
The bigger picture...
Commentary on
Somato-dendritic vasopressin and oxytocin secretion in endocrine and autonomic regulation
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Dendritic secretion of regulatory peptides: The bigger picture by Lee E. Eiden

One of the most useful simplying generalizations arising from the many and varied microscopical observations of the Cajal era of neuroscience was the so-called law of dynamic polarization, i.e. that dendrites and soma of neurons collect and integrate information from upstream neuronal input; the axon receives this collated information at the initial segment; the axon conducts it to the nerve terminal in the form of action potential propagation at varying frequencies; and the nerve terminal conveys that information across the synapse via quantally released neurotransmitters. This generalization of linear reception, conduction and application has however been increasingly beset with exceptions, as most useful generalizations are. An intriguing update of dendritic secretion of the neuropeptide oxytocin and vasopressin from magnocellular neurons of the hypothalamus by Brown and colleagues highlights an important one (Brown, Ludwig et al. 2020).

The magnocellular neurons of the hypothalamus are the 'gift that keeps on giving' in this process of dogmatic simplification and generation of more nuanced (and, importantly, more accurate) conceptualizations of how neurons actually work. The neurosecretory neuron was once the example 'par excellence' of the polarized neuron. In fact, it was given the name neurosecretory neuron, or MNN (we generally call these neurons MNNs, however Brown and colleagues refer to them as MNCs, or magnocellular neurosecretory cells, and we follow this nomenclature here), to distinguish its morphologically spectacular polarization. The MNCs have few, but prominent dendrites that collect information from multiple neuronal inputs throughout the brain, integrate these inputs within compact groups of massively-sized soma, and propagate action potentials at frequencies directly proportional to the release of oxytocin and vasopressin from secretory vesicles contained in nerve terminals located mainly in the posterior pituitary and into the general circulation as hormones. However, microscopists early on noted that the characteristic hormone-containing vesicles (large dense-core vesicles, or DCVs, sometimes called LDCVs) could also be visualized in the dendrites of MNCs (Morris and Pow 1988). Brown and colleagues have now summarized the case for oxytocin and vasopressin secretion not only from the 'secretory end' of the cell (in the posterior lobe of the pituitary), but also from secretory vesicles within the dendritic tree of these cells. Is the notion of neuronal polarization of neurotransmitter/ neurohormone secretion upended by, or refined by, these observations? And are these observations restricted to MNCs, or is MNC dendritic release indicative of a bigger picture of neuronal function throughout the CNS?

The release of oxytocin and vasopressin from dendrites seems to have two functions: one by now relatively well-established, and the other still controversial. As to the first, nerve terminals seems to endow OT and AVP MNNs with more highly-tuned regulation in response to uterine contraction via noradrenergic neurons in NTS projecting to SON/PVN. Both NTS neurons impingent upon OT MNC soma, and the MNC soma themselves, possess OT receptors. Activation of these enhances NE release from NTS projections and sensitizes OT MNCs to further stimulation from the NTS. The end result is that, once having been triggered by uterine contraction, secretion rates of OT from the posterior pituitary are amplified, and stabilized, by OT secretion from the MNC dendritic OT stores. Importantly, physiological and neurochemical signals can differentially affect OT release from dendrites within hypothalamus and axons in posterior pituitary. Unlike OT MNCs, AVP receptors (V1aR) are found on cells (astrocytes) near dendrites releasing AVP, rather than on dendrites (or soma) of MNCs releasing AVP. And AVP dendritic release does not appear to 'prime' vasopressin MNCs for further AVP release. Rather ghrelin acts on GHSRs (growth hormone stimulating receptor, the cognate G-protein coupled receptor for ghrelin, a hoone released in the gut) of AVP MNC soma which acts upon astrocyte V1a receptors to release ATP onto nearby GABAergic interneurons, which in turn exert inhibition on AVP axonal secretion.

Other neurotransmitters and hormones act upon OT and AVP MNCs at the soma to elicit OT and AVP dendritic release, which in turn helps to shape, by the autocrine and paracrine mechanisms described above, the phasic firing of both types of MNCs to optimize OT and AVP release from the nerve terminals of the posterior pituitary. One example is galanin, which is preferentially packaged in DCVs that traffic preferentially to dendrites, rather than axon terminals of AVP MNCs, and, upon its own dendritic release, interacts with kappa opiate receptors (KORs) on AVPs to modulate both timing and intensity of AVP hormonal release. In general, it may be that the fundamental purpose of dendritic release is the coordination of the SON and PVN as a cohort of cells from which AVP and OT release into the circulation must be controlled with respect to both speed of response to meet physiological needs, and upper and lower limits on basal (tonic) and phasic secretion to remain in harmony with other hormones acting on fundamental processes such as electrolyte balance and smooth muscle contraction during labor and other hard work. This of course implies a need for continuously setting a 'gain' of MNCs that preserves elasticity in modulating secretion rate of both AVP and OT under varied physiological circumstances. CB-1/2-AG system acts in this way: as illustrated in their Figure 6, the authors show the important role of presynaptic CB1 receptors on GABAergic and glutamatergic synapses on MNCs, whose ligands 2-AG and anandamide are released at the OT MNC soma in response to ambient steroid hormone levels as well as basal autocrine OT. Such a system allows the 'definition' of basal OT or AVP secretion, as well as the dynamic range of stimulated secretion, to rise and fall so that physiological regulation of electrolyte levels is reliably delivered to the organism despite changes in gonadal status or ability to choose between water imbibition or kidney-mediated conservation (in the case of AVP).

Single-cell transcriptomics and high-resolution dual and triple ISH is beginning reveal specific neuronal populations in which a neuropeptide, and its cognate receptor, are co-expressed in a neuron , and this can be an initial clue for autocrine function, either at the nerve terminal upon axonal release, as for galanin, NPY and other neuropeptides, or at the cell body, as for the examples of OT and AVP in MNCs reviewed by Brown et al. Furthermore, autocrine/paracrine function may not be restricted to promoting 'autologous' neuropeptide secretion, but may also promote or otherwise regulate the nerve terminal secretion of co-expressed glutamate or GABA, when the nerve terminals of interest are found not in the posterior lobe of the pituitary, but presynaptically within extended amygdala, hippocampus, epithalamus, or brain stem.

There are other systems in which chemoanatomical considerations suggest that regulatory peptides control the activities of the neurons in which they are expressed by either pre-synaptic or dendritic release. Some examples are the TIP39-expressing neurons of the hypothalamus and their projections (Dimitrov, Kim et al. 2011), oxytocinergic nerve terminals in the nucleus accumbens that modulate the perception of reward (Schwartz, Temkin et al. 2014), and galanin release from noradrenergic neurons of the locus coeruleus (Hokfelt, Barde et al. 2018). In general, a role for dendritically released neuropeptides can be envisioned unless actually ruled out: one way to tell is by direct anatomical observation of peptides in both dendrites and nerve terminals of a given cell in the brain. In fact it was the observation of DA staining in SNc dendrites, along with their decoration with antibody specific for VMAT2 at the EM level, that led Pickel and colleagues to postulate a role for dendritic release of DA in nigrostriatal function (Nirenberg, Chan et al. 1996).

What is the full extent of dendritic peptide release in brain physiology, and will it fundamentally alter the concept of 'dynamic polarization'? How can this question be explored experimentally in areas in which it is not so easy to directly assess dendritic release using, for example, in vivo dialysis, as can be done for the massively secreted and measurable AVP and OT? Finally, what of the final question: dendritic release leading to quasihormonal effects (i.e. neuropeptides released from dendrites and acting at a distance in the brain after passage through the interstitial or cerebrospinal fluid)? It seems likely that this will remain a controversial area for both OT and AVP for quite some time, and even more so for other neuropeptides. In the meantime, dendritic release reminds us of the undeniable bipolarity of information transfer in the CNS, and how much there is to learn about it through chemoanatomical and ex vivo electrophysiological and functional studies.

Control of nerve terminal release of OT and AVP from MNC projections which go, not to the posterior pituitary, but to brain, including hippocampus, habenula, extended amygdala, and brainstem (denoted as 'collateral's in Figure 1 of Brown et al.) is also enabled by dendritic paracrine release of MNC OT or AVP. In fact it might be said that the need to modulate the tempo and intensity of release of AVP and OT from CNS-projecting nerve terminals 'goes double' compared to posterior pituitary secretion, since their synapses help orchestrate the allostatic control required for anticipation when physiological drives must be delayed (re-prioritized) under conditions of threat, sex, or other important organismic considerations. In fact, preferential action of dendritically-released OT or AVP on the action potentials propagated to nerve terminals in the posterior pituitary gland, compared to those of the collaterals projecting elsewhere, might well reveal an unlooked for way that AVP or OT released from dendrites can act 'at a distance' within the brain.

Further understanding will depend in part on knowing exactly what dendritic release looks like in terms of the radius of action of peptides released by this mechanism (Chini, Verhage et al. 2017). This in turn will be enabled by more precise understanding of the process of DCV exocytosis itself at dendrites compared to nerve terminals. Brown et al. strongly hint that the multimolecular assemblies mediating DCV release at dendrites are different from the set of classical SNARE proteins comprising exocytosis 'nanomachines' for small synaptic vesicles (SSVs) (Bruns and Jahn 2002). This opens up an entire 'nanoverse' of biochemical inquiry that might ultimately lead to the molecular tools required to put this mode of regulatory peptide signaling into a bigger picture in which neurons auto-regulate their own behavior, and elicit cooperation from neighboring vasculature and glial cells for optimal function, ultimately in the service of the 'dynamic polarity' from which dendritic secretion seems such a dramatic departure.

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