-neurohypophysial system (HNS) in premature and at-term children. From the youngest fetus of our study onwards, so from a gestational age of 26 weeks, adult vasopressin and oxytocin cell numbers were found in both the SON and the PVN (Fig. 7; Wierda et al., 1991; Van der Woude et al., 1995). This is in agreement with the estimation of Dörner and Staudt (1972) that the hypothalamic nuclei are already completely formed around 25 weeks of gestation, on the basis of the disappearance of the matrix layer around the third ventricle at that age (Staudt and Stüber, 1977). The fetal HNS, however, is far from mature at term, in spite of the adult cell numbers. This is apparent, for example from the neuronal densities which are still decreasing after this period. Rinne et al. (1962) found a gradual increase in nuclear volume in the SON and PVN during fetal development, but he did not distinguish between oxytocin and vasopressin neurons. Judging by the strongly increasing nuclear size of the oxytocin neurons in the fetus during the last part of gestation (our unpublished data), these neurons seem to become gradually strongly activated towards term. This should, however, be confirmed by better measures of neuronal activity,

Fig. 7. Vasopressin (light bars) and oxytocin (dark bars) cell numbers in the PVN of premature (26–37 weeks) and mature (37–42 weeks) fetuses and in adults. Adult numbers were already present around 26 weeks gestation (from Goudsmit et al., 1992, with permission).

such as in situ hybridization for oxytocin-mRNA. So it seems quite possible that less mature oxytocin neurons in premature children would be, at least partly, responsible for the increased incidence of obstetrical problems. The idea of an active fetal role of oxytocin neurons in delivery is reinforced by a number of clinical observations. Firstly, human anencephalics do not have a neurohypophysis and have an impaired oxytocin and vasopressin release (Visser and Swaab, 1979; Oosterbaan and Swaab, 1987). In anencephalics expulsion takes twice as long and the birth of the placenta even takes three times longer, suggesting a role of fetal neuroendocrine mechanisms in speeding up the course of labor. In addition, the observation that about half of the anencephalics dies during the course of labor is a strong indication for the importance of an intact fetal brain to withstand the stress of birth (Honniebier and Swaab, 1973; Swaab et al., 1977). The second observation is derived from children suffering from Prader-Willi syndrome (see below). These children have considerable obstetrical problems (Wharton and Bresman, 1989), and we found that adult Prader-Willi patients have

only 58% of the normal number of oxytocin neurons in adulthood but their number of vasopressin neurons is normal (Swaab et al., 1995). The third argument is based on the frequent perinatal problems found in septo-optic dysplasia (De Morsier, 1956) in which the fetal hypothalamo-neurohypophyseal system is often damaged (Roessmann et al., 1987) (Fig. 8a,b). Moreover, prolonged labor and breech delivery have been documented in 50–60% of the idiopathic growth hormone-deficient children, a disorder that seems to be based on congenital hypothalamic pituitary abnormalities (Maghnie et al., 1991). The causality of the relationship between obstetric complications and neurological or psychiatric diseases such as schizophrenia (Geddes and Lawrie, 1995), might thus be quite the reverse from what is generally thought. A disturbed labor might be the first symptom of a brain disorder (see citation from Freud, before). How the fetal hypothalamus might play a role in fetal presentation is not known at present.

Immaturity at term may also affect the function of vasopressin neurons, though to a lesser degree than oxytocin neurons since the vasopressin neurons are already further advanced in the developmental process, something that has also been reported for other species. This is in agreement with the vasopressin levels in fetal cord, which are extremely high after delivery (Oosterbaan and Swaab, 1989). The adaptive vasopressin response (Pohjavuori and Fyhrquist, 1980) has been said to be induced by the stress of birth (Chard et al., 1971), by hypoxemia, acidemia (Daniel et al., 1983; Parboosingh et al., 1982) or by a rise in intracranial pressure associated with delivery. Perinatal hypoxia stimulates the vasopressin neurons in particular, as became apparent from their co-expression of tyrosine-hydroxylase (Panayotacopoulou et al., 1994). The physiological importance of neuroendocrine adaptive responses may also be deduced from the fact that two-thirds of the anencephalic children die during the course of labor (Honniebier and Swaab, 1973). These children do not have a functional neurohypophysis (Visser and Swaab, 1979). The observation that hereditary hypothalamic diabetes insipidus children from ditto mothers without vasopressin did not have a history of difficult labor at first sight seemed to suggest that the

Fig. 8. Septo-optic dysplasia (De Morsier syndrome) in a girl of 4 years and 5 months. (A) The PVN is absent. Scale bar, 0.5 mm. (B) Only a few small PVN neurons were present that stained for the vasopressin precursor by means of an antiglycopeptide antibody (Boris Y-2). Scale bar, 100 μ m.

absence of vasopressin alone does not seem to prevent an adequate neuroendocrine adaptive response of the fetus during labor (Swaab et al., 1982). However, later it became clear that vasopressin production in these children may be quite normal up to the age of 9 years or so (Bahnsen et al., 1992), so that these children do not give useful information on the putative involvement of fetal vasopressin.

Drinking disorders

As to the function of the posterior lobe, the experimental evidence is unequivocal. Its

removal causes no symptoms. Moreover, its structure is non-glandular. Camus and Roussy were quite justified in speaking of it as an atrophied nervous lobe.... We have, therefore, no evidence that pituitrin is anything more than a pharmacologically very interesting extract

*(Bailey and Bremer, 1921
cited by Anderson and Haymaker, 1974).*

Pathology of the neurohypophysis

The neurohypophysis consists of (1) the pars nervosa (neural or posterior lobe), (2) the infundibular process (pituitary stalk), that contains the nerve tracts from the supraoptic and paraventricular

nucleus (SON and PVN), a thin tongue of anterior pituitary tissue (pars tuberalis containing predominantly gonadotrophs) and the vessels of the portal system and (3) the pars infundibularis (infundibulum). Clinically, pathology of the neurohypophysis may lead to diabetes insipidus or to inappropriate secretion of vasopressin (Schwartz–Bartter syndrome). Apart from disturbances of water metabolism, abnormalities in the posterior pituitary, particularly space-occupying lesions, may cause symptoms such as headache and visual disturbances. In addition, the intracranial pressure may increase, producing anterior-pituitary compression. Damage to the pituitary stalk may interrupt the portal circulation and lead to infarction of the anterior lobe and thus to endocrine impairments. Congenital malformations in the neurohypophysis have also been described, such as persistence of the infundibular recess by which the third ventricle is protruding into the neurohypophysis. The infundibular recess in the neurohypophysis normally disappears in human embryos by the 45 mm stage (Cabanes, 1978). Moreover, duplication of the pituitary, of the adenohypophysis as well as the neurohypophysis have been described (Hori, 1983). In addition, loss of the infundibulum or pituitary stalk due to traumatic damage has been reported (Grossman and Sanfield, 1994). Dystopia of the neurohypophysis may either be asymptomatic or go together with anterior pituitary anomalies (Aydin and Ghatak, 1994). In the empty-sella syndrome the intrasellar CSF does not seem to influence posterior lobe function (Zucchini et al., 1995). No patients have been reported with isolated diabetes insipidus or other hypothalamic-pituitary disorders who also had an empty sella (Cacciari et al., 1994).

The following histopathological phenomena may be found in the neurohypophysis (for reviews see Kovacs, 1984; Treip, 1992; Horvath et al., 1997):

- Basophilic ACTH and β MSH containing cell invasion (Osamura and Watanabe, 1978) is generally not present before the age of 20 years. This phenomenon does not occur before puberty and is frequently (in 30%) seen in older subjects, especially in aging men. It is generally not related to any endocrine abnormality (Sheehan and Kovacs, 1982; Sano et al., 1993). However, some authors consider these cells to be one of the possible origins of basophil pituitary adenomas. In the literature two cases of basophil adenomas in the posterior lobe have indeed been recorded (Kuebber et al., 1990).
- Glandular structures (Rasmussen, 1933), i.e. ectopic salivary gland tissue resembling serous acinar and duct cells (Schochet et al., 1974; Osamura and Watanabe, 1978; Horvath et al., 1997) and lymphocytic foci (Shanklin, 1951) are common incidental findings in the posterior lobe or stalk without clinical consequences. Chronic inflammation with infiltration of lymphocytes, predominantly of the T cell and CD4+ type, and plasma cells are found in the case of lymphocytic infundibulo-neurohypophysitis and may cause diabetes insipidus. In the case of lymphocytic infundibulo-neurohypophysitis, thickening of the pituitary stalk, enlargement of the neurohypophysis and absence of the hyperintense MRI signal of the posterior pituitary are found.
- The commonest finding in the infundibular stem and process is acute haemorrhage, often petechial, but sometimes large enough to cause appreciable damage to the infundibular process. Necrosis within the infundibular process itself is very rare. Haemorrhages and necroses may be associated with traumatic head injuries, postpartum necrosis of the anterior pituitary, increased cranial pressure, shock, disseminated intravascular coagulation, septicemia, and various hematological disorders. Accumulation of neurosecretory material and retraction bulbs are evidence of ruptured axons. In the case of thrombotic thrombocytopenic purpura, vessels in the neural lobe may contain hyaline thrombi. Agonal thrombi may also be seen in the vessels of the infundibular stem.
- Chronic changes following lesions are atrophy and loss of pituicytes. Haemosiderin deposition may be found in longstanding cases and can appear within 8 days of injury.
- Cystic changes in the infundibular process have been described.
- Hypovolaemic shock of the mother at the time of delivery may not only cause pituitary necrosis, but may also affect the tuber cinereum, pituitary stalk, SON and PVN. Hypopituitarism of pregnancy may

be accompanied by diabetes insipidus of sudden onset following severe postpartum haemorrhage. However, true diabetes insipidus is rare in Sheehan's syndrome, and lesions may be present in the posterior lobe without corresponding clinical symptoms. Probably the amount of damage to the SON and PVN will determine whether or not diabetes insipidus will occur, but other factors are certainly not excluded (Sheehan and Kovacs, 1982). And indeed, in cases of postpartum hypopituitarism considerable degeneration in the SON and PVN has been reported. The estimated numbers of SON neurons remaining was often only some 20–25%. In some cases the accessory SON may disappear as well. The PVN is sometimes as strongly affected as the SON, but sometimes retains its normal neuronal numbers. In addition, nearly all cases had petechial haemorrhages in the hypothalamus, apparently related to the terminal coma (Whitehead, 1963).

- Granulomas may be present on the basis of tuberculosis, neurosarcoidosis, syphilis or Wegener's granulomatosis. The neurohypophysis is also frequently involved in histiocytosis. Diabetes insipidus may be an early sign of this disease (Catalina et al., 1995). On MRI a thickened stalk may be seen as expression of preclinical histiocytosis (Zucchini et al., 1995). Numerous eosinophilic leukocytes and lipid-laden foamy macrophages may be present or fibrosis may prevail.
- Infections and fibrosis may also be found in the neurohypophysis. Patients with septicaemia sometimes have foci of leucocytes in the posterior lobe.
- Granular cell tumors (termed choristomas by Sternberg in 1921), and granular cell myoblastomas or tumorettes by Shanklin in 1947) are the most common primary neurohypophysial tumors. They occur in some 5–17% of the pituitaries (Shanklin, 1953; Sano et al., 1993) and are found after the second decade in some 6% of the pituitary glands (Luse and Kernohan, 1955). They consist of large cells with granular, lightly eosinophilic cytoplasm (Fig. 9). They are mostly small, 1–2 mm or even smaller, and are not evident on gross inspection. They grow slowly, are histologically benign, well demarcated, but unencapsulated. The majority remains asymptomatic. In those rare cases that granule cell tumors are symptomatic they may

give diabetes insipidus, hypopituitarism, visual impairment or headache (Symon et al., 1971; Massie, 1979; Barrande et al., 1995; Ji et al., 1995). Histologically, granular cell tumors are composed of loosely apposed, large, spherical, oval or polygonal cells with eccentrically located nuclei and abundant acidophilic cytoplasm, containing PAS positive neuramic acid and carbohydrate containing granula that appear to be lysosomes under the EM. The brown cytoplasmic granules (Fig. 9) may be sufficiently numerous to impart a brown pigmented appearance to the tumor (Massie, 1979). The cells probably originate from pituicytes (Luse and Kernohan, 1955; Jenevein, 1964; Massie, 1979; Müller et al., 1980; Horvath et al., 1997). Granular cell tumors label with lectin,

Fig. 9. Cells of a granular cell tumor (choristoma) in the neurohypophysis. Note the brown pigmented cytoplasmic granules (NHB # 92-001). Scale bar, 100 μ m.

S-100 and not with neuron-specific enolase, myelin basic protein, vimentin, keratin or desmin and mostly not with GFAP. Some showed reactivity, however, for α -1-antitrypsin, α -1-antichymotrypsin and cathepsin B. The latter marker suggests a lysosomal disorder. The fact that GFAP is usually negative does not support the pituicyte as a progenitor of granular cell tumors, but it also does not exclude this possibility (Nishioka et al., 1991). Indeed, Barrande et al. (1995) and Lafitte et al. (1994) both reported a granular cell tumor to be positive for GFAP.

- Metastatic carcinomas in the posterior pituitary constitute the most important neoplasms. They may be derived from, e.g. carcinomas of the bronchus, breast, colon, prostate, malignant melanoma, sarcomas, lymphoma, Hodgkin's disease, or leukemia and may give rise to diabetes insipidus.
- Only seldom are other neoplasms found in the neurohypophysis, i.e. gliomas that are only rarely derived from pituicytes. A few cases of pilocytic pituitary astrocytomas or pituicytomas have been described. MRI shows extension of the tumor into

the pituitary stalk. Panhypopituitarism may be an early manifestation of this tumor, but diabetes insipidus may be absent, suggesting vasopressin release to take place above the level of the tumor (Nishizawa et al., 1997). In addition, gangliogliomas, hamartomas (Fig. 10), epidermoids, suprasellar germinomas, craniopharyngiomas and lipomas have been reported (Hurley et al., 1994). The first abnormal MRI sign in case of germinoma in children and adolescents was pituitary stalk thickening (Mootha et al., 1997). One case of a meningioma of the pituitary stalk has been described that must have originated from the arachnoid membrane since it had no dura attachment (Hayashi et al., 1997). A few cases of gangliocytomas have also been reported. Neoplasms of the infundibulum are described under various names, i.e. infundibuloma, hamartoma, glioma or astrocytoma.

An early stage of cytoskeletal alterations as revealed by antibodies against abnormally phosphorylated tau (e.g. AT8, PHF-1 and Alz-50) are found in fibers and Herring-body-like swellings in

Fig. 10. Asymptomatic hypothalamic hamartoma (NHB # 84186; 29 years of age) in the median eminence/pituitary stalk region stained for its strong vasopressin innervation. The tumor was less densely innervated by oxytocin fibers and did not stain for LHRH. Scale bar, 1 mm.

some aged patients, even if the brain was devoid of Alzheimer changes. Such changes are difficult to detect with the sensitive silver method. The relationship between these early Alzheimer changes in the neurohypophysis and those in the SON, PVN and the rest of the brain should be further investigated. In addition, the functional implications of these cytoskeletal changes are not yet clear (Schultz et al., 1997).

Pathological states of the neurohypophysis may be reflected in changes in the MRI high intensity signal of the posterior pituitary that is normally present in 90% of the subjects (Brooks et al., 1989; Tien et al., 1991). It was first thought to be caused by fat within the sella turcica, but the source of the hyperintense MRI signal is now presumed to be the neurosecretory granules containing vasopressin (Fujisawa et al., 1989). No attention has been paid so far to the contribution of oxytocin-containing granules. It should be noted that also in the case of persistent elevation of vasopressin plasma levels as found in diabetes mellitus and hemodialysis, the hyperintense MRI signal in the neurohypophysis may be decreased, possibly due to depletion of vasopressin storage. When treating for hyperglycaemia, plasma levels of vasopressin promptly decrease and the hyperintense MRI signal reappears within 1–2 months (Fujisawa et al., 1996;

Sato et al., 1995). The high intensity MRI signal is frequently absent in the case of macroadenoma of the anterior pituitary, craniopharyngioma, traumatic stalk transection, patients with empty sella syndrome, and diabetes insipidus. In both primary idiopathic diabetes insipidus and secondary diabetes insipidus due to e.g. germinoma, teratoma (Mootha et al., 1997), Wolfram syndrome or histiocytosis-x, the normal high intensity MRI signal was not detected. In some patients with macroadenomas, a small, high signal intensity region was seen above the pituitary gland without any high intensity from within the gland itself (Colombo et al., 1987; Fujisawa et al., 1987b), suggesting the presence of a newly formed 'miniature-posterior lobe' above the level of the neurohypophysis.

Diabetes insipidus

The brain secretes thoughts as the kidney secretes urine.

Jakob Moleschott (1822–1893)

Diabetes insipidus is characterized clinically by polyuria and polydipsia and may be due to vasopressin deficiency, a lack of kidney receptors for vasopressin or primary polydipsia.

Fig. 11. Pedigree of the Dutch hereditary hypothalamic diabetes insipidus family comprising five generations. Black symbols denote affected individuals. Females are indicated by circles and males by squares. Samples were available from individuals marked by the arrows (from Bahnsen et al., 1992, with permission).

Familial diabetes insipidus

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, and they respond to substitution therapy with exogenous vasopressin or analogues. Urine production may amount to some 20 litres per day. Members of a Dutch family suffering from this disease (Fig. 11) appeared to have a point mutation in one allele of the affected gene, based upon a G to T transversion at position 17 of the neurophysin encoding exon B on chromosome 20 (Bahnsen et al., 1992) (Fig. 12). In a Japanese diabetes insipidus family a G to A transition has been described in the same exon (Ito et al., 1991). A number of other mutations have now been found in familial hypothalamic diabetes insipidus (Fig. 13), i.e. two missense mutations that altered the cleavage region of the signal peptide, seven missense mutations in axon 2, one nonsense mutation in axon 2 and 3 nonsense mutations in axon 3 (Miller, 1993; Yuasa et al., 1993; Nagasaki et al., 1995; Rittig et al., 1996). Raug et al. (1996) found a point mutation in the carboxy-terminal domain of

neurophysin II. Both in primary idiopathic diabetes insipidus and secondary diabetes insipidus, e.g. due to germinomas, teratoma, Langerhans cell histiocytosis, or Wolfram syndrome, the normal high MRI signal of the posterior lobe is generally not detected (Fujisawa et al., 1987b; Tien et al., 1991; Rutishauser et al., 1996), although there seem to be exceptions to this rule (Miyamoto et al., 1991; Maghnie et al., 1992, 1997). The source of the hyperintense MRI signal of the posterior pituitary is most probably the neurosecretory granules that contain vasopressin (Fujisawa et al., 1989). It has, however, so far not been studied what the contribution of oxytocin and its precursor might be to the bright spot. Increased release due to persistent elevation of plasma vasopressin levels, as found in diabetes mellitus, may also go together with a decreased MRI signal intensity of the neurohypophysis (Fujisawa et al., 1996). The presence of a bright spot in diabetes insipidus may thus depend on the type of mutation, the turnover of neuropeptides in the neurohypophysis and the amount of oxytocin.

The few available postmortem histological observations in families with hereditary hypothalamic diabetes insipidus point to severe neuronal

Fig. 12. DNA sequencing gel demonstrating the difference in exon B between the normal and the mutated vasopressin-neurophysin gene allele of the individual IV-3 (see Fig. 11). The missense mutation G-T is indicated by arrows. Numbering of the deduced amino acid sequence corresponds to human neurophysin (from Bahnsen et al., 1992, with permission).

Fig. 13. Schematic diagram of the coding regions of the vasopressin (AVP)-neurophysin (NP) gene containing the glycopeptide (GP) moiety and the primary structure of the preprohormone, showing location and type of mutations identified in familial hypothalamic diabetes insipidus (from Rittig et al., 1996 with permission).

death in the SON and PVN associated with a loss of nerve fibers in the posterior pituitary (Hanhart, 1940; Braverman et al., 1965; Green et al., 1967; Bergeron et al., 1991) suggesting that the mutated product might be toxic to the neurosecretory cell. Slowly acting toxicity would also explain the variable age at onset of the disease (Schmale et al., 1993) such as in our observations that diabetes insipidus did not strike until an individual reached the age of approximately 9 years (Bahnsen et al., 1992). Other observations, too, indicate that vasopressin secretion is normal for the first few years of life, but that diabetes insipidus then develops rapidly, after which it may continue to aggravate slowly for a decade or more (McLeod et al., 1993). In one case, a 44-year-old man with hereditary diabetes insipidus, no clear cell death was found in the SON and PVN, but immunocytochemically the nuclei hardly stained for vasopressin in the PVN (Nagai et al., 1984). One can perhaps consider this as an early phase of degeneration.

When the mutant of the Dutch kindred was stably

expressed in a mouse pituitary cell line, the mutant precursor was synthesized, but processing and secretion were dramatically reduced and the protein did not seem to reach the trans-Golgi network (Olias et al., 1996). Studies in which various other human mutant vasopressin precursors were expressed in cell lines also showed an accumulation of the mutated vasopressin precursor in the endoplasmic reticulum and a reduced viability of the cells (Ito et al., 1997). This may thus be the mechanism that causes the neurosecretory neurons in hereditary hypothalamic diabetes insipidus to degenerate.

Autoimmune diabetes insipidus

Recently an autoimmune form of hypothalamic diabetes insipidus has been described with circulating autoantibodies against the vasopressin cell surface (Fig. 14). Such autoantibodies could not be demonstrated in hereditary forms of diabetes insipidus. It has not yet been established whether the autoantibodies observed in diabetes insipidus

are indeed cytotoxic and might destruct the vasopressin cell bodies (Scherbaum, 1992), but the presence of such antibodies might go together with partial diabetes insipidus, possibly even for a long period of time (De Bellis et al., 1994). In addition, a case of diabetes insipidus caused by non-specific chronic inflammation of the hypothalamus was reported. As acute multifocal placoid pigment epitheliopathy with an immunogenic predisposition was found, and human leucocytic antigen class I antigen A2 and class II antigen DR4 were observed it might be a case of autoimmune reaction (Watanabe et al., 1994). In patients with idiopathic diabetes insipidus, thickening of the pituitary stalk, enlargement of the neurohypophysis and absence of the hyperintense MRI signal were found. Biopsies of the neurohypophysis or pituitary stalk revealed chronic inflammation with infiltration of lymphocytes predominantly of the CD4+ subpopulation and plasma cells. The natural course of the lymphocytic infundibulo-neurohypophysitis generally seems to be self-limited (Imura et al., 1993; Koshiyama et al., 1994; Paja et al., 1994). However, cases with necrotizing infundibulo-hypophysitis and a combination of diabetes insipidus and hypopituitarism have been described. It is possible that this disorder as described by Ahmed et al. (1993) represents an end stage of lymphocytic infundibulitis, but alternatively it may be a unique syndrome. Wegener's granulomatosis is a systematic necrotizing vasculitis with neurological symptoms in some 50% of the cases. Anti-neutrophil cytoplasmic antibodies are present. A few cases have been described in which the disease remained

confined to the anterior and posterior pituitary, causing hypopituitarism and diabetes insipidus. The patients did not respond to immunosuppressive therapy with cyclophosphamide but in some patients corticosteroids gave a clinical remission (Roberts et al., 1995; Rosete et al., 1991). In addition, it should be noted that iatrogenic antibodies may be raised by treatment with vasopressin or pituitary snuff.

Pregnancy induced diabetes insipidus

During pregnancy a transient form of diabetes insipidus sometimes occurs. This may be partly due to the presence of vasopressinase during pregnancy. Vasopressinase of pregnancy is the same enzyme as cystine-aminopeptidase (CAP) or oxytocinase, and is produced by the placenta. It may, at least partly, be responsible for the fact that the metabolic clearance of vasopressin during pregnancy increases 4-fold. The enzyme decreases to undetectable levels in several days postpartum. Cases have been described with a transient diabetes insipidus during pregnancy due to extraordinary high plasma CAP. However, a more likely cause of polydipsia and polyuria during pregnancy is the unmasking of subclinical forms of either central or nephrogenic diabetes insipidus. Apart from the presence of CAP, a decreased threshold for thirst contributes to the aggravation of diabetes insipidus. When, during pregnancy, thirst increases, more water is consumed and the urine volume becomes unacceptable. The lowering of the thirst threshold is accompanied by a similar lowering of the osmotic threshold for the release of vasopressin. The

Fig. 14. (a) Autoantibodies to hypothalamic vasopressin cells. An unfixed 7 μ m cryostat section of human hypothalamus at the level of the supraoptic nucleus (SON) was incubated with native serum from a patient with idiopathic hypothalamic diabetes insipidus and stained with FITC-labeled anti-human-IgG. Note that the cytoplasm of large cells is stained. It could be shown by the four-layer double-fluorochrome immunofluorescence test with anti-vasopressin in the second sandwich that vasopressin cells were stained (magnification: $\times 250$). (b) The same area of the SON as in (a) incubated with normal human serum and FITC-labeled polyvalent anti-human immunoglobulin. Note that the background is brighter than the dark neurosecretory cell bodies (magnification: $\times 400$). (c) The same area of the SON as in (a) incubated with the serum of a patient with systemic lupus erythematosus containing the rare anti-ribosomal antibodies visualized by FITC-labeled anti-human IgG which may in a very rare case disturb the detection of vasopressin cell antibodies. Note the coarsely granulated cytoplasmic staining of the two large cell bodies (magnification: $\times 400$). (d) A cryostat section (7 μ m) of human hypothalamus at the level of the SON. The specimen was obtained from a donor aged 50 years. The section was incubated with normal human serum and FITC-labeled polyvalent anti-human immunoglobulin. The autofluorescent lipofuscin deposits in the cell bodies of large neurosecretory cells hamper the evaluation of test results (magnification: $\times 250$) (from Scherbaum, 1992, with permission).

response is that pregnant women drink more water that is subsequently retained. The mechanism for the altered osmoregulation in pregnancy is obscure, but the combination of changes in water homeostasis and vasopressin metabolism that occurs in normal pregnancy seems to provide an explanation for the transient expression of diabetes insipidus in pregnant women, especially in case of latent forms of neurogenic or nephrogenic diabetes insipidus (Durr et al., 1987; Iwasaki et al., 1991; Robinson and Amico, 1991; Treip, 1992; Williams et al., 1993; Van der Post et al., 1994; Lindheimer and Davison, 1995; Naruki et al., 1996).

Other causes of diabetes insipidus

Diabetes insipidus has also been observed as part of a midline developmental anomaly, e.g. in septo-optic dysplasia (Fig. 8), in dystopia of the neurohypophysis, in hypothalamic Langerhans cell histiocytosis, following skull fracture, hypoxic/ischaemic brain damage, hemorrhage, infarcts, inflammation and abscess formation, tumors of the hypothalamus, including metastases, following traumatic injuries and after surgical manipulations affecting either the SON and PVN or, more frequently, following sectioning of the hypothalamo-neurohypophysial tract. Lesions of the neurohypophysis alone may not result in diabetes insipidus when the neurosecretory nuclei remain intact. In addition, diabetes insipidus may occur in neurosarcoidosis (Treip, 1970; Rudelli and Deck, 1979; Stern et al., 1985; Fujisawa et al., 1987b; Bell, 1991; Laing et al., 1991; Arisaka et al., 1992; Catalina et al., 1995). A syndrome of partial diabetes insipidus has been reported in anorexia nervosa, where vasopressin seems to be secreted erratically, independent of plasma sodium levels (Gold et al., 1983). Structural lesions of the hypothalamus in children may go together with weight gain, diabetes insipidus, osmoreceptor dysfunction (hypernatraemia with absent thirst), pituitary deficiencies and hyperprolactinaemia (Cianfarani et al., 1993).

The hypothalamic forms of diabetes insipidus should be distinguished from a molecular defect in the vasopressin V2-receptor gene causing nephrogenic diabetes insipidus, a rare X-linked disease (Bichet et al., 1988; Holtzman et al., 1993). It is characterized by normal or elevated

concentrations of vasopressin and an insensitivity to exogenously administered vasopressin analogues. In masked diabetes insipidus, polyuria in nephrogenic diabetes insipidus is completely concealed by concomitant adrenal failure. Polyuria immediately starts following corticosteroid replacement, probably based on an intrarenal mechanism. Cortisol seems to be required for an optimal excretion of water (Iwasaki et al., 1997). On the other hand, we observed a strongly decreased vasopressin staining in the SON and PVN following corticosteroid treatment (Erkut et al., 1998), indicating a lack of free vasopressin that may also contribute to unmask diabetes insipidus.

Wolfram syndrome (acronym: DIDMOAD: diabetes insipidus, diabetes mellitus, optic atrophy and deafness; MIM222300) was first described by Wolfram and Wagener (1938). We found in the two Wolfram patients with diabetes insipidus, that the SON contained hardly any neurosecretory neurons in a thionin staining and no neurons that stained processed vasopressin. The PVN did not contain vasopressin-expressing neurons either (Fig. 15). However, using a potent antibody against the vasopressin precursor (anti-glycopeptide 22-39 Boris Y-2) a considerable number of vasopressinergic neurons was present in the PVN, although the cells were clearly too small (Fig. 15). No vasopressinergic neurons were found in the SON with Boris Y-2. The oxytocin expression in the SON and PVN seemed normal. In the two Wolfram patients who did not have vasopressin staining there was also an absence of protein convertase (PC)-2 and the molecular chaperone 7B2, strongly suggesting the presence of a processing disturbance of the vasopressin precursor (Gabreëls et al., 1998).

Lesion of the pituitary stalk

Following surgical hypophysectomy or pituitary stalk sectioning, the SON and PVN show a marked nerve cell loss that is usually more pronounced in the SON than in the PVN (Daniel and Prichard, 1975) (Figs. 16 and 17). Similar changes are found in the SON and PVN when the stalk is interrupted by metastasis (Duchen, 1966). Pituitary stalk sectioning has been employed to inhibit hypothalamic stimulation of the pituitary, e.g. in the treat-

Fig. 15. Paraffin sections through the paraventricular nucleus (PVN) of a Wolfram syndrome patient # 94-133 (A) with the antibody #III-D-7 that recognizes processed vasopressin no immunoreactivity is found. (B) No immunoreactivity is present either with the antibody # PS41 predominantly recognizing the processed form of NP, but (C) many positive cells are stained with the antibody Boris Y-2 recognizing the glycopeptide part of the VP precursor. These data indicate a processing disorder. Scale bar, 25 μ m (from Gabreëls et al., 1998, with permission).

Fig. 16. Effect of hypophysectomy on the SON. Nissl stained sections through the SON of a normal subject (a), and of two patients who had been hypophysectomized for 4 months (b) and 8 years (c). Note the great loss of nerve cells in the nucleus after hypophysectomy (from Daniel and Prichard, 1975, with permission).

Fig. 17. Effects of hypophysectomy and of pituitary stalk section on the paraventricular nucleus. Parasagittal Nissl stained sections through the paraventricular nucleus of a normal subject (a), and of a patient who died 8 years after hypophysectomy (b). AC, anterior commissure; F, anterior column of fornix; IF, interventricular foramen; PV, paraventricular nucleus; SR, supraoptic recess of third ventricle.

ment of metastatic cancer of the breast or diabetic retinopathy. Many of the SON and PVN neurons are disintegrating and dying by the end of the second week after the operation and at 3 weeks a loss of nerve cells was definitely apparent. After 3 months, dying cells were seldom seen (Daniel and Prichard, 1972, 1975). Morton (1970) found a cell loss of 25% at 3 weeks after the operation, and after 3 months, 50% of the nerve cells had disappeared. In contrast to Daniel and Prichard (1975), Morton (1961, 1970) found a continuing cell loss until about a year after the operation, when approximately 20% of the nerve cells remained. Some discrepancies in literature concerning cell loss may be due to the fact that individual variability in cell number in the SON and PVN is considerable

(see before). No close relationship has been found between the length of the remaining stalk and the number of residual cells in the SON and PVN. In the SON and PVN of stalk sectioned patients gliosis has been reported. An accumulation of Chomori positive neurosecretory material within a week after operation was reported; this increased staining disappeared after a month (Daniel and Prichard, 1972, 1975).

Following suprasellar removal of the pituitary or stalk sectioning, a polyuria starts usually one day after the operation due to the acute damage of the hypothalamo-neurohypophysial system (Seckl et al., 1990). This phase was followed by a period of normal urine levels that could be explained by the release of preformed vasopressin. The occurrence

of permanent polyuria was frequent but unpredictable. After a month, the stalk has regenerated and has a nearly normal appearance. Patchy innervation and haemosideration granules are observed. After a year, the stalk is reinnervated throughout, although less abundantly and with a finer calibre fiber than can be found in a normal stalk. From animal experiments it is estimated that if less than 5–15% of the SON cells remained in the SON, polyuria would occur (Lipsett et al., 1956). In some cases where the pituitary stalk has been transected a newly formed small ectopic 'miniature neurohypophysis' is found at the proximal stump of the transected stalk. The ectopic posterior lobe secretes vasopressin and shows a high intensity signal on T1-weighted MRI images (Fujisawa et al., 1987a; Daniel and Prichard, 1975).

The immediate effect of stalk sectioning is a venous infarction of the neural tissue of the stump that is due to thrombosis of the long portal vessels. Because the arterial blood flow is not cut off by the operation, an intense congestion of the blood vessels in the stump occurs, as well as an extravasation of blood. Necrosis of neuronal tissue may involve irregular areas higher up, up to the junction of the stalk and the optic chiasm. The cells of the pars tuberalis usually survive. Haemorrhages may extend into the hypothalamus, around the infundibular recess (Daniel and Prichard, 1972, 1975).

Depression

Currently at least four hypothalamic peptidergic systems are considered to be involved in symptoms of depression, but the decreased activity of the suprachiasmatic nucleus and the alterations in the thyroid regulation will not be discussed here.

Corticotrophin-releasing hormone (CRH) and vasopressin-expressing neurons in depression

An increasing proportion of CRH neurons express also vasopressin as a sign of activation during the course of aging (Fig. 18). Major depressed patients and patients with a bipolar depression showed a much stronger CRH neuron activation than controls or Alzheimer's disease patients as appears from the increased total number

Fig. 18. Age-related increase in the ratios of the number of CRH neurons showing colocalization with AVP over those of CRH neurons not showing colocalization with AVP. Control subjects (●), Alzheimer patients (○). Correlations between age and ratio are highly significant ($P=0.02$) in controls and Alzheimer's disease patients and show Spearman's correlation coefficients of 0.71 and 0.72, respectively. Note that the majority of CRH neurons colocalize AVP above the age of approximately 60 years (from Raadsheer et al., 1994b, with permission).

of cells expressing CRH, the increased total number of CRH neurons showing vasopressin colocalization and the increased amount of CRH-mRNA in the PVN (Raadsheer et al., 1994c, 1995). The observation that the number of non-vasopressin-coexpressing CRH neurons increased more in major and bipolar depression than the number of vasopressin-coexpressing CRH neurons (Raadsheer et al., 1994c) seems to indicate that different subtypes of CRH neurons are present in humans and that these are activated differentially in depressed patients (Raadsheer et al., 1995). This view is supported by the finding of two subtypes of CRH neurons in the PVN of experimental animals (Whitnall et al., 1993). One type colocalized AVP and, in human, increases in activity with aging and projects to the median eminence, whereas the other type does not coproduce AVP and projects to the brain stem and spinal cord (Sawchenko and Swanson, 1982). However, this principle still has to be confirmed for the human

brain. Although in the rat these non-neuroendocrine neurons represent only a minor subpopulation of the CRH neurons in the PVN (Mezey et al., 1984; Swanson et al., 1983), our data indicate that, if the same principle goes for humans, this fraction may be considerably larger in our species.

At present there are various arguments suggesting that CRH might be a causal factor in the development of symptoms of depression. Firstly, there is a strong increase of CRH activity in major depression (Raadsheer et al., 1994c, 1995); the total number of CRH neurons of the major depressed patients was four times higher than in controls (Raadsheer et al., 1994c). In addition CRH-mRNA, as determined by quantitative *in situ* hybridization, was strongly activated in major depression (Raadsheer et al., 1995). Increased plasma cortisol levels and disturbed dexamethasone suppression, enhanced adrenal response to ACTH, blunted pituitary ACTH response to CRH and adrenal and pituitary enlargement in depression also indicate increased HPA-axis activity in this disorder (Krishnan et al., 1991a,b; O'Brien et al., 1996; Rubin et al., 1996). A second argument for the crucial role of CRH is that symptoms resembling depression, e.g. decreased food intake, decreased sexual activity, disturbed sleep and motor behavior and increased anxiety can be induced in experimental animals by intracerebroventricular injection of CRH (Holsboer et al., 1992). Thirdly, antidepressant drugs attenuate the synthesis of CRH (Fischer et al., 1990; Brady et al., 1991, 1992; Delbende et al., 1991; Reul et al., 1993) and the CRH concentrations in CSF in healthy volunteers (Veith et al., 1993) and the CRH levels in CSF of depressed patients (De Bellis et al., 1993). Lastly, a transgenic mouse model which has an overproduction of CRH appeared to have increased anxiogenic behavior, i.e. symptoms that are usually related with major depression that could be counteracted by injection of CRH antagonist (Stenzel-Poore et al., 1994).

The sum of these arguments leads to the CRH-hypothesis of depression, i.e. that the hyperactivity of a subgroup of CRH neurons that sometimes colocalizes AVP and does not project to the median eminence but into the brain may be activated in depression and cause symptoms in this disorder.

Oxytocin and vasopressin neurons

CRH and vasopressin are colocalized in an increased number of PVN neurons in depressed patients (Raadsheer et al., 1994c). We not only found an increased number of vasopressin coexpressing CRH neurons in depression, but also an increase in the total number of vasopressin and oxytocin expressing neurons in the PVN, of 56% and 23% respectively, indicating an increased production and a release of these peptides (Purba et al., 1996). Our observations thus confirm the postulation of Von Bardeleben and Holsboer (1989) that the action of CRH in depression is enhanced by vasopressin. Recently Van London et al. (1997) indeed reported increased levels of vasopressin in depressed patients. The melancholic patients had higher plasma levels than the non-melancholic patients. There appeared to be a slight relationship between plasma vasopressin levels and psychomotor retardation and a significantly inverse relationship between these levels and neuroticism. The oxytocin plasma levels of depressed patients showed only a trend towards higher levels in this study.

It should be noted that not only vasopressin, but also oxytocin may potentiate the effects of CRH (Yates and Maran, 1974; Gillies and Lowry, 1979; Carlson et al., 1982; Gillies et al., 1982; Vale et al., 1983; Muir and Pfister, 1988; Makara, 1992). In the rat, oxytocin neurons that coexpress CRH are present in the PVN (Sawchenko et al., 1984; Pretel and Piekut, 1990), but in the human PVN this coexistence has not been studied. Such a coexistence may be of particular importance, since animal experiments have implicated oxytocin as a possible central mediator of CRH-induced anorexias (Olson et al., 1991a,b). In addition to their endocrine actions, CRH and vasopressin may also act synergistically on behavior. In this way, increased vasopressin and oxytocin cell activity might contribute to mood changes, decreased food intake, and cognitive impairment (Legros and Ansseau, 1992; Swaab et al., 1995). A recent study showed that patients displaying clearly increased activity of the HPA-axis in mid-afternoon had elevated vasopressin levels, as did patients who had attempted suicide. These data therefore support the possible

synergistic effects of vasopressin and CRH, both at the level of the pituitary and of behavior (Inder et al., 1997). The activation of oxytocin neurons might also contribute to the decreased food intake observed in depressed patients, since the oxytocin cells of the PVN are putative satiety neurons of the brain (Swaab et al., 1995).

The idea that activation of the CRH and vasopressin neurons is related to the symptoms of depression, is reinforced by the observation of De Bellis et al. (1993), who found a significant decrease, not only of CRH, but also of vasopressin levels, accompanied by a decrease in the Hamilton Depression Scale ratings following fluoxetine treatment. The therapeutic effects of this serotonin reuptake inhibitor may thus be related to diminution of these two arousal-promoting neuropeptides.

Schizophrenia

Schizophrenia is considered to be a developmental disturbance due to genetic, viral or metabolic factors during pregnancy, or to obstetric complications (Geddes and Lawrie, 1995; Squires et al., 1995; Susser and Lin, 1992; Susser et al., 1996). The large number of structural abnormalities reported in schizophrenia agrees with the developmental hypothesis. Various changes in vasopressin and oxytocin have been reported in schizophrenia. Mai et al. (1993) observed strongly decreased numbers of neurophysin containing neurons in the PVN of untreated schizophrenic patients, but not in their SON. Unfortunately, these authors could, however, not distinguish between vasopressin- or oxytocin-neurophysin. Indeed, changes of water metabolism with possible involvement of vasopressin have been reported in schizophrenia. Compulsive water drinking is frequently found in chronic schizophrenics (Legros and Ansseau, 1992). Water intoxication may be a serious problem in many patients suffering from a chronic psychiatric illness, as are polydipsia and hyponatremia (Goldman et al., 1988; Verghese et al., 1993). These phenomena seem to be due to unexplained defects in urinary dilution, osmoregulation or water intake and the secretion of vasopressin. Upregulation of vasopressin receptors in the kidney has been presumed (Goldman et al., 1988). For reasons that are not

quite clear, 3–5% of the chronic schizophrenic patients are hyponatremic and experience life-threatening episodes of water intoxication that may lead to seizures, delirium, irreversible neurologic defects, and death. Psychotic exacerbations are associated in this group of polydipsic schizophrenic patients with chronic hyponatremia with enhanced plasma levels of vasopressin. The exacerbated psychosis seemed to be responsible for the enhanced vasopressin release. In a group of closely matched normonatremic schizophrenic patients vasopressin levels rose a little, if at all (Goldman et al., 1997). In one patient with schizophrenia and inappropriate secretion of antidiuretic hormone, the hyponatremia ended after recovery from psychosis by electroconvulsive therapy (Suzuki et al., 1992). However, Frederiksen et al. (1991) did not observe a difference in hypothalamic vasopressin content in schizophrenic patients. There is, moreover, no consensus as far as circulating levels of neurohypophyseal hormones in schizophrenic patients are concerned (Legros and Ansseau, 1992). On the one hand, reduced vasopressin levels and their corresponding neurophysin levels have been observed in CSF and plasma (Sarai and Matsunaga, 1989). By contrast, schizophrenic patients have been reported to excrete less water after water loading, which suggests vasopressin hypersecretion (Goldman et al., 1988; Legros and Ansseau, 1992). Plasma vasopressin levels were reported to be increased in acutely psychotic patients (Raskind et al., 1978). On the other hand, Beckmann et al. (1985) did not find differences in vasopressin levels in cerebrospinal fluid in schizophrenia. Increased oxytocin levels in schizophrenic patients have been confirmed by Legros and Ansseau (1992). However, it should also be noted that antipsychotic medicines might affect the activity of the hypothalamo-neurohypophyseal system. Oxytocin levels increased after three weeks of treatment with neuroleptic drugs (Legros and Ansseau, 1992). Psychotropic drugs such as thiothixene, amitriptylene, thioridazine and chlorpromazine might cause inappropriate antidiuretic hormone secretion. Irreversible neurological symptoms and even coma have been reported as a result of such effects (Ajlouni et al., 1974; Tildesley et al., 1983; Ananth and Lin, 1987). Also animal experiments point to a stimula-

tion of supraoptic and paraventricular nuclei in rats treated with neuroleptics (Ireland and Connell, 1990). In addition, electroconvulsive therapy (ECT) results in a rise of vasopressin levels both immediately after ECT and one week after the last ECT (Narang et al., 1973). One must thus try to distinguish disease- and treatment-related effects in the reported hypothalamic alterations in schizophrenic patients.

The SON and PVN in aging and Alzheimer's disease

*It's a fortunate person whose brain
Is trained early, again and again,
And who continues to use it
To be sure not to lose it,
So the brain, in old age, may not wane
Rosenzweig and Bennett, 1996*

Various observations have provided evidence in support of our hypothesis that activation of neurons interferes in a positive way with the process of aging and with Alzheimer's disease, and may thus prolong the life span of neurons or restore their function. This hypothesis is paraphrased as 'use it or lose it' (Swaab, 1991). The neurons of the SON and PVN have been instrumental in the formation of this hypothesis, since they form a population of extremely stable cells in normal aging and in Alzheimer's disease. The classical Alzheimer changes are generally absent in the SON and PVN (Saper and German, 1987; Ishii, 1966). Despite the use of several antibodies, neither cytoskeletal alterations nor β /A4 plaques are generally found in the neurons of the SON of Alzheimer patients (Standaert et al., 1991; Swaab et al., 1992). Only in 5–8% of the old subjects studied were Alzheimer changes observed in the PVN and SON respectively (Schultz et al., 1997). These observations are in accordance with the idea that there was a relationship between metabolic activity and protection against aging and Alzheimer's disease. Although in the PVN of Alzheimer patients some neuronal and dystrophic neurite staining can be observed with cytoskeletal antibodies (Swaab et al., 1992), no β /A4 plaques are present (Standaert et al., 1991) and the total cell number in the PVN

remains unaltered (Goudsmit et al., 1990). SON and PVN neurons are not only metabolically highly active throughout life, but are extra 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 (Lucassen et al., 1993; Lucassen et al., 1994) (Fig. 19), and from the enhanced plasma levels of vasopressin (Frolkis et al., 1982; Rondeau et al., 1982) and neurophysins (Legros et al., 1980). It should be noted, though, that there are also reports that do not confirm an increased basal vasopressin plasma level in aging (Helderman et al., 1978; Rowe et al., 1980). The number of vasopressin-expressing neurons in the PVN increases during the course of aging, a change that is also interpreted as hyperactivation, and remains stable in Alzheimer patients (Van der Woude et al., 1995; Fig. 20). The increased activity of the SON and PVN during aging is most probably also the basis of the age-related decline in the frequency of the posterior pituitary bright spot found by MRI, a frequency estimated to decline with a rate of approximately 1% per year (Brooks et al., 1989).

Although after 24 h of water deprivation there is a deficit in thirst in healthy elderly men, osmoreceptor sensitivity as estimated by the vasopressin response to hypertonic saline increases with age, which is in agreement with the increased neurosecretory activity we observed. However, there is a failure of elderly people to release vasopressin in response to orthostasis and a paradoxical response to ethanol (Helderman et al., 1978; Robertson and Rowe, 1980; Rowe et al., 1980; Kirkland et al., 1984; Phillips et al., 1984). Alzheimer patients are at risk of dehydration due to a loss of the protective 'thirst' response. Plasma vasopressin levels were not different from controls after overnight dehydration, but these levels can be considered as inappropriately low for the level of serum osmolality (Albert et al., 1994).

The observation that the plasma vasopressin response to osmotic stimulation by hypertonic saline infusion is intact in Alzheimer patients. Peskind et al. (1995) supports the idea that this system remains largely unaffected in this condition. This observation also questions the impor-

Fig. 19. Photomicrograph depicting Golgi apparatus staining in vasopressinergic SON neurons of the hypothalamus of (A) a 43-year-old control subject, (B) an 82-year-old control subject, (C) a 49-year-old Alzheimer patient and (D) an 81-year-old Alzheimer patient. Note the activation with age both in controls and Alzheimer patients as shown by the increased size of the Golgi apparatus. Scale bar, 28 μm (from Lucassen et al., 1994, with permission).

tance of the cholinergic system in the osmotic response of vasopressin neurons since this system was previously shown to be seriously affected in Alzheimer's disease. As appeared from animal experiments, the increased activity of SON and PVN neurons during the course of aging might be considered as a compensatory activation due to a loss of vasopressin receptors in the kidney (Fliers and Swaab, 1983; Ravid et al., 1987; Goudsmit et al., 1988; Herzberg et al., 1989). However, such a loss of kidney receptors for vasopressin still has to be proved in human aging. In normal elderly people thirst is significantly reduced. Water conservation and excretion are also impaired. However, the relationship between vasopressin and osmolality is

unchanged, which suggests that the increased plasma osmolality seen in elderly people may be due to the kidney's reduced response to vasopressin (Ravid et al., 1987; Goudsmit et al., 1988). In this respect it is of interest that plasma osmolality may be a predictor of outcome in acutely ill elderly patients (O'Neill et al., 1990).

The number of oxytocin-expressing neurons in the PVN remains unaltered in aging and Alzheimer's disease (Wierda et al., 1991) (Fig. 21). In some projection areas, i.e. the hippocampus and temporal cortex of Alzheimer patients, the oxytocin concentrations even increased, whereas they remained unaltered in other areas (Mazurek et al., 1987), which is also in agreement with a stable oxytocin neuron population in aging.

Fig. 20. Linear regression between vasopressin (AVP) cell number in the PVN and age. Data of male (Δ) and female ($\circ$) control subjects did not differ and were pooled. A significant correlation between age and cell number was found in control subjects ($r = 0.583$, $P < 0.01$; $n = 20$). Old control subjects had a significantly higher cell number compared with young controls. Values of male ($\blacktriangle$) and female ($\bullet$) Alzheimer's disease patients are delineated by a minimum convex polygon and were reduced compared to old controls. Note that the rise in AVP cell number with age in controls does not occur in Alzheimer patients (from Van der Woude et al., 1995, with permission).

Conclusions and summary

Vasopressin is produced in the human SON, PVN, SCN, diagonal band of Broca, bed nucleus of the stria terminalis, oxytocin is produced in the PVN and SON. Vasopressin and oxytocin are not only released as neurohormones in the neurohypophysis, to regulate kidney function and reproduction, in the median eminence together with CRH to release ACTH, but also as neurotransmitters or neuromodulators in other parts of the brain, influencing e.g. blood pressure, temperature regulation, cognitive functions, social attachment, paternal behavior, food intake and sexual behavior. Fetal vasopressin and oxytocin play a role in the adaptation to the stress of labor, and in speeding up the course of labor. In Prader-Willi syndrome the 50% drop in the number of oxytocin-expressing neurons is thought to be related to the insatiable hunger of these patients.

Developmental disorders affecting the vasopressin and oxytocin neurons include septo-optic dysplasia and anencephaly, while dystopia of the neurohypophysis rarely affects neurohypophysial function. Chronic alcohol consumption affects the vasopressin neurons mainly in the SON, but also in the PVN. Stalk sectioning causes a strong loss of neurons in both the SON and PVN. Pathology of the neurohypophysis includes acute haemorrhage and hypovolaemic shock, which may cause not only pituitary necrosis, but also a lesion of the SON and PVN, and granulomas, infections, granular cell tumors, metastatic carcinomas, hamartomas and other tumors. In addition, cytoskeletal Alzheimer alterations are sometimes found.

Diabetes insipidus might be of a primarily hypothalamic-familial nature due to mutations or, secondarily, to tumors, Langerhans cell histiocytosis, Wolfram syndrome, autoimmune processes, increased levels of cystine-aminopeptidase during pregnancy, septo-optic dysplasia, trauma, cerebrovascular lesions. It might also be caused by a molecular defect in the V_2 -receptor, causing nephrogenic diabetes insipidus. Other drinking

Fig. 21. Linear regression between oxytocin (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 Alzheimer disease patients (closed symbols) are delineated by a minimum convex polygon and were within the range of the controls (from Wierda et al., 1991, with permission).

disorders are primary polydipsia, adipsic or hypodipsic hypernatraemia, nocturnal diuresis, vasopressin hypersecretion in diabetes mellitus, inappropriate secretion of vasopressin (Schwartz-Bartter syndrome) and cerebral salt wasting.

In depression the increased number of CRH neurons that coexpress vasopressin may be related to mood disorder, the oxytocin cell activation to the eating disorder, the vasopressin increase to the risk of suicide and the decreased activity of the SCN to sleep disturbances. In schizophrenia changes in vasopressin and oxytocin have also been observed.

In aging, also in Alzheimer patients, the SON and PVN neurons are activated and remain generally intact. This supports the idea that activation of neurons interferes in a positive way in the process of aging and Alzheimer's disease, a concept that was paraphrased by us as 'use it or lose it'.

Acknowledgements

I am very grateful to Ms. W.T.P. Verweij for her excellent secretarial assistance, to Dr. J. Kruisbrink for her bibliographical help, to Mr. G. van der Meulen for his photographic work, and to the Netherlands Brain Bank (coordinator Dr. R. Ravid) for the hypothalami.

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