OXYTOCIN-messages via the CEREBROSPINAL FLUID: behavioral effects; a review.

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Running Head:

Behavioral effects of CSF-Oxytocin.

Abstract
VEENING, J.G.,T. DE JONG AND H. P. BARENDREGT. Oxytocin-messages via the cerebrospinal fluid: behavioral effects; a review. PHYSIOL BEHAV 0000000
The cerebrospinal fluid (CSF) usually is considered as a protective 'nutrient and waste control' system for the brain. Recent findings suggest, however, that the composition of CSF is actively controlled and may play an influential role in the changes in brain activity, underlying different behavioral states. In the present review, we present an overview of available data concerning the release of oxytocin into the CSF, the location of the oxytocin-receptive brain areas and the behavioral effects of intracerebroventricular oxytocin. About 80% of the oxytocin-receptive areas are located close to the ventricular or subarachnoid CSF, including the hypothalamic 'Behavior Control Column' (L.W.Swanson, 2003). As a conclusion we suggest that 'CSF-oxytocin' contributes considerably to the non-synaptic communication processes involved in hypothalamic-, brainstem- and olfactory brain areas and behavioral states and that the flowing CSF is used as a 'broadcasting system' to send coordinated messages to a wide variety of nearby and distant brain areas.

Keywords:
- Cerebrospinal Fluid
- Oxytocin
- Behavioral state
- Non-synaptic communication
- Dendritic release
- Olfaction

Contents of the review:

1: INTRODUCTION

2. OXYTOCIN AND CSF

- **2.1 Peripheral and CSF-OT-levels are regulated differentially.**
- **2.2 General neuroanatomy of the oxytocin system**
- **2.3 Diffusion after Dendritic Release from PVH and SON**
- **2.4 Supra-ependymal Release**
- **2.5 Synchronisation and Cross-talk of OT neurons**
- **2.6 OT released into the CSF: are the levels functionally relevant?**
- **2.7 Oxytocin Receptors and the CSF**

3. BEHAVIORAL EFFECTS OF OXYTOCIN ARE ELICITED IN THE CSF.

- **3.1 Social Behavior**
- **3.2 Sexual Behavior**
- **3.3 Parental Behavior**
- **3.4 Food Intake**
- **3.5 Grooming Behavior**
- **3.6 Pain**

4. CSF-OXYTOCIN MAY AFFECT VARIOUS PARTS OF THE CNS.

- **4.1 OT- effects on hypothalamic 'Behavioral Control Column'.**
- **4.2 OT- effects on brainstem ('core'- and 'paracore'-) areas.**
- **4.3 OT- effects on cortical areas.**
- **4.4 OT- effects on olfactory areas.**
- **4.5 OT- effects on olfactory sensory neurons (OSNs).**

5. CONCLUSIONS AND THEORETICAL FRAMEWORK.

1: INTRODUCTION

Animal and human behavior can be described as ‘goal-directed’ with a succession of different behaviors leading to different goals (feeding and drinking, or ‘social activities’ like aggression or sex) over time. Such changes in behavior require adaptive physiological mechanisms and complex changes in neural activity in a wide variety of brain areas and have been described as switches of the ‘behavioral state’ of the organism. Such states regulate the input-output repertoire of the organism and have been described and defined as motivational, emotional or mental states [1-6] in animal and human behavioral studies. Obviously, the hypothalamus, embedded in the limbic system is necessarily involved when motivational states change [1, 3, 6-8], but other brain areas, ranging from cortical regions to spinal cord, must be involved as well in order to accomplish the coordinated adaptations in the neural (sensory, motor and autonomic) as well as hormonal systems, underlying goal-directed behavior.

Since the early eighties, the occurrence of ‘non-synaptic communication’ or ‘volume transmission’ has been described as a new mechanism in addition to ‘wiring transmission’ [9-13]. ‘Volume transmission’ has been proposed as a mechanism to change neuronal activity in more than a single brain area, for an extended period of time [1, 7, 8, 14-23], which are basic requirements for motivational changes. Many descending neuropeptidergic fiber systems containing mostly unmyelinated varicose fibers and lacking synaptic contacts [1, 6-8, 20, 22, 24-26] are in an excellent position for changing the weight factors in the neural network involved in keeping or switching between

behavioral states. Remarkably, many of these descending fibers are running close to the ventricular system [24-27], which raises the question in how far the cerebrospinal fluid (CSF), flowing through the ventricular system and the arachnoid space surrounding the brain, could be involved in behavioral changes.

In early studies of Cushing [28] the term *'third circulation'* was coined for the CSF, flowing caudally through as well as around the CNS. Friedman and Friedman [29] showed already that oxytocin-levels in the CSF were sufficiently high to induce contractions of the rabbit uterus, which makes it legitimate to ask in how far the circulating CSF can play a role in physiological and behavioral changes and - states.

Previously, Sewards and Sewards [30, 31] have argued, in our view convincingly, that vasopressin and cortocotropin-releasing-factor (CRF) are released into the CSF in order to induce their behavioral effects via activation of the appropriate receptors in distant brain areas. In a previous paper [23] we have discussed the available evidence that the flow of the CSF through and around the CNS provides a fast and specific substrate for sending neuropeptidergic as well as other 'messages' to appropriate receptive brain areas. Especially the local release of melatonin into the dorsal part of the third ventricle and the release of 'gonadotropin hormone releasing hormone' (GnRH) into the basal part of the 3rd ventricle, each with their own specific target brain areas [32-37] strongly support the hypothesis that the CSF may be involved in 'broadcasting messages' as a special kind of 'volume transmission'.

In the present review we intend to explore the available evidence that oxytocin (OT)-producing neurons are using the CSF as a 'broadcasting system' to communicate with a variety of other nearby as well as distant brain areas. For the assumption that OT distributed via the CSF is relevant for behavioral changes, at least the following kinds of supporting evidence are necessary:

- OT can be released into the CSF, 'to go with the flow';
- OT-levels in the CSF are regulated independently and different from the peripheral levels in the blood;
- OT-levels in the CSF are sufficiently high to activate OT-receptive areas alongside the ventricular or arachnoid spaces;
- OT-receptive 'target'-areas are located alongside the ventricular and arachnoid spaces of the brain;
- OT-administration into the CSF induces behavioral effects not obtained by peripheral administration;
- behavioral effects of intra-cerebro-ventricular (icv) -OT-administration can be linked, anatomically and/or functionally, to the OT-receptive brain areas.

For each of these aspects, the available evidence will be presented and discussed in the next sections of the present review.

2. OXYTOCIN AND CSF

Oxytocin is a nonapeptide, synthesized by Du Vigneaud in 1953, after its isolation and clarification [38]. Since then, OT has been implicated in a dazzling variety of widely diverging functions. Many reviews are available summarising and highlighting the relevant specific findings in detail: in each of

the years 2007 and 2008 at least 20 reviews appeared focusing on specific OT-functions.

2.1 Peripheral and CSF- OT-levels are regulated differentially.

OT has been detected in the cerebrospinal fluid of many species, although the levels vary considerably both diurnally and between species [39-43].

It has been shown extensively that OT levels in the CSF are different from plasma OT levels and react very differently upon natural or experimental challenges. Natural and experimentally manipulated circadian rhythms are much more visible in the CSF than in the blood plasma [39-42, 44]. Effects of pregnancy and labor in humans [45], of parturition in sheep or rats [46, 47], of hand-milking in the goat [48] or of suckling in the guinea pig [49] are very different in CSF compared to plasma levels of OT. Experimental challenges like opioid or naltrexone administration in rats [50] and sheep [51], partner preference test [52], stress [53], vagino-cervical stimulation in the goat [54], electrical stimulation of the hypothalamus or neural lobe in the rat [55], chemical stimulation of the paraventricular hypothalamic nucleus (PVH) by the excitatory amino acid glutamate [56] and hypophysectomy [57] all affect OT-levels in CSF differently from plasma OT-levels. Many additional findings are available from the literature to draw the conclusion that CSF and peripheral levels of OT are not only different but, more importantly, are controlled by different largely independent, mechanisms [42]. The finding that peripheral OT-levels contribute only 0.002% to the OT-CSF-levels [58], supports the functional independency. Peripheral levels may not be completely

independent, however, since CSF-OT may play a regulatory role in the control of peripheral OT levels [48].

In addition to the differentially regulated levels, the half-life values of OT are completely different: about 28 minutes in CSF compared to 1-2 minutes in the blood plasma [49, 58-60], which suggests that the behavioral effects of OT inside the CNS use a radically different time-scale compared to the peripheral effects on specific organs.

From the multiple functional differences in the control of CSF and plasma OT levels, we propose that it is certainly allowed to explore the possibility that ventricular release of OT into the CSF may compose a message for other parts of the brain, because, once released, it may 'follow the flow' and reach many widespread brain areas within minutes. In the following parts of this review, the possible origins and destinations of the 'CSF-OT-message' will be discussed.

In summary: CSF-OT levels are not controlled by peripheral systemic levels but by independent mechanisms controlling both levels and temporary peaks in the CSF. Combined with the about 20 times longer half-time values of OT in the CSF, this suggests that independent 'OT-messages' to other brain areas are possible, without involvement of peripheral effects on specific organs.

2.2 General neuroanatomy of the oxytocin system

The production and subsequent central or peripheral release of OT is executed by partly overlapping and interconnected groups of neurons. The majority of OT-producing neurons is located in the paraventricular hypothalamic nuclei (PVH), with a dorsal extension into the bed nucleus of the

stria terminalis, and in the supraoptic hypothalamic nuclei (SON). Several additional perivascular clusters of OT-immunoreactive (OT-IR) neurons can be observed consistently in the rostral hypothalamus, 'scattered' between the SON and PVH. These clusters are interesting because of the special role of the perivascular spaces for the rapid distribution of CSF-messages [61-64].

Parvocellular neurons in the dorsal part of the PVH release OT from their axons in distant CNS sites [65, 66]. Interestingly, many of these axonal projections reach areas bordering, surrounding and/or functionally related to the ventricular system [65-71]. Magnocellular neurons in the paraventricular and supraoptic nuclei of the hypothalamus release OT directly from their axons into the blood stream via the neurohypophysis. Many morphological and functional aspects of both types of OT-neurons (projections, afferent connections, co-localisation with other neuropeptides, plasticity, etc) have been discussed in a lengthy series of review papers since 1983 [66], and can be left out of focus for the present purpose.

Production of OT occurs in 2 hypothalamic cell groups (the paraventricular and the supraoptic nuclei) as well as in a few perivascular clusters in between. Both brain areas border the CSF directly, (at the third ventricle or the arachnoid space, respectively) and contain magnocellular neurons that release OT via the pituitary directly into the systemic circulation. The parvocellular OT-neurons of the PVH send their axonal projections to many distant brain areas, including the spinal cord, often at a small distance from the ventricular system.

2.3 Diffusion and Dendritic Release from PVH

Hoistad et al. [72] have convincingly shown that neuropeptides like beta-endorphin, released at a distance, eventually appear in the CSF, with a peak-delay of about half an hour. Their finding shows two important matters: on the one hand that axonally-released neuropeptides eventually reach the CSF through diffusion and/or extracellular fluid (ECF-) flow [73]; on the other hand that peptidase-levels in the ECF and CSF are apparently too low to prevent the appearance of peptides in the CSF, half an hour later. Apparently, in the CNS extracellular neuropeptides are distributed and may remain effective over considerable distances for an extended period of time. On the other hand, however, the appearance of neuropeptides into the CSF is slow and levels remain generally low, when released at such distances from the ventricular system. In agreement with this suggestion, a recent paper showed that only about 10 to 15% of the ECF is drained into the CSF [74]. As a mechanism for 'switching behavioral states' such ECF-CSF-exchange is probably too weak and too slow but 'sustaining effects' cannot be excluded. Therefore, the notion of Landgraf & Neumann [69] may be generally right, that 'neuropeptide levels in the CSF essentially reflect the more or less "global" activity of the corresponding neuropeptide in the brain'. However, in the case of OT, a 5-fold daily increase in primate CSF-OT [40] has been observed. Without specific release mechanisms, such strong fluctuations cannot be explained by 'axonal/terminal release at a distance'. Interestingly, over the last few years, appropriate mechanisms have been described and investigated that are capable of releasing large amounts of OT specifically into the CSF.

This fascinating role might be played by dendritic release and subsequent diffusion of oxytocin in the PVH and the SON [69, 75-77]. Inside the PVH, it is

remarkable to observe how the dendrites of the magnocellular (as well as other) parts of the PVH generally run in parallel to the outer borders of the PVH(-subdivisions) and show a strong preference to extend into the central-medial parts of the PVH (**Fig 1)**. Some of the medially directed dendrites not only reach and penetrate (Fig 1A,B) the ventricular lining but some of them have been observed to cross the dorsal side of the third ventricle, potentially to influence the contralateral PVH as well (Fig 1B) [78-81]. In combination with the lateral cell-free border zone, along the ventrolateral side of the PVH, which limits diffusion in a ventrolateral direction (pers.obs.), this particular 'internally directed' dendritic organisation strongly suggests a specific function in the 'internal' communication inside the PVH as well as towards the CSF. (**Fig 2**). The dendrites of the OT-neurons inside the SON show an even stronger preference to extend in a ventral direction, towards the subarachnoid space. All of these magnocellular dendrites have been shown to release OT [76, 82, 83] and have been described as 'prototypic receiver/transmitters' [84, 85]. (**Fig 3**)

Since OT has a strong excitatory effect on the activity of (surrounding) OT-neurons [84, 86, 87], dendritic exocytosis turned out to form the basis for a chain reaction of massive OT-activation and release of OT inside the PVH and SON leading to a thousand-fold increase of extracellular OT [69, 75, 76], inevitably followed by increases in CSF-levels because of the missing ECF-CSF-barriers. This specific type of release may contribute to coordinate the action of large groups of OT neurons via positive feedback mechanisms, and may also play a role to functionally separate the peripheral release, in the neural lobe of the pituitary, from the central effects inside the hypothalamic

nuclei. Dendritic release itself occurs at a millisecond time scale, but the size of the effects on surrounding neurons is strongly depending on the hormonal state of the animal [88, 89] and appears to be controlled by the presence of oestradiol and estrogen receptivity [89, 90], by specific changes in neuron-glia interactions, by numbers of plasmalemma juxtapositions and by priming effects [75, 76, 84, 91-93]. In addition, dendritic release of OT may be self-sustaining and long-lasting (up to 90 min). These dendritic release mechanisms are in a complex way supported by specific priming effects [93], and by the twentyfold elongated half-life values in CSF compared to blood plasma [49, 58-60]. Mechanisms controlling the receptive properties of surrounding neurons by insertion of receptor proteins into postsynaptic membranes, [84] contribute to the complexity.

For the cellular mechanisms involved in the differential regulation of dendritic versus axonal release of OT, the reader is referred to an extensive series of recent review papers [69, 76, 83, 85, 94].

In summary: neuropeptides released elsewhere in the brain will eventually appear in the CSF, sometimes after considerable delay. The thousand-fold increases of OT-levels in the PVH and SON as a result of massive and coordinated dendritic release mechanisms will, however, strongly and almost immediately affect OT-levels in the CSF. Since the dendritic and the terminal release mechanisms of the magnocellular neurons appear to be functionally independent, dendritic release mechanisms are the best candidates to regulate CSF-OT levels independently from systemic release.

2.4 Supra-ependymal Release

In addition to the dendritic release followed by diffusion of OT into the CSF, another source of OT-release is composed by the 'supra- and sub-ependymal structures'.

It has been observed that OT-IR dendrites run subependymally along the 3rd ventricular wall, in a rostral or caudal direction [95], and that supraependymal fibers run along the ventricular surface to terminate in the supraependymal plexus on the floor of the 3rd ventricle [96]. Large numbers of 'neural nitric oxide synthase (nNOS)-positive cerebrospinal fluid-contacting neurons' have been observed in the rat, with somas, dendrites and axons situated at sub- and supraependymal levels along the 3rd ventricular wall. 88% of these neurons were OT-IR [97]. In addition, in mice OT-immunoreactive cells with cilia extending into the 3rd ventricle from the lower part of the anterior ventricular wall near the suprachiasmatic nucleus, showed a significant daily rhythm in immunostaining, regulated by environmental lightning [44]. These effects were 'OT-specific' since no effects on calbindin or vasopressin immunostaining were observed.

Combining these data with older data concerning neurophysin (a carrier protein involved in the axonal transport of PVH-OT) [98], with the supposed general role of CSF-contacting neurons as reviewed by [99, 100], and with some of the data concerning the magnocellular PVH-neurons, as discussed above, it is only a small step to suggest that oxytocinergic fibers and 'CSF-contacting-neurons' surrounding the ependymal layer of the 3rd ventricle, may directly and actively contribute to the OT-levels in the CSF.

There are no data available to estimate the size, or importance, of this contribution relative to the amounts released by the magnocellular PVH- and

SON dendrites. It may be questioned, however, whether it makes sense to discuss these contributions as separate entities. The release of massive amounts of any peptide along the ventricular wall (either by dendritic release inside the PVH or by axonal release from the varicosities of fibers running in parallel to the ventricular surface [25, 26, 101-103]) will immediately affect CSF-levels. 'Short-distance-diffusion' will occur without delay in the direction of the lower concentrations in the CSF, because there are no intervening barriers. Diffusion will remain 'CSF-directed' ('CSF-petal') as long as the CSF-levels are the lowest [72]. (The supposed 'waste-removal'-function of the CSF is fully based on this assumption!) If, however, levels of OT (or any other neuroactive substance) are increased in the CSF, relative to the local extracellular-fluid (ECF) -levels, due to release at some 'upstream' location, diffusion will 'change direction' and become 'ECF-directed'('CSF-petal'). (All experiments based on icv-administration are based on this assumption!)

Therefore, increased CSF-levels will sustain and elongate the effects of locally released OT. Because of the free and bidirectional CSF-ECF exchange, all OT-release mechanisms, whether axonal alongside the ventricular walls or via the CSF, are mutually supportive, the main difference being the (short) delay for the CSF-messages.

The exact size and place of the 'cumulative' effects' of CSF-, ECF- and axonally released OT will be dependent on the location and on the local structure of the brain areas involved. The presence of glial cells, astrocyte extensions or fiber layers etc, (all contributing to 'tortuosity') may be hindering diffusion in some of the possible directions (leading to 'anisotropy') [104-106]. We have been studying tracer injections into the rat brain over the years and

we observed frequently that many ‘barriers’ exist that prevent an expected “spherical” diffusion of the injected substances into the surrounding brain tissue (pers.obs, Veening). But if diffusion is hindered in certain directions, it will be enhanced in the other directions, especially towards the barrier-free CSF.

In summary: supra- and sub-ependymal release of OT may contribute to the CSF-OT levels elevated by dendritic release of OT. The many varicose OT-fibers running alongside and terminating in brain areas bordering the ventricular system, suggest a ‘mutual support’-relationship between axonal/terminal released OT and CSF-OT by enhancing and elongating the effects of OT-peaks.

2.5 Synchronisation and Cross-talk of OT neurons

Synchronization of OT-neurons seems to be the underlying mechanism for pulsatile release of OT into the blood stream when triggered by suckling [107-109]. However, measurements inside the supraoptic nucleus have shown that synchronisation of dendritic release of OT results in 100 to 1000 times higher levels in the ECF compared to plasma levels [69, 110]. In primates OT levels in the CSF may be considerably higher than the peripheral levels and, as mentioned, show an independent rhythm, not observed in plasma levels [40-42]. Circadian CSF rhythms of OT are endogenously generated, leading to five-fold increases in primates [40], synchronized by the daily light-dark cycle [39, 40] These findings suggest that strong positive feedback and synchronizing mechanisms are working during the coordinated dendritic release of OT.

In addition to the remarkable mechanisms involved in the co-activation of OT neurons inside each PVH or supraoptic nucleus, another interesting phenomenon has been observed: cross-talk ('synchronisation') between OT-neurons in different brain areas. Most research has been aimed at OT-neurons in the supraoptic nucleus, where it was shown that unilateral activation of specifically OT neurons (and not the vasopressin neurons!) especially in lactating females induce activation in the contralateral supraoptic OT cells [108]. Apparently, all magnocellular OT cells are being synchronized in their activity and OT release, including those in the PVH [111]. Despite the fact that direct reciprocal connections between both supraoptic nuclei have not been observed with the available techniques, there is convincing evidence to exclude diffusion effects [108]. In a careful series of experiments, Moos et al. [109] have shown that ventromedial medullary neurons are involved in the synchronization of OT neurons, including those in the PVH. Interestingly, the ventral medullary brain areas receive messages from the CSF very rapidly because of fast CSF-transport and the 'vascular pump-mechanisms' [61-64], and are therefore in an excellent position to provide the appropriate signals for a rapid 'long-distance-synchronization'. In addition, for the bilateral synchronization of PVH-OT neurons, short axonal collaterals and dendritic extensions across the upper border of the 3rd ventricle [80], (See Figs 1, 2) or even volume transmission from one PVH/ventricular wall across the 3rd ventricle to the opposing PVH/ventricular wall (small distance, no intervening barriers) have to be considered alongside the other hypothalamic and extrahypothalamic synchronization sources.

In summary: synchronisation of dendritic OT-release does not only occur between the neurons in a single hypothalamic nucleus, but happens bilaterally for both the PVH and SON, to produce maximal amounts of OT, if necessary.

2.6 OT released into the CSF: are the levels functionally relevant?

Because of the intervening blood-brain-barrier, peripheral OT contributes only a negligible amount (0.002%) to the OT-levels in the CSF [58]. Therefore, OT-levels in the CSF arise from the paraventricular and supraoptic hypothalamic nuclei, directly by dendritic and supraependymal release into the CSF and/or indirectly by terminal release from OT-fibers in other brain areas from where OT may diffuse towards and into the CSF. What do we know about the relative contribution of these sources?

We have to consider that in the magnocellular OT neurons, up to 95% of OT is present in and released from the dendrites [112] which makes this contribution many times more effective in regulating OT-CSF levels than the relative small amounts released by the terminals of the parvocellular neurons projecting to a variety of brain areas. While terminal release, for instance in the central amygdaloid nucleus, may induce a five-fold local increase in extracellular OT [113], it is hard to imagine how such minimal amounts at a considerable distance from the ventricular system could play a role, compared to the 1000-fold increases observed in PVH and SON [83] in the direct vicinity of the ventricular borders. The more so as diffusion over long distances disperses OT in more directions than only towards the CSF. In addition, ‘diffusion takes time’, which means that the amounts of extracellular OT steadily decrease over time and distance. While the half-life-time for OT in the

CSF is about 10 to 20 times longer than in the blood, the ECF-half life-times are probably similar but remain to be determined. Anyway, both time and distance will decrease the amounts of OT reaching the CSF from 'terminal release sites at a distance' to some extent. We propose that the contribution of terminal release of OT elsewhere in the brain (apart from the OT-fibers running along the ventricular system to release their contents along or even purposefully into the CSF) to varying OT-CSF levels will be, at the most, very limited and thereby the idea that varying OT-CSF levels reflect only 'OT-waste-disposal' as utmost improbable.

This raises the question: are the amounts of OT becoming available from the well-coordinated dendritic release in PVH and SON sufficient to explain the varying OT-CSF levels and to induce behavioral/physiological effects? All available evidence suggests: yes, they are! Under resting conditions, basal OT-CSF levels tend to be in the range of 5 to 10 fmol/ml=pg/ml [49, 56, 114-116], though occasionally higher basal levels have been reported [58, 117]. These basal levels tend to increase from about three- up to five-fold higher levels at night in the rat, [39] or at daytime in the human, [41], after osmotic stimulation [116, 118], after ejaculation [115] as well as during nursing in guinea pig [49] and sheep [119]. Such increases in OT-levels turned out to be sufficient and have been causally related to effects on nursing [119], learning processes [58] as well as pain-suppression [117]. In the latter publication it was shown that after electrical stimulation of the caudal PVH OT-levels were only increased in the CSF, while after rostral PVH-stimulation increased peripheral OT-levels were induced as well [120], a remarkable case of goal-specific release.

Concerning the amounts of OT necessary to induce such 3 to 5-fold increased OT levels, it was shown by Robinson and Jones [49] that an injection of 100 pg OT into the ventricular system of the guinea pig induced an eightfold increase from about 5 to 40 pg/ml, obviously in the range of the behavioral effects, discussed before. It has been calculated that the SON contains 3.2 ng OT [112, 121]. Adding the magnocellular PVH neurons, the total amount of OT 'bordering' the CSF can be estimated as about 5 or 6 ng OT, of which 95% is available for dendritic release [112]. These amounts are 'huge' compared to the 100 pg necessary for an eightfold increase, which in itself seems to be two times higher than necessary to induce a physiological or behavioral effect. Amounts like 100 pg have, indeed, been shown to become readily available. The concentration of OT in the cisterna magna of the rat increases up to about 300 pg/ml after morphine withdrawal, with the SON as the sole source of this 'subarachnoid OT', because lesioning the PVH was without effect [60, 83]. In addition, during acupuncture analgesia in the rat, the SON may release as much as 750 pg/mg protein, completely on its own without support from the PVH, with clearcut analgesic effects [122].

The available evidence suggests that OT neurons in the PVH are perfectly in a situation to work synchronously (by positive feedback as well as by cross-talk between left and right PVH), to release considerable amounts of OT specifically into the rostral 3rd ventricle, without concomitant release in the blood stream, providing potentially an independent message to other brain areas, in addition to the 'parvocellular OT-projections', without peripheral involvement. OT-neurons in the SON may provide a similar message to brain areas at the outer surface of the brain, bordering the subarachnoid space.

In view of these neuroanatomical and functional characteristics of the OT system described above, we prefer to consider the CSF not as a ‘drain’ by which superfluous amounts of OT are removed, but, following Sewards and Sewards [31], as an actively regulated system carrying variable amounts of OT, as a message to widespread ‘downstream’ brain areas.

In summary: since systemic OT does not contribute to CSF-OT, all CSF-OT must be derived from PVH and SON by dendritic release, supported by release via supraependymal elements and parvocellular terminals. The amounts of available and experimentally released OT into the CSF seem to be amply sufficient to compose a relevant signal or to ‘send a message’ to sensitive brain areas.

2.7 Oxytocin Receptors and the CSF

Questions about ‘sensitive brain areas’ focus on the distribution and density of OT receptors, that have been studied by a variety of techniques, in different animals and at different ages [123-131] including the human brain [132, 133] and genetically modified lacZ gene- and Venus cDNA-expressing mouse brains [124, 131]. In an extensive review, Gimpl and Fahrenholz [134] discussed the OT-receptor system, and they listed about 50 brain areas showing detectable levels of OT-mRNA-expression or the occurrence of OT-binding, in the rat and human brain. A few points, related to the subject of the present review, have to be addressed more specifically.

An OT-message consisting of a single or a few successive peaks in the ventricular OT-levels contains in itself a very limited amount of ‘content’, hard to reconcile with the many and variable effects of icv-administration of OT, as

described in the literature (see below). Necessarily, it has to be conceived that the ‘receptive system’ (OT-receptors and binding sites) is a variable and plastic part of the communication system. It is hardly surprising, therefore, to see that an extensive set of controlling factors determines the ‘reactive state’ of the OT-receptive system, with long- and short-term changes occurring both globally and in a site-specific way. It is the variability in the OT-receptive target areas that explains the differentiated behavioral effects of single icv-OT injections [135] (**Fig4**). Recently, it has been shown experimentally that genetic manipulation of the ‘receptive system’ and viral vector-mediated changes in receptor expression induce impressive long-term behavioral changes [136-140].

As observed by Tribollet et al, [129], the distribution and local densities of OT-receptors are strongly depending on the age of the individual and on existing species differences [129]. Changes in expression of OT-receptors concur with important behavioral changes, while neonatal manipulations induce long-lasting behavioral effects [128, 141, 142]. Some species-differences are clearly related to social conditions (living monogamously or polygamously) [140, 143], but for other differences the functional context is not immediately clear. OT-receptors appear to be under extensive regulatory control, however, exerted by a variety of steroids, circulating in the blood stream. It has been shown that cholesterol [144, 145], gonadal steroids [146-149] and corticosteroids [150, 151] all play a regulatory role in the density and sensitivity of the OT-receptors. Since steroid levels are constantly changing, due to a large variety of internal as well as external control mechanisms, so will be the case for local OT-receptivity. These steroid effects are not involving

the whole population of OT-receptors irrespectively, but seem to be targeting specific brain areas, as shown by the specific variations during the estrous cycle on OT-receptor densities in the ventromedial or the preoptic hypothalamus in the rat [149, 152-158]. In this way, a picture of constantly changing patterns of OT-receptivity emerges when several brain areas are considered together. Additional indirect regulatory effects, like those described for opioids [159, 160] may add considerably to the observed variations in OT-receptor densities and distribution. Finally, the 'common use' of the AVP1 receptor makes the OT-message partially depending on the state of the AVP-receptive system, adding to local variations in sensitivity for the 'OT-message'.

Taken together, the 'OT-receptive system' impresses as an extremely flexible congregation of brain areas, of which 'OT-sensitivity' constantly changes over time, short-term and/or long-term, as well as over location. Apparently, OT-sensitivity should be described as variable patterns. Such a variable patterning of OT-sensitivity over time and location seems to be amply sufficient to understand how a single 'one-dimensional' message may have such a variety of effects.

Among the 50 OT-receptive rat brain areas listed by Gimpl and Fahrenholz [134], at least 25 are located at a distance of less than 1 mm from the ventricular walls surrounding the CSF, and when the outer surface of the brain is taken into consideration as well, including the cortical areas, this number increases to about 40, revealing that 80% of the brain areas containing OT-receptors are potentially influenced by volume-transmission via CSF-OT, within a matter of minutes (**Fig5**).

‘Mismatch’ is a well known phenomenon in the brain, meaning that the distribution of immunoreactive fibers for a given neuroactive brain substance is not congruent with the distribution of its receptors [161, 162]. In the case of OT, it is clear that many of the areas containing OT-receptors receive direct OT-projections from mainly the parvocellular part of the PVH. However, some remarkable exceptions seem to be present, suggesting a considerable ‘mismatch’ between the density of the innervating fibers and the density of OT-binding sites. When comparing the distribution of OT-IR fibers in the rat [65, 67] and guinea pig brain [163] with the brain areas showing the highest ‘OT-receptivity’ [127, 129, 130, 134, 135, 143, 164] several remarkable differences become apparent. Some ‘OT-receptive’ brain areas hardly receive any OT-innervation, while some other brain areas may contain OT-IR fibers of parvocellular origin, but their close proximity to the ventricular system or subarachnoidal space suggests that interactive neuronal-CSF-OT-effects, as discussed before, most probably occur all the time.

The most interesting brain areas have been indicated in **Fig 5.** This figure shows the flow of CSF with the OT ‘going with the flow’ and 5 areas have been indicated specifically, where functional behavioral effects of OT might be of considerable importance. These brain areas will be discussed in more detail below, in section 4, but comprise medial hypothalamic regions, with important behavioral functions, brainstem areas involved in general and visceral functions, cortical areas and olfactory regions.

In summary: if OT-releasing neurons use the CSF-system for distant messages, the variable, plastic part must be at the receptive side of such a ‘messaging-system’ and relevant brain areas should be bordering the

ventricular and subarachnoid spaces. The great majority of OT-receptive brain areas are found along the ventricular and arachnoid surfaces and some of them do not even contain any OT-IR-fibers ('mismatch'). Density and sensitivity of OT-receptors are extensively controlled by all kinds of steroid hormones and other factors, in a localised and specific way, resulting in a very variable pattern of receptivity of brain areas.

3. BEHAVIORAL EFFECTS OF OXYTOCIN ARE ELICITED IN THE CSF.

Functionally, OT and its receptors are involved a wide variety of behaviors like maternal-, sexual-, aggressive-, affiliative-, anxiety-, grooming and feeding behavior, as well as in nociception [134].

The OT-involvement in a particular behavioral system is usually intertwined with other neurotransmitter or endocrine changes, as well as peripheral physiological phenomena. Most of the effects on organs or bodily systems can be understood as adaptive changes, supporting the behavioral effects, mentioned above. Some of the behavioral effects can be induced by (large amounts of) peripheral OT but, generally, peripheral administration induces only peripheral effects, due to the blood-brain-barrier. However, small amounts of icv-OT are remarkably effective to induce behavioral effects, while in some cases, direct neuronal connections of parvocellular OT-neurons seem to be indispensable.

The hypothesis that, besides local release from axons, OT distributed by CSF plays a role in behavior is supported by the many effects found after intracerebroventricular injection of the neuropeptide.

3.1 Social Behavior

Social behaviors exist in many forms and have been described as including parental behavior, affiliative behavior, social attachment, sociosexual behavior and monogamy, and all of these share the involvement of OT [140, 165-177]. In rodents, sheep and goats, olfactory and other cues, guiding social recognition, are obviously under oxytocinergic control. Several reviews appeared recently and showed the OT-involvement in a series of brain areas, like the olfactory bulb, the medial amygdala, the medial preoptic area, the ventral tegmental area and the nucleus accumbens,[166, 177-186]. Repeatedly, the similarities between the effects of disturbed OT systems and clinical syndromes like autism have been pointed out and recently the beneficial clinical effects of OT-treatment on positive social interactions as well as for autism were reported [167, 187-191]. Interestingly, underlying the different behavioral reactions to cues to be approached or to be avoided [177], there seems to be a balance between OT and the pituitary-adrenal axis activity [147, 192-196]. In this interaction, OT has stress-reducing effects, which even appear to be transmittable to a conspecific cage mate by olfactory cues [197, 198]!

Intranasal administration of a variety of substances has been shown to be effective in inducing physiological, behavioral and clinical effects [199-207]. In humans, intranasal administration of oxytocin causes a substantial increase in trust among humans and decreases anxiety [208-213], thereby greatly increasing the benefits from social interactions. Oxytocin specifically affects an individual's willingness to accept social risks arising through interpersonal interactions [214]. Oxytocin also improves ‘mind reading’: the ability to infer

the mental state of others from physical cues of the eye region [215]. Interestingly, the effects of intranasal administration of OT (as well as many other neuroactive substances) seem to originate not from the 'olfactory system' itself, but from the 'perineuronal spaces' surrounding the olfactory fibers while penetrating the cribriform plate, to reach the olfactory bulb and surrounding liquor space. The identity of and the relationships between these 'perineuronal spaces' and the spaces functioning during the CSF-release into the 'nose-lymphatics', certainly deserve more attention and additional research[199-201, 210-212, 216, 217].

3.2 Sexual Behavior

An overwhelming amount of data shows that OT stimulates erection, with both central and peripheral mechanisms involved [218-228]. In the succeeding phases of the copulatory sequence of the male rat, OT significantly reduced mount and intromission latencies only in aging (20-month-old) rats [229], but the reduction in ejaculation latency as well as in the duration of the post-ejaculatory interval were observed also in young vigorous males, most consistently after icv-administration [230, 231]. Recently, a case of male anorgasmia was treated successfully by intranasally applied OT [232]. Peripherally, OT stimulates only some specific aspects of the ejaculatory process, like sperm transport [225, 233-235]. Generally, peripheral interactions and the integrity of the pelvic nerve seem to be necessary, at least for the effects of systemically administered OT [236].

Interestingly, OT has antidepressant effects in several animal models for depression [237]. Antidepressant drugs, like specific-serotonin-inhibitors (SSRI's) may induce inhibition of masculine behavior [238]. OT may reverse this SSRI-induced inhibition [239, 240]. Moreover, oxytocin is released centrally during sexual activity and mating with a receptive female, and this seems to be involved in the reduction of anxiety and the increase in risk-taking behavior in male rats that continues for several hours after copulation [77].

In contrast to the generally stimulating effects of OT on male sexual behavior, inhibitory effects of OT have also been observed, after high doses, especially after icv-administration. These inhibitory effects on penile erection [241] as well as on later phases of masculine behavior [242, 243] suggest that larger dosages of OT, administered centrally, may 'create a physiological state, analogous to sexual satiety' [244, 245]. Concerning the brain areas involved in these effects on male sexual behavior, the OT-neurons in (and adjoining) the paraventricular hypothalamic nucleus play a crucial role [246], but hippocampal involvement in erection has been described as well [227, 228, 247].

In addition, OT has been shown to play a facilitatory role in female sexual behavior [230, 245, 248-253], possibly due to its involvement in the efferent control of the (rodent) clitoris and vagina [254].

Ovarian hormones as well as sexual interaction strongly influence the distribution and intensity of immunoreactivity of OT neurons [255] and OT+Fos-IR neurons have been observed after sexual activity in female rats [256]. Defining the neural substrate for these behavioral effects is

complicated, however, although the medial preoptic area and the lateral part of the ventromedial hypothalamic nucleus seem to be involved [257], precisely the brain areas where OT-receptors are influenced by gonadal hormones ([154-158], (see section 2.7)! Part of the OT effects may be indirect by increasing the tolerance of the female rat for tactile stimulation or by actions on affiliative behaviors (see below) associated with sexual behavior [244]. Finally, species differences, even between rodents, may be considerable, because in the prairie vole no facilitatory effects could be demonstrated. Instead, high dosages resulted in immediate and long-lasting inhibition of female sexual behavior, but only after icv and not after systemic administration [244, 245].

3.3 Parental Behavior

Especially in the peri- and postpartum period, a remarkable set of physiological and behavioral changes is induced, including parturition and lactation [168, 258]. To mention just a few of the adaptive changes described: olfactory changes, related to olfactory/social recognition [114, 181], changes in brain activation patterns [259, 260], morphological and excitatory changes in specific brain areas [92, 261] as well as changes in OT release concurrent with receptor expression [262, 263]. During parturition, the brain of the newborn is protected by the elevated OT levels [264], while afterwards the anxiolytic effects of OT become more manifest, supporting maternal defence [265]. A recent fMRI study showed the modulating effects of OT on unconditioned fear responses in lactating dams [266]. Apparently, the integrative role of OT around parturition is highly complex and affects several

behavioral and physiological levels in order to adjust the physiological mechanisms to the necessary changes in behavior. Many of the changes described have been related to functional changes in the 'OT-receptive' target areas occurring in this time period.

In ewes, intracerebroventricular infusions of oxytocin significantly increased the frequency of some or all of the maternal behaviors scored, while aggressive and negative behaviors significantly decreased in frequency [119]. In vivo microdialysis showed that OT concentrations increased significantly in the region of PVH at birth in multiparous ewes. When OT was retrodialysed bilaterally into the PVH, maternal behavior was induced [267].

3.4 Food Intake

In relation to food intake, OT has been shown to affect both peripheral physiological aspects like gastric motility [268, 269], gastric acid secretion [270] and insulin secretion [271] as well as central behavioral aspects. OT generally seems to inhibit food intake while OT-knockout mice show enhanced intake of palatable carbohydrate solutions [272]. OT seems to play a special role in linking 'long-term'-satiety signals (leptin) to meal size control. The cells of origin for these inhibitory effects are OT-neurons located in the paraventricular nucleus, and their descending fibers may exert a tonic inhibitory influence via (parts of) the nucleus of the solitary tract. Interestingly, icv-administration of OT induces also strong feeding-related effects, especially via the 4th ventricle, where application of an OT-antagonist was shown to be about 1000-fold more effective than in the 3rd ventricle [273, 274]. Taken together, these data are strongly suggesting a conjoined and mutually

supporting effort of neuronal and CSF-messaging influencing the brainstem areas that control food intake. Additional effects on more rostral brain areas, like the activation of the ventromedial hypothalamic nucleus [275], previously known as ‘satiety center’, may further contribute to a subtle differential inhibitory control of food intake.

3.5 Grooming Behavior

Grooming behavior can be induced by an icv injection of OT [276-279], even in transgenic ‘OT-null’-mice [280]. These effects were thought to be initiated via the paraventricular hypothalamic nucleus and/or ventral tegmental area [281, 282], whereas the nucleus accumbens was associated with inhibition of OT-icv-induced grooming [283].

3.6 Pain

OT has been reported to influence pain control mechanisms [117, 122, 284-288], modulation of the sympathetic nervous system [289, 290], and cerebral hemodynamics [291], suggesting even further going indirect adaptive control functions for OT. Concerning the effects on pain regulating mechanisms, it turned out that only i.c.v.-administration of OT was effective in elevating the pain threshold, which could be blocked by an OT-antagonist, while peripheral administration was completely ineffective [122]. Increased OT-levels in the CSF, induced by central release of OT after PVH-stimulation, were directly involved in and causally related to the pain suppression [117].

In summary, icv-injections of OT induce many different behavioral as well as pain-reducing effects. Apparently, the state of the ‘OT-receptive-system’

determines the effect of an experimental 'CSF-OT-peak'. Systemic administration of OT frequently induced no behavioral effects at all and was completely ineffective in pain suppression.

4 CSF-OXYTOCIN MAY AFFECT VARIOUS PARTS OF THE CNS.

The multiple and variable behavioral effects of icv-injections of OT suggest a specific role for the CSF in distributing OT-messages to distant destinations. **Fig 5** summarizes how OT, released from the PVH into the ventricular system and from the SON into the subarachnoidal space, reaches many OT-receptive parts of the brain by 'going with the flow'. Some of these brain areas deserve special attention, because of their strong involvement in a variety of physiological, behavioral and cognitive functions. These areas have been numbered 1 to 5 in Fig 5, and will be discussed successively.

4.1 OT- effects on hypothalamic 'Behavioral Control Column'

(Nr 1 in Fig 5, Fig 6)

Over the last years, Larry Swanson has developed the concept of a 'behavioral control column' [1, 292]. This column consists of a longitudinal series of nuclei extending from the most rostral (preoptic) to the most caudal (premammillary and mammillary) parts of the medial hypothalamus, including the anterior and ventromedial nuclei. Nuclei of this hypothalamic 'behavioral control column' turn out to play a keyrole in the organisation of behavior. (**Fig 6**). Many neurons of this 'column' are steroid sensitive and Pfaff and co-workers have shown over the years that circulating gonadal hormones directly

affect OT-receptivity in the lateral part of the ventromedial hypothalamic nucleus, involved in the lordosis-circuitry of the female rat [154-156, 158, 256, 257, 293-300]. This impressive line of research shows very clearly how steroid hormones influence OT-receptivity, allowing the gonadal endocrine systems regulatory control over a range of other behaviors. As an example: female rats readily switch their response to a male from a soliciting proceptive attitude when in estrous to an aggressive response when in non-estrous, showing how different hormonal states induce radically different reactions towards the same approaching stimulus. In this kind of behavioral reactions, the 'behavioral control column' plays a keyrole together with some closely (and mostly reciprocally) connected parts of the bed nucleus of the stria terminalis, the amygdaloid complex and maybe other medial and cortical parts of the ' limbic system' [30].

As mentioned before, OT and its receptors induce a complex set of behavioral changes, especially peri- and postpartum, involving effects on maternal, sexual and affiliative behavior, female aggression, anxiety, nociception and social memory [134]. One or more of the hypothalamic nuclei of the 'behavioral control column' are always involved in these behavioral changes, as supported by numerous Fos- and other studies from our group [301-306] as well as from many others. Each of the nuclei of the 'behavioral control column' is located closely to the ventricular walls (in rats (much) less than a mm) and contains neurons provided (sometimes densely) with OT-receptors [130].

From these facts we propose that some major target areas of CSF-OT are located in the medial-hypothalamic 'behavioral control column' as defined by

Swanson. The strong effect of icv-OT on ventromedial hypothalamic neuronal activity [275] is a nice demonstration of such hypothalamic targets. Suppression of aggressive reactions, normally obtained from the anterior hypothalamic nucleus, or the adjoining 'hypothalamic attack areas' [307-311] could obviously be another OT-effect realised in the 'behavioral control column'. In addition to possible CSF-effects, some rostral (preoptic) and some caudal (pre)mamillary nuclei may receive a direct OT-innervation as well, supporting the idea of mutually supporting messages.

N.B. Our conclusion regarding the importance of these paracrine OT-effects are neither meant to indicate that these paracrine effects are the only ones influencing these target areas, nor that the target areas are restricted to this behavioral control column!

4.2 OT- effects on brainstem ('core'- and 'paracore'-) areas. (Fig 5, nr 2)

Since there is no reason to assume that the caudal flow of CSF-OT becomes ineffective at the entrance of the cerebral aqueduct, the receptive parts of the periaqueductal gray (PAG), raphe nuclei, locus coeruleus and the solitary tract nucleus [30, 31, 134, 312, 313] may all add their contribution to the behavioral changes observed. Especially the PAG seems to be easily accessible for all kinds of substances passing the cerebral aqueduct, as apparent from all studies concerning the penetration depth of substances added to the CSF [161, 314-316] as well as those concerning GnRH effects on the PAG [317, 318].

However, brain areas more remote from the ventricular or subarachnoidal space may also have easy access to (the contents of) the CSF as well, and

tanycytes seem to play a crucial role here. Tanycytes are specialised bipolar ependymal cells contacting the CSF [319-324], especially in the mediobasal hypothalamus. However, brainstem areas like locus coeruleus, raphe nuclei and the paragigantocellular nucleus in the ventral brainstem are also provided by tanycytes [325-329]. Very recently it was shown that the raphe nuclei may be reached by CSF-influences via such specialised tanycytes [330] and that the locus coeruleus accumulates nerve growth factor, about 50% of it not by neuronal transport mechanisms but obtained from the CSF [331]. Assuming that these findings form part of an increasing series of similar findings, it is interesting to recognize that the raphe nuclei and the locus coeruleus form part of the 'medial and lateral paracore areas' respectively, as defined by Nieuwenhuys [7, 20, 22]. These 'paracore areas' extending through the brainstem are characterized by their content of numerous unmyelinated peptidergic fibers, apparently involved in non-synaptic communication and subserving the physiological adaptations necessary for appropriate emotional and behavioral reactions [7]. We hypothesize that CSF-messages may become effective in these brainstem areas in cooperation with the many unmyelinated fibers, releasing neuropeptides in many brainstem areas, frequently running close and parallel to the ventricular system, especially the cerebral aqueduct.

4.3 OT- effects on cortical areas. (Fig 5, nr 3)

Another specific and important part of the brain influenced by the OT-CSF-flow, is the cortical mantle, covering most of the telencephalon. Interestingly, a direct cortical innervation by OT-fibers seems to be virtually or totally lacking

in many cortical areas. Nevertheless, quite a few cortical areas are OT-receptive, with the highest densities of OT-receptors located in cortical layers 2 and 3 [127, 130, 134, 135]. Since cortical neurons located in layers 2 and 3 are mostly involved in the intracortical connectivity, the following picture emerges: OT arriving via the CSF, has easy and rapid access to cortical and deeper brain areas via the perivascular spaces. OT may spread over the whole extension of the cortical mantle, to influence OT-receptive neurons in layers 2 and 3, not only to influence cortical development [332] but also to induce changes in local or overall cortical activity or functional 'connectivity'. Experimental data, confirming that OT affects cortical activity, including attenuation of memory and learning [333] are not difficult to find, despite the fact that these cortical effects of OT received considerably less attention, so far, than the subcortical behavioral effects [334-337].

Recent findings show the key role of OT in phenomena like 'affective evaluation' and 'trust' [338-340]. In the human brain, 'Von Economo neurons' play an important role in autism, intuition and social behavior [341-343]. The possibility of effective treatment regimens by intranasal OT-application offers exciting new opportunities [215, 338, 344-346] and it will certainly be possible to define the role of cortical OT much more specifically, in the near future.

4.4 OT- effects on olfactory areas. (Fig 5, nr 4)

If most of the CSF and OT is drained into the olfactory lymphatics, it means that the olfactory bulbs as well as all adjoining superficial olfactory areas are fully exposed to the surrounding CSF-OT, which makes it less surprising that electrical stimulation of the paraventricular hypothalamic nucleus (PVH)

induces the same inhibitory effect on the mitral cells in the olfactory bulb as microinfusion of oxytocin in the lateral ventricle (icv) [347]. While there are some OT-fibers directly innervating the bulbs and other olfactory areas, unilateral transections between PVH and olfactory bulb failed to block the stimulation effects and the authors suggested explicitly that the CSF was the way of communication [347]. Anyway, the density of OT-receptors in the olfactory areas is generally high [130, 134, 135, 348] and easily accessible for 'CSF-OT'.

Taking into account the location of the easily accessible olfactory bulbs, completely surrounded by CSF, it is no longer surprising that OT is very effective in influencing in 'olfaction-related-behaviors' and or can be used as a target for intranasal-OT sprays [344, 346].

4.5 OT- effects on olfactory sensory neurons (OSNs). (Fig 5, nr 5)

Drainage of CSF via the numerous small lymphatic vessels of the nose, opens the possibility that eventually even the olfactory sensory neurons (OSNs) themselves could be affected by the temporarily elevated OT-levels, while at the same time linking the brain to the lymphatic system [349]. Such a hypothetical effect of OT on the OSNs would serve the function of adapting olfactory sensitivity to the hormonal and behavioral state of the animal. This idea seems attractive for a number of reasons: 1) changes in the motivational state are known to induce temporary adaptive changes in the somatosensory, gustatory, visual and auditory sensations, and there is no reason to assume that the olfactory sense would be an exception to what seems to be a general rule: motivational changes induce sensory adaptations. 2) gonadal hormones

have been shown to influence olfactory sensations extensively (factors like estrous vs anestrous, or effects of castration [350-352]. 3) direct effects of neuropeptides on olfaction are harder to find, but in 'behavioral states' like hunger vs satiety, two neuropeptides play a prominent role: orexin (of hypothalamic origin and stimulating food intake) and leptin (of peripheral origin and inhibiting food intake) [353-357]. Note that these peptides not only affect hypothalamic/limbic mechanisms regulating food-intake but also show direct effects on the olfactory sensations themselves, just like the motivational states hunger and satiety have been shown to induce changes in olfactory sensitivity [358-360]. 4) for OT to exert direct effects on the OSNs, the latter necessarily would need to be in the possession of the appropriate receptors. This information is hard to find in the literature, which reflects a general lack of knowledge about possible modulating effects of neuropeptides on OSNs. However, Levasseur et al. [361] have studied cultured OSNs and they showed not only the presence of several types of receptors on OSNs, but also direct effects of vasopressin and OT on OSNs. Especially the effect of OT, at this cellular level, turned out to be strong!

Several other neuropeptides have been shown to affect OSN sensitivity: in addition to orexin and leptin, mentioned above, substance P [362], natriuretic peptides [363] and GnRH [364]. These findings strongly suggest that it is probably the rule, and not an exception, that neuropeptides involved in motivational changes, concurrently modulate olfactory sensitivity into a state optimally adapted to the current behavioral state.

Finally we would like to ask attention again for the puzzling findings of Agren et al, who showed that the stress-reducing effects of OT are apparently

transmitted to a conspecific cage mate by olfactory cues [197, 198]. Could it be that the OT in the nose-lymphatics and nasal epithelium is playing a role here?

There is much experimental work to be done in this field of the functional relations between olfactory bulbs, the surrounding CSF, the olfactory fibers and adjoining lymph vessels and the possible direct modulating effects of neuropeptides as well as other substances on OSNs. Since each of these structures may also be involved in the effects of 'intranasal administration' of drugs and neuropeptides, which treatment is growing more and more important as an alternative route for drug administration, to circumvent the blood-brain-barrier, it is to be expected that considerably more experimental data and more conclusive evidence will come available over the next few years.

In summary: The most interesting brain areas, potentially targeted by OT-messages via the CSF, comprise the medial hypothalamus and several brainstem, cortical and olfactory regions. For each of these regions, the available evidence that OT might be involved in functional and/or behavioral changes is presented. Apparently, there remains a lot of work to be done.

5. CONCLUSIONS AND FUTURE DIRECTIONS.

In the previous sections we have stated that the CSF is used for communication in the central nervous system, that oxytocin is released into the CSF, that oxytocin in the CSF contains a meaningful message and reaches many brain areas that contain functional oxytocin receptors and that oxytocin in the CSF has multiple marked behavioral effects.

The question that remains is: what is the functional significance and the specific contribution of this relatively uncontrolled and broad-spectrum oxytocin release system, in addition to the targeted axonal release from parvocellular OT-neurons and the peripheral release of the magnocellular OT-neurons? We support and propose the view that broadcasting messages via the CSF is an appropriate way to put several parts of the CNS into a 'behavioral state', subserving the performance of specific behaviors or groups of behavioral elements sharing a common motivational system including the temporary suppression of specific behavioral or physiological reactions. These 'CSF-messages' have to be considered as a partially independent signal, while at the same time constantly supporting, sustaining and in mutual exchange with the ECF-contents released by axon terminals all over the brain, but mostly in brain areas adjoining the CSF. This signaling pathway has been described recently as an 'undervaluated pathway of neuroendocrine signaling into the brain' [365]. The presence of nanostructures, from various brain sources, appears to support such signaling functions in the human CSF [366].

Sewards and Sewards [31] proposed that the presence of elevated CSF-levels of corticotropin releasing factor (CRF) and vasopressin generate fear and 'power-dominance' drive motivation, respectively. They hypothesized that the elevated neuropeptide levels in the CSF are detected and transduced into neuronal activities by, predominantly, hypothalamic neurons in the vicinity of the third ventricle. The purpose of this system was proposed to be maintaining a state of fear or anger and consequent vigilant or aggressive behavior after the initial fear- or anger-inducing stimulus itself is no longer perceptible [31]. In

other words, CSF-messages prolong the duration of a motivated state. Interestingly, important destination areas for this transmission (the medial hypothalamus, periaqueductal gray, midline thalamus and medial) prefrontal cortex are all bordering the CSF-liquor system, at the inner- or outer surface of the brain. In addition, each of these destination areas is extensively connected to other parts of the limbic system and functionally involved in a range of differently motivated behaviors [31]

We propose that a similar (but compared to CRF opposite) role is being played by a CSF-OT-message-system. OT-release into the CSF upon stimuli like parturition, suckling or hand-milking, vagino-cervical stimulation or mating, can lead to a number of behavioral effects: facilitation of sexual behavior, inducing partner preference or pair bonds, facilitation of maternal behavior, decrease of aggressive behavior, increase of physical contact, increase of proximity and coherence in a group of huddling pups, increase in trust, improvement of social 'mind-reading' and elevation of the pain threshold, amongst others.

Although the complete scope of behaviors related to CSF-oxytocin release may not yet be complete, the general pattern that emerges is one of an increase in social behavior, contacts and 'trust', combined with a decrease in stress and anxiety'.

In summary: We propose that OT-messages are broadcasted via the CSF in order to maintain for a prolonged period of time a 'pro-social' behavioral state, allowing and increasing bodily contacts, while at the same time modulating a variety of other behaviors, depending on the sensitivity (or 'OT-receptive state') of numerous brain areas involved.

Considering all available evidence we propose that:

- OT levels in the CSF are being regulated actively;

- OT levels in the CSF contain a meaningful message for brain areas in the appropriate receptive state;

- OT-messages via the CSF are effective at an appropriate timescale to induce behavioral changes as well as to support and sustain the effects of OT released by axonal terminals in many 'behavior-relevant' brain areas bordering the ventricular and subarachnoidal spaces;

- the 'behavioral control column' in the hypothalamus, brainstem areas ('core' and 'paracore' as well as ventral superficial) and the cortical and olfactory areas bordering the subarachnoid space and most probably including the olfactory sensory neurons, can be considered as the main target areas for the CSF-OT messaging system.

Legends to the Figures

Fig 1 shows the location of paraventricular hypothalamic neurons and dendrites with their characteristic extensions in the medial direction, towards the ventricular surface, with exceptionally few dendrites leaving the confines of the paraventricular hypothalamic nucleus. Fig 1A is reprinted from: Rho and Swanson [81], with permission of the Society of Neuroscience. Abbreviation: pv: periventricular part of the PVH, bordering the 3rd ventricle; Figs B, C and D clearly show the medialward preference of the dendritic extensions towards the 3rd ventricle on the left. In Fig B the 2 upper medial neurons show dendritic extensions that may cross the tip of the 3rd ventricle to extend to (dendrites from) the contralateral paraventricular nucleus, maybe contributing to bilateral PVH-synchronisation. Figs B,C and D are reprinted from: Armstrong et al. [80], with permission of Elsevier.

Fig 2 is reprinted from Dubois-Dauphin et al. [163], with permission of Elsevier. Figs A and B show clearly how close OT-immunoreactive neurons are bordering the third ventricle in the guinea pig, in an excellent position to release their dendritic contents into the CSF. In addition, Fig B shows many OT-IR fibers penetrating the ependymal lining of the 3rd ventricle and the intermingling of OT dendrites from the right and left side of the ventricle. Since dendritic OT-release stimulates

dendritic activity of other OT-neurons, the bilateral proximity of OT-IR dendrites will contribute to the synchronised release of OT by the left and right PVH simultaneously. Abbreviations: *: 3rd Ventricle; f: fornix; AH: anterior hypothalamic nucleus; Pa: paraventricular hypothalamic nucleus (=PVH).

Fig 3 is reprinted from Ludwig and Pittman [85], with permission from Elsevier. It shows clearly (a) how many OT-IR neurons in the Supraoptic nucleus (SON) extend their dendrites towards the ventral surface of the brain (b). These dendrites (D) are loaded with OT-IR vesicles, sometimes trapped at the moment of dendritic release (small arrows)(c).

Fig 4 is reprinted from: Ostrowski [135], with permission of Elsevier. It shows the distribution of OT-receptor mRNA in the rat brain. The ample occurrence in medial hypothalamic, superficial cortical layers as well as the olfactory regions is immediately clear.

Fig 5 is based on a midsagittal section of the rat brain, kindly provided by L.W. Swanson. It shows dendritic OT release-sites, from where OT 'goes with the flow'. An 'internal flow' caudalward from the PVH, followed by a rostralward flow along the outside of the brain. The supraoptic nucleus (SON), at the ventral surface of the hypothalamus, mainly contributes to this 'external flow'. The main regions containing OT-receptors and potentially influenced by 'OT-messages' arriving with the

CSF, have been indicated and numbered 1 to 5 as follows: 1,‘Behavioral control column’ in the hypothalamus; 2 ‘core’ and ‘paracore’- brainstem areas; 3, cortical areas; 4, olfactory regions; 5, olfactory sensory neurons. Each of the regions is discussed in the text. OT released in the CSF starts flowing caudally along the dorsal and ventral side of thalamic adhesion, to enter the cerebral aqueduct (AQ) and fourth ventricle; a small part of the CSF may continue flowing caudally through the central canal of the spinal cord, but most of the CSF leaves the ventricular system via the lateral apertures to start flowing through the subarachnoid space, surrounding the brain. This ‘external-flow’ is indicated here along the dorsal and ventral surface but occurs along all external brain surfaces. The destination of the arachnoid flow is the cribriform plate of the ethmoidal bone, containing the penetrating olfactory fibers, where CSF is released in small lymphatic vessels. The picture suggests that the ventricular bulk-flow of CSF is caudalward and arachnoid flow mainly rostralward. Abbreviations: IVF: interventricular foramen; PVH: paraventricular hypothalamic nucleus; SON: supraoptic hypothalamis nucleus; V3(p,h,m,t,pl): parts of the third ventricle; V4: fourth ventricle; 1-6: circumventricular organs; 5: Pineal organ;

Fig 6 is a horizontal reconstruction of the rat brain, kindly provided by L.W. Swanson. The concept of a ‘Behavioral Control Column’ [1, 292, 367]

is represented by the series of hypothalamic nuclei, extending from the rostral preoptic part to the caudal premammillary region.

While the number of OT-IR fibers traversing the medial hypothalamus is very limited, the presence of OT-receptors is generally abundant, as indicated by the orange arrows in the lower part of the figure, that are based on Vaccari [130]. As discussed in the text, this situation suggests that the ‘Behavioral Control Column’ can be considered as one of the main target regions for OT-messages flowing with the CSF.

Abbreviations: MPN: medial preoptic nucleus; AHN: anterior hypothalamic nucleus; PVHd: paraventricular hypothalamic nucleus; VMH: ventromedial hypothalamic nucleus; PMv & PMd: ventral and dorsal premammillary nuclei; VTA: ventral tegmental area.

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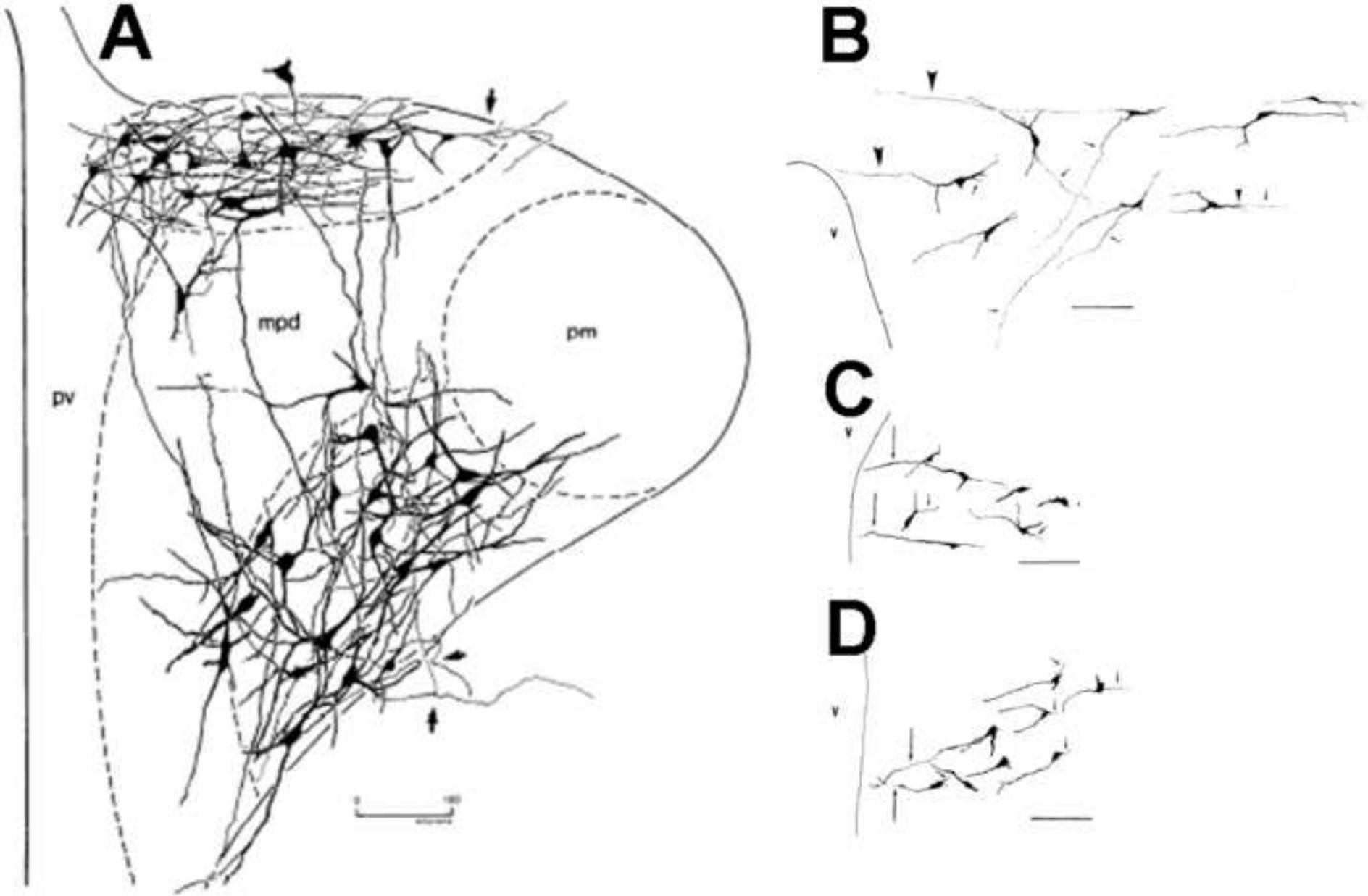

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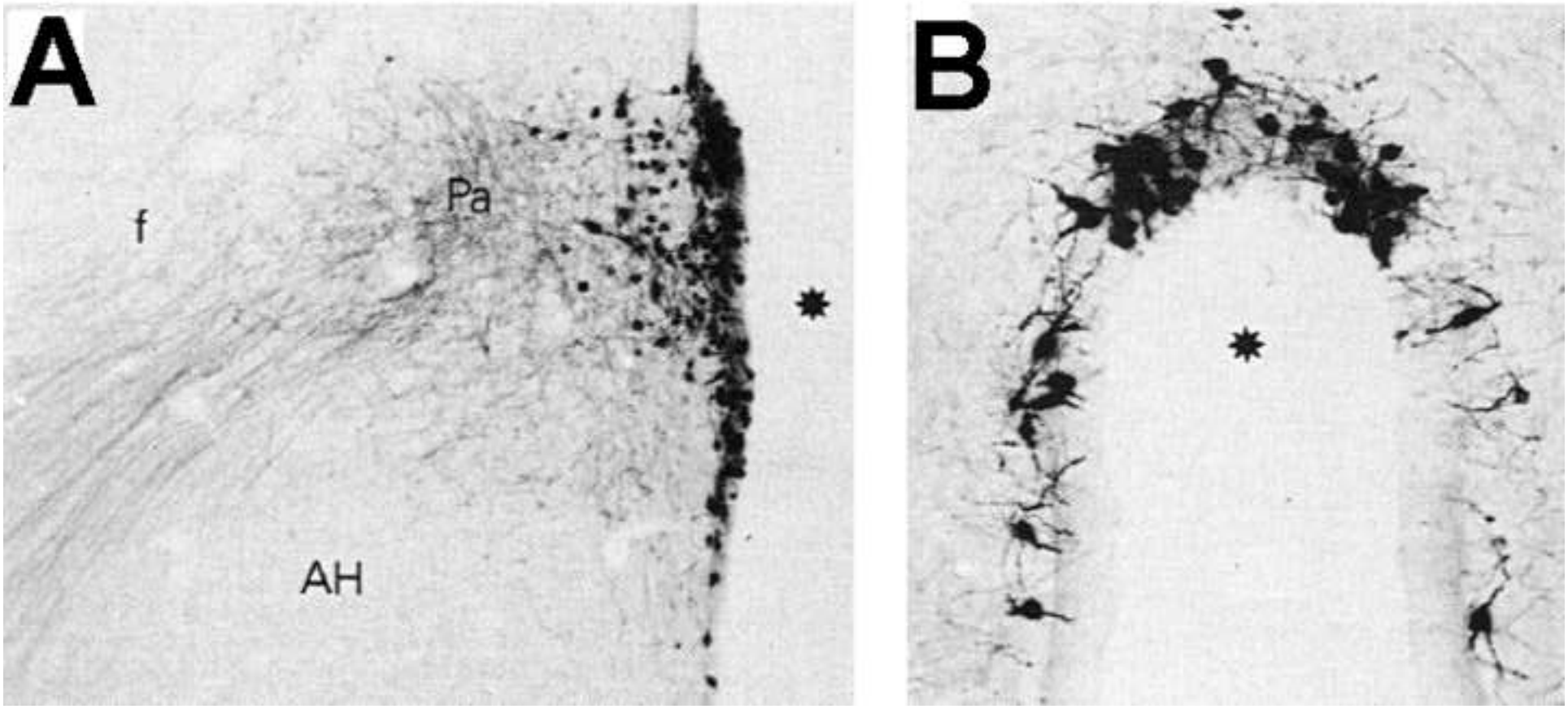

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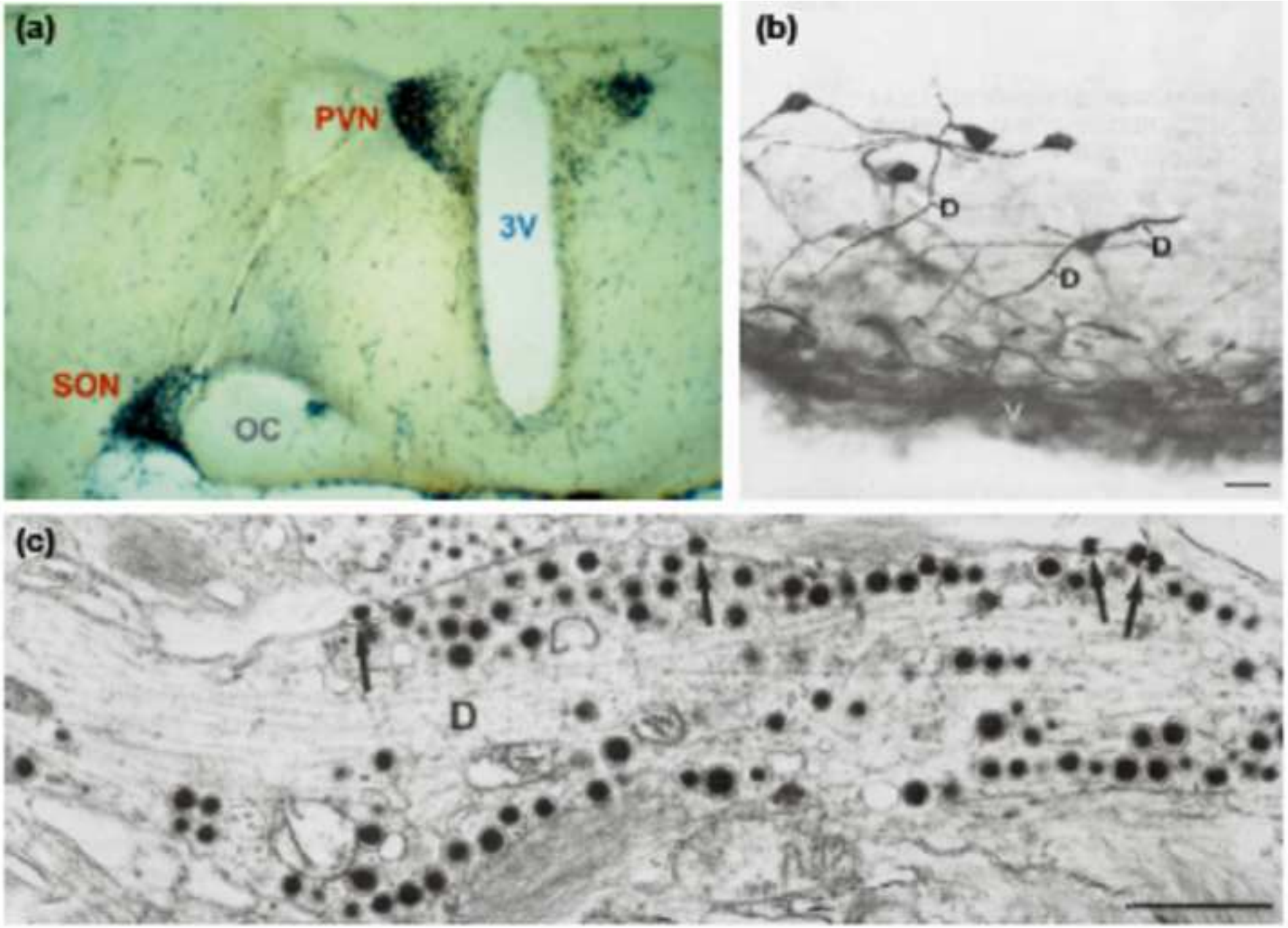

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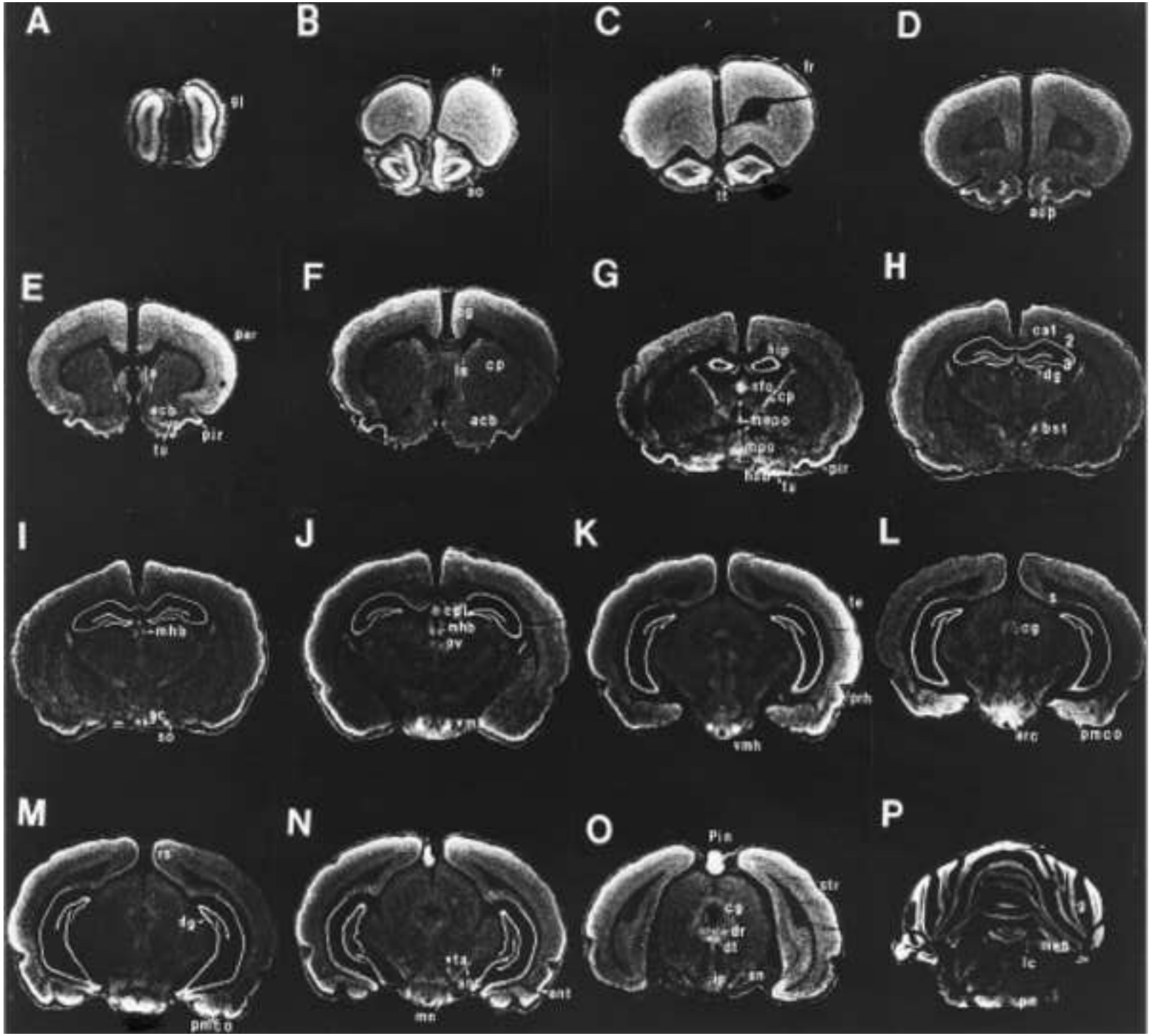

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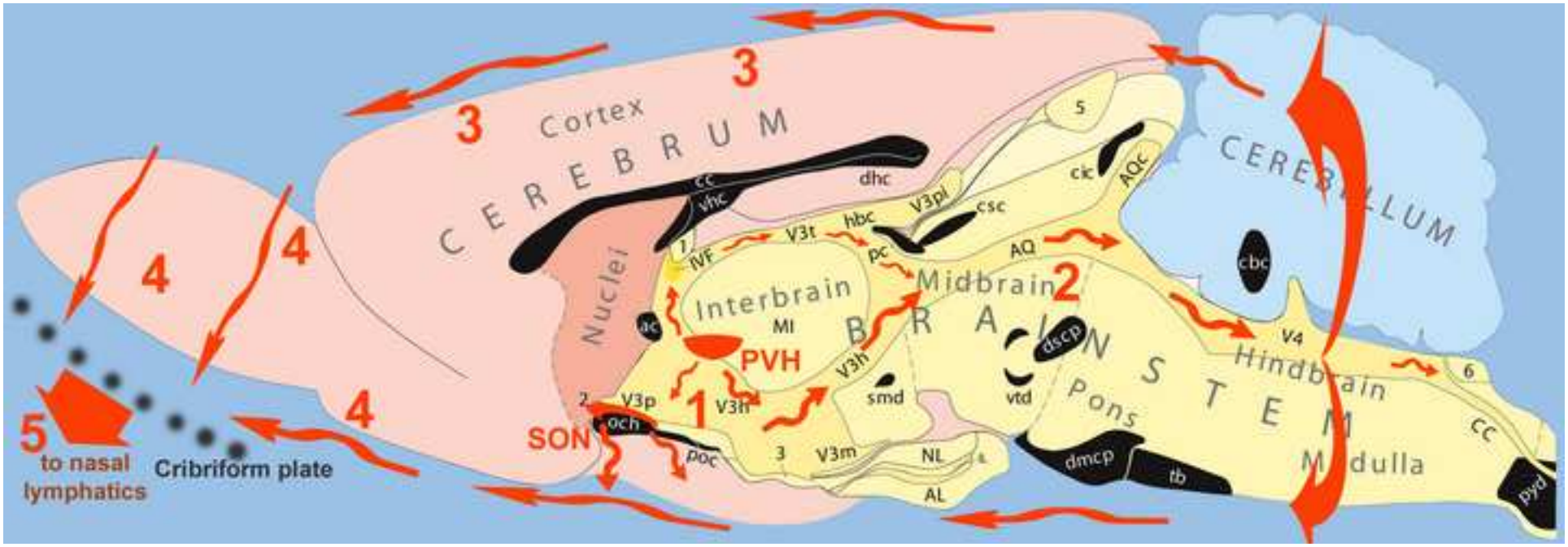

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