CHAPTER 9

Neuropeptide changes in aging and Alzheimer’s disease

E. Fliers and D.F. Swaab

Netherlands Institute for Brain Research, Meibergdreef 33, 1105 AZ Amsterdam ZO, The Netherlands

Introduction

Neuropeptides are an ever growing group of putative neurotransmitters. Although the exact function of any of these peptides is not known at present, they are capable of eliciting a variety of effects upon central or peripheral administration (for a review see Swaab, 1982). Neuropeptide effects have also been demonstrated on functions, which are known to change in aging and Alzheimer’s disease, such as cognitive functions. This is one of the reasons why interest in changes in neuropeptide systems in senescence and Alzheimer’s disease has increased over the past decade. In addition, research on peptidergic changes in brain areas which are known to exhibit changes in other neurotransmitter systems such as acetylcholine (Candy et al., 1986) or monoamines (Gottfries, 1986), may yield information with respect to the specificity of alterations in neurotransmitter systems with aging or in Alzheimer’s disease. Any selectivity in neurotransmitter changes in Alzheimer’s disease may contribute to a better understanding of its pathogenesis, which is a prerequisite for the development of a rational therapeutic approach (Swaab and Fliers, 1986).

In various earlier studies, changes were demonstrated in neuropeptide systems which in general seemed to be indicative of degeneration. For instance, the level of somatostatin (SOM) was found to be reduced in a number of cortical areas in patients with Alzheimer’s disease (Davies et al., 1980; Rossor et al., 1980a). These findings were confirmed in later studies (Davies and Terry, 1981; Arai et al., 1984). Ferrier et al. (1983) reported decreased SOM levels in several cortical areas in Alzheimer’s disease, without significant reductions in neurotensin (NT) or substance P (SP) levels. However, the decrease in SOM did not simply reflect the pattern of neuropathological changes, since in the hippocampus no difference was observed between patients with Alzheimer’s disease and controls. Furthermore, there was no close correlation between changes in the cholinergic system and SOM changes in the cortical areas studied, suggesting a rather indirect relationship between these two systems. This was also illustrated by the fact that in the substantia innominata, where a 50% reduction in choline acetyltransferase (CAT) activity was found, concentrations of SOM were increased, which points towards selective neuropeptide changes in Alzheimer’s disease, that are probably not directly related to changes in e.g. the cholinergic system.

Spatial selectivity of changes in neuropeptide systems also appeared from a study of Sanders et al. (1982), showing increased concentrations of glucagon in the grey matter of the temporal cortex in Alzheimer’s disease, without differences in the occipital cortex. Other examples of reduced peptide concentrations in Alzheimer’s disease are vasoactive intestinal polypeptide (VIP) in insular and angulate cortex (Arai et al., 1984) and, in contrast to the study of Ferrier et al. (1983), cortical substance P (Crystal and Davies, 1982).

Neuropeptide concentrations in brain areas
reflect, however, only a balance between the rates of production, transport, release and degradation. Consequently, changes in neuropeptide concentrations do not give any indication with respect to the direction in which the activity of peptidergic neurons has changed. Conversely, the absence of a decreased concentration does not rule out a marked reduction in the total number of afferent fibers, for example in the case of cortical atrophy. Consequently, it seems impossible to interpret changes in concentrations in terms of functional integrity of a particular peptidergic system. In that respect it might, however, be of interest that also in the cerebrospinal fluid (CSF), decreased neuropeptide concentrations have been reported in Alzheimer's disease e.g. for oxytocin (OXT) (Unger et al., 1971), ACTH (Facchinetti et al., 1984) and SOM (Oram et al., 1981; Soininen et al., 1984).

**Vasopressin, aging and Alzheimer’s disease**

One peptide which has received much attention in relation to aging and Alzheimer's disease is vasopressin (VP), in view of its effects on certain aspects of memory as originally demonstrated by the group of De Wied (for review see De Wied, 1983). VP cells are present in the supraoptic and paraventricular nuclei (SON and PVN), from which they project to the neurohypophysis, where the peptide is released into the blood. These are the 'classical' neurosecretory cells of the hypothalamo-neurohypophyseal system (HNS), involved in the maintenance of water and salt homeostasis. VP cells are also present in the suprachiasmatic nucleus (SCN), both in the rat (Swaab et al., 1975; Vandesande et al., 1975) and in man (Dierickx and Vandesande, 1977; Swaab et al., 1985). VP fibers are present in many extrahypothalamic brain areas both in the rat and in man (Buijs et al., 1978; Fliers et al., 1986), where they most probably act as neurotransmitters (Buijs, 1982). Recent work in the rat showed that in many of these extrahypothalamic areas of termination, VP fibers are dependent upon the levels of circulating androgens (De Vries et al., 1985). Many of the areas of termination contain VP fibers that are derived from the bed nucleus of the stria terminalis (BST), which, along with the dorsomedial hypothalamus, medial amygdaloid nucleus and locus ceruleus, was found to contain VP-immunoreactive cells in colchicine-pretreated rats (Van Leeuwen and Caffè, 1983; Caffè and Van Leeuwen, 1983). The human BST was also found to contain VP neurons, but the pattern of extrahypothalamic VP fiber distribution was found to be different from that in the rat (Fliers et al., 1986).

With respect to the neurosecretory pathway, degenerative changes with aging were proposed by Legros (1975), who showed decreased blood levels of neurophysins in a group of healthy men aged 50–60, as compared with younger age groups. In aged rodents, neurohypophyseal failure was proposed already in the 1950's (Friedman and Friedman, 1957). Effects of aging on the regulation of VP secretion were also observed. An increased VP response to hypertonic saline infusion has been reported (Helderman et al., 1978; Robertson and Rowe, 1980), while VP secretion in response to hemodynamic stimuli was found to decrease with aging (Rowe et al., 1982). However, these observations may give information regarding receptor sensitivity rather than the integrity of the HNS as such.

Because of the importance of salt and water homeostasis for the organism, the effects of treatment of aged rats with suspensions of posterior pituitary extracts on lifespan were tested. A significant prolongation of the mean lifespan was indeed observed after long-term treatment of old rats (Friedman and Friedman, 1963). However, in later experiments, this effect turned out to be due to OXT rather than to VP (Bodanszky and Engel, 1966). This surprising observation has not had any recent follow-up.

Legros' observations (1975), together with results of experiments indicating effects of VP on memory functions (see De Wied, 1983) have led to a number of clinical trials, in which VP or its analogs were administered to patients with Alzheimer's disease (for review see Jolles, 1983; Jolles,
Moderate improvement of certain aspects of cognition was found in some studies, involving mildly impaired AD patients. However, major improvement of memory functions was not found (Jolles, 1986).

With respect to the integrity of centrally projecting VP cells in senescence and Alzheimer’s disease, only very few data were available until recently. Rossor et al. (1980b) reported a non-significant decrease in VP concentrations in a number of extrahypothalamic brain areas in Alzheimer’s disease, while a significant decrease was found in globus pallidus. In the aged rat brain, Dorsa and Bottemiller (1982) reported decreased VP concentrations in a number of extrahypothalamic areas. However, again these data were hard to interpret in terms of activity changes (see before). In human CSF, lower (Sundquist et al., 1983; Sørensen et al., 1983) as well as higher (Tsuji et al., 1981) VP levels in Alzheimer’s disease have been reported, making unequivocal conclusions impossible.

In our studies on VP and OXT in the human brain, we have tried to circumvent the methodological pitfalls mentioned before by studying both cells of origin and areas of innervation, and by applying morphometric techniques that would indicate the direction of functional changes to immunocytochemically identified neurons. VP cells were studied from early infancy into senescence, while also brain material from patients with neuropathologically verified Alzheimer’s disease was studied.

**Hypothalamic VP cells in aging and Alzheimer’s disease**

In the SON and PVN, the size of immunocytochemically identified VP and OXT neurons and their nucleoli was measured as a parameter of neurosecretory activity (cf. Zambrano and De Robertis, 1968; Russel, 1983). No significant changes were observed in cellular profile areas of OXT cells from early infancy into senescence. However, VP cellular profile area was significantly increased both in the PVN and in the SON from 80–100 years of age, pointing to activation of VP neurons. The Alzheimer’s disease patients showed similar values as controls (Fliers et al., 1985a). A similar differential pattern of changes was found for the size of nucleoli of VP and OXT cells, viz., a significant increase in nucleolar size of VP cells after 80 years of age without changes in nucleolar size of OXT cells. The values of the Alzheimer’s disease patients were commensurate with their age-matched controls (Hoogendijk et al., 1985). A highly significant correlation was found between mean nucleolar diameter and mean cellular profile area per patient of VP cells in the SON and PVN (p < 0.001). These results were indicative of increased neurosecretory activity of VP cells in senescence, as opposed to earlier reports in the literature (cf. Legros, 1975; Rowe et al., 1982). Two arguments plead against the possibility that the observed activation of neurosecretory VP cells has to be considered as a compensatory mechanism for cell loss from the PVN or SON: (a) recent studies reported elevated plasma levels of VP, both in the aged rat and in man (Frolkis et al., 1982; Fliers and Swaab, 1983; Miller, 1985; Kirkland et al., 1984), (b) determination of total cell numbers in the SON and PVN in the same material revealed no cell loss during normal aging. Cell numbers in the SON of Alzheimer’s disease patients were somewhat lower than in age-matched controls, but this difference was not statistically significant. In the PVN, similar cell numbers were found in Alzheimer’s disease patients and controls (Goudsmit et al., 1986; Swaab et al., 1986).

In aged rats, a strongly diminished VP binding in renal distal convolutes and collecting ducts was found (Ravid et al., 1986a). This opens the possibility of the activation of neurosecretory VP cells being a consequence of decreased renal sensitivity for VP in senescence. Another factor of possible causal importance is changes in gonadal function in senescence. Blood levels of testosterone decrease during aging, both in man (Deslypere and Vermeulen, 1984) and in the rat (Kaler and Neaves, 1981; Ravid et al., 1986b). Since castration of male rats has been shown to result in increased
neurosecretory activity in the SON and PVN (Swaab and Jongkind, 1970) and in increased VP blood levels (Skowsky et al., 1979), the decreased levels of testosterone in senescence may contribute to the activation of neurosecretory VP cells in senescence. In addition, changes in the afferent innervation of the SON and PVN may play a role in the observed age-related changes. Sladek et al. (1983) observed a decrease in the catecholaminergic innervation of the SON in aged rats. No data are available on the human SON and PVN in this respect.

A completely different pattern of age-related changes was found in another VP cell containing hypothalamic nucleus, viz., the suprachiasmatic nucleus (SCN). This nucleus is considered to be the major circadian pacemaker of the mammalian brain, coordinating hormonal and behavioral circadian rhythms (e.g. Rusak and Zucker, 1979). Age-related changes in circadian rhythms have been reported in man as well as in other species (for review see Van Gool and Mirmiran, 1986). Among the most prominent changes is a fragmentation of sleep-wake patterns which occurs in senescence (Van Gool and Mirmiran, 1983), a phenomenon that is even more obvious in Alzheimer’s disease patients (Prinz et al., 1982). Since the human SCN is hardly recognizable in conventionally stained material (Lydic et al., 1980), immunocytochemical staining of VP cells was used in order to visualize the nucleus, making it accessible to morphometric investigation.

A marked decrease in SCN volume, VP cell number and total cell number was found in subjects aged 80–100, while in Alzheimer’s disease patients these changes were more pronounced than in age-matched controls (Swaab et al., 1985). Since the size of the SCN has been shown to be directly related to the expression of its pacemaker properties (Pickard and Turek, 1983), the observed decrease in SCN volume and cell number in senescence and Alzheimer’s disease suggests a causal relationship between degenerative changes in the SCN and disturbances of circadian rhythmicity in these conditions.

The observations of increased activity of neurosecretory VP cells in senescence and Alzheimer’s disease without concomitant cell loss in the SON and PVN, and of decreased SCN volume and cell number point towards differential changes with aging within one brain area, viz., the anterior hypothalamus, even among neurons of one peptidergic type, viz., VP neurons. The fact that all morphometric analyses were performed in one series of brain material gives extra support to this point. Since in the SCN, neither VP-cell density nor total cell density showed any significant changes with aging or in Alzheimer’s disease, it can be concluded that determination of cell density does not necessarily give information with respect to cell loss. Apparently, marked cell loss may go together with unaltered cell density in case the volume of a particular structure decreases.

The pronounced changes observed in the SCN in senescence and Alzheimer’s disease at first glance suggest that neurotransmitter changes in these conditions are not restricted to the cholinergic system. However, data concerning a possible cholinergic innervation of the human SCN are lacking. Therefore, our observations at present do not rule out cholinergic involvement in the disrupted circadian organization in Alzheimer’s disease.

**Changes in extrahypothalamic VP fibers in the aging brain**

In order to investigate what the consequences of the differential changes with aging in VP cells are for the vasopressinergic innervation of extrahypothalamic brain areas, young and old Brown-Norway rats were compared with respect to the density of VP fibers in a number of brain areas. A marked decrease of VP fiber density was found in 34-months-old rats as compared with the 5-months-old control animals in the vertical limb of the diagonal band, the basal nucleus of Meynert (Fig. 1), the lateral habenular nucleus, the medial amygdaloid nucleus, the substantia nigra, the ventral hippocampus, the central grey, the locus
Fig. 1(A and B). Transverse sections of the basal nucleus of Meynert (B) and medial amygdaloid nucleus (MA) of a young (1A) and old (1B) rat. Note the low VP fiber density in both areas in 1B. Arrows point towards weakly staining VP immunoreactive cells that were found in both MA and B of young animals only. OT, optic tract; ST, stria terminalis. Bar represents 100 µm.
neurosecretory activity in the SON and PVN (Swaab and Jongkind, 1970) and in increased VP blood levels (Skowiansky et al., 1979), the decreased levels of testosterone in senescence may contribute to the activation of neurosecretory VP cells in senescence. In addition, changes in the afferent innervation of the SON and PVN may play a role in the observed age-related changes. Sladek et al. (1983) observed a decrease in the catecholaminergic innervation of the SON in aged rats. No data are available on the human SON and PVN in this respect.

A completely different pattern of age-related changes was found in another VP cell containing hypothalamic nucleus, viz., the suprachiasmatic nucleus (SCN). This nucleus is considered to be the major circadian pacemaker of the mammalian brain, coordinating hormonal and behavioral circadian rhythms (e.g. Rusak and Zucker, 1979). Age-related changes in circadian rhythms have been reported in man as well as in other species (for review see Van Gool and Mirmiran, 1986). Among the most prominent changes is a fragmentation of sleep-wake patterns which occurs in senescence (Van Gool and Mirmiran, 1983), a phenomenon that is even more obvious in Alzheimer’s disease patients (Prinz et al., 1982). Since the human SCN is hardly recognizable in conventionally stained material (Lydic et al., 1980), immunoocytochemical staining of VP cells was used in order to visualize the nucleus, making it accessible to morphometric investigation.

A marked decrease in SCN volume, VP cell number and total cell number was found in subjects aged 80–100, while in Alzheimer’s disease patients these changes were more pronounced than in age-matched controls (Swaab et al., 1985). Since the size of the SCN has been shown to be directly related to the expression of its pacemaker properties (Pickard and Turek, 1983), the observed decrease in SCN volume and cell number in senescence and Alzheimer’s disease suggests a causal relationship between degenerative changes in the SCN and disturbances of circadian rhythmicity in these conditions.

The observations of increased activity of neurosecretory VP cells in senescence and Alzheimer’s disease without concomitant cell loss in the SON and PVN, and of decreased SCN volume and cell number point towards differential changes with aging within one brain area, viz., the anterior hypothalamus, even among neurons of one peptideergic type, viz., VP neurons. The fact that all morphometric analyses were performed in one series of brain material gives extra support to this point. Since in the SCN, neither VP-cell density nor total cell density showed any significant changes with aging or in Alzheimer’s disease, it can be concluded that determination of cell density does not necessarily give information with respect to cell loss. Apparently, marked cell loss may go together with unaltered cell density in case the volume of a particular structure decreases.

The pronounced changes observed in the SCN in senescence and Alzheimer’s disease at first glance suggest that neurotransmitter changes in these conditions are not restricted to the cholinergic system. However, data concerning a possible cholinergic innervation of the human SCN are lacking. Therefore, our observations at present do not rule out cholinergic involvement in the disrupted circadian organization in Alzheimer’s disease.

Changes in extrahypothalamic VP fibers in the aging brain

In order to investigate what the consequences of the differential changes with aging in VP cells are for the vasopressinergic innervation of extrahypothalamic brain areas, young and old Brown-Norway rats were compared with respect to the density of VP fibers in a number of brain areas. A marked decrease of VP fiber density was found in 34-months-old rats as compared with the 5-months-old control animals in the vertical limb of the diagonal band, the basal nucleus of Meynert (Fig. 1), the lateral habenular nucleus, the medial amygdaloid nucleus, the substantia nigra, the ventral hippocampus, the central grey, the locus
Fig. 1(A and B). Transverse sections of the basal nucleus of Meynert (B) and medial amygdaloid nucleus (MA) of a young (1A) and old (1B) rat. Note the low VP fiber density in both areas in 1B. Arrows point towards weakly staining VP immunoreactive cells that were found in both MA and B of young animals only. OT, optic tract; ST, stria terminalis. Bar represents 100 μm.
Fig. 2(A and B). Transverse cryostate section, stained for VP, of the locus ceruleus of a 74-year-old subject. (B), detail from (A). Note the dense VP fiber network in the LC between the neuromelanin-containing cell bodies. Arrow points towards structure, suggestive of perineuronal innervation. LC, locus ceruleus; V, fourth ventricle. Bars represent 100 $\mu$m (A) and 50 $\mu$m (B), respectively.
ceruleus and the ambiguus nucleus. The VP innervation of the lateral septum and the dorsomedial hypothalamic nucleus was moderately, although not significantly reduced. No age difference was found in the VP innervation of the paraventricular thalamic nucleus or in the nucleus of the solitary tract. OXT fiber density did not differ in any of the brain areas studied. Thus, the aging process appeared to affect centrally projecting VP cells in a differential way as well (Fliers et al., 1985b).

There is a remarkable similarity between the pattern of decrease in VP fiber density with aging and that observed following castration (cf. De Vries et al., 1985). In view of this parallel and since testosterone levels decrease during aging in rats of various strains (Kaler and Neaves, 1981; Chambers and Phoenix, 1984; Ravid et al., 1986b), the observed decrease in VP fiber density might be explained in part by age-related decline in testosterone levels. Therefore, long-term testosterone treatment of aged rats may yield interesting information with respect to the possible reversibility of these innervation changes and its potential behavioral consequences.

Also in the human brain a start was made with the investigation of the VP innervation of extrahypothalamic brain areas. Until recently, only little information was available on the morphologic distribution of VP fibers in the human brain, since most of the studies so far were performed by radioimmunoassay (RIA) (Rossor et al., 1981; Jenkins et al., 1984). However, also by means of immunocytochemistry as applied to post-mortem brain tissue, VP fibers could be demonstrated in the brain stem and spinal cord (Sofroniew et al., 1981), while the presence of VP fibers in the septum and spinal cord was found already by 17 weeks of gestation (Swaab and Ter Borg, 1981).

In a recent study, the VP and OXT innervation in brain material of human subjects aged 18–90 was investigated by means of immunocytochemistry (Fliers et al., 1986). In contrast to the rat brain, VP fibers were found only in low numbers in the septum, where, in contrast to the situation in rat, no sex difference in VP fiber density was found. Very few VP fibers were found to be present in the amygdala and in the hippocampus. By contrast, the locus ceruleus contained dense networks of VP fibers over its entire rostro-caudal extension (Fig. 2). The extrahypothalamic VP innervation thus appears to be quite different from that seen in the rat, in that the innervation of human limbic structures is less pronounced than in the rat, whereas the innervation of the locus ceruleus is denser in the human brain as compared with the rat brain. As opposed to the rat, no effects of age on VP fiber density was found in any of the brain areas studied.

In future studies, the extrahypothalamic VP innervation will be investigated in brain material from Alzheimer's disease patients as well.

**Summary and conclusions**

In the present chapter, the pattern of peptidergic changes in Alzheimer's disease is reviewed and compared with changes during normal aging. Many peptides have been measured in Alzheimer's disease brain tissue and age-matched control material. Reduced cortical levels of SOM have been reported consistently, while reports of reductions in other neuropeptide systems (e.g. substance P) were not consistent. VP was reported to be reduced in a number of extrahypothalamic brain regions, although statistical significance was reached only in the globus pallidus. In the CSF, ACTH, SOM and OXT have been reported to be reduced in Alzheimer's disease. It is argued, however, that the mere determination of peptide concentrations in brain areas is not sufficient to investigate age-related or disease-related changes in peptidergic systems, since the observed changes cannot be interpreted in functional terms.

A different approach towards the elucidation of peptidergic changes during aging and Alzheimer's disease is the assessment of parameters that indicate changes in cell function, i.e. cell size or nucleolar size, in immunocytochemically identified peptidergic neurons. Application of such pro-
cedures to VP and OXT neurons in the human SON and PVN revealed increased neurosecretory activity of VP, but not of OXT cells in senescence and Alzheimer’s disease. By contrast, extensive cell loss was found in the SCN, a VP cell containing hypothalamic area which is essential for the coordination of hormonal and behavioral circadian rhythms. Therefore, changes in VP cells during aging and Alzheimer’s disease were found to be specific for the hypothalamic area studied. A topographic selectivity of age-related changes was also found in the VP innervation of the rat brain. The VP innervation of the human brain was found to differ from the rat brain, without any apparent age differences being found so far.

From these data it can be concluded that:

(a) changes in neurotransmitter systems in senescence and Alzheimer’s disease are not restricted to cholinergic or monoaminergic neurons, but also include neuropeptides;

(b) changes in peptidergic neurons show a strong topographic selectivity, even among neurons of one peptidergic type;

(c) marked species differences may exist with respect to the neuroanatomy of peptidergic systems.

For these reasons, and in particular because there is no animal experimental model for Alzheimer’s disease so far, it is essential to investigate such neurotransmitter changes in the human brain in order to obtain an insight into the neurotransmitter changes occurring in this disease.

Acknowledgements

The authors are indebted to the Foundation for Medical Research (FUNGO) and the Stichting Onderzoek op het gebied van de Ouder wordende Mens (SOOM) for financial support, to Dr. F. Van Haaren for checking the English and to Ms. T. Eikelboom for typing the manuscript.

References


Discussion

R. S. J. FRACKOWIAK: Do you think your observation of differential sensitivity of neurons in one neurotransmitter system (which though anatomically distinct are spatially closely related) has any pathogenic implication or gives us any insight into pathogenic mechanisms in Alzheimer's disease?

ANSWER: Indeed, we are currently trying to elucidate the mechanisms underlying these differential changes. In the SCN a change in ACh innervation belongs to the possibilities. However, recent immunocytochemical staining with CAT antibodies failed to reveal a cholinergic innervation of the human SCN. Studies in rat have shown a reduction in both amplitude and period of circadian rhythm in senescence (Van Gool and Mirmiran, 1986), which may be related to a reduction in cell numbers in the SCN. Current experiments in aged rats are directed towards environmental manipulation of the age related changes in circadian rhythms. For the changes which we observed in the extrahypothalamic VP innervation of the rat brain, decreased blood levels of testosterone may be responsible, since the VP innervation of a number of brain areas has been shown to be dependent upon the levels of circulating androgens, both during development and in adulthood (De Vries et al., 1985). Recent experiments involving immunocytochemical staining of VP binding sites in the kidney suggest a role for the kidney in the increased neurosecretory activity of VP cells in senescence. All of these possibilities will be tested in future research.

D. M. GASH: What was the range in the number of vasopressin neurons in the SCN of AD patients? Was there an overlap between cell numbers found in AD patients and in the normal aged population?

ANSWER: There was an overlap. However, a comparison of AD patients with age- and sex-matched controls revealed a statistically significant difference in the number of SCN neurons between AD patients and controls.

R. D. TERRY: I do not believe that replacement of one or several neurotransmitters will provide effective improvement in Alzheimer's disease. Only finding and preventing the etiologic agent would seem to offer major help. L-DOPA's success in Parkinson's disease seems actually to have delayed research on the cause of that disease.

ANSWER: I fully agree with your point regarding replacement therapy in Alzheimer's disease, but I do think that our immunocytochemical approach towards the elucidation of changes in certain neurotransmitter systems may help us in obtaining a better insight into parts of the pathogenesis of AD.

A.J. CROSS: Two points about Dr. Terry's comments: (1) In Parkinson's disease there are many transmitter disturbances present in the brain at autopsy, yet L-DOPA still proves to be a useful therapeutic agent.

(2) I do not think that the relationship between plaques and the presence of dementia has been proved. In scrapie in animals, in some models one can get a proliferation of plaques without any obvious behavioral changes.

D.F. SWAAB: There are also theoretical reservations with respect to the proposed substitution therapies with neurotransmitters. It may be somewhat naive to think that we can replace the integrating capacity of the lost neurons by administrating their neurotransmitters. The brain is more than a solution of 1.5 litres of neurotransmitter!

P.W.M. RAJIMAKERS: Do you know of any changes in afferents to the VP cells in SON and PVN that might be causing the age-dependent increase in VP that you find?

ANSWER: In aged rats, a decrease in the catecholaminergic innervation of the SON has been demonstrated (Sladek et al., 1983). However, we do not have data on age-related changes in other afferents to the PVN and SON in the rat. No data are available on the human brain in this respect. However, endocrine factors may be of importance as well. Recent results showed that VP binding to renal collecting ducts and distal convolutes is strongly diminished in aged rats. Hence, the activation of neurosecretory VP cells in the senescent brain might be secondary to decreased renal sensitivity for VP. A third factor of possible importance for the observed activation of VP cells is decreased levels of testosterone in senescence, since castration of adult rats has been shown to induce elevated VP blood levels (Skowsky et al., 1979) and increased neurosecretory activity of VP cells in the SON and PVN (Swaab and Jongkind, 1970). These possibilities will be investigated in future research.

References


