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PHILOSOPHICAL TRANSACTIONS B

Phil. Trans. R. Soc. B.
doi:10.1098/not yet assigned

Multiple signalling modalities mediated by dendritic exocytosis of oxytocin and vasopressin

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Keywords: hypothalamus, supraoptic nucleus, paraventricular nucleus, priming, calcium, homeostasis

Summary

The mammalian hypothalamic magnocellular neurons of the supraoptic and paraventricular nuclei are among the best understood of all peptidergic neurons. Through to their anatomical features, vasopressin- and oxytocin-containing neurones have revealed many important aspects of dendritic functions. Here we review our understanding of the mechanisms of somato-dendritic peptide release, and the effects of autocrine, paracrine and hormone-like signalling on neuronal networks and behaviour.

Of secret messages and public announcements.

Forms of information processing and intercellular communication in the brain may be classified, at least in part, according to distinct spatio-temporal features. At one end of the spectrum is classical chemical synaptic transmission. Chemical synapses are structurally organized units with a well-defined physical substrate, and have evolved to transfer information between pairs of neurons efficiently, in a precise, spatially constrained and rapid manner. The strength and time course of this "hard-wired" communication is dependent on the probability of presynaptic transmitter release, the affinity of the postsynaptic receptors for the transmitter, the density of postsynaptic receptors clustered at highly specialized sites, and the rate of diffusion/uptake of the neurotransmitter at/from the synaptic cleft [1-4].

At the opposite end of the spatio-temporal spectrum, paracrine or hormone-like signalling modalities mediate transfer of information between entire populations of neurons, which in some cases may be located relatively distant from each other, acting in a more diffuse, less spatially constrained manner and on a slower time scale. In the hard-wired chemical synapse, the "secrecy" of the communication is largely determined by the spatially constrained structure of the synapse. Conversely, in paracrine transmission, specificity is solely determined by the specificity of the signal/receptor interaction. Examples of signalling mechanisms acting at more distant sites include release of catecholamines and acetylcholine from en passant boutons on axonal segments [5], and gaseous neurotransmitters including nitric oxide and carbon monoxide [6]. However, the prototypes for hormone-like signalling within the brain are many neuropeptides, including vasopressin and oxytocin, released from their somata and dendrites. They are public announcements; they are messages not from one cell to another, but rather a message that is directed from one population of neurons to another [7-9].

The hypothalamo-neurohypophysial axis – a model system to study dendritic

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peptide release

The dendrites of magnocellular neurons (MCNs) of the hypothalamic supraoptic nucleus (SON) and paraventricular nucleus (PVN) have some unique characteristics compared to other neurons in the central nervous system. They are aspiny, branch sparsely, in many cases are aggregated in bundles, and are relatively thick and varicose. Dendrites in MCNs are structurally dynamic, undergoing activity-dependent remodelling, including shrinkage/elongation, altered branching patterns and increased bundling [10, 11]. Another salient feature is that in more than 60% of MCNs, axons arise from a dendrite rather than more conventionally from the soma [10, 12]. These axon-bearing dendrites may not only be privileged in their ability to influence spiking initiation and overall neuronal output [13], but they could be in turn more efficiently affected by back-propagating action potentials (see below).

The MCNs of the SON and PVN themselves are large and can easily be identified. Their cell bodies and dendrites are aggregated into compact and homogenous nuclei located in and receiving input from the central nervous system. Their axons project to the posterior pituitary gland, which lacks an effective blood-brain barrier allowing secretion from this site to enter the systemic circulation. MCNs dendrites are known to store the majority of the neuropeptide content present in the SON and PVN, and studies of dendritic release using push-pull perfusion or microdialysis [14, 15] can be accomplished without contamination by local synaptic release or reuptake of peripherally-released peptides (since the blood-brain barrier effectively blocks reuptake), dividing the brain and its periphery into two separate compartments. Simultaneous microdialysis and blood sampling *in vivo* has provided evidence that there is sometimes a clear dissociation between release of peptides into these two compartments, and these seem to be both stimulus-dependent and peptide-specific [16]. For example, a dissociation between dendritic and axon terminal oxytocin release is evident from the effects of alpha melanocyte-stimulating hormone (α-MSH). Activation of melanocortin 4 receptor receptors on oxytocin cells by α-MSH mobilizes intracellular calcium and stimulates dendritic oxytocin release, but the electrical activity of the cell is inhibited, leading to less oxytocin release into the periphery [17]. Another example of dissociated release patterns is that of vasopressin release into the periphery to counteract water-loss from the kidneys in response to increased plasma osmolality. The axon terminal release of vasopressin after a systemic hypertonic saline injection increases immediately, but dendritic release of vasopressin in the SON starts only an hour later, when peripheral release is subsiding, illustrating a separation in time between release events in the dendrites and the terminals of the same neurons [18].

Whereas the SON only contains MCNs, the PVN houses many sets of functionally distinct neurons, classified into two major groups: MCNs and parvocellular neurons. Parvocellular neurosecretory neurons send their axons to the median eminence, from where they release hypophysiotropic hormones that control the function of the anterior pituitary and the major hypothalamo-pituitary axes. Parvocellular preautonomic neurons send long descending projections to sympathetic and parasympathetic centres in the brainstem and spinal cord, modulating sympathetic and parasympathetic outflows to a variety of target organs, including the heart, the peripheral vasculature and the kidneys [19-21]. In addition to neurosecretory and autonomic targets, the PVNs also include neurons that project to hierarchically higher centres in the brain, including the central amygdala, projections recently shown to modulate fear-conditioned responses [22]. These distinctive anatomical and physiological features make the PVN an ideal model to study the role of neuropeptides as signaling molecules in mediating communication within and between different neuron populations in the brain [8, 9].

Dendritic peptide release

Modulation of neuronal function by dendritic transmitter release is a widespread phenomenon, and is specific neither to a localized part of the brain nor to a particular subtype of signalling molecule [23-26]. As mentioned above, the best-characterised sites of dendritic peptide release are the hypothalamic SON and PVN, where the MCNs release vasopressin and oxytocin from their somato-dendritic compartment. At the ultrastructural level, large dense-cored vesicles (LDCVs) are broadly distributed throughout vasopressin and oxytocin neurons and it has been shown that their contents can be released from any part of the neurons, including the cell body and especially the dendrites (Fig. 1). The first unequivocal evidence of LDCV release from dendrites came from the visualization of exocytotic profiles in electron-microscopic studies on

sympathetic and hypothalamic neurons [27-29]. Pow and Morris [29] revealed the classical LDCV morphology in the dendrites and soma of MCNs and omega-shaped fusion profiles at the plasma membrane. The authors also visualized dendritic exocytosis from oxytocin and vasopressin neurons when they treated hypothalamic tissue with tannic acid to "freeze" aggregations of the exocytosed peptide granules [29-31]. Later microsampling techniques *in vivo* confirmed and amplified the data on dendritic vasopressin and oxytocin release and revealed many aspects of its control [32].

The LDCVs often contain more than one neuropeptide, and in fact many neurons release a mixture of neuropeptides [33, 34]. For instance, vasopressin co-exists with dynorphin [35], galanin [36], pituitary adenylate cyclase activating polypeptide (PACAP) [37] and secretin in MCNs of the SON and PVN. On the other hand, oxytocin in the SON co-exists with encephalin and dynorphin [38, 39]. Other peptides, for example apelin is also synthesized in MCNs, but it is packed and released from separate LDCVs [40].

Mechanisms of release

Actin cytoskeleton

Since peptide release from MCNs is not restricted to any particular part of the plasma membrane [29, 30], regulation of exocytosis may rely on controlling the access of the vesicles to the plasma membrane [41]. This led to the suggestion that this control may be exerted by cytoskeletal elements, as in classical endocrine cells. In addition to a network throughout the cytoplasm, the cell bodies of MCNs possess a network of filamentous protein (F-actin) beneath the plasma membrane, usually referred to as cortical F-actin. In endocrine cells, this F-actin engulfs secretory vesicles, segregating them from the plasma membrane. As F-actin undergoes fast, transient and reversible depolymerization during hormone secretion, and as areas of exocytosis have been found to be lacking F-actin, cortical F-actin has long been proposed to act as a *barrier*, restricting the movement of secretory vesicles to their release sites at the plasma membrane [42, 43].

MCNs possess F-actin structures in the subcortical regions of somata and dendrites [44, 45]. The F-actin of the somata/dendrites is rapidly and reversibly depolymerized by factors that stimulate secretion. Moreover, depolymerization of F-actin stimulates oxytocin and vasopressin release from the dendrites and acute exposure to drugs that polymerize F-actin inhibits stimulated dendritic peptide release. Thus the evoked release from the dendrites requires depolymerization of F-actin [45].

However, there is evidence that the F-actin cortex, classically viewed as a barrier that hinders the movements of LDCVs to the plasma membrane, might also play a positive role either by providing 'tracks' that permit docking at appropriate sites, or by spatially constraining components of the release machinery. This suggests that activation of secretion does not simply trigger the disassembly of the barrier, but rather a reorganization of F-actin, which allows the LDCVs access to the release sites and provides the structural support necessary for exocytosis [43]. In MCNs, it appears that F-actin remodelling plays a part in regulating the availability of functionally mature and readily releasable vesicles in different parts of the cell and thus is involved in the differential control of release from different parts of the cell. In contrast to neuronal synapses, release of vesicles from both the somata/dendrites and axon terminals in MCNs does not appear to occur at morphologically distinct active zones [30]. Thus, actin filaments could provide transport, tethering, barriers and support structures at different times and locations [45].

Exocytosis proteins

The stimulated release of both LDCVs and synaptic vesicles involves the soluble N-ethylmaleimide sensitive factor attachment receptor (SNARE) complex, which allows the membrane of the vesicle to fuse with the plasma membrane and release its cargo into the extracellular space. There is evidence for the involvement of SNARE proteins in the release of LDCVs from dendrites, with the majority of the data arising from studies of substantia nigra dopamine cells [46-48]. Data from several other brain regions, including hippocampus [49, 50], olfactory bulb [51], cerebellum [52] and neocortex [53] indicate the requirement for SNARE variants in dendritic transmitter release.

Sensitivity of somato-dendritic release to tetanus toxin which cleaves VAMP-2 (a vesicular component of the SNARE complex) was described in isolated MCNs [54], suggesting that VAMP-2 proteins similar to

those operating in synapses may regulate dendritic exocytosis of oxytocin and vasopressin. Many SNARE proteins have been identified in the terminals of the posterior pituitary [55, 56]. However, immunofluorescence studies have shown a surprising lack of some of the core proteins, such as VAMP-2 and SNAP-25 in the somata and dendrites of the SON. Perhaps there are more members or isoforms of the existing members to be identified, but, at present, the somato-dendritic peptide release from MCNs appears to occur in the absence of the full complement of exocytosis machinery that is generally considered to be mandatory for regulated exocytosis [57].

Action potentials

Exocytotic release of vasopressin and oxytocin from the axonal terminals in the posterior pituitary gland is linked to electrical activity, resulting from Ca^{2+} entry through voltage-gated channels following depolarization of the terminals by invading action potentials [58]. The available stores of small electron-lucent vesicles (ELVs) at synapses are replenished by endocytotic recycling and they are quickly re-filled with neurotransmitter by transporter-mediates uptake [59]. However, neuropeptides, which are not recycled after release have to be synthesized and the LDCVs loaded in the cell body. Compared to ELVs, LDCVs differ by requiring sustained increases in intracellular Ca^{2+} to release their contents. As a consequence, LDCVs have longer latencies to release and require stronger stimulation for exocytosis, such as, for example, bursts of electrical activity. The LDCVs also differ from ELVs in that the associated Ca^{2+}-sensor that triggers release has a higher affinity for calcium. Consequently it is not necessary for LDCVs to be located in close proximity to membrane calcium channels to undergo exocytosis, and synaptic specializations are not a prerequisite for release [60-64].

As it is the case in many neurons, the membrane properties of the dendrites support action potentials allowing them to propagate into the dendrites [65]. A rise in dendritic free Ca^{2+} content initiated by action potential back-propagation has been suggested to trigger dendritic dopamine release within the substantia nigra [46]. While action potentials may propagate into the dendrites of MCNs [66] dendritic release of vasopressin and oxytocin can occur independently of action potential firing [67, 68] .

Role of calcium and its sources

Calcium-dependent exocytosis represents a universal mechanism underlying release of neurotransmitters from presynaptic terminals and release of neurohormones from neuroendocrine cells. Similar to the calcium-dependent release of neuropeptides from MCNs axonal terminals in the neurohypophysis [58], dendritic release of these same neuropeptides has also been shown to be dependent on a rise in intracellular free Ca^{2+} in the dendrites [54, 69, 70].

The spatio-temporal properties and dynamics of the intracellular Ca^{2+} signal are key determinants of transmitter release in classical synapses [71]. These are in part determined by the source of Ca^{2+} and its proximity to the release machinery, as well as the different Ca^{2+} buffering mechanisms available to influence the magnitude and time course of the calcium signal. In this sense, a variety of different sources of Ca^{2+} have been shown to efficiently trigger dendritic release of oxytocin and vasopressin from MCNs.

Calcium channels

A major route of entry of Ca^{2+} involved in dendritic neuropeptide release is through voltage-operated Ca^{2+} channels (VOCCs) [58, 72]. MCNs express several types of VOCCs [73], but the N-type channels appear to be particularly important for dendritic release. Although the current carried by N-type channels is comparatively small in the somata of MCNs compared to the other VOCC types or indeed the whole-cell Ca^{2+} current [74, 75], release of oxytocin from SONs is most sensitive to blockade of N-type channels. As stated above, these channels can be activated in both in somatodendritic and axonal compartments as a consequence of membrane depolarization evoked by anterograde or back-propagated action potentials [58]. However, some chemical signals, notably oxytocin and vasopressin, can themselves trigger dendritic peptide release without increasing the electrical activity of the neurons. Oxytocin- and vasopressin-neurons express oxytocin- and vasopressin-receptors, respectively [76], and the peptides act at these receptors to produce a cell-type-specific rise in intracellular Ca^{2+} concentration. For example, the response induced by vasopressin in vasopressin cells requires an influx of external Ca^{2+} through voltage-gated calcium channels, particularly of the

L-, N- and T-types [77]. The requirement of somato-dendritic release for Ca^{2+} entry through mainly L- and N-type channels has been shown for other transmitters, including dynorphin [78], dopamine [79, 80], serotonin [25] and pituitary adenylate cyclase activating polypeptide (PACAP) [70].

NMDA receptors

Another major source of free calcium in neurons are the Ca^{2+}-permeable glutamate N-methyl-D-aspartate (NMDA) receptors. NMDA receptors are particularly important in MCNs, in which they not only influence overall MCN excitability, but also contribute to the adoption of burst-firing, optimizing in turn hormonal release from neurohypophysial terminals [81, 82]. Moreover, activation of NMDARs in MCNs results in large increases in dendritic free Ca^{2+} levels [8, 83] efficiently evoking dendritic release of both oxytocin [84] and vasopressin [8]. In addition to their conventional location at postsynaptic sites, functional NMDARs, with unique molecular and functional properties, have been also recognized to be located at extrasynaptic sites [85, 86]. In a series of recent studies, we showed the presence in MCNs of functional extrasynaptic NMDA receptors, which play a major role in regulating MCN excitability [87, 88]. Extrasynaptic NMDA receptors also contribute to increases in intracellular Ca^{2+}, and unlike synaptic NMDARs, they are selectively coupled to other Ca^{2+}-dependent signalling mechanisms, including voltage-gated potassium channels and gamma-aminobutyric acid ($GABA_A$) receptors [88-90]. However, whether synaptic and extrasynaptic NMDARs selectively or differentially affect dendritic release of neuropeptides is at present unknown.

Intracellular calcium stores

Another important source of Ca^{2+} shown to evoke and regulate dendritic release of neuropeptides are intracellular calcium stores. This is particularly the case for oxytocin autocrine effects. Binding of oxytocin to its receptors on oxytocin neurons mobilizes Ca^{2+} from intracellular stores in the endoplasmic reticulum [91] This increase in intracellular Ca^{2+} is sufficient to induce oxytocin release from dendrites, without affecting the firing activity of neurons and without inducing release from nerve terminals [67]. Once triggered, dendritic peptide release can be self-sustaining and hence long-lasting [67]. Other agents that mobilize intracellular calcium stores, such as thapsigargin, can also evoke dendritic release of neuropeptides [67, 68, 92].

Calcium buffering mechanisms

Intracellular Ca^{2+}-buffering mechanisms constitute additional critical factors influencing the shape and time course of intracellular Ca^{2+} signals. MCNs are endowed with numerous calcium buffering/clearance mechanisms, including plasmalemmal and endoplasmic reticulum calcium transport ATPases, the mitochondrial calcium selective uniporter (10), and Ca^{2+}-binding proteins, including calbindin and calretinin [93, 94]. Most of these mechanisms have been shown to efficiently restrain calcium transients in MCNs [83, 93, 95, 96]. Moreover, blockade of these Ca^{2+}-buffering mechanisms prolonged K^+-evoked increases in intracellular free Ca^{2+}, concomitantly enhancing somatodendritic vasopressin release [95]. Interestingly, the portfolio of available Ca^{2+}-homeostatic systems differ in somatodendritic and axonal compartments of MCNs [93, 95], further supporting the notion of independent regulation of these two neuronal compartments during neuropeptide release by MCNs.

Calcium-dependent priming of dendritic release

In addition to directly activating dendritic release, elevation of intracellular free Ca^{2+} concentrations has another important consequence: it can *prime* dendritic stores of peptides to make them available for subsequent activity-dependent release [67]. Spike activity in oxytocin or vasopressin neurons *in vivo* does *not* result in measurable dendritic peptide release, but agents that mobilize Ca^{2+} from intracellular stores, such as thapsigargin or cyclopiazonic acid, or some peptides, including oxytocin itself and α-MSH, consistently induce dendritic release directly [17, 67]. It seems possible that any signal that mobilizes Ca^{2+} from intracellular stores might prime dendritic secretion. Moreover, after exposure to agents that mobilize intracellular calcium, peptide release in response to many stimuli (such as osmotic stimulation, depolarization with high K^+ or electrical stimulation) is dramatically potentiated. *In vitro*, this priming persists for at least 90 min. Priming involves *preparing* a system for some anticipated trigger that will come at some uncertain time in the future; it

involves making the secretory pool of the target cell available for rapid release in response to that future trigger. The mechanisms of priming in MCNs involve recruitment of vesicles from a reserve pool into a readily-releasable pool [92], probably through changes in the actin skeleton. Priming also involves recruitment of VOCCs, suggesting that a stimulus that produces an increased secretory responsiveness with an intermediate time scale (30-90min) may cause MCNs to recruit N-type calcium channels to the plasma membrane, allowing them to respond to a subsequent depolarization with a larger secretory response [75]. However, priming does not appear to require either *de novo* gene transcription or translation [97].

Actions of dendritically released neuropeptides

Autocrine effects

The physiological functions of dendritically released neurotransmitters include a local autocrine effect on the neurons from which they are released, as well as effects on surrounding neurons and glia. The overall consequences can be a dramatic change in firing rate, because these autocrine effects can change both the inputs to oxytocin cells and also the way that the oxytocin cells respond to those inputs. A striking example of this is the way that dendritically released oxytocin promotes the milk ejection reflex as described below.

A far more common autocrine effect of dendritic release is *auto-inhibition*. Vasopressin neurons discharge in a characteristic phasic pattern that optimizes the efficiency of stimulus-secretion coupling at the nerve terminals. Vasopressin released from dendrites modulates this phasic activity by a predominantly inhibitory action. Interestingly, vasopressin, like oxytocin, can facilitate its own dendritic release [98]. This may explain the time dissociation between peripheral and intra-SON release of vasopressin after a hyperosmotic stimulus. Although systemic secretion of vasopressin occurs rapidly after an osmotic stimulus, the dendritic release of vasopressin evolves as a delayed and prolonged response [18]. Mimicking dendritic release by retrodialysis of vasopressin onto vasopressin neurons inhibits the vasopressin neurons by reducing their firing rate [99]. Thus, dendritic vasopressin release may activate adjacent dendrites to facilitate its own release until the local concentration has reached a threshold sufficient to hyperpolarize the neuron and/or modulate inhibitory inputs. The auto-inhibitory action of dendritic vasopressin may therefore limit the extent of systemic vasopressin secretion in response to osmotic stimuli or volume depletion.

Local paracrine effects

Exogenously applied or endogenously released oxytocin also acts on afferent nerve endings. As presynaptic oxytocin receptors are not found in the SON, this paracrine action was likely to be indirect and indeed has been shown to be mediated by oxytocin-dependent endocannabinoid release from the oxytocin neuron [100, 101]. Cannabinoid receptors (CB1) have been localized by immunohistochemistry to both excitatory and inhibitory axon terminals innervating dendrites in the SON, and the cannabinoid agonist presynaptically inhibits spontaneous excitatory and inhibitory postsynaptic currents in SON neurons recorded in slices. Thus, dendritic oxytocin release may act on oxytocin receptors leading to Ca^{2+} release from intracellular stores and the 'on-demand' generation of endocannabinoids. The endocannabinoids pass through the membrane, diffuse and bind to presynaptic CB1 receptors, inhibiting both GABAergic and glutamatergic afferents onto MCNs. This signalling probably has a very short radius of action due to the lipophilic nature of cannabinoids. However, both oxytocin and vasopressin can spread over larger areas, effectively broadcasting their message throughout the nucleus.

An example of such longer-radius paracrine action of dendritically-released neuropeptides is highlighted by our recent study showing that dendritically-released vasopressin is able to modulate the activity of neighbouring presympathetic neurons within the PVN [8]. We found that activity-dependent dendritic release of vasopressin from MCNs resulted in a concomitant increase in the firing activity of RVLM-projecting PVN neurons. This interpopulation crosstalk involved the diffusion of vasopressin in the extracellular space, and binding and activation of V1a receptors in presympathetic neurons. We found that in contrast to conventional synaptic transmission, the efficiency and strength of this diffuse paracrine action of vasopressin was dependent on the overall extracellular levels of vasopressin (dependent in part on the average activity of the entire vasopressin population and on factors regulating vasopressin half-life in the

extracellular space) as well as the ability of vasopressin to diffuse and reach relatively distant targets (e.g., tortuosity of the extracellular space).

Hormone-like signals in the brain

Oxytocin- and vasopressin-induced effects on behaviours are exerted at sites that, in some cases, richly express receptors but are innervated by few peptide-containing projections. Could dendritically released peptides act at distant brain targets to evoke long-lasting behavioural effects? Although extracellular neuropeptide concentrations differ from site to site, similar changes are often seen at widely separated sites [16]. Peptide release within the brain is not specifically targeted to synapses, and as the half-lives of peptides in the central nervous system can be up to 20 min [102], there is time for considerable movement of peptides by diffusion and bulk flow in the extracellular fluid and cerebrospinal fluid. The dendrites of MCNs project towards the brain surface and make close contact with ependymal cells that line the ventricular spaces. The reason for this may be twofold. The dendrites can register the neurochemical composition of the CSF and they can send their messages into the CSF circulation. Neuropeptides administered intracerebroventricularly lead to coherent and purposeful behaviours.

Physiological functions

The milk ejection reflex

Priming appears to be the key phenomenon underlying the intermittent burst discharge that oxytocin cells display in response to suckling during the milk-ejection reflex. Under basal conditions, oxytocin neurons are continuously active, but, in the pregnant animal during parturition and in the lactating animal in response to suckling, oxytocin cells discharge approximately synchronously with brief, intense bursts of action potentials; these bursts release into the circulation large boluses of oxytocin which result in intense contractions of the pregnant uterus or milk let-down from the mammary glands. For oxytocin neurons, dendritic release of oxytocin, which is up-regulated during parturition and in lactation, has an essential role in the generation of these intermittent synchronized bursts [103]. The bursting activity can be blocked by administration of oxytocin antagonists into the SON, and can be facilitated by local administration of oxytocin agonists [104].

After a priming signal, activity-dependent oxytocin release from dendrites might lead to positive-feedback coupling between oxytocin cells, producing the intense synchronized bursts observed during parturition and suckling. In each of these cases, the actions of the dendritically-released oxytocin are not restricted to the cell of origin, but are also exerted on the dendrites of other oxytocin cells, possibly to facilitate homotypic interactions.

Generation of multimodal neurohumoral homeostatic responses

Control of body homeostasis by the PVN requires the generation of complex but orchestrated neurohumoral responses, generally consisting of a "neuronal" component (i.e., changes in sympathetic/parasympathetic outflows to different target organs) along with a "humoral" response, represented by the release of different neurohormones, including vasopressin, angiotensin and endothelins among others [105-107]. These neurohumoral responses generated by the PVN are critically important for the maintenance of cardiovascular and fluid balance homeostasis. A characteristic example of such an integrative homeostatic response is that following a central osmotic challenge, which evokes a coordinated increase in renal symapathetic nerve activity together with a concomitant increase in circulating levels of vasopressin. These responses are coordinated by the PVN, and result in proper adjustments in water and Na+ reabsorption by the kidneys, leading in turn to reestablishment of fluid/electrolyte balance in response to the osmotic challenge [108]. We recently demonstrated that dendritically released vasopressin plays a pivotal role in this homeostatic response. We found that a central osmotic challenge evoked an increase in dendritic release of vasopressin from MCNs, which on diffusion in the extracellular space, participated in the recruitment of

neighbouring presympathetic PVN neurons. This interpopulation crosstalk resulted in turn in a in a proper renal sympathoexcitatory homeostatic response. Thus, dendritic release of vasopressin is a critical signalling modality contributing to the ability of the PVN to orchestrate the activity of distinct populations of neurons, and thus, the generation of multimodal homeostatic response.

Formation of short-term social odour memories in the olfactory system

Both peptides evoke specific effects on behaviour [109-111]. For example, oxytocin is involved in social behaviours, including bonding and maternal behaviour, and vasopressin acts in the brain to affect social recognition and aggression. We recently identified populations of vasopressin-expressing neurons in the main and accessory olfactory bulb and in the anterior olfactory nucleus, a region of olfactory cortex that transmits and processes information in the main olfactory system [112-114]. Both vasopressin and oxytocin modulate conspecific social recognition at the level of the olfactory system and we proposed a model by which the somato-dendritic priming and release of vasopressin in main olfactory regions may facilitate the formation of short-term social odour memories [112].

Acknowledgments

We thank Dr Rafael Pineda (Edinburgh) for help with the production of the immuno-fluorescence pictures.

Funding Statement

Work was supported by grants from Biotechnology and Biological Sciences Research Council, UK (ML) and National Heart, Lung, and Blood Institute R01 HL-090948 and HL112225 (JES)

Competing Interests

We have no competing interests.'

Authors' Contributions

Both authors contributed to the writing of the review.

Figures

Figure 1) Vasopressin and oxytocin system of the hypothalamus:
A) Coronal section through the rat hypothalamus at the level of the supraoptic (SON) and paraventricular nuclei (PVN); vasopressin cells are immunostained with fluorescent green and oxytocin cells with fluorescent red. A**i)** In the SON the dendrites project towards the ventral surface of the brain where they form a dense plexus (arrow). **B)** LDCVs in a coronal section of a SON dendrite. **C)** An 'omega' fusion profile at the plasma membrane (arrow) indicates exocutosis. **D)** Close anatomical relationships among the dendrites of MCNs vasopressin (green) and retrogradely labeled presympathetic neurons from the rostral ventrolateral medulla (red) in the PVN. **Di-Dii)** Progressively higher magnification of D showing thick and varicose immunoreactive dendrites from MCN vasopressin cell dendrites in close apposition with the somata and dendrites of presympathetic neurons. Modified from [8, 16].

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