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VASOPRESSIN AND OXYTOCIN—THEIR ROLE IN NEUROTRANSMISSION

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1. INTRODUCTION

Chemical transfer of information in the brain is at present a well accepted phenomenon for quite a number of substances already. It is less than fifty years ago that Dale (1935) put forward this theory for the central nervous system. He had fierce opposition to overcome (Eccles and O'Connor, 1939) and it was not until 1954 that Dale's former opponent proved this theory to be true for the spinal cord (Eccles *et al.*, 1954). Since that time it has generally been accepted that transfer of information from one neuron to another can occur via release of a chemical substance (the neurotransmitter) at the synaptic terminal—in such a way changing the postsynaptic membrane potential.

An apparently completely different idea with regard to the transfer of central information was the concept of neurosecretion, as put forward by Scharrer and Scharrer (1937). They suggested that certain neurons would be capable of releasing their product into the bloodstream in order to reach distant target structures. This theory was likewise welcomed 'not only with scepticism, but mostly with outright rejection' (Scharrer, 1974). According to the critics these neurosecretory cells were "nothing more than signs of postmortem changes of degenerative processes". The concept of neurosecretion was only fully accepted after Bargmann (1949) had applied Gomori's pancreas staining to brain sections and thus stained the neurosecretory cells of the hypothalamus and their fiber tracts into the neural lobe. In a combined publication Bargmann and Scharrer (1951) concluded that the stainable material contained the antidiuretic and oxytocinergic principles which were transported from the neurosecretory cells towards the neural lobe via the hypothalamo-neurohypophyseal tract.

In the neuroendocrinological literature much emphasis has been put on the 'unique' characteristics of the neurosecretory neuron. 'The crucial issue in the definition of what is now often referred to as "classical neurosecretory neuron", was that it fails to engage in synaptic chemical transmission, but instead manufactures (and discharges) substantial amounts of peptidergic neurohormones in the manner of classical protein-secreting cells' (Scharrer, 1974). In view of this, it is even more remarkable that Barry proposed, as early as 1954, the existence of Gomori-positive terminations within the central nervous system, which he thought originated from the paraventricular nucleus and which he called 'des synapses neurosecretoires' (Barry, 1954). However, because (1) the synaptic nature of these terminations could only be proved with electron microscopy that could not be combined with the Gomori technique (Barry, personal communication), (2) these observations were so different from the at that time only recently neurosecretory character of the Gomori-positive cells, (3) such terminations could not be fitted into any known neurobiological function and (4) as the publications were in French, these excellent studies were neglected or overlooked. Yet observations in the thirties already suggested central effects of pituitary hormones. Cushing (1932) demonstrated pronounced central effects of an extract of the neurohypophysis following an injection into the cerebral ventricles of hypophysectomized patients, and Popa (1938) distinguished two centrally active pituitary principles: 'cerebrostimuline' and 'cerebrolaxine' in his experiments on frogs.

It was de Wied, however, who opened up the experimental field on the effects of pituitary hormones on the brain, while studying the role of ACTH in acquisition and extinction of avoidance behavior. Posterior lobectomy facilitated the extinction in a conditioned shuttle-box avoidance response. Administration of an extract of the neurointermediate lobe of the pituitary restored the extinction rate (de Wied, 1965). An active principle of this preparation appeared to be vasopressin (Lande *et al.*, 1971) since it was found that a subcutaneous injection of vasopressin to intact animals resulted in the consolidation of the acquired behavior (de Wied, 1971). Because of the apparently pure endocrine nature of this phenomenon—the effect of removal of the endocrine ‘gland’ was abolished by peripheral administration of the hormone (de Wied, 1965)—the peripheral circulation (Thompson and de Wied, 1973) or the cerebrospinal fluid (van Wimersma Greidanus *et al.*, 1975) were proposed as the routes via which vasopressin would reach the central sites of action. In order to investigate these putative routes for centrally active vasopressin, Dogterom (1977) measured neurohypophyseal hormone levels in plasma and CSF of rats under various experimental conditions. No correlation was found, however, between vasopressin blood levels and the acquisition of passive avoidance (van Wimersma Greidanus *et al.*, 1979). Moreover, peripherally injected vasopressin antiserum did not influence the passive avoidance behavior (van Wimersma Greidanus *et al.*, 1975).

The possibility that CSF was the (main) transport route for centrally active vasopressin and oxytocin was also not experimentally supported. The inhibition of passive avoidance behavior by administration of anti-vasopressin was interpreted as a neutralization of vasopressin in the CSF (van Wimersma Greidanus *et al.*, 1975). However, immunocytochemical observations revealed that the antisera penetrate the CNS with a spread of approximately 300 $\mu\text{m/hr}$ (Swaab and Boer, 1980), suggesting that neutralization in brain tissue is another possibility. Radioimmunoassay measurements in CSF of oxytocin and vasopressin in intact and hypophysectomized rats indicated the presence of these peptides in the CSF, but no distinction could be made whether this was before or after the hormones had executed their central effects. High vasopressin levels in the CSF of hypophysectomized rats (Dogterom *et al.*, 1977) were, however, apparently contradictory with the absence of avoidance response, which suggested that the CSF neurohypophyseal hormone content was not of primary importance for this behavioral paradigm. This condition was recently supported by the finding that vasopressin CSF levels did not change during acquisition and retention of a passive avoidance response (Mens *et al.*, 1983). However, it may be that changes in vasopressin CSF levels occur as a result of behavioral manipulation within a short period of time, i.e. at other time points than those used by Mens *et al.* (1983).

At present immunocytochemical techniques have provided evidence that a direct transport of vasopressin and oxytocin within the brain via nerve fibers might be a physiological route through which these peptides reach their site of action (Buijs, 1978; Buijs and Swaab, 1979; Sofroniew and Weindl, 1978; Swanson, 1977). The present review will deal with these and other recent observations that led to the conclusion that vasopressin and oxytocin execute their central action via these exohypothalamic fibers and might be regarded as neurotransmitters. The basis for these assumptions can be found in the following evidence.

2. VASOPRESSIN AND OXYTOCIN AS NEUROTRANSMITTERS IN THE CNS

2.1. LOCALIZATION AND ORIGIN OF VASOPRESSIN AND OXYTOCIN FIBERS

Vasopressin and oxytocin fibers have been demonstrated by means of immunocytochemistry, in a large number of brain regions from the olfactory bulb down to the spinal cord (Figs 1 and 2) (Buijs *et al.*, 1978; Swanson, 1977; Sofroniew and Weindl, 1978). The densest networks have been demonstrated in subcortical brain structures, though in the cortex and cerebellum scattered—fibers (mostly vasopressinergic) are found (Buijs,

FIGS 1 and 2. The major vasopressin and oxytocin pathways in the rat brain projected in the sagittal plane.

1

Vasopressin

FIG. 1. Demonstrates the major vasopressinergic pathways in the brain with their most likely origin (see text). The pathways of the paraventricular nucleus are indicated by (— · — · —). Pathways of the suprachiasmatic nucleus (SCN)(triangle) are indicated by (· · · · ·). The vasopressinergic cell groups found only after colchicine treatment are indicated by large black dots, while the pathways of the bed nucleus of the stria terminalis (BST) are indicated by (-----). The question mark indicates that the source of the vasopressin innervation in this area is still unknown.

2

Oxytocin

FIG. 2. Demonstrates the major oxytocinergic pathways largely arising from the PVN (see text). A—amygdala; DBB—diagonal band of Broca; DMH—dorsomedial nucleus of the hypothalamus; DVC—dorsal vagal complex; LC—locus coeruleus; LH—lateral habenula; LS—lateral septum; MB—mammillary body; ME—median eminence; MFB—medial forebrain bundle; MS—medial septum; NA—nucleus ambiguus; OB—olfactory bulb; OVLT—organum vasculosum of the laminae terminalis; P—pineal; PBN—parabrachial nucleus; PVG—periventricular grey; PVS—periventricular nucleus; RD—dorsal raphe nucleus; SC—superior colliculus; SN—substantia nigra; SON—supraoptic nucleus; TT—taenia tectae; VHI—ventral hippocampus; VTA—ventral tegmental area.

1980). Especially limbic system brain structures, such as septum, lateral habenular nucleus and amygdala, are heavily innervated by vasopressin containing fibers (Fig. 3), while in the brain stem and spinal cord oxytocin fibers are prevalent (Buijs, 1978; Swanson and McKellar, 1980). Extrahypothalamic fibers, which are already present at fetal day 17 (Buijs *et al.*, 1980), were found to innervate the lateral septum and lateral habenular nucleus from day 10 in a sexual dimorphic way (De Vries *et al.*, 1981). In male rats a much denser vasopressin innervation was found, which appeared to be dependent on the presence of androgens in early postnatal development. However, even in adulthood the female innervation pattern of the lateral septum could still be changed into a male one by the administration of a large dose of testosterone, thus demonstrating the plasticity of the innervation of this area (De Vries *et al.*, in preparation). In various other mammalian species the presence of a vasopressinergic and oxytocinergic innervation of the brain has

FIG. 3. Transversal section of the rat brain, demonstrating an extensive network of vasopressin fibers in the lateral septum (arrows). MS—medial septum. Bar = 50 μ m.

been demonstrated; for example, human subcortical brain structures are extensively innervated by vasopressin and oxytocin containing fibers (Figs 4, 5 and 6) that can already be found in the spinal cord of human fetuses of only 19 weeks after conception (Swaab and Ter Borg, 1982). That the extrahypothalamic neurohypophyseal hormone containing fibers were not only present in the mammalian brain was recently demonstrated by Van den Dungen *et al.* (1982), who found an even more extensive vasotocin and isotocin containing fiber system in the trout brain, while also the brains of lampreys were extensively innervated by vasotocin-containing fibers. Consequently the presence of neurohypophyseal hormone containing extrahypothalamic fibers is certainly not a phenomenon merely acquired by higher vertebrates but is also present in animal species that are phylogenetically considered to be older, which stresses the possible importance of this system for a wide variety of species.

The origin of the extrahypothalamic vasopressin and oxytocin containing fibers in the rat brain was thought to be the paraventricular (PVN) and possible also the supraoptic nucleus (SON). Moreover, also the parvocellular, vasopressin containing suprachiasmatic nucleus (SCN) would project with a large number of vasopressin fibers into various brain regions (Buijs *et al.*, 1978; Buijs, 1978; Sofroniew and Weindl, 1978b). Originally, the anatomy of the vasopressin and oxytocin pathways was established mainly by following them in serial sections. This proved to be an unreliable technique. After lesioning the SCN it showed that its vasopressin fiber system was much less widespread than had been

assumed earlier. It demonstrated that vasopressin fibers from the SCN reach the organum vasculosum of the lamina terminalis (OVLT), the dorsomedial hypothalamic nucleus and the periventricular nucleus (Hoorneman and Buijs, 1982) (Fig. 2). Apart from the projections from the SCN only the projections from the PVN towards the nucleus of the solitary tract seem to be well established, as has been demonstrated by means of retrograde transport of HRP or fluorescent dyes (Hosoya and Matsushita, 1979; Ono *et al.*, 1978; Schober, 1978)—sometimes even in combination with the establishment of the peptidergic content of the cell bodies (Sawchenko and Swanson, 1982; Sofroniew and Schrell, 1981; Swanson and Kuypers, 1980). Lesioning the PVN indeed resulted in the disappearance of vasopressin and oxytocin containing fibers in several regions of the brain stem. Surprisingly, it was not followed by a diminution in vasopressinergic fibers in the various regions where the PVN was thought to project to, viz. the amygdala, dorsal raphe nucleus etc. (De Vries and Buijs, 1983). Recently Van Leeuwen and Caffé (1983) demonstrated, after an intraventricular injection of colchicine, numerous vasopressin containing cell bodies in other brain regions, viz. in the bed nucleus of the stria terminalis, the amygdala, locus coeruleus, and in the dorsomedial nucleus of the hypothalamus. This opened the possibility that these nuclei could form the source of a substantial part of the vasopressinergic innervation in the brain. Indeed, both lesioning the cell groups in the bed nucleus of the stria terminalis and isolating the septum by knife-cuts followed by the immunocytochemical demonstration of vasopressin resulted in a drastic decrease in

FIG. 4. Demonstrates the localization of vasopressin cell bodies in the suprachiasmatic nucleus (SCN) in a transversal section of the human hypothalamus. Note the abundance of fibers arising from this nucleus. E—ependyma of the third ventricle. Bar = 50 μ m.

FIGS 5, 6 and 7. Demonstrate vasopressin fiber terminations in transversal sections of the human (5-6) and rat (7) brain.

FIG. 5. Vasopressin fibers from extensive contacts with a neuron (n) and its processes in the region of the nucleus of the solitary tract. Bar = 50 μ m.

FIG. 6. A similar perineuronal contact in the region of the ventral tegmental area; each process of the neuron seems to be innervated by vasopressin fibers (arrows); Bar = 25 μ m.

FIG. 7. Vasopressin containing fibers forming extensive ramifications and bouton-like terminations in the rat lateral septum (arrows). Bar = 10 μ m.

vasopressin fiber innervation of the lateral septum. In addition, since small cell bodies in the bed nucleus of the stria terminalis were found to be labeled after injection of HRP and fluorescent tracers in the lateral septum, it is likely that the vasopressinergic cells in the bed nucleus will project towards the septum. Other areas, to which the vasopressin neurons in the bed nucleus of the stria terminalis most probably project to, are: the lateral habenular nucleus, the periventricular grey and locus coeruleus (De Vries and Buijs, 1983).

Because lesions might also result in the interruption of passing vasopressin fibers, ultimate proof for these projections can, however, only be obtained after retrograde tracing in combination with the demonstration of vasopressin in the labeled neuron.

Nevertheless, a new picture emerges with respect to the origin of the vasopressin containing fibers, *viz.* that the PVN and SCN contribute only for a small part to the extrahypothalamic fibers and that their origin must lie elsewhere, most probably in the vasopressinergic cell bodies that could be demonstrated only after colchicine treatment. Herewith vasopressin has lost one of its characteristics that had distinguished it so far from other peptides, in that its cell bodies were confined to the hypothalamus and were readily visible without colchicine treatment. As it appears now, a combination of both cell groups occurs. In addition, also the vasopressin cell bodies are much more widespread over the brain than has been assumed hitherto.

In contrast to vasopressin, practically all oxytocin fibers seem to be derived from the PVN. Lesioning of this nucleus resulted in an almost complete disappearance of the oxytocin innervation of the brain (De Vries and Buijs, 1983). In addition, in colchicine-treated rats no additional oxytocin-containing neurons were detected, which reduces the probability of an alternative source. It will be clear that from its much more widespread sites of origin and terminal areas alone, vasopressin can already be involved in the regulation of far more functions than oxytocin. This will undoubtedly be a vital lead in unravelling putative functions of these two neurohypophyseal peptides in the central nervous system.

2.2. ELECTRONMICROSCOPIC LOCALIZATION

The assumption of Barry (1954) that neurosecretory fibers containing Gomori-positive material would terminate by means of 'des synapses neurosecretoires' seemed to be plausible, as in many brain regions vasopressin and oxytocin containing fibers are found to form extensive ramification and perineuronal structures (Figs 5, 6 and 7). To verify this assumption immunoelectronmicroscopy was performed on regions in the limbic system and medulla that are densely innervated by, respectively, vasopressin and oxytocin containing fibers. As in the immunoelectronmicroscopical study using post-embedding staining on ultrathin sections gave a false-positive result, pre-embedding staining was used instead (Buijs and Swaab, 1979; Voorn and Buijs, 1983). It appeared that in these regions vasopressin and oxytocin were localized within synapses mostly terminating on dendrites (Fig. 8) and infrequently on cell bodies. On no occasion were vasopressin or oxytocin containing structures found to be either pre- or postsynaptic to axonal processes. Therefore, results that suggest a 'modulating' action of vasopressin on monoamine metabolism in terminal regions of monoaminergic and vasopressinergic fibers (Tanaka *et al.*, 1976; Versteeg *et al.*, 1979) may probably be explained via an indirect mechanism and not via a direct postsynaptic action of vasopressin on the monoamine containing axon or terminal. The absence of presynaptic terminals on vasopressin and oxytocin containing fibers suggest that presynaptic modulation of vasopressin and/or oxytocin release will not be a widespread phenomenon, at least not in the areas investigated.

In spite of the fact that for the visualization of these structures it is necessary to use Triton X-100, thus hampering the preservation of ultrastructure of the tissue, these synapses were found to contain clear, and sometimes also 80–100 nm dense, core vesicles (Buijs and Swaab, 1979; Voorn and Buijs, 1983).

The presence of these 80–100 nm dense core vesicles in extrahypothalamic brain regions suggests that the vasopressin and oxytocin fibers in these areas are derived from other neurons than those projecting towards the neural lobe, where 140 nm vesicles are found (Van Leeuwen and Swaab, 1977). The presence of small vesicles might indicate a different processing mechanism from that present in the hypothalamo–neurohypophyseal system. The fact that in the brain stem immunoreactive neurophysin is present predominantly in a high-molecular weight precursor, in contrast to the precursor found in the hypothalamo–neurohypophyseal system (Sinding *et al.*, 1982) supports this idea. Another

FIG. 8. Vasopressin containing terminal forming a synapse with an unlabelled dendrite in the lateral habenular nucleus of the rat brain. Note the DAB deposit around the clear vesicle-like structures. Bar = 0.25 μ m (from Buijs and Swaab, 1979).

possibility is a different release mechanism of these peptides in the brain or in the pituitary, resulting in much more clear vesicles and fewer (and smaller) dense core vesicles.

Both in the human and in the trout and lamprey brain the extrahypothalamic neurohypophyseal hormone containing fibers form ramifications similar to those which were found in the rat, which suggesting that also these fibers terminate synaptically. Since recently such synaptic terminations were also demonstrated in the human brain (Kerkhoven and Buijs, unpublished observations), there seems to be little doubt that these neurohypophyseal peptides will influence neuronal structures via synaptic terminals in a wide variety of species. However, after the synaptic localization of vasopressin and oxytocin was established, it was still an open question whether these peptides were indeed released, or some other, unknown, substances.

2.3. CENTRAL RELEASE OF VASOPRESSIN AND OXYTOCIN

As far back as 1910 Cushing and Goetsch were able to demonstrate the presence of neurohypophyseal hormones in the human cerebrospinal fluid (CSF). With the contemporary anatomical knowledge this presence was explained as a release from the neural lobe, either directly or via the bloodstream into the CSF. Especially the latter theory persisted

over a great many years until first Zaidi and Heller (1974), and later many other authors demonstrated the improbability of such a route for physiological amounts of vasopressin and oxytocin. In addition, it appeared on various occasions that vasopressin and oxytocin levels in the CSF were not related to the level of these peptides in the blood (Dogterom *et al.*, 1977; Robinson and Jones, 1982; Mens *et al.*, 1982). Thus apparently a different route exists via which vasopressin and oxytocin reach the CSF. In line with the demonstrated synaptic terminals it is likely that vasopressin and oxytocin in the CSF originate from synaptic release. Consequently, the demonstration of a regular fluctuation (Perlow *et al.*, 1982) in levels of vasopressin and oxytocin in the CSF might reflect release patterns in central brain regions. However, the amount of vasopressin and oxytocin in CSF will also depend on turnover mechanisms which are unknown at present.

In order to demonstrate that vasopressin and oxytocin containing synapses were indeed able to release their peptide content upon a depolarizing stimulus, an *in vitro* release procedure was set up (Buijs and Van Heerikhuize, 1982). For this purpose various brain regions, together with the neurointermediate lobe, were selected. Using high potassium or veratridine as a depolarizing stimulus, release from the septal area and NTS, which are the target areas for vasopressin and oxytocin fibers, respectively, was compared with the release of these peptides from the neural lobe.

Thus a calcium-dependent potassium- or veratridine-stimulated release of vasopressin and/or oxytocin could be demonstrated in those brain regions where there fibers terminate synaptically on neuronal structures. The veratridine-stimulated release of oxytocin from the NTS ($6.1\% \pm 0.9$) of the tissue stores in 10 min.) or the neural lobe ($7.7\% \pm 0.6\%$ in 10 min.) is more pronounced than that of AVP from the septum ($3.6\% \pm 0.7\%$ in 10 min.) (Fig. 9) or neural lobe ($1.4\% \pm 0.1\%$ in 10 min.) (Buijs and Van Heerikhuize, 1982). The

FIGS 9 and 10. The release of vasopressin from septal slices (9) and from the region between the paraventricular (PVN) and supraoptic (SON) nuclei. The initial release during the dissection of the material is indicated in the hatched column. $-Ca^{2+}$ no calcium the medium. $+K^+$ high potassium (56 mM); Ver—use of veratridine in the incubation buffer. The detection limit of the assay is indicated. The total sum of the amounts present in the tissue after the experiment and the peptide released are indicated by the 100% volume (from Buijs and Van Heerikhuize, 1982).

FIG. 9. Veratridine-stimulated vasopressin release is not different from potassium-stimulated release. The 100% volume indicates the amount of AVP from 3 septi.

FIG. 10. No potassium- or veratridine-stimulated release could be observed for vasopressin from this region, where vasopressin fibers do not exhibit synaptic termination. The 100% value indicates the amount from 3 PVN/SON regions.

information (cf. Swanson and Sawchenko, 1980). The role of vasopressin and oxytocin in the connection between the PVN and the hindbrain will probably lie in the regulation of processes in which these peptides are also involved in the periphery—such as the control of blood pressure and lactation. The fact that vasopressin concentrations are affected in brain stem and neural lobe in spontaneously hypertensive rats (Mohring *et al.*, 1980), and that both vasopressin and oxytocin influence blood pressure, especially in caudal brain regions (Bohus, 1980; Matsuguchi *et al.*, 1982; Pittman *et al.*, 1982; Versteeg *et al.*, 1980), supports this theory. This possible coupling of central and peripheral actions of vasopressin and oxytocin seems to be a general phenomenon of hypothalamic peptides (Swaab, 1982).

An example of such peripheral and central coupling might be found in the action of vasopressin in limbic brain areas such as the lateral septum and the amygdala. Both areas are densely innervated by vasopressin containing fibers, and send direct projections to the PVN and/or the SON (Pittman *et al.*, 1981a; Poulain *et al.*, 1981; Silverman *et al.*, 1981; Tribollet and Dreifuss, 1981). Also here it awaits elucidation whether the neurons that project to the PVN and SON are in fact innervated by vasopressin containing fibers. The demonstration of a simultaneous vasopressin release, following a hypertonic saline injection, both in the periphery and in the septum and amygdala (Pittman *et al.*, 1981b), supports at least the idea that central and peripheral release of vasopressin in some instances might be coupled. More studies have appeared, however, in which no such coupling could be found (Mens *et al.*, 1980; Robinson *et al.*, 1982).

Yet there is still a possibility that via the connections from septum to PVN and SON central vasopressin might influence the release of hormonal vasopressin into the periphery. The simultaneous central and peripheral release will probably occur only upon very specific stimuli and will result in the initiation of processes, both centrally and peripherally, that help the animal adapt to this stimulus. The importance of such a coupled action can be found in the effect of vasopressin in temperature control. Vasopressin release in the septal region of sheep measured by push-pull perfusion correlated negatively with a change in body temperature. That is, the release of vasopressin increases when body temperature falls, while by raising body temperature release of vasopressin decreases (Cooper *et al.*, 1979; Kasting *et al.*, 1982). Moreover, the addition of vasopressin to the perfusate resulted in a drop in body temperature. In separate experiments it was demonstrated that peripheral vasopressin levels are enhanced when body temperature is elevated (Cooper *et al.*, 1979; Kasting *et al.*, 1982). Thus vasopressin might exert an antipyretic effect in the CNS, while in the periphery it prevents the loss of water via the kidney to prevent dehydration by the perspiration induced by a rise in temperature. Via such mechanisms indeed central and peripheral actions of vasopressin are coupled. Whether this will be a general rule for vasopressin and oxytocin or even for all hypothalamic releasing hormones will certainly be a point of future investigation.

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information (cf. Swanson and Sawchenko, 1980). The role of vasopressin and oxytocin in the connection between the PVN and the hindbrain will probably lie in the regulation of processes in which these peptides are also involved in the periphery—such as the control of blood pressure and lactation. The fact that vasopressin concentrations are affected in brain stem and neural lobe in spontaneously hypertensive rats (Mohring *et al.*, 1980), and that both vasopressin and oxytocin influence blood pressure, especially in caudal brain regions (Bohus, 1980; Matsuguchi *et al.*, 1982; Pittman *et al.*, 1982; Versteeg *et al.*, 1980), supports this theory. This possible coupling of central and peripheral actions of vasopressin and oxytocin seems to be a general phenomenon of hypothalamic peptides (Swaab, 1982).

An example of such peripheral and central coupling might be found in the action of vasopressin in limbic brain areas such as the lateral septum and the amygdala. Both areas are densely innervated by vasopressin containing fibers, and send direct projections to the PVN and/or the SON (Pittman *et al.*, 1981a; Poulain *et al.*, 1981; Silverman *et al.*, 1981; Tribollet and Dreifuss, 1981). Also here it awaits elucidation whether the neurons that project to the PVN and SON are in fact innervated by vasopressin containing fibers. The demonstration of a simultaneous vasopressin release, following a hypertonic saline injection, both in the periphery and in the septum and amygdala (Pittman *et al.*, 1981b), supports at least the idea that central and peripheral release of vasopressin in some instances might be coupled. More studies have appeared, however, in which no such coupling could be found (Mens *et al.*, 1980; Robinson *et al.*, 1982).

Yet there is still a possibility that via the connections from septum to PVN and SON central vasopressin might influence the release of hormonal vasopressin into the periphery. The simultaneous central and peripheral release will probably occur only upon very specific stimuli and will result in the initiation of processes, both centrally and peripherally, that help the animal adapt to this stimulus. The importance of such a coupled action can be found in the effect of vasopressin in temperature control. Vasopressin release in the septal region of sheep measured by push-pull perfusion correlated negatively with a change in body temperature. That is, the release of vasopressin increases when body temperature falls, while by raising body temperature release of vasopressin decreases (Cooper *et al.*, 1979; Kasting *et al.*, 1982). Moreover, the addition of vasopressin to the perfusate resulted in a drop in body temperature. In separate experiments it was demonstrated that peripheral vasopressin levels are enhanced when body temperature is elevated (Cooper *et al.*, 1979; Kasting *et al.*, 1982). Thus vasopressin might exert an antipyretic effect in the CNS, while in the periphery it prevents the loss of water via the kidney to prevent dehydration by the perspiration induced by a rise in temperature. Via such mechanisms indeed central and peripheral actions of vasopressin are coupled. Whether this will be a general rule for vasopressin and oxytocin or even for all hypothalamic releasing hormones will certainly be a point of future investigation.

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