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## **Dendritic release of neurotransmitters**

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**Release of neuroactive substances by exocytosis from dendrites is surprisingly widespread and is not confined to a particular class of transmitters: it occurs in multiple brain regions, and includes a range of neuropeptides, classical neurotransmitters and signaling molecules such as nitric oxide, carbon monoxide, ATP and arachidonic acid. This review is focused on hypothalamic neuroendocrine cells that release vasopressin and oxytocin and midbrain neurons that release dopamine. For these two model systems, the stimuli, mechanisms and physiological functions of dendritic release have been explored in greater detail than is yet available for other neurons and neuroactive substances.**

### **Introduction**

The dendrites of many neural populations transmit information back to their synaptic inputs by releasing neuroactive substances (89, 99, 128). Indeed, 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. In addition to membrane-permeant substances such as carbon monoxide, arachidonic acid and nitric oxide, classical transmitters can be released from dendrites to signal in a retrograde fashion. For example, somatodendritic release of dopamine, which is the exemplar small molecule transmitter emphasized in this review, modulates the firing rate and excitability of midbrain dopamine neurons. In

addition, the amino acids GABA and glutamate act as retrograde transmitters in the olfactory bulb, hippocampus, cortex and cerebellum (90, 119, 226, 266). However, the most numerous class of signalling molecules in the brain is the neuropeptides and there is ample evidence for their dendritic release. There is convincing evidence for somatodendritic release of the neurohypophysial peptides, oxytocin and vasopressin, in the hypothalamus (111, 116, 120, 127), which are the exemplar peptides covered in this review. Notably, there are also reports for this mode of release for other peptides, including dynorphin, enkephalin and cholecystinin (19, 46, 216).

### **The hypothalamo-neurohypophysial peptide system**

Oxytocin and vasopressin (antidiuretic hormone, ADH) enter the circulation following exocytotic release from magnocellular neurosecretory cells (MCNs), components of hypothalamic supraoptic (SON) and paraventricular nuclei (PVN) that project into the posterior pituitary gland. Oxytocin is required for milk ejection, and produces uterine contractions, and so has a role in parturition and lactation (4, 19, 81, 114, 202), whereas vasopressin is involved in the regulation of water excretion and blood pressure. In addition, both peptides have effects on behavior (see below). Both are released at axonal synapses, but also from the somata and dendrites of MCNs (99, 111, 116, 120, 127, 128, 155, 168). The cell bodies and dendrites of MCNs form densely packed and homogeneous nuclei, whereas their axons project into the posterior pituitary gland. As there is no blood-brain barrier in the posterior pituitary, peptide secretion from axons swiftly enters the bloodstream. The dendrites of adult rat MCNs are characteristically smooth (aspiny), thick and varicose, with little branching, and are often associated in bundles (147, 221). Most of the neuropeptides expressed in the SON and PVN are stored within MCN dendrites. Dendritic release can be studied in these regions by push-pull perfusion or microdialysis (150, 256). Importantly, these methods can be used to study dendritic release independently of axonal release, because re-entry of peripherally released peptide into the brain is prevented by the blood-brain barrier.

Although the SON contains only MCNs, the PVN contains both MCNs and many other morphologically and functionally distinct cell types. Parvocellular *neurosecretory* neurons make axonal contact with the median eminence and they release hypophysiotropic hormones that regulate functions of the anterior pituitary and the major hypothalamo-pituitary axes. Parvocellular *preautonomic* neurons modulate sympathetic and parasympathetic outflow to several organs, including the heart, the peripheral vasculature and the kidneys (31, 223, 262), through long descending projections into sympathetic and parasympathetic centers in the brainstem and spinal cord. Some neurons within the PVN also project into other limbic areas, including the central amygdala, and have recently been shown to modulate fear-conditioned (103).

Because of these features, the PVN is a particularly useful system for studying communication within and between different neuronal populations in the brain (218, 220), and particularly the role of neuropeptides in this process.

### **The nigrostriatal and mesolimbic dopamine systems**

Another transmitter system that relies on somatodendritic release is dopamine, which is released from midbrain dopamine neurons. Dopamine neurons of the substantia nigra pars compacta (SNc) give rise to the nigrostriatal dopamine pathway, which is essential for motor learning and motor control. Indeed, loss of dopamine in this system impairs neuronal output from the basal ganglia (76), leading to the motor impairments that characterize Parkinson's disease (1, 24, 134, 251). In addition, dopamine from this pathway, and from the ventral tegmental area (VTA), also in midbrain, influences a number of other brain functions including reward, emotion, cognition and memory (25, 181, 193).

Dopamine neurons of the SNc and VTA send axon projections that densely innervate the striatal complex in the forebrain (139): the nigrostriatal dopamine pathway projects from the SNc preferentially to the dorsal striatum (caudate-putamen, CPu), whereas the mesolimbic dopamine pathway projects from the VTA preferentially to the ventral striatum (nucleus accumbens, NAc). In addition, VTA dopamine neurons project via the mesocortical pathway to the prefrontal cortex, hippocampus and amygdala

(80, 246).

Like that of all catecholamines, the synthesis of dopamine originates from the amino acid precursor L-tyrosine, which is transported across the blood brain barrier into dopamine neurons. Tyrosine is converted to L-dihydroxyphenylalanine (L-DOPA) by the rate-limiting enzyme tyrosine hydroxylase (TH) and then to dopamine by L-aromatic amino acid decarboxylase (Fig. 1B). Notably, unlike many transmitters/neuromodulators that are synthesized in the cell body and transported to distant release sites in axons, TH protein expression in dopamine neurons can be seen throughout the soma, dendrites and axons (254). Moreover, regulation of TH activity by phosphorylation occurs in both somatodendritic compartments and terminal fields, thereby indicating that dopamine is synthesized locally for either somatodendritic or axonal release (209).

The release of dopamine from axonal sites is fairly well characterized. However, dopamine release from the somata and dendrites of midbrain dopamine neurons in the SNc and VTA remains incompletely understood, despite extensive research over decades (9, 10, 17, 26, 29, 32, 40, 69, 74, 169, 184, 196, 198). Because the somata and dendrites are intermingled in these regions, their individual contributions to dopamine release cannot be distinguished easily, so the term “somatodendritic” is used to describe non-axonal evoked dopamine release in SNc and VTA. Mechanistic studies of somatodendritic dopamine release have been conducted primarily in the SNc, in which dopamine release is exclusively somatodendritic (95, 249). In contrast, the VTA has collaterals from its own axons, as well as from those that arise in the SNc (7, 56).

## **Experimental methods used to study somatodendritic release**

### **Oxytocin and vasopressin**

Ideally, experimental methods to study somatodendritic release of oxytocin and vasopressin should have sufficient resolution to define the location and time course of release. Although the number of techniques that meet these criteria is limited, the use of hypothalamic explants containing the SON, sometimes with the pituitary gland attached (217), has provided insights

into the regulation of somatodendritic release by steroids, changes in intracellular  $\text{Ca}^{2+}$  concentrations, the activation of autoreceptors and second messenger pathways (33, 105, 121, 129, 204, 206, 252)-

The most widely used approach is to monitor changes in neuropeptide concentrations in the plasma, through the use of sensitive chemical assay techniques such as radioimmunoassay (RIA) and enzyme-linked immunosorbent assay (ELISA). RIA, in particular, offers the high sensitivity required for the quantification of neuropeptides collected *in vivo* using push-pull perfusion (110, 150, 160) and microdialysis (98, 256). With these methods, samples can be collected from the extracellular space of defined brain structures in unrestrained animals, with timescales of minutes to days (62, 110, 255). Other *in vivo* sampling techniques have also been employed, including the simultaneous detection of hormones secreted into the blood, using specialized microdialysis probes (166) or chronically implanted jugular venous catheters (257). In anesthetized animals, simultaneous electrophysiological recording has been combined with microdialysis (126).

Other approaches for measuring neuropeptides in microdialysates include immunosensing with microdialysis probes containing antibody-based electrodes and capillary liquid chromatography combined with electrospray ionization-mass spectrometry (37, 131). Although these techniques have comparable sensitivity to that of RIA they have not yet been widely applied.

## **Dopamine**

The first studies of somatodendritic dopamine release involved either the measurement of  $^3\text{H}$ -dopamine overflow from *in vitro* midbrain slices (74) or *in vivo* measurements in midbrain using push-pull perfusion (32, 169). Subsequently, microdialysis coupled with electrochemical detection was used for *in vivo* studies of dopamine release (11, 13, 61, 83, 97, 199, 211). The use of microdialysis offered the advantage of a separation step, enabling dopamine, its metabolites and in some cases other neurotransmitters to be assayed simultaneously. A problem with this or any *in vivo* method, however, is that systemically or locally applied drugs may affect regulatory processes, which could be mediated by extended pathways; because of this, *in vitro* cell culture preparations and midbrain slices have been used in most recent

mechanistic studies of somatodendritic dopamine release, with dopamine overflow in culture typically measured by HPLC or RIA (70, 143).

In slices, the approaches primarily used to detect somatodendritic dopamine release are fast-scan cyclic voltammetry (FCV) and amperometry with carbon-fiber microelectrodes. These methods permit the quantification of changes in extracellular dopamine concentration ( $[DA]_o$ ) with high temporal and spatial resolution, on scales of milliseconds and micrometers, respectively (146, 183). This is crucial for the rapid detection of release evoked in small discrete regions of the brain, including the SNc and VTA ((29, 40, 69, 184, 196, 198). In these methods, the target molecule (dopamine) is oxidized at the surface of the carbon-fiber microelectrode with a suitable applied potential, and the resulting current, which is directly proportional to the rate of oxidation of transmitter molecules, is recorded. With FCV, the applied potential is ramped up and down, enabling identification of released dopamine from its characteristic voltammogram (26, 196). The release of dopamine can also be verified by the effects of pharmacological agents; for example the response is increased by inhibitors of the plasma membrane dopamine transporter (DAT) (29, 42) and decreased by inhibitors of the vesicular monoamine transporter (VMAT2) (198).

In amperometry, a potential is applied at a constant value that is sufficient to oxidize dopamine. This method has been used to examine quantal release of dopamine from neuronal somata (91, 102). One drawback of voltammetric and amperometric methods is the possibility of signal contamination by contributions from other endogenous electroactive substances. For example, in FCV studies of somatodendritic dopamine release in the substantia nigra of some rodent species, including rats and mice, the voltammetric signal is heavily contaminated by locally released serotonin (5-hydroxytryptamine, 5-HT). Given that microdialysis studies include a chemical separation step, that technique avoids this lack of specificity. Interestingly, this is not a concern when detecting dopamine release in the VTA because the VTA of mice, rats and guinea pigs lack 5-HT innervation and thus the voltammetric signal arises exclusively from dopamine (26, 38, 42, 93).

Most recently, Williams and colleagues applied electrophysiological

techniques to detect somatodendritic dopamine release. By using whole-cell voltage-clamp recording from midbrain dopamine neurons, it is possible to record D2 dopamine autoreceptor-dependent inhibitory currents (D2ICs) to monitor evoked dopamine release in the SNc and VTA (9, 10, 38, 68, 69).

### **Vasopressin and oxytocin are released by exocytosis**

Vasopressin and oxytocin are stored in and released from large dense-cored vesicles (LDCVs). Classical morphological evidence for somatodendritic release was provided by electron-microscopic studies on hypothalamic neurons, which showed LDCVs within the dendrites and somata of MCNs, together with omega-shaped fusion profiles at the plasma membrane (189). Exocytosis from the dendrites of oxytocin and vasopressin neurons was also demonstrated by treatment of hypothalamic tissue with tannic acid to fix exocytosed peptide granules (155, 157, 189). Since peptide release from MCNs is not restricted to any particular region of the plasma membrane (157, 189), regulation of exocytosis may occur simply by controlling the access of vesicles to the sites of fusion (151). In classical neuroendocrine cells, control of this type is exerted by cytoskeletal elements, and such control may also occur in MCNs, as their cell bodies contain an actin network proximal to the plasma membrane, usually referred to as cortical F-actin. In neuroendocrine cells, this network surrounds the secretory vesicles.

The actin network undergoes rapid, transient and reversible depolymerization during exocytosis, and F-actin is depleted close to fusion zones. The cortical F-actin network has long been proposed to restrict the movement of secretory vesicles to fusion zones on the plasma membrane (57, 245). The subcortical regions of somata and dendrites in MCNs contain polymerized F-actin (238, 248), which is rapidly and reversibly depolymerized when secretion is stimulated, and drugs that depolymerize F-actin stimulate dendritic peptide release. Thus, evoked release of peptides from the dendrites requires the depolymerization of F-actin (Fig. 1A) (238).

However, although cortical F-actin has historically been viewed as a barrier that restricts the movement of LDCVs to the plasma membrane, it might also have an enabling role in exocytosis, either by providing 'tracks' for LDCV movement to fusion zones, or by constraining some components of the



fusion machinery. This would suggest that during secretion the F-actin network is not simply disassembled, but reorganized to allow the access of LDCVs to fusion sites and to provide or assemble the molecular machinery necessary for membrane fusion and exocytosis (57). In MCNs, F-actin remodeling appears to be involved in the trafficking of functionally mature, release-competent vesicles to fusion sites, and it may therefore be critical in the differential control of release from different parts of the cell. However, in contrast to release from neuronal synapses, vesicle fusion in both the somata/dendrites and axon terminals in MCNs does not appear to occur at morphologically distinct fusion zones (157). In summary, actin filaments may have several roles in exocytosis, including functions in LDCV trafficking and tethering, acting as a barrier to fusion, and transporting membrane fusion machinery (238).

Exocytosis of vesicles is a multi-step process, involving a network of interacting proteins at various locations (Fig. 1A), including on the LDCVs themselves and at the active zones of the plasma membrane, where membrane fusion occurs (229). Exocytosis of both LDCVs and synaptic vesicles involves the soluble N-ethylmaleimide-sensitive factor attachment receptor (SNARE) complex, which opens the fusion pore and catalyzes the fusion of the vesicle membrane with the plasma membrane, resulting in the release of its cargo into the extracellular space. There is also evidence for the involvement of SNARE proteins in dendritic release, much of the data coming from work on dopamine cells in the substantia nigra (12, 180, 254) (see below). Studies of other brain regions, including the hippocampus (132, 133), olfactory bulb (140), cerebellum (59) and neocortex (266) also indicate the requirement for SNARE variants in dendritic transmitter release.

Clostridial neurotoxins, after binding to peripheral neurons and undergoing reverse axonal transport, are the precursors of zinc proteinases that specifically cleave components of the SNARE complex. Tetanus toxin (TeTX) cleaves VAMP-2 (synaptobrevin 2, an intrinsic protein component of LDCV membranes and part of the SNARE complex). Sensitivity of somatodendritic release to TeTX has been described in isolated MCNs (53), implying involvement of VAMP-2 in dendritic release of oxytocin and vasopressin, as well as in transmitter release at synapses. Although many

SNARE proteins have already been identified in the terminals of the posterior pituitary (96, 263), immunofluorescence studies have failed to detect core proteins, including VAMP-2 and SNAP-25, in the somata and dendrites of the SON. Somatodendritic peptide release from MCNs thus appears to occur without all of the machinery that is needed for regulated exocytosis in other cell types (235), but it is probable that the functions of the missing protein components are fulfilled by other variants.

### **Does somatodendritic dopamine release occur by exocytosis?**

Studies of the subcellular anatomical characteristics of dopamine neurons have raised questions about the mechanism and regulation of somatodendritic dopamine release.

First, dopamine axons in the striatum contain abundant clusters of vesicles near the plasma membrane at presumed release sites (171, 185). Although early anatomical studies also observed vesicle clusters in dopamine somata and dendrites within the SNc (253), subsequent studies, including those using immunogold labeling of VMAT2 profiles, concluded that SNc dopamine somata generally lack such clusters (170). as do dopamine dendrites within the substantia nigra pars reticulata (SNr) (79, 249, 253). Nonetheless, evidence for exocytosis is provided by reports of quantal dopamine release from somata in the SNc, the estimated quantal size being 14,000 molecules per vesicle (91), which is of similar magnitude to that seen in adrenal chromaffin granules (117) and axonal varicosities of dopamine neurons in culture (188, 219).

Second, although some dopamine is stored in small electron-lucent vesicles (ELVs) and in LDCVs (170), somatic dopamine in both SNc and VTA appears to be mainly stored in 'tubulovesicles', saccules of smooth endoplasmic reticulum (SER) that express VMAT2 (Fig. 1B) (170, 253). In addition, VMAT2 can be visualized on the outer membranes of organelles that may be involved in recycling vesicular membrane proteins (170). Whether dopamine is released directly from tubulovesicles or whether they can provide a rapid on-demand source of vesicles for release is not currently known. Inhibitors of VMAT2 block dopamine release, confirming the importance of dopamine uptake and storage, but not necessarily the involvement of

exocytosis *per se*. Third, although dendro-dendritic dopamine synapses are present in both SNc and VTA, they are also rare (79, 170, 249, 253), and are virtually absent from the dopamine-dendrite rich SNr (79).

Studies using botulinum toxins to target specific SNARE proteins suggest that somatodendritic dopamine release occurs primarily by exocytosis (13, 70, 180). However, immunohistochemical studies indicate that TH-positive somata and dendrites in the substantia nigra lack some typical intrinsic vesicle membrane proteins, including synaptophysin, the sv2a and sv2b isoforms of synaptic vesicle protein 2, and the  $\text{Ca}^{2+}$ -sensors synaptotagmin 1 and 2 (254). These findings are consistent with the relative absence of conventional synaptic vesicles in dopamine neurons. Moreover, several of the conventional SNARE proteins involved in vesicle docking, including the vesicle membrane protein VAMP-1 (synaptobrevin 1) and the plasma membrane protein syntaxin 1a, are also absent. On the other hand, SNAP-25 and some non-conventional SNARE protein isoforms, including VAMP-2 and the plasma membrane protein syntaxin 3b, are expressed throughout dopamine somata (143, 254).

Overall, the molecular organization involved in dopamine release in the SNc appears to differ markedly from that of conventional synaptic vesicular release, with the SNARE triad having the unusual composition of VAMP-2, SNAP25 and syntaxin 3b (Fig. 1B). Importantly, although dopamine somata and dendrites in the SNc lack synaptotagmin 1 and 2 (143, 254), which are low-affinity isoforms of the vesicular  $\text{Ca}^{2+}$ -sensors found at fast synapses (259), they do possess two isoforms with higher  $\text{Ca}^{2+}$ -affinity, namely synaptotagmin 4 and 7 (143), which may play a role in the high  $\text{Ca}^{2+}$  sensitivity of somatodendritic release (28). It should be noted, however, that the dopamine neurons express mRNA for synaptotagmin 1, presumably because synaptotagmin 1 is involved in axonal dopamine release in the striatum. Indeed, consistent with the notion that synaptotagmin 4 and 7, but not synaptotagmin 1, are involved in somatodendritic dopamine release, down-regulation with siRNA of synaptotagmin 4 and 7, but not of synaptotagmin 1, decreases dopamine release from cultured midbrain neurons (143).

Despite the presence of SNARE complex components (syntaxin 3b, SNAP-25 and VAMP2) throughout dopamine somata and dendrites, levels of VMAT2 and V-ATPase, the vacuolar-type H<sup>+</sup>-translocating ATPase that generates the transmembrane electrochemical proton potential gradient required for active amine uptake through VMAT2, decrease from somata to distal dendrites of dopamine neurons (254). This suggests that release and storage mechanisms for dopamine may differ between cell bodies and proximal dendrites in the SNc and those in distal dendrites in the SNr. As discussed further below, the regulation of dopamine release by intracellular Ca<sup>2+</sup> stores may also differ between these locations: dopamine dendrites in the SNr have low levels of the sarco/endoplasmic reticulum Ca<sup>2+</sup>-ATPase (SERCA), which translocates cytosolic Ca<sup>2+</sup> into the ER, and also low levels of regulatory inositol 1,4,5-triphosphate receptors (IP<sub>3</sub>Rs) and ryanodine receptors (RyRs) in the ER (184).

These data, together with the limited number of dendro-dendritic synapses and the small population of 'classical' LDCVs (79, 145, 170, 249, 253), suggest that some somatodendritic dopamine release might occur by mechanisms other than exocytosis, including release from the cytoplasmic pool by reverse transport through the plasma membrane DAT (60, 63, 79, 170, 177). Cytoplasmic dopamine concentrations are normally too low for DAT reversal, unless enhanced by displacement of dopamine from vesicles by pharmacological agents such as amphetamine (118, 230). However, dopamine storage in tubulovesicles introduces the possibility that dopamine leakage from these organelles might raise the cytoplasmic dopamine concentration sufficiently for DAT reversal and release into the extracellular space (Fig. 1B). Importantly, given that evoked increases in [DA]<sub>o</sub> are usually enhanced, rather than abolished, by DAT inhibitors (10, 29, 40), this cannot be the primary release mechanism in the SNc. Furthermore, release by direct transport through the plasma membrane cannot account for the observed quantal transmitter release in the SNc recorded by amperometry (91). In contrast, release from distal dendrites in the SNr is abolished by inhibition of DAT when stimulated by glutamate released from subthalamic nucleus afferents (63), and has been proposed to occur by activation of metabotropic

glutamate receptors (mGluR1), with subsequent PKC-induced reversal of the DAT (63, 177).

## **Ca<sup>2+</sup> dependence of somatodendritic release**

### **Somatodendritic oxytocin and vasopressin release**

As described above, release of neurotransmitters from presynaptic terminals and of neuropeptides from neuroendocrine cells occurs by the ubiquitous process of Ca<sup>2+</sup>-dependent exocytosis. Like the release of oxytocin and vasopressin from axonal terminals in the neurohypophysis (65), dendritic release of these neuropeptides depends on a local increase in intracellular free Ca<sup>2+</sup> concentration ([Ca<sup>2+</sup>]<sub>i</sub>) (53, 167, 215).

In classical synapses the patterns of neurotransmitter release depend critically on the spatio-dynamics of the [Ca<sup>2+</sup>]<sub>i</sub> transients (142), which are themselves determined by the origin of Ca<sup>2+</sup> and its proximity to the release machinery, as well as by the various intracellular Ca<sup>2+</sup> buffering mechanisms that control the amplitude and duration of [Ca<sup>2+</sup>]<sub>i</sub> transients. The Ca<sup>2+</sup> that triggers the dendritic release of oxytocin and vasopressin from MCNs can originate from a number of extracellular and intracellular sources (Fig. 1A).

### **Ca<sup>2+</sup> channels**

Voltage-gated Ca<sup>2+</sup> channels (VGCCs) (65, 247) are responsible for the entry of much of the extracellular Ca<sup>2+</sup> that triggers dendritic neuropeptide release. MCNs express several types of VGCCs (67). Despite the fact that the Ca<sup>2+</sup> current carried by N-type channels is small compared to those of the other types of VGCC or to the whole-cell Ca<sup>2+</sup> current in the somata of MCNs (94, 236), N-type channels appear to be particularly important for dendritic release, as release of oxytocin from SONs is most sensitive to blockade of N-type channels, N-type channels in both in somatodendritic and in axonal compartments can be opened in response to the depolarization evoked by action potentials (65). However, some signaling molecules, including oxytocin and vasopressin, can trigger dendritic peptide release without increasing the electrical activity of the neurons, via their receptors on oxytocin and vasopressin neurons (71). These peptides act at their respective receptors to

produce a cell-type specific rise in intracellular  $\text{Ca}^{2+}$  concentration that can promote transmitter release. Vasopressin-dependent vasopressin secretion depends on  $\text{Ca}^{2+}$  influx through VGCCs, particularly of the L-, N- and T-types (205). Similarly,  $\text{Ca}^{2+}$  entry, mainly through L- and N-type channels, is also the trigger for somatodendritic release of other transmitters, including dynorphin (216), dopamine (101, 143), serotonin (241) and pituitary adenylate cyclase activating polypeptide (PACAP) (215).

### *NMDA receptors*

Extracellular  $\text{Ca}^{2+}$  can also enter neurons through  $\text{Ca}^{2+}$ -permeable ionotropic glutamate receptors, including N-methyl-D-aspartate receptors (NMDARs). In MCNs NMDARs influence overall MCN excitability and are also involved in the control of burst-firing of these cells, which optimizes hormonal release from neurohypophysial terminals (66, 86, 162, 173). Opening of NMDARs results in  $\text{Ca}^{2+}$  entry and in large increases in dendritic  $[\text{Ca}^{2+}]_i$  in MCNs (218, 222), with consequent dendritic release of both oxytocin (51) and vasopressin (218). Consistent with this, functional NMDARs with unique molecular and functional properties have been found at extrasynaptic, as well postsynaptic, sites (113, 207) in MCNs. Extrasynaptic NMDARs are also coupled to other  $\text{Ca}^{2+}$ -dependent signaling mechanisms, including voltage-gated  $\text{K}^+$  channels and ionotropic gamma-aminobutyric acid ( $\text{GABA}_A$ ) receptors (162, 186, 187), unlike synaptic NMDARs. However it is not yet known whether dendritic release of neuropeptides is differentially regulated by synaptic *versus* extrasynaptic NMDARs.

### *Intracellular $\text{Ca}^{2+}$ stores*

As well as being triggered by the entry of extracellular  $\text{Ca}^{2+}$ , dendritic neuropeptide release can be evoked by  $\text{Ca}^{2+}$  release from intracellular stores (Fig. 1A). An example of this is the autocrine release of oxytocin, in which binding of oxytocin to its receptors on oxytocin neurons causes  $\text{Ca}^{2+}$  to be released from its major intracellular store in the endoplasmic reticulum (ER) (107). The increase in  $[\text{Ca}^{2+}]_i$  triggers the release of oxytocin from dendrites, without inducing release from nerve terminals or affecting the firing of neurons (129). Through this autocrine mechanism, dendritic peptide release, once

triggered, can become self-sustaining and thus long-lasting (129). Other agents that mobilize intracellular  $\text{Ca}^{2+}$  can also evoke dendritic release of neuropeptides. One example is thapsigargin, an inhibitor of SERCA, which can inhibit uptake of  $\text{Ca}^{2+}$  into the ER, raising cytoplasmic  $[\text{Ca}^{2+}]$  and thereby triggering  $\text{Ca}^{2+}$ -induced  $\text{Ca}^{2+}$  release from the ER, through ryanodine receptors (RyRs) (121, 129, 237).

#### *Ca<sup>2+</sup> buffering mechanisms*

Intracellular  $\text{Ca}^{2+}$ -buffering mechanisms influence the amplitude and duration of cytoplasmic  $\text{Ca}^{2+}$  transients. Various mechanisms of  $\text{Ca}^{2+}$  buffering and clearance mechanisms operate in MCNs, including  $\text{Ca}^{2+}$ -translocating ATPases both in the ER and in plasma membranes, the mitochondrial  $\text{Ca}^{2+}$ -uniporter (221) and  $\text{Ca}^{2+}$ -binding proteins such as calbindin and calretinin (50, 148). The operation of these buffering and transport systems damps  $[\text{Ca}^{2+}]_i$  transients in MCNs (50, 105, 214, 222), whereas their blockade prolongs the transient rise in  $[\text{Ca}^{2+}]_i$  that accompanies depolarization by  $\text{K}^+$ , and thereby enhances somatodendritic vasopressin release (105). Interestingly, the repertoire of  $\text{Ca}^{2+}$ -homeostatic systems differs between the somatodendritic and axonal compartments of MCNs (50, 105), providing further evidence to support independent regulation of neuropeptide release by these two compartments.

#### *Ca<sup>2+</sup>-dependent priming of dendritic release*

As well as triggering the final membrane-fusion step in exocytosis, elevation of intracellular free  $[\text{Ca}^{2+}]$  also *primes* vesicular stores of peptides within the dendrites, rendering them 'release-ready' and available for subsequent  $\text{Ca}^{2+}$ -dependent fusion (Fig. 1A) (129). Spike activity in oxytocin or vasopressin neurons *in vivo* is not itself sufficient to trigger dendritic peptide release unless the stores have been primed, but agents that deplete intracellular  $\text{Ca}^{2+}$ -stores, such as thapsigargin or cyclopiazonic acid (SERCA inhibitors), or some peptides, including oxytocin itself and alpha melanocyte-stimulating hormone ( $\alpha$ -MSH), consistently induce dendritic release directly (129, 204). It is possible that any signal that mobilizes  $\text{Ca}^{2+}$  from intracellular stores might prime dendritic secretion. Moreover, exposure to agents that

mobilize  $\text{Ca}^{2+}$  from intracellular stores greatly stimulates the peptide release evoked by many stimuli such as electrical or osmotic stimulation and  $\text{K}^{+}$ -induced depolarization. *In vitro*, such priming persists for at least 90 min. During priming, neuropeptide-storing vesicles become competent to respond to the fusion trigger that will arrive at some point in the future, in other words, priming increases the size of the secretory pool available for rapid release in response to a future trigger of the target cell. One mechanism by which vesicles in MCNs leave the reserve pool and enter the release-ready pool (237) may be the remodeling of actin. Priming also involves the recruitment of VGCCs to the plasma membrane, suggesting that stimuli that increase secretory responsiveness on a relatively slow time scale (30-90 min) may act by stimulating the recruitment of N-type  $\text{Ca}^{2+}$  channels to release sites, where they potentiate the secretory response subsequent depolarizations (236). This priming of exocytosis appears not to require either gene transcription or *de novo* protein synthesis (234).

### **Somatodendritic dopamine release**

In the very first report of somatodendritic dopamine release, Geffen and colleagues proposed that, in a manner similar to axonal dopamine release, dopamine release in the SNc occurs by exocytosis of storage vesicles (74). However, details of the precise release mechanism remain incomplete. Although the somata and dendrites of SNc dopamine neurons lack conventional synaptic structures, dopamine release from the somatodendritic compartment occurs by  $\text{Ca}^{2+}$ -dependent exocytosis. Moreover, somatodendritic dopamine release requires  $\text{Na}^{+}$ -dependent action potentials (29, 210), and is prevented by inhibitors of VMAT2 (10, 83, 198). However as mentioned above, the effect of VMAT2 inhibitors alone does not confirm that dopamine release occurs from conventional storage vesicles, as VMAT2 is also expressed by other subcellular organelles in dopamine neurons (170).

### ***Ca<sup>2+</sup> entry***

The requirement for extracellular  $\text{Ca}^{2+}$  in somatodendritic dopamine release has become a matter of debate. Although somatodendritic release is



prevented by the removal of extracellular  $\text{Ca}^{2+}$  (in  $\text{Ca}^{2+}$ -free media containing the  $\text{Ca}^{2+}$ -chelator EGTA) or by blocking  $\text{Ca}^{2+}$ -channels in the plasma membrane with  $\text{Cd}^{2+}$  (28, 184, 196, 198), release can still occur at low (submillimolar) extracellular  $\text{Ca}^{2+}$  concentrations ( $[\text{Ca}^{2+}]_o$ ) that do not trigger detectable axonal dopamine release, at least in guinea-pig SNc. Indeed, in studies using FCV to detect single-pulse evoked increases in  $[\text{DA}]_o$  in guinea pig midbrain and striatal slices (28), the  $[\text{Ca}^{2+}]_o$  required for half-maximal release ( $\text{EC}_{50}$ ) is markedly lower in the SNc (0.3 mM) than in the CPu (2.3 mM); similar differences were observed in the VTA *versus* NAc shell. It should be noted that although these studies were done in the presence of glutamate and GABA receptor antagonists, it is possible that  $\text{EC}_{50}$  values for the  $\text{Ca}^{2+}$  dependence for striatal dopamine release could be influenced by powerful regulation through ACh acting at nAChRs. However, when nAChRs are blocked the  $\text{EC}_{50}$  for calcium dependence in the CPu is remarkably similar (1.9 mM) (18). Furthermore, unlike in the striatum where axonal dopamine release is abolished by a cocktail of VGCC blockers, somatodendritic dopamine release in the SNc persists in the presence of these blockers (11, 14, 27, 29, 60, 70, 85). The resistance of release to VGCC blockers presumably reflects the incomplete blockade of these channels, along with the minimal cytoplasmic  $\text{Ca}^{2+}$  concentration required to trigger exocytosis via the high  $\text{Ca}^{2+}$ -sensitivity synaptotagmin isoforms involved in fusion. Somatodendritic dopamine release is therefore only weakly dependent on  $[\text{Ca}^{2+}]_o$  and  $\text{Ca}^{2+}$  entry. Interestingly, the dependence on  $[\text{Ca}^{2+}]_o$  for somatodendritic dopamine release has been reported to be stronger in rat and mouse than in guinea pig (38, 69).

Which VGCCs are required for  $\text{Ca}^{2+}$  entry in somatodendritic dopamine release? N- and P/Q-type, but not L-type, channels appear to be involved in basal somatodendritic dopamine release measured by RIA in mesencephalic cultures (143). L- and T-type channels, but not N- or P/Q-type channels, are involved in  $\text{K}^+$ -evoked dopamine release in the same preparation (60), as well as in  $\text{K}^+$ -induced dopamine release detected by amperometry in dissociated dopamine cells (102). Therefore, the VGCC types involved in providing  $\text{Ca}^{2+}$  entry to trigger somatodendritic dopamine release appear to depend on the experimental conditions, including the species studied, the type of preparation

and the stimulation procedure employed. These factors all contribute to the complexity of elucidating the precise mechanisms involved in somatodendritic dopamine release and its regulation.

### *Intracellular Ca<sup>2+</sup> stores*

The ability to detect evoked somatodendritic dopamine release with nominally zero  $[Ca^{2+}]_o$  raises the possibility that there may be mechanisms by which small increases in  $[Ca^{2+}]_i$  are amplified. An obvious mechanism is  $Ca^{2+}$ -induced  $Ca^{2+}$  release from intracellular ER stores (129, 184, 242), as discussed above for oxytocin and vasopressin. Within neurons, the ER forms a large network extending from the soma to dendrites and dendritic spines, and to axons and presynaptic release sites (244). In SNc dopamine neurons, this system propagates  $Ca^{2+}$  release from somatic ER stores to dendrites (34).

Immunohistochemical studies have identified ER membrane proteins associated with  $Ca^{2+}$  mobilization from ER stores in SNc somata and proximal dendrites, including SERCA-2 and inositol tris-phosphate receptors (IP<sub>3</sub>R) and RyRs (184), which are ligand-gated  $Ca^{2+}$ -channels. Each of these facilitate somatodendritic dopamine release evoked in the SNc by local pulse-train stimulation and detected by FCV (184). In dopamine neurons, RyRs assemble in clusters that are closely apposed to the plasma membrane, a location that maximizes their activation with the entry of extracellular  $Ca^{2+}$  through VGCCs (Fig. 1B). This enables somatodendritic dopamine release to be amplified at physiological  $[Ca^{2+}]_o$ . This amplification, however, is not necessary when  $Ca^{2+}$  entry is sufficiently large, as occurs with higher  $[Ca^{2+}]_o$ . In contrast, facilitation of SNc dopamine release by IP<sub>3</sub>R does not necessarily require  $Ca^{2+}$  entry through VGCCs but can occur downstream from metabotropic receptors, including mGluR1 (Fig. 1B) (184).

The role of intracellular  $Ca^{2+}$  stores in amplifying somatodendritic dopamine release is complex, and also can vary with the experimental conditions and rodent species used (38, 69, 143). Moreover, whether intracellular  $Ca^{2+}$  stores contribute to release in the VTA is not yet known. Exocytosis involves several  $Ca^{2+}$ -dependent steps with proteins that exhibit

different  $\text{Ca}^{2+}$  sensitivities. The final fusion event may require a very rapid elevation in  $[\text{Ca}^{2+}]_i$  close to the secretory vesicle to trigger release, whereas a slower, less localized increase in  $[\text{Ca}^{2+}]_i$  could enhance priming of secretory vesicles, as seen in the release of oxytocin from the dendrites of hypothalamic neurons (129), discussed above. Although most evidence suggests that dopamine release in the SN or the VTA is not primed by the SERCA inhibitor thapsigargin, the possible involvement of other intracellular  $\text{Ca}^{2+}$  stores remains unknown (12). Whether the differential expression of RyR at sites close to the plasma membrane and the cytoplasmic location of  $\text{IP}_3\text{R}$  reflect these different functions also remains unresolved.

### **Is somatodendritic release triggered by action potentials?**

Action potentials are usually initiated at the junction between cell body and axon, the axon hillock. In the classical model of synaptic neurotransmitter release, the action potential is propagated down the axon to its terminal where it opens VGCCs, resulting in the fusion of synaptic vesicles with the pre-synaptic plasma membrane. However, an action potential can travel in any direction from its point of initiation, and into dendrites if the electrical properties of the dendrite support this, as is the case in many neurons (39, 227).

Exocytotic release of vasopressin and oxytocin from axonal terminals in the posterior pituitary gland is linked to electrical activity in the somata and is produced by the opening of VGCCs following depolarization of the terminals by invading action potentials (65). At classical fast, glutamatergic synapses, the available stores of small ELVs are maintained by endocytotic membrane recycling and are quickly reacidified by the V-type  $\text{H}^+$ -ATPase and re-filled with neurotransmitter by secondary active transport mediated by  $\text{H}^+$ -linked antiporters (190). However, unlike small neurotransmitters, neuropeptides are not taken up and repackaged after release – they must be synthesized in the rough ER and concentrated in LDCVs in the soma. Compared to ELVs, LDCVs require a more sustained increase in  $[\text{Ca}^{2+}]_i$  to trigger exocytosis. Consequently, LDCVs have longer latencies to release and require stronger stimulation for exocytosis, for example bursts of electrical activity. LDCVs also differ from ELVs in that the associated variants of synaptotagmin, the  $\text{Ca}^{2+}$ -

sensor that triggers release, have a higher affinity for  $\text{Ca}^{2+}$ , as discussed above for dopamine. Consequently it is not necessary for LDCVs to be located close to membrane  $\text{Ca}^{2+}$  channels to receive a  $\text{Ca}^{2+}$  pulse sufficient to produce exocytosis, and synaptic specializations are not necessary (2, 6, 135, 136, 208).

In many neurons, the properties of the dendritic membranes support the propagation of action potentials (227). However, dendritic release of vasopressin and oxytocin in MCNs can occur independently of action potentials (121, 129), even though action potentials can propagate into the dendrites (5). Accordingly, neuropeptide release from dendrites is not linked to release from terminals within the same neurons, and this uncoupling seems to be both stimulus-dependent and peptide-specific (127). An example of this is provided by the effects of alpha melanocyte-stimulating hormone ( $\alpha$ -MSH): binding of  $\alpha$ -MSH to melanocortin 4 receptors on oxytocin cells releases  $\text{Ca}^{2+}$  from intracellular stores, stimulating dendritic oxytocin release, but inhibits the electrical activity of the cell and so inhibits oxytocin release into the periphery (204). Dissociation of dendritic and axonal release patterns is also seen in the effects of increased plasma osmolality. Systemic hypertonic saline injection immediately increases vasopressin release from axon terminals, but dendritic release of vasopressin in the SON starts an hour later, when peripheral release is subsiding. In this case there is a separation in time between transmitter release from dendrites and terminals within the same neurons (124).

In SNc dopamine neurons, the axon initial segment arises from a proximal dendrite rather than from the cell body; action potentials originate in the dendritic tree and single action potentials back-propagate into dendrites (82). However, during burst-firing of these neurons, and particularly if dopamine D2 receptors are activated, back-propagation of action potentials may not occur (75), suggesting that dopamine can influence the spread of action potentials, thereby down-regulating its own release from dendrites. Thus, burst-patterned firing, which promotes dopamine release from axon terminals, does not necessarily promote dendritic release (78). Consequently, dopamine release from distal dendrites is likely to be semi-independent of the electrical activity of the neuron. As mentioned above, dopamine release from

distal dendrites has been proposed to be triggered through local glutamatergic activation of mGluRs (177). Interestingly, serotonin neurons in the dorsal raphe nucleus also exhibit somatodendritic release. Action potentials in these neurons also do not back-propagate very far; however, local activation of NMDARs can lead to dendritic release in the absence of action potentials (52). This is yet another example of the dissociation of dendritic release of monoamines from action-potential-dependent axonal release.

## **Modulation of somatodendritic release by synaptic inputs**

### ***Vasopressin and oxytocin***

Vasopressin (and in the rat, oxytocin) is involved in the control of plasma electrolyte balance. Systemic injection of hypertonic saline stimulates vasopressin and oxytocin release from axon terminals in the neural lobe and from dendrites within the SON. Vasopressin neurons respond directly to the osmotic pressure of their environment (137, 176), but systemic osmotic stimuli also activate central receptors on cells that project, directly or indirectly, to the SON and PVN, including afferent neural pathways from the rostral forebrain anterior 3<sup>rd</sup> ventricle region (AV3V). The response to systemic osmotic stimulation is blocked by tetrodotoxin, which blocks voltage-gated Na<sup>+</sup>-channels, and by lesions of the AV3V, suggesting that somatodendritic release is part of a cascade of events initiated by osmotic activation of synaptic pathways, rather than by the direct effect of hyperosmolarity on the MCNs (122, 123).

The afferent pathways from the AV3V include an inhibitory GABA component (174) and excitatory components mediated by amino acids and several peptides, including angiotensin II (92). Intracerebroventricular (icv) administration of angiotensin increases both systemic and somatodendritic vasopressin release within the SON and PVN (152). While somatodendritic release is unaffected by retrodialysis of the GABA agonist muscimol into the SON, the GABA<sub>A</sub>R antagonist bicuculline increases somatodendritic release (109), suggesting tonic inhibition by endogenous GABA. Furthermore glutamate stimulates dose-dependent release of angiotensin II from isolated fragments of magnocellular dendrites (158) and also increases

somatodendritic release when retrodialysed into the SON, whereas kynurenic acid, a glutamate antagonist, is inhibitory (109).

Somatodendritic release of vasopressin following acute osmotic stimulation is inhibited by salt loading but not by water deprivation, while the systemic response is unaffected (130), suggesting that somatodendritic release is regulated by afferent inputs from both osmo- and baro-receptors. The control of central peptide release by volume and pressor stimuli is also revealed by studies of hemorrhage and baroreceptor denervation; concentrations of vasopressin both in the plasma and in the PVN increase markedly in response to hemorrhage (179). Hemorrhage-induced decrease of arterial blood pressure stimulates vasopressin secretion through inhibition of baroreceptors and activation of chemoreceptors in the aortic arch and carotid body, while sinoaortic baroreceptor denervation increases the osmotically-induced release of vasopressin and oxytocin from the posterior pituitary (159) and also increases somatodendritic vasopressin release stimulated by direct or peripheral hypertonic saline stimulation (22).

Systemic oxytocin release increases during parturition and lactation, in parallel with increased electrical activity involving the synchronous burst firing of oxytocin neurons. That oxytocin, but not vasopressin, is released within the SON and PVN in response to suckling has been demonstrated in push-pull perfusion studies in anaesthetized lactating rats (19) and microdialysis studies in conscious parturient and lactating animals (22). Somatodendritic suckling- or parturition-induced oxytocin release is inhibited by oxytocin antagonists infused into the SON, suggesting the receptor-mediated autoregulation of oxytocin release (163, 164).

The systemic secretion of oxytocin during suckling is also subject to noradrenergic regulation, arising mainly from the brainstem. Suckling increases both noradrenaline turnover and local oxytocin levels within the SON (47), and phentolamine, an  $\alpha$ -adrenergic antagonist, blocks oxytocin release into the SON and PVN during suckling, indicating that suckling stimulates noradrenaline release, with subsequent stimulation of somatodendritic oxytocin release through the action of  $\alpha$ -adrenergic receptors (8).

Systemic and somatodendritic peptide release are also controlled by other neurotransmitters released by nerve fibers terminating in the hypothalamic nuclei. GABA and glutamate have already been discussed. Acetylcholine is also involved in regulating systemic vasopressin release (217), and also stimulates somatodendritic vasopressin release in hypothalamic explants (excluding axon terminals) (138, 178). Both somatodendritic and systemic release of oxytocin appear to be regulated by noradrenaline (165), since systemic administration of cholecystinin (CCK), which acts via the vagus nerve to excite the A2 noradrenergic brainstem projection to magnocellular oxytocin neurons (243), stimulates release. CCK may also directly regulate somatodendritic peptide release; intra-SON administration of CCK increases somatodendritic oxytocin and vasopressin levels (165), and also the expression of Fos in SON neurons (125).

Pituitary adenylate cyclase activating polypeptide (PACAP) receptor mRNA and PACAP-like immunoreactivity are present within the SON and PVN (161) and PACAP appears to participate in the regulation of the MCNs by opening VGCCs and increasing cytoplasmic  $[Ca^{2+}]$ , thereby stimulating the somatodendritic release of vasopressin *in vitro* (215).

Dendritic oxytocin release from MCNs is inhibited by endogenous opioids in ovariectomized (87) and late-pregnant rats, although this inhibition does not occur during parturition (58, 163). In addition, in morphine-dependent rats, the opioid antagonist naloxone, introduced into the SON either by systemic injection or by retrodialysis, increases somatodendritic oxytocin release (20, 203). This 'morphine withdrawal excitation' also involves somatodendritic oxytocin, the release of which is increased under these conditions, while icv administration of an oxytocin antagonist reduces this increase (20).

During late pregnancy, sex steroids promote oxytocin synthesis and storage within the dendrites of the MCNs (156), and steroids have also been proposed to exert direct, rapid, non-genomic effects on neurons (232).

### **Dopamine**

Synaptic input to midbrain dopamine neurons comes predominantly from glutamate and GABA, with GABAergic input dominating in the SNc and

glutamatergic input dominating in the VTA (154, 197). Consequently, the net influence of excitatory *versus* inhibitory regulation of dopamine neurons differs between the SNc and VTA. In *ex vivo* midbrain slices, somatodendritic dopamine release evoked by a single stimulus pulse is unaltered by ionotropic glutamate or GABA receptor antagonists (27), suggesting the absence of tonic regulation by these transmitters in slices. However, during stimulation by multiple pulses, regulation by concurrently released glutamate and GABA is seen in both the SNc and VTA (30). In the SNc, dopamine release evoked by local pulse-train stimulation is inhibited by concurrently released glutamate acting on AMPA- and NMDA-receptors. This inhibition is prevented by GABA receptor antagonists, which is consistent with anatomical data showing AMPARs on inhibitory input to the SNc (182, 260), (30). In contrast, the increase in dopamine release produced by NMDA-receptor antagonists during pulse-train stimulation is unaffected by a cocktail of GABA receptor antagonists, suggesting the involvement of another inhibitory mediator. One possible candidate is endogenously generated  $H_2O_2$ , which has been shown to inhibit dopamine release in the SNc (26) and may be generated downstream from NMDAR activation.

In the VTA, pulse-train evoked dopamine release is unaffected by blocking  $GABA_{A-}$ ,  $GABA_{B-}$  or AMPA-receptors. By contrast, NMDA-receptor blockade suppresses evoked  $[DA]_o$ , consistent with a glutamate-dependent facilitation of dopamine release (30). Importantly, however, blockers of either AMPA- or NMDA-receptors decrease evoked dopamine release when applied in the presence of GABA-receptor antagonists, thereby unmasking the conventional direct excitatory effect of glutamate input to VTA dopamine neurons.

Regulation by glutamate of somatodendritic dopamine release in the SNc also occurs through the metabotropic, G-protein coupled receptor mGluR1 (184). mGluR1 $\alpha$  is highly expressed in dopamine neurons and, as described above, mGluR1 activation produces  $IP_3R$ -mediated  $Ca^{2+}$  release from ER stores, which facilitates evoked dopamine release. However, with large increases in intracellular  $Ca^{2+}$ , inhibition of dopamine neuron excitability and consequently dopamine release may occur from activation of  $Ca^{2+}$ -activated  $K^+$  channels (64, 153). Therefore, the net effect of dopamine release



regulation by mGluR1s will depend on exogenous mGluR1 agonist concentration or on stimulus intensity for endogenous glutamate release (48, 184). As already noted, activation of mGluR1s can also facilitate dendritic dopamine release in the SNr, possibly from elevated dopamine levels in the cytoplasm and subsequent DAT reversal (177).

#### *Possible role of co-released glutamate and GABA*

The increasing recognition that dopamine neurons co-release multiple transmitters including glutamate and GABA provides a novel concept in the idea of “autoreceptor” regulation. Initial studies using cultured dopamine neurons established that they can both synthesize and release glutamate (36, 55). In support of this, subsequent optogenetic methods using selective expression of channelrhodopsin (ChR2) in dopamine neurons have demonstrated that glutamate released from dopamine axons produces glutamate receptor-dependent excitatory post-synaptic currents in striatal neurons in slices (35, 106, 225, 228, 231, 240) and mediates behavioral effects *in vivo* (16). Similar approaches have been used to show co-release of GABA from dopamine axons; although these neurons synthesize GABA using a non-conventional enzyme, aldehyde dehydrogenase 1a1 (100), and they can also obtain GABA by uptake from the extracellular space (225, 240). Thus, if also co-released with dopamine from somata or dendrites, glutamate and/or GABA could autoregulate somatodendritic dopamine release. This possibility is supported by the presence of vesicular glutamate transporters (vGluT2) in VTA dopamine neurons (55, 84), and co-released GABA appears to be accumulated in secretory vesicles through VMAT2 (240), which is present in all midbrain dopamine cell bodies and proximal dendrites (170).

### **Actions of dendritically released oxytocin, vasopressin and dopamine**

#### ***Autocrine effects***

Dendritically released neurotransmitters exhibit autocrine effects on the neurons from which they are released, and also affect surrounding neurons and glia. These effects can change both the inputs to cells and the cellular response to these inputs. A good example of this occurs in oxytocin cells, in

which dendritically released oxytocin enhances the milk ejection reflex, as described below.

More commonly, somatodendritic release is auto-inhibitory and thus self-limiting. Vasopressin neurons discharge in a characteristic phasic pattern that maximizes stimulus-secretion coupling at the nerve terminals, but this activity is modified by the inhibitory autocrine effects of vasopressin released from dendrites. Like oxytocin, vasopressin can also facilitate its own dendritic release (258), which may explain the temporal separation of peripheral and central release of vasopressin following a hyperosmotic stimulus. Osmotic stimulation is followed immediately by systemic secretion of vasopressin, whereas dendritic release is delayed and the response prolonged (124). Increase of extraneuronal vasopressin concentrations by retrodialysis inhibits vasopressin neurons, reducing their firing rate (126). Thus, dendritic vasopressin release may stimulate vasopressin release from adjacent dendrites until the local external concentration reaches a threshold sufficient to hyperpolarize the neuron or else to modulate inhibitory inputs, thereby limiting the extent of systemic vasopressin secretion following osmotic stimuli or volume depletion.

Understanding of these autocrine effects is further complicated by the fact that within a single LCDV, several other peptides have been co-localized with either vasopressin or oxytocin. For example, the endogenous opioid dynorphin is co-localized with vasopressin in the same vesicles (250) and dendritic vasopressin release will therefore be accompanied by the release of dynorphin to provide feedback inhibition of vasopressin cell activity (21). In addition many other neuropeptides, such as galanin, apelin, PACAP and secretin, are synthesized in MCNs (54, 72, 77, 112). Accompanying receptor expression for these peptides on MCNs provides mechanisms for autocrine feedback regulation by these co-released neuropeptides (19).

Autocrine effects of somatodendritic dopamine release are central to the consequences of this process. Locally released dopamine binds to inhibitory D2 autoreceptors on dopamine neurons in the SNc and VTA, and thereby regulates the rate and pattern of firing of dopamine neurons (10, 73, 75, 191, 265), which ultimately influences the level and pattern of axonal dopamine release in CPu and NAc (211). Somatodendritic dopamine release

in SNc and VTA is also controlled by local feedback via D2 autoreceptors (41).

### ***Paracrine effects***

Exogenously applied or endogenously released oxytocin also acts on afferent nerve endings. The SON does not contain presynaptic oxytocin receptors, suggesting that this paracrine action is indirect. One indirect mechanism involves oxytocin-dependent endocannabinoid release from oxytocin neurons (104, 175), mediated by the action of dendritically released oxytocin on oxytocin receptors, release of  $Ca^{2+}$  from intracellular stores and consequent 'on-demand' synthesis of endocannabinoids. Endocannabinoids are arachidonate-based lipids that are hydrophobic enough to diffuse passively through plasma membranes; their binding to presynaptic cannabinoid receptors (CB1) inhibits both GABAergic and glutamatergic afferents onto MCNs. Indeed, CB1 receptors have been found using immunohistochemistry on both excitatory and inhibitory axon terminals that innervate dendrites in the SON. In SON slices, cannabinoid agonists presynaptically inhibit spontaneous excitatory and inhibitory postsynaptic currents.

The milk-ejection reflex during suckling provides an interesting example of local paracrine control by oxytocin. Oxytocin neurons are continuously active under basal conditions but during parturition and in response to suckling in lactating animals, discharge brief, intense bursts of action potentials. These bursts release large boluses of oxytocin into the circulation, producing intense contractions of the pregnant uterus or milk ejection from the mammary glands. The bursts are blocked by administration of oxytocin antagonists into the SON, and facilitated by oxytocin agonists (108). Dendritic release of oxytocin is up-regulated during parturition and in lactation, and has an essential role in the generation of these intermittent synchronized bursts (201). Its effects are not restricted to the cell of origin, but are also exerted on the dendrites of other oxytocin cells, possibly to facilitate homotypic interactions

Dendritically-released vasopressin modulates the activity of neighboring presympathetic neurons within the PVN (218), providing another example of a long-distance, paracrine action of dendritically-released neuropeptides. Activity-dependent dendritic release of vasopressin from MCNs concomitant increases the firing activity of neurons projecting from the PVN to the rostroventrolateral medulla. This interpopulation crosstalk involves extracellular diffusion of released vasopressin to V1a receptors in presympathetic neurons. Consequently, unlike conventional synaptic transmission, the efficiency and strength of this diffuse paracrine action of vasopressin depends on the extracellular vasopressin concentration, which in turn depends on the average activity of the entire vasopressin neuron population. It also depends on the half-life of vasopressin in the extracellular space, as well as on the ability of vasopressin to reach relatively distant targets by diffusion (e.g. the tortuosity of the extracellular space). These examples illustrate the importance of dendritic release of vasopressin in the ability of the PVN to control the activity of distinct populations of neurons, and thus, to produce a multimodal homeostatic response (218, 220).

Given the structural characteristics of midbrain SNc and VTA dopamine neurons, somatodendritic dopamine release is likely to be at least partly non-synaptic. Moreover, dopamine receptors and reuptake transporters on dopamine cell bodies and dendrites are largely extrasynaptic (171, 172, 213, 261), as are D1 receptors on non-dopaminergic terminals in these regions (23, 261). Thus, somatodendritically released dopamine must act through volume transmission via the extracellular fluid (194, 195). Extracellular dopamine concentrations are in turn regulated by diffusion, by uptake through the DAT and by the (probably negligible) effects of enzyme-catalysed degradation (43, 195). Diffusion measurements in *ex vivo* guinea pig midbrain slices reveal that the extracellular volume fraction in the SNc, SNr and VTA is ~50% larger than that in forebrain structures, including the striatum (43), which would lead to lower extracellular concentrations in midbrain than forebrain for a given number of molecules released. Of course, net  $[DA]_o$  is also influenced by other regulators, especially uptake, which is greater in the striatum than in the midbrain, so that absolute concentrations in these regions do not differ as much as predicted by diffusion characteristics alone (195). Interestingly, DAT

activity is greater in SNc than VTA, as well, leading to greater effects of DAT inhibitors on evoked increase in  $[DA]_o$  in SNc than in VTA (40, 43).

In contrast to evidence for diffusion-based volume transmission of dopamine in the SNc and VTA from anatomical and voltammetric studies, evaluation of evoked D2ICs in dopamine neurons suggests that the actions of dopamine are not only largely diffusion-independent, but also synaptic (9, 10, 38). These conclusions are based on several observations. First, the concentration of *exogenous* dopamine required to induce D2ICs of similar magnitude to those produced by endogenously released dopamine is in the micromolar range. This is in contrast to the nanomolar concentrations expected for D2 autoreceptors in the high-affinity state. Given that the external dopamine concentration declines sharply with distance from a site of release (38, 44, 195), an interpretation of this result is that the dopamine detected by D2 receptors is immediately post-synaptic, or at least peri-synaptic. Synaptic dopamine release does occur in the VTA, given the presence of axon collaterals (7, 28). Second, the time-course of evoked D2ICs is relatively constant across stimulations, as might be expected for a postsynaptic response. However, the kinetics of the G-protein coupled, inwardly-rectifying  $K^+$  (GIRK) channel activated by dopamine are likely to be the rate-limiting factor in this autoreceptor-mediated process. Indeed, modeling studies of quantal dopamine release indicate that the peak concentration is reached  $\sim 10$  ms after a release event, even at a distance of 5  $\mu m$  from the release site (43, 44, 195), whereas the D2 IPSC peak occurs several hundred ms after stimulation (38, 68). Thus, the debate about synaptic transmission vs. volume transmission for somatodendritic release of dopamine remains open (68, 195).

### **Functional roles for somatodendritic oxytocin, vasopressin and dopamine and other diffusible messengers in the brain**

Oxytocin and vasopressin exert specific behavioral effects: oxytocin is involved in maternal behavior and social bonding, while vasopressin has actions in the brain that affect social recognition and aggression (88, 168, 224). The sites at which these behavioral effects are exerted show, in some cases, high levels of receptor expression but little innervation by peptide-

containing projections. Could dendritically released peptides exert long-lasting behavioral effects by acting on distant targets within the brain? Similar changes in neuropeptide concentrations often occur at widely separated sites, even though the absolute values vary between sites (127). Dendritic peptide release is not targeted specifically to synapses, but peptides may travel to their targets by bulk flow through the extracellular fluid and cerebrospinal fluid. The half-life of oxytocin in the CSF is about 20 min (144), in contrast with the typically subsecond lifetime of dopamine, which limits the range of its action after both axonal and somatodendritic release (38, 44, 195).

Somatodendritic dopamine release also plays a role in animal behavior, including motor activity. The action of dendritically released dopamine on D1 dopamine receptors in the terminals of the striatonigral direct pathway enhances GABA release from axons in the SNr, thereby amplifying inhibition of the principal cells of the SNr (149, 192, 239). Through these pathways, somatodendritic, as well as axonal dopamine release regulates motor behavior (3, 15, 45, 56, 141, 200, 212, 233).

The paracrine or hormone-like actions of neuropeptides and dopamine can enable signaling between entire populations of neurons, some of which may be relatively distant from each other. Thus these transmitters act in a more diffuse, less spatially constrained manner – and on a longer time scale – than those involved in classical fast synaptic transmission. At chemical synapses, the “secrecy” of signal transmission is maintained by the structure of the synapse and by the surrounding network of reuptake transporters. In contrast paracrine transmission has evolved so as to maximize spillover, and its specificity depends only on that of the signal/receptor interactions. In addition to the transmitters that are the focus of this review, other biogenic amines and acetylcholine are released from *en passant* boutons on axonal segments (264). Extending this concept further are gaseous neurotransmitters such as nitric oxide and carbon monoxide (49). It is likely that all of these molecules transmit chemical signals not simply from one cell to another, but from one population of neurons to another (115, 116, 127), while maintaining signal specificity by actions at transmitter-specific receptors.

## **Conclusions**

Somatodendritic oxytocin and vasopressin release from hypothalamic neurons provides paracrine signals that are critical in several key physiological events, including birth, milk let-down and social bonding. Somatodendritic release and volume transmission of neuropeptides represents a form of hormonal action. These neurohormones can act in a temporally coherent way at discrete brain sites to establish and co-ordinate complex behaviors.

Somatodendritic dopamine release from midbrain dopamine neurons provides an autocrine signal that regulates dopamine neuron activity, and thus contributes to axonal release regulation in target regions. Equally importantly, dopamine released within these cell body regions contributes to the regulation of release of other transmitters, including GABA and glutamate. Through these actions, somatodendritic dopamine release contributes to motor regulation, as well as to plasticity in rewards circuits, including aberrant plasticity in response to drugs of abuse.

Recent studies provide evidence about the mechanism and regulation of somatodendritic release of oxytocin, vasopressin and dopamine, including underlying commonalities and differences. There is no reason to believe that somatodendritic release is restricted to these systems, and study of this process in other neuronal types is likely to be fruitful. How well we can understand somatodendritic release in the healthy brain necessarily influences how well we can harness these processes to treat disorders involving these pathways. The goal of future work into the somatodendritic release of peptides, dopamine and related molecules will be to provide this understanding.

Figure Legend

**Figure 1: Comparison of the mechanisms of somatodendritic release of oxytocin and vasopressin in the hypothalamus (A) and dopamine in the substantia nigra (B).**

**A)** Neuropeptides are synthesized and packaged in the soma and stored in

dendrites in a reserve pool (RP) containing large numbers of large dense-cored vesicles (LDCVs) in dendrites. Depolarization-induced  $\text{Ca}^{2+}$  entry through voltage-gated calcium channels (VGCCs) stimulates peptide release by exocytosis of LDCVs. This requires the depolymerization of F-actin to G-actin. Furthermore, the stimulation of G-protein coupled receptors, such as the oxytocin receptor, stimulates the mobilization of  $\text{Ca}^{2+}$  from  $\text{IP}_3$ -dependent intracellular stores and an increase in both the number of LDCVs and N-type VGCCs at the plasma membrane, thus priming the exocytosis machinery for subsequent activity-dependent release. Although some members of the SNARE family are detectable by immunocytochemistry, there appears to be a lack of VAMP, SNAP-25 and synaptotagmin-1 in the somata-dendrites, with their function presumably being replaced by other SNARE proteins. TG, thapsigargin; CPA, cyclopiazonic acid

**B).** Features of somatodendritic dopamine release. Dopamine is synthesized in the intracellular compartment from tyrosine via tyrosine hydroxylase (TH). This process generates L-DOPA which is converted to dopamine by aromatic amino acid decarboxylase (AADC). Synthesized dopamine is stored in tubulovesicular structures that are part of the endoplasmic reticulum (ER); these structures are the primary site of VMAT2, the vesicular monoamine transporter expressed in dopamine soma and proximal dendrites. Dopamine dendrites contain few vesicles, but those present appear to bud from tubulovesicles. Somatodendritic dopamine release is action potential dependent. Release also requires  $\text{Ca}^{2+}$  entry via VGCCs, but is amplified by both ryanodine receptors (RyRs) and metabotropic glutamate receptor (mGluR)-dependent activation of  $\text{IP}_3$ Rs that release  $\text{Ca}^{2+}$  from intracellular ER stores. Immunohistochemical evidence suggests that a novel constellation of SNARE proteins may be involved in the release, including SNAP-25, VAMP2, and syntaxin3b. Release from dendrites has also been suggested to involve reversal of the dopamine transporter (DAT). Released dopamine is taken up and recycled via the DAT.

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