Vasopressin and Oxytocin Localization and Putative Functions in the Brain

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Introduction

In this chapter a description will be given of the widespread occurrence of vasopressin (VP) and oxytocin (OT) neurons in the rodent brain. In addition, an attempt will be made to describe, on the basis of its origin, possible functions of VP and OT in the various parts of the central nervous system (CNS).

The availability of antibodies to VP, OT and neurophysin permitted the localization of these hormones in separate cell bodies in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) and later on in the suprachiasmatic nucleus (SCN) (Vandesande *et al.* 1974, Swaab *et al.* 1975). Recently, other sites of VP synthesis were revealed after pretreatment of a rat with cholchicine: in cell bodies of the bed nucleus of the stria terminalis (BST), dorsomedial hypothalamus, medial amygdala and locus coeruleus (Caffé and Van Leeuwen 1983, Van Leeuwen and Caffé 1983).

Improvement of immunocytochemical techniques resulted in the demonstration of extensive VP and OT pathways in the central nervous system. The presence of this central VP innervation suggested that VP is able to reach neuronal structures by other routes than via the general circulation or the cerebrospinal fluid. Indeed, the presence of extensive fiber arborizations and perineuronal structures suggested that these fibers actually terminate in many such areas. Immunoelectron-microscopy applied to the lateral septum, lateral habenular nucleus, amygdala and nucleus tractus solitarius (NTS) showed that VP fibers indeed terminate synaptically on other neuronal structures (Buijs and Swaab 1979, Voorn and Buijs 1983).

At present, a number of reports have appeared showing the synaptic release of VP or OT in a number of different brain regions (Cooper *et al.* 1979, Buijs and

Van Heerikhuize 1982, Pittman *et al.* 1984). The conclusion seems justified that VP and OT will be released with a specific stimulus and will act in only those areas where synaptic specializations are present. In addition, the actions of this peptide on neuronal firing in several brain regions, (Zerihun and Harris 1981, Mühlethaler *et al.* 1982, Joëls and Urban 1982), together with the demonstration of VP and OT binding in the same brain regions (Baskin *et al.* 1983, Van Leeuwen and Wolters 1983, Biegon *et al.* 1984), shows that these peptides are able to act as neurotransmitters in these brain regions (Buijs 1983). With a neurotransmitter role of VP or OT basically being established, it is necessary to determine the functional meaning of these transmitters and how and where these functions can be executed. Therefore it became of crucial importance to determine the origin of the VP and OT fibers in the various brain regions. Fig. 1 summarizes the anatomical picture of the organization of the different VP systems that can be found in the rat brain, while Fig. 2 does the same for OT. It will be clear that based on the widespread distribution of VP fibers and the different origin of these fibers, VP is involved in a large number of different brain functions.

For OT the picture seems to be far less complex, most innervations being derived from the PVN, and apart from projections to the circumventricular organs the brain stem and spinal cord are largely reached by OT fibers.

De Vries *et al.* (1981) detected the presence of a sexually dimorphic innervation of VP fibers in the lateral septum. From postnatal day 12 onwards, a male rat had a much denser VP innervation in the lateral septum than a female rat. Moreover, the presence of gonadal hormones, either testosterone or oestradiol, appeared to be of crucial importance for the mainte-

Vasopressin

Fig. 1. Sagittal scheme of the rat brain representing the major vasopressinergic pathways with their most likely origin. The pathways of the paraventricular nucleus are indicated by (---). Pathways of the suprachiasmatic nucleus are indicated by (·····). The vasopressin cell groups found after cholchicine treatment are indicated by black dots, while the pathways of the bed nucleus of the stria terminalis are indicated by (—). 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; ME median eminence; NA nucleus ambiguus; OVLT organum vasculosum of the laminae terminalis; PVG paraventricular grey; PVS periventricular nucleus; RD dorsal raphe nucleus; SCN substantia nigra; VHi ventral hippocampus; VTA ventral tegmental area

nance of the VP fiber innervation of, *e.g.*, the lateral septum (De Vries *et al.* 1985). Gonadectomy of adult male or female rats resulted in a gradual decrease in VP fiber density over a period of 15 weeks to a point where hardly any fibers were found (De Vries *et al.* 1984). These results indicate that apart from the possibility of dividing the extrahypothalamic pathways on the basis of their origin, it is also possible to divide them on the basis of their sensitivity to gonadal hormones.

At present, the morphology and origin of the various VP systems is well established and it may be possible to make a few assumptions on the putative functions of VP in the brain.

Each of the sites where VP is produced will be influenced by different stimuli, a spatially controlled release of VP. Therefore the approach of the present chapter is to take into account the source of VP fibers when it comes to distinguishing between the different VP systems of the brain.

Paraventricular Nucleus

The PVN supplies the largest contingent of VP and OT fibers, the latter predominating, in the caudal brain, *viz.*, brain stem and spinal cord (Buijs 1978, Swanson and McKellar 1979). The OT projection to the A1 and A2 areas and to the intermediolateral column in the

spinal cord have been the most eye-catching of the PVN OT projections, suggesting that these peptides from the PVN are involved in the control of autonomous functions. It has been shown that especially A1 (noradrenergic) neurons (Sawchenko and Swanson 1981, Sladek and Zimmerman 1982) densely innervate the magnocellular VP and OT containing neurons in the SON and PVN. Day and Renaud (1984) have shown by a combination of lesioning with 6-hydroxy-dopamine and stimulation of the A1 area that this noradrenergic innervation provides a stimulatory input for the VP containing neurons of the SON and PVN, thus promoting the neurohypophyseal release of VP into the bloodstream. The innervation of A1 and A2 neurons by OT containing fibers suggests that OT as a neurotransmitter can be involved in, for example, the control of the release of VP from the HNS into the general circulation. Infusions of small amounts of OT in this area indeed induce elevated levels of vasopressin in the general circulation (Hermes, unpublished observation).

Suprachiasmatic Nucleus

The SCN, which is the major endogenous pacemaker, functions as the major clock in synchronizing the circadian rhythms (Stephan and Zucker 1972, Moore 1979). It seems only logical to assume that VP from the SCN is involved, one way or another, in this syn-

Fig. 2. Sagittal scheme of the rat brain representing the major oxytocinergic pathways originating largely from the paraventricular nucleus. For abbreviations used, see Fig. 1

chronizing function. The fact that a VP-deficient Brattleboro rat, which lacks VP also in the SCN, seems to have a normal sleep-wake rhythm (Peterson *et al.* 1980), does not necessarily lead to the conclusion that VP is of no importance to the circadian synchronization of certain behaviors. These mutant rats are likely to have compensatory systems that, at least partially, take over the function of VP.

In the CSF, VP has a pronounced day-night rhythm that seems to be dependent on the activity of the SCN (Reppert *et al.* 1982, Schwartz *et al.* 1983). Södersten *et al.* (1983, 1985) have shown that VP injected into the CSF during low VP night levels inhibits lordosis behavior in ovariectomized female rats, while an antagonist injected during the day period enhance lordosis behavior. Their observations led them to the conclusion that VP inhibits lordosis behavior, and to the suggestion that the SCN is involved in the regulation of this behavior.

Bed Nucleus for the Stria Terminalis and Medial Amygdala

The reason for discussing these nuclei together is that they are both influenced by gonadal steroids and probably both project to the same areas (Holstege *et al.* 1985). The sexually dimorphic innervation, and the fact that replacement of oestrogen and testosterone restores the original VP innervation (in gonadectomized females and males respectively; De Vries *et al.* 1981, 1984) suggests that VP in these limbic brain regions is involved in the regulation of sex-linked functions. This does not imply, however, that VP is involved in the regulation

of reproductive behavior, for a number of other behaviors such as feeding, drinking, temperature regulation and aggressive behavior is sexually dimorphic as well (Goy and McEwen 1980, Beatty 1984). Thus, the sexually dimorphic VP innervation may be involved in non-reproductive behavior-linked sexually dimorphic functions.

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