Somato-Dendritic Secretion of Neuropeptides

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Abstract

In addition to classical neurosecretion at the synapse, many neurons also secrete neurotransmitters from their cell bodies and dendrites. In contrast to synaptic transmission, somato-dendritic secretion is best characterized as modulating the overall excitability of the target cells over a longer time course via actions at presynaptic and extrasynaptic receptors. Magnocellular neurons of the hypothalamic supraoptic and paraventricular nuclei synthesize the neuropeptides, vasopressin and oxytocin, and were among the first neurons shown to secrete neurotransmitters from their cell bodies and dendrites by exocytosis. These neuropeptides modulate the activity of the neurons from which they are secreted, as well as the activity of neighboring neurons, to provide intra- and interpopulation signals that coordinate the endocrine and autonomic responses for control of cardiovascular and reproductive physiology, as well as behavior.

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4.1 Introduction

The prevailing view of neuronal communication in the brain is of point-to-point transmission at synapses within neural networks. However, knowledge of other modes of communication has rapidly expanded in recent years, providing insight into the complexity of information transfer in the nervous system. These other modes of communication are all paracrine communication that are broadly categorized in neuroscience as volume transmission because they involve neurotransmitter diffusion through the extracellular space to activate extrasynaptic receptors, or intracellular effectors (Sykova 2004). While synaptic transmission allows for specific one-on-one interactions between individual neurons, volume transmission lends itself to communication at the population level. Many neurons have been shown to release neurotransmitters from their cell bodies, and *dendrites* of *magnocellular neurons* (also known as magnocellular neurosecretory cells) of the hypothalamic *supraoptic and paraventricular nuclei* are among those for which the mechanisms and consequences of somato-dendritic exocytosis are best characterized.

4.2 Magnocellular Neurons

Magnocellular neurons secrete the hormones, *vasopressin* (aka, antidiuretic hormone) or *oxytocin*, into the general circulation. Vasopressin maintains body fluid balance and blood pressure by activation of renal V_2-receptors to increase water reabsorption from the urine and, when blood pressure/volume is decreased, by activation of vascular V_1-receptors to cause vasoconstriction (Brown 2016). Oxytocin triggers uterine contractions during birth and milk ejection during lactation (Brown 2016).

Each magnocellular neuron extends a single axon (that typically arises from the primary dendrite) to the posterior pituitary gland (neurohypophysis), where each axon branches extensively into several thousand neurosecretory axon swellings and terminals that are tightly packed with dense core vesicles containing either vasopressin or oxytocin, as well as lesser amounts of other neurotransmitters/neuromodulators (Brown et al. 2008). Some magnocellular neurons extend axon collaterals to other brain areas to modulate behavior (Knobloch et al. 2012).

Most magnocellular neurons extend between one and three simple dendrites that are smooth (i.e., do not have dendritic spines), thick, varicose, and a few hundred micrometers in length. Magnocellular neuron dendrites are also tightly packed with dense core vesicles that undergo *exocytosis* (Pow and Morris 1989) to release vasopressin or oxytocin, along with other neurotransmitters/neuromodulators (Fig. 4.1). The dendrites of supraoptic nucleus magnocellular neurons largely extend

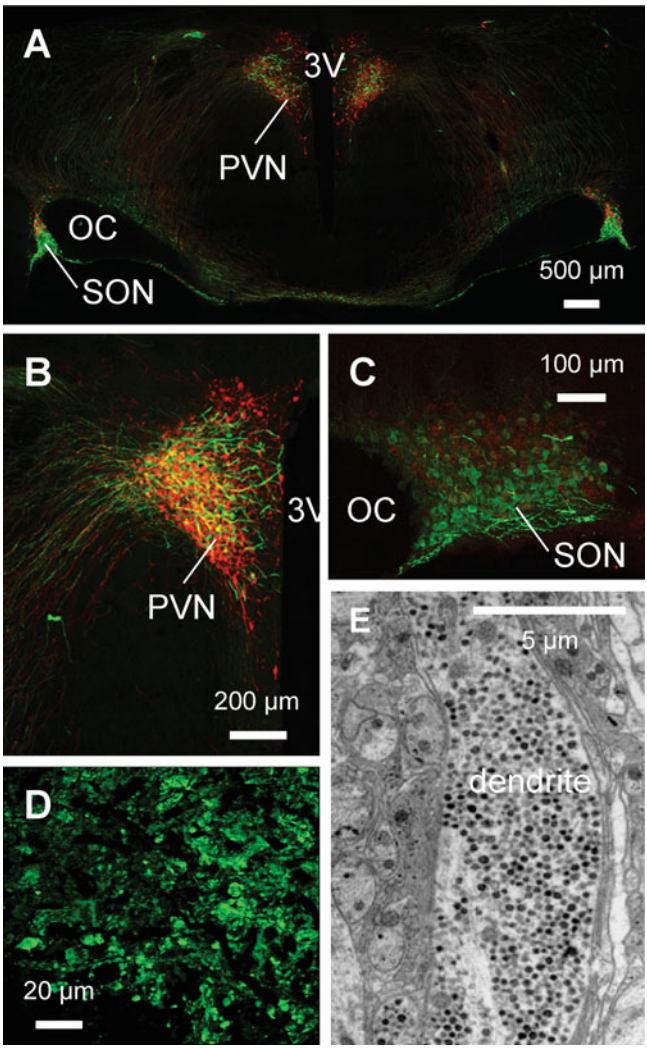

Fig. 4.1 The magnocellular neurosecretory system. (**a**–**c**) Photomicrographs of coronal sections of rat hypothalamus (**a**), in which vasopressin neurons are immunostained with fluorescent green and oxytocin neurons with fluorescent red. Magnocellular cell bodies are principally found in the hypothalamic supraoptic nucleus (SON) (**b**), lateral to the optic chiasm (OC), and paraventricular nucleus (PVN) (**c**), lateral to the third cerebral ventricle (3V). The SON contains only magnocellular neurons that project predominantly to the posterior pituitary gland, whereas the PVN also contains parvocellular oxytocin and vasopressin neurons (as well as other parvocellular neurons) that project elsewhere in the brain. (**d**) Photomicrograph of vasopressin axon terminals in the posterior pituitary gland. (**e**) Electron micrograph showing magnocellular dendrites densely packed with dense core neurosecretory vesicles (small black dots). Reproduced from Brown et al. (2013), with permission

to the ventral surface of the nucleus where they bundle together within the ventral glial lamina (a layer of astrocytes within the supraoptic nucleus) and the dendrites of paraventricular nucleus magnocellular neurons extend toward the subependymal region of the third ventricle (Brown 2016).

4.3 Regulation of Somato-Dendritic Secretion in Magnocellular Neurons

While axons of magnocellular neurons have morphological structures (swellings and terminals) from which release occurs, somato-dendritic secretion appears to occur from any part of the cell body or dendrites (Morris and Pow 1991), more reminiscent of endocrine cells than synaptic transmission. Similarly to magnocellular neuron terminals in the posterior pituitary gland, the cell bodies and dendrites contain a network of sub-plasmalemmal filamentous actin (cortical F-actin) that might limit access of dense core vesicles to the plasma membrane for secretion (Fig. 4.2). Again similarly to secretion from the terminals, F-actin depolymerization increases somato-dendritic vasopressin and oxytocin secretion and F-actin polymerization inhibits stimulated somato-dendritic secretion (Tobin and Ludwig 2007), although it remains to be determined whether specific sites in the cortical F-actin network provide dense core vesicles privileged access to the surface membrane.

Somato-dendritic exocytosis from magnocellular neurons appears to be mediated by the soluble *N*-ethylmaleimide-sensitive factor attachment receptor (SNARE) complex, which allows vesicle fusion with the plasma membrane. Tetanus toxin cleaves vesicle-associated membrane protein-2 (VAMP-2, a core SNARE complex protein) and inhibits secretion from isolated magnocellular neurons (bereft of axons and dendrites, so secretion presumably is only from cell bodies) (de Kock et al. 2003). While many SNARE proteins have been identified in magnocellular neuron axon terminals, labeling for VAMP-2 and synaptosomal-associated protein 25 (SNAP-25, another core SNARE complex protein) is not evident in the cell bodies and dendrites of magnocellular neurons (Tobin et al. 2012). Hence, somato-dendritic exocytosis from magnocellular neurons might involve other isoforms of the core SNARE complex proteins than those involved in axon terminal release.

While neuropeptides can be released by partial (kiss-and-run) fusion with the plasma membrane, this is unlikely to occur in magnocellular neurons because their dense core vesicles are tightly packed with ~10,000 neuropeptide molecules, which is near the maximum possible due to physicochemical constraints. Indeed, tannic acid perfusion fixation shows that the entire vesicle core is exocytosed (Pow and Morris 1989). Hence, it is not surprising that magnocellular neurons might express a noncanonical suite of exocytotic machinery.

The dendrites of magnocellular neurons support back propagation of action potentials (Bains and Ferguson 1999), and it has been proposed that single action potentials trigger somato-dendritic exocytosis from magnocellular neurons from studies of membrane capacitance (de Kock et al. 2003). However, a one-to-one relationship between action potential firing and somato-dendritic dense core vesicle

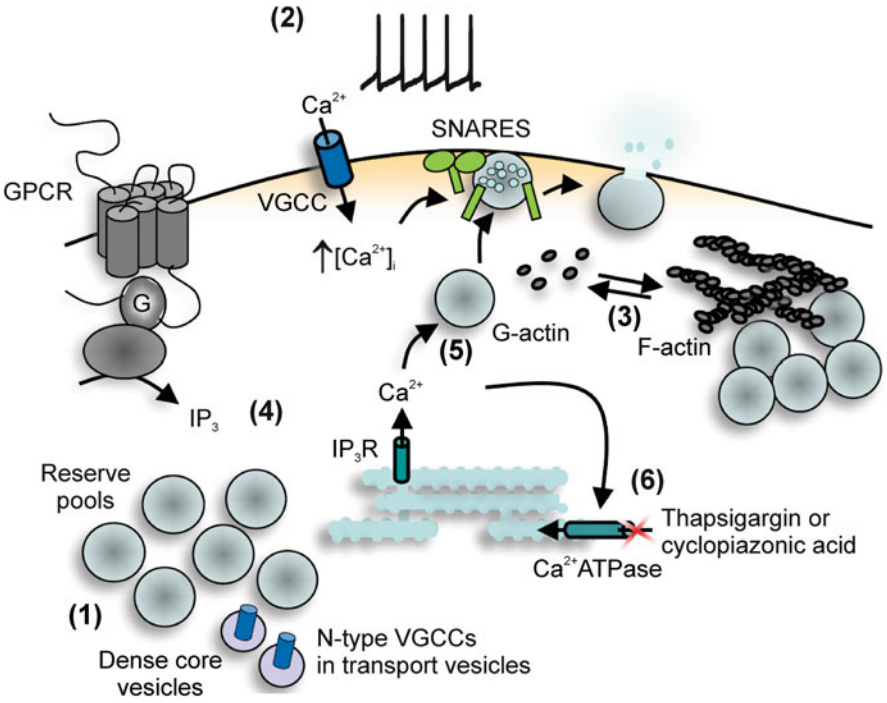

Fig. 4.2 Somato-dendritic neuropeptide secretion from magnocellular neurons. Neuropeptides are synthesized and packaged in the cell body and stored in a reserve pool (RP) containing large numbers of dense core vesicles in the cell body and dendrites (1). Depolarization-induced calcium influx through voltage-gated calcium channels (VGCCs) stimulates exocytosis to secrete neuropeptide into the extracellular space (2). Access of dense core vesicles to the plasma membrane requires the depolymerization of F-actin to G-actin (3). In addition, activation of G_q-protein coupled receptors (GPRs), including the oxytocin receptor, mobilizes calcium from inositol triphosphate (IP_3)-dependent intracellular stores (4) and increases the number of dense core vesicles and N-type VGCCs at the plasma membrane (5), priming the exocytotic machinery for subsequent activity-dependent release. Direct stimulation of calcium release from intracellular stores with thapsigargin or cyclopiazonic acid also causes priming (6). Although some members of the SNARE family are detectable by immunocytochemistry, there appears to be little or no VAMP, SNAP-25, and synaptotagmin-1 in the cell bodies and dendrites of magnocellular neurons, with their function presumably being replaced by other SNARE proteins. Modified from Ludwig et al. (2017), with permission

exocytosis is unlikely because exocytosis of ~6000 vesicles per second would be sufficient to maintain effective concentrations of vasopressin and oxytocin within the hypothalamus (Brown et al. 2007). There are ~10,000 magnocellular neurons in the rat hypothalamus (and over 100,000 in the human) and so each magnocellular neuron would need to release (on average) only one vesicle every couple of seconds to maintain basal hypothalamic vasopressin and oxytocin concentrations. However, magnocellular neurons have a mean firing rate of ~5 action potentials per second. Hence, a one-to-one relationship between action potential firing and dense core

vesicle exocytosis would flood the extracellular space with vasopressin and oxytocin. Indeed, somato-dendritic oxytocin secretion can occur in some cases when action potential firing is reduced (Sabatier et al. 2003).

Increased intracellular calcium is obligatory for exocytosis. In contrast to classical synaptic transmission, exocytosis from somato-dendritic dense core vesicles requires a sustained increase in intracellular calcium and the associated calcium sensor has a high calcium affinity. Therefore, specialized release sites are likely not essential for somato-dendritic exocytosis to occur because the dense core vesicles do not need to be close to membrane calcium channels, but this remains to be confirmed.

Magnocellular neurons express a suite of voltage-operated calcium channels that can be activated by action potential firing or by smaller sustained membrane depolarization. $Ca_{v2.2}$ (N-type) channels carry a comparatively small current in magnocellular neurons compared to other voltage-operated calcium channels but nevertheless are most important for somato-dendritic oxytocin release (Tobin et al. 2011). While action potential activity can activate voltage-operated calcium channels, vasopressin and oxytocin neurons express receptors for their cognate neuropeptides and the neuropeptides activate these receptors to produce a cell-type specific rise in intracellular calcium concentration (Dayanithi et al. 2000) that could drive somato-dendritic exocytosis. Calcium permeation through extrasynaptic *N*-methyl-D-aspartate (NMDA) receptors provides another means to trigger somato-dendritic exocytosis of vasopressin and oxytocin from magnocellular neurons (Son et al. 2013; de Kock et al. 2004). While the initial signal is calcium influx from the extracellular space, calcium release from intracellular stores also evokes somato-dendritic secretion of neuropeptides from magnocellular neurons (Ludwig et al. 2002, 2005) and calcium buffering mechanisms regulate somato-dendritic exocytosis from magnocellular neurons through a variety of mechanisms that limit increases in intracellular calcium (Dayanithi et al. 2012).

In addition to triggering somato-dendritic secretion, increased intracellular calcium also "primes" somato-dendritic secretion by promoting movement of dense core vesicles toward the cell surface (Tobin et al. 2004) and by recruitment of $Ca_{v2.2}$ channels. Priming increases the somato-dendritic secretory response to other signals that mobilize intracellular calcium, such as vasopressin or oxytocin themselves. Without a priming stimulus, vasopressin and oxytocin elicit little somato-dendritic secretion, but after priming each neuropeptide elicits robust somato-dendritic secretion from their respective neuronal phenotypes (Ludwig et al. 2002, 2005).

4.4 Physiological Functions of Somato-Dendritic Neuropeptide Secretion

The physiological functions of somato-dendritic secretion include autocrine effects on the activity of the neuron from which neurotransmitters are released, as well as paracrine effects on neighboring neurons and glia. While it has been proposed that somato-dendritic secretion of vasopressin and oxytocin might act as hormone-like signals in the brain (Ludwig and Leng 2006), it has yet to be established whether

neuropeptides released from the cell body and dendrites can impact neurons in distant brain areas, although there is some evidence that magnocellular neuron dendrites might mediate vasopressin and oxytocin activation of nearby neurons.

4.4.1 Autocrine Regulation of Vasopressin Neuron Activity

Vasopressin-containing dense core vesicles express V_{1a} and V_{1b} receptors (Hurbin et al. 2002). These receptors are presumably inserted into the cell membrane during somato-dendritic exocytosis of vasopressin and so will be exposed to high vasopressin concentrations, providing an ideal system for autocrine feedback regulation of vasopressin neuron activity.

While vasopressin neurons express a range of activity patterns, many display rhythmic "phasic" activity, in which they alternate between periods of activity (bursts) and silence that each last tens of seconds and that increase the efficiency of vasopressin secretion from the posterior pituitary gland. Autocrine feedback regulation of phasic activity has been largely characterized by microdialysis drug application directly into the supraoptic nucleus while recording spontaneous action potential discharge in anesthetized rats (Box 4.1, Movie 4.1).

Box 4.1 In Vivo Extracellular Single-Unit Recording from the Supraoptic Nucleus with Microdialysis Drug Application in Anesthetized Rats

In vivo recording of the activity of magnocellular neurons in anesthetized rats allows the impact of (patho)physiological and pharmacological manipulations on the neuronal activity to be measured, without the confounding influence of uncontrolled variables evident in conscious animals. The anatomical separation of magnocellular cell bodies from their secretory terminals in the posterior pituitary gland allow for electrophysiological identification of the neurons (by antidromic stimulation from the posterior pituitary) and recording from the cell body (Movie 4.1), and the localization of magnocellular neurons to the hypothalamic supraoptic nucleus makes these neurons amenable to microdialysis drug administration during in vivo electrophysiological experiments (Movie 4.1) without disruption of their afferent inputs or cellular integrity. We have used this technique to apply various drugs into the supraoptic nucleus while recording phasic activity, which has identified several dendritically released factors as modulators of this activity pattern (Brown et al. 2008).

While application of exogenous vasopressin has been reported to drive all vasopressin neurons toward phasic activity (Gouzenes et al. 1998), this is unlikely to occur naturally because it would increase circulating vasopressin concentrations to levels that would cause robust vasoconstriction that is not evident under basal conditions. Indeed, antagonism of V_{1a}-receptors within the supraoptic nucleus

consistently increases the activity of phasic neurons throughout the active period (Ludwig and Leng 1997), indicating that endogenous vasopressin is inhibitory, probably via V_{1a}-receptor-mediated inhibition of excitatory postsynaptic potential (EPSP) amplitude (Kombian et al. 2000) and increased inhibitory postsynaptic potential frequency (Hermes et al. 2000). While vasopressin neurons express vasopressin receptors, the simplest explanation for the effects of vasopressin on synaptic potentials is that vasopressin also acts as a retrograde modulator of synaptic transmission as well as an autocrine feedback inhibitor of activity. Overall, somato-dendritic vasopressin secretion contributes to the generation of phasic activity patterning in vasopressin neurons necessary for efficient release of vasopressin into the bloodstream under basal conditions (Fig. 4.3).

In addition, somato-dendritic vasopressin secretion functions as a negative feedback mechanism to restrain excitation of vasopressin neurons at a population level. This hypothesis is supported by the observation that osmotic stimulation of vasopressin neurons increases vasopressin release into the blood and brain. However, central release is delayed (perhaps while priming is established) and prolonged compared to peripheral release (Ludwig et al. 1994), such that central release is increasing while peripheral release is decreasing, as would be expected by negative feedback regulation of vasopressin neuron activity by somato-dendritic vasopressin secretion.

4.4.1.1 Autocrine Regulation of Vasopressin Neuron Activity by Co-released Neurotransmitters

Magnocellular neurons synthesize and secrete a number of neuropeptides in addition to vasopressin and oxytocin, although in much lower quantities than the principal neuropeptides. For vasopressin neurons, these neuropeptides include apelin, dynorphin, galanin, neuroendocrine regulatory peptides (NERPs), pituitary adenylate cyclase activating polypeptide (PACAP), and secretin (Brown et al. 2008).

While most neuropeptides in magnocellular neurons are found within the same dense core vesicles as vasopressin or oxytocin, at least apelin and galanin appear to be segregated from vasopressin. Apelin is packaged in a distinct group of dense core vesicles from vasopressin, while some dense core vesicles contain only galanin or vasopressin (although others contain both galanin and vasopressin). Clearly, segregation might allow for differential release of vasopressin or oxytocin and their co-expressed neuropeptides. Indeed, this does appear to be the case because the co-expressed neuropeptides and galanin-containing vesicles are preferentially trafficked to the dendrites rather than the axons (Landry et al. 2003).

It is not known whether co-expressed neuropeptides other than apelin and galanin are also differentially segregated in dense core vesicles of vasopressin neurons, but, if so, differential release of co-expressed neuropeptides might reinforce or restrain peripheral secretion of vasopressin because apelin, PACAP, and secretin excite vasopressin neurons while dynorphin, NERPs, and galanin inhibit vasopressin neurons (Brown 2016).

While it is possible that there is some segregation of dynorphin and vasopressin, it is clear that dynorphin and vasopressin are present in many of the same dense core

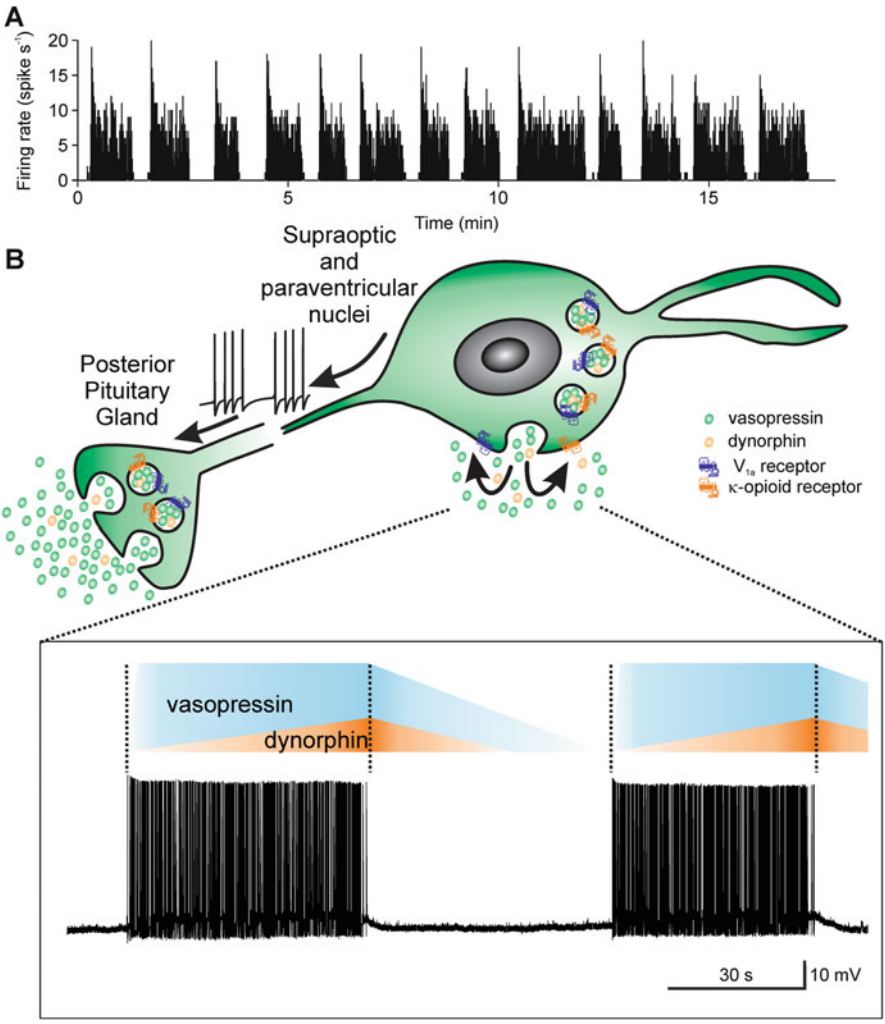

Fig. 4.3 Autocrine inhibition of phasic activity in vasopressin neurons by somato-dendritic neuropeptide secretion. (**a**) In vitro extracellular recording of the firing rate (averaged in 1 s bins) of a vasopressin neuron. The neuron displays the highly organized phasic activity pattern characteristic of vasopressin neurons, with periods of activity (bursts) and silence that each lasts tens of seconds. (**b**) Schematic representation of autocrine feedback inhibition of phasic activity in vasopressin neurons. Once a burst starts, somato-dendritic vasopressin and dynorphin secretion occurs with concurrent insertion of V_{1a} and κ-opioid receptors into the cell membrane. The inset illustrates the temporal profile of vasopressin and dynorphin feedback. Vasopressin inhibition reaches maximum in within the first few seconds of burst initiation and is maintained through the burst. Dynorphin inhibition progressively increases during the burst, eventually helping to terminate firing. After burst termination, vasopressin and dynorphin are cleared by diffusion and extracellular peptidases and the cycle restarts with the beginning of the next burst

vesicles and that these vesicles also express κ-opioid receptors (Shuster et al. 2000), for which dynorphin is the canonical agonist, and κ-opioid receptors are inserted into the plasma membrane along with vasopressin receptors during somato-dendritic exocytosis. Similarly to vasopressin, with which it will be co-secreted, dynorphin inhibits phasic activity in vasopressin neurons, but unlike vasopressin, dynorphin inhibition is activity dependent; i.e., it is absent at the onset of phasic bursts and increases over the course of bursts, even during osmotic stimulation (Fig. 4.3) when prodynorphin mRNA expression is upregulated (Scott et al. 2009). Hence, somato-dendritic secretion of dynorphin appears to be involved in generation of phasic activity in vasopressin neurons. While the membrane current that sustains activity during phasic bursts in vasopressin neurons is inhibited by endogenous dynorphin (Brown and Bourque 2004), similarly to vasopressin, dynorphin also acts as a retrograde modulator of synaptic transmission (Iremonger and Bains 2009), and this too might contribute to activity patterning.

Remarkably, differential somato-dendritic secretion of dynorphin might also contribute to the adoption of different activity patterns across the population of vasopressin neurons. Similarly to phasic neurons, action potential firing in vasopressin neurons displaying irregular activity is robustly excited by administration of a κ-opioid receptor antagonist, indicating that they are also under κ-opioid inhibition (Scott et al. 2009). By contrast, action potential firing in continuously active vasopressin neurons is unchanged by κ-opioid receptor antagonist administration despite being strongly inhibited by κ-opioid agonist administration (Scott et al. 2009), indicating that continuously active vasopressin neurons express functional κ-opioid receptors but do not release dynorphin. Hence, it appears that vasopressin neurons that escape autocrine dynorphin inhibition enter continuous activity.

Overall, it appears that autocrine regulation of activity patterning in vasopressin neurons regulates phasic activity under basal conditions. Intuitively, it could be hypothesized that a relaxation of autocrine inhibition is a mechanism by which vasopressin neurons increase their activity under stimulated conditions. However, this does not appear to be the case, at least for dynorphin feedback, which counter-intuitively increases during chronic osmotic stimulation by dehydration (Scott and Brown 2010). Hence, autocrine inhibition of vasopressin neurons by somato-dendritic secretion probably functions as a restraining mechanism to prevent increased activation of afferent inputs precipitating oversecretion of vasopressin into the bloodstream, providing for a graded hormonal response to graded (patho) physiological stimuli.

4.4.2 Paracrine Regulation of Preautonomic Neuron Activity by Somato-Dendritic Vasopressin Secretion

Unlike the supraoptic nucleus, which essentially comprises only magnocellular neurons (and glia), the paraventricular nucleus also contains parvocellular neurons that are involved in the regulation of hormone secretion from the anterior pituitary gland and autonomic function through projections that control activity of autonomic regulatory (preautonomic neurons) and behavior.

Preautonomic neurons modulate sympathetic and parasympathetic nerve activity to a variety of organs, including the heart, blood vessels, and kidneys to ultimately influence cardiovascular function and body fluid homeostasis, among other physiological systems. As their name implies, preautonomic neurons do not project directly to the target organs in the periphery. Rather, they project to sympathetic and parasympathetic centers in the brainstem and spinal cord, including the nucleus tractus solitarius, rostral ventrolateral medulla, and dorsal motor nucleus of the vagus in the brainstem and preganglionic sympathetic neurons in the intermediolateral cell column of the spinal cord that project outside the central nervous system to regulate autonomic function.

While there is some anatomical compartmentalization of magnocellular and parvocellular neuron cell bodies within the paraventricular nucleus, some vasopressin neuron dendrites approach the cell bodies of preautonomic neurons in the parvocellular division of the paraventricular nucleus and preautonomic neurons express vasopressin receptors (Son et al. 2013), providing a framework for somato-dendritic vasopressin secretion from magnocellular neurons to modulate autonomic function by paracrine actions within the paraventricular nucleus. Indeed, activation of individual vasopressin neurons by uncaging *N*-methyl-D-aspartate (NMDA) to activate individual vasopressin neurons increased action potential firing in neighboring preautonomic neurons retrogradely labeled from the rostral ventrolateral medulla (Son et al. 2013). The responses of preautonomic neurons to activation of magnocellular vasopressin neurons occur with a delay of several seconds, depend on intracellular calcium, and are blocked by superfusion of a vasopressin receptor antagonist. Taken together, these observations strongly suggest that the excitation is mediated by diffusion of somato-dendritic vasopressin through the extracellular space. Most remarkably, excitation of a single vasopressin neuron excites several neighboring preautonomic neurons, suggesting that this represents a population-to-population communication rather than point-to-point communication between individual neurons. Indeed, administration of a vasopressin receptor antagonist alone reduces the activity of preautonomic neurons and the effectiveness of the antagonist depends on the activity level of the vasopressin neuron population; when the vasopressin neurons are more active, the antagonist is more effective at reducing the firing rate of preautonomic neurons. Hence, it appears that preautonomic neurons are under tonic modulation by neighboring magnocellular vasopressin neurons that likely coordinates the humoral (vasopressin) neuronal (sympathetic) responses to (patho)physiological perturbations (Fig. 4.4).

Box 4.2 Retrograde Labeling of Axon Projections

This technique allows the identification of the cell bodies of the neurons with axons that terminate in the brain area of interest by injecting retrograde label (e.g., fluorescent microspheres) into the region of interest. It is important that a retrograde label is used that is only taken up at axon terminals to prevent confounding results caused by label that could be taken up by projections

(continued)

Box 4.2 (continued)
passing through the area of interest. After several days, the retrograde label can be visualized in the cell bodies of projecting neurons, which can be double labeled using immunohistochemistry to identify the phenotype of the projecting neurons. Or, as we have done (Son et al. 2013), retrograde labeling can be completed in animals that have the neuronal phenotype of interest labeled by genetic modification (e.g., enhanced green fluorescent protein, eGFP) to allow identification of retrogradely labeled neurons of a particular phenotype to be studied (e.g., by patch-clamp electrophysiology in brain slices).

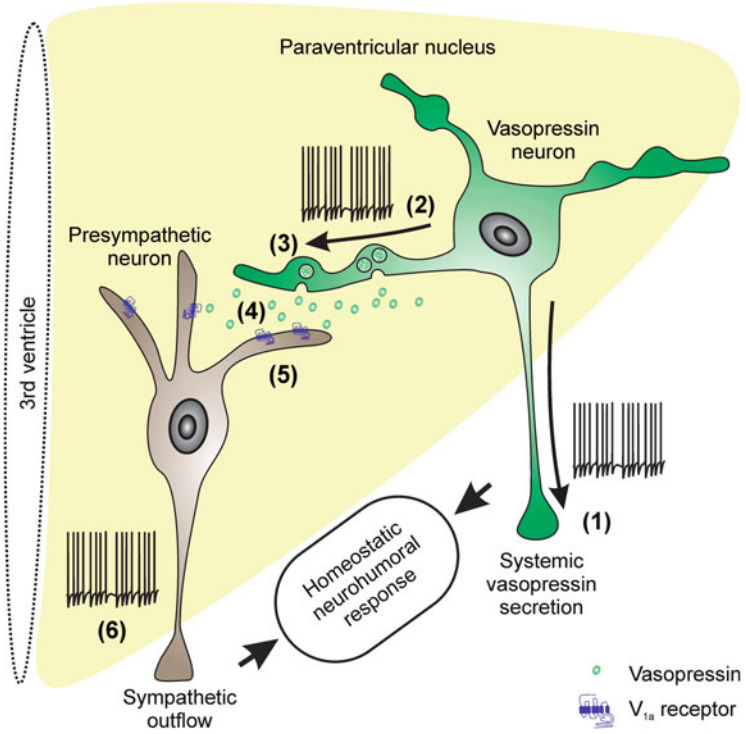

Fig. 4.4 Autonomic activation by somato-dendritic vasopressin secretion. (1) Activation of magnocellular vasopressin neurons leads to a burst of action potentials that increase vasopressin secretion into the circulation from the posterior pituitary gland. (2) Concurrently, the action potentials also back-propagate into the dendrites to (3) trigger somato-dendritic vasopressin release into the paraventricular nucleus. (4) Vasopressin passively diffuses through the extracellular space and (5) binds to V_{1a} receptors on presympathetic paraventricular nucleus neurons to cause membrane depolarization and thus increased firing, leading in turn to increased sympathetic outflow to peripheral organs. Somato-dendritic vasopressin secretion contributes to the coordination of the neurohumoral response to physiological challenges that is required to maintain homeostasis. Reproduced from Stern (2015) with permission

4.4.3 Autocrine Regulation of Oxytocin Neuron Activity

Similarly to somato-dendritic vasopressin secretion, somato-dendritic oxytocin secretion also has autocrine paracrine effects. However, in contrast to vasopressin, the paracrine effects of somato-dendritic oxytocin secretion on oxytocin neurons are mediated by endocannabinoids that are liberated after autocrine receptor activation to cause retrograde inhibition of synaptic transmission (Hirasawa et al. 2004). While endocannabinoid retrograde inhibition of synaptic transmission is triggered by somato-dendritic oxytocin secretion, the overall effect of somato-dendritic oxytocin secretion is excitation, but only under specific (patho)physiological conditions.

4.4.3.1 Burst Firing in Oxytocin Neurons

Under basal conditions, magnocellular oxytocin neurons typically fire slowly and continuously at 1–5 action potentials per second to sustain circulating concentrations of 1–3 pg per ml, with higher concentrations during sleep. However, as a hormone, oxytocin is best known for its stimulation of uterine contraction during birth and of milk ejection during suckling. Indeed, oxytocin comes from the Greek, *oxutokia*, meaning "sudden delivery." Both uterine contraction and contraction of the mammary ducts for milk ejection are episodic, with each contraction occurring several minutes apart. It is the coordinated secretion of pulses of oxytocin by the population of oxytocin neurons that generates the pattern of contractions required for normal birth and for milk delivery to the offspring, and somato-dendritic secretion plays a fundamental part in generating the pulsatile secretion pattern through its influence on oxytocin neuron activity.

Pulsatile oxytocin secretion during birth and suckling results from bursts of action potentials in oxytocin neurons (Brown 2016). Unlike phasic bursts in vasopressin neurons, bursts fired by oxytocin neurons are generally much faster (up to 100 action potentials per second), are relatively short (1–3 s), and, most remarkably, are coordinated across the population of oxytocin neurons in the bilateral supraoptic and paraventricular nuclei (Belin et al. 1984).

While oxytocin neurons do not normally fire bursts under basal conditions, they can be induced to do so in brain slices by treatment with an α_1-adrenoceptor agonist in a low calcium medium (Wang and Hatton 2005), suggesting that noradrenergic inputs might trigger bursts. Indeed, the number of noradrenergic inputs to oxytocin neurons is increased in late pregnancy and lactation and norepinephrine levels are increased in the supraoptic nucleus during birth. However, noradrenergic excitation of bursts in oxytocin neurons is likely mediated via stimulation of somato-dendritic oxytocin secretion because noradrenergic receptor stimulation is required for suckling-induced somato-dendritic oxytocin secretion, which might be part of a positive feedback loop that builds toward bursts because oxytocin increases norepinephrine levels within the supraoptic nucleus. Indeed, oxytocin levels rise within the supraoptic nucleus immediately preceding bursts in lactating rats (Moos et al. 1989) and bursts are blocked by oxytocin receptor antagonist administration, suggesting that (regardless of what the initiating event might be) somato-dendritic secretion of oxytocin is required for bursts to occur.

Bursts can also be evoked in oxytocin neurons of anaesthetized virgin rats by coordinated activation of neighboring oxytocin neurons, and this is enhanced by agents that induce priming by mobilization of intracellular calcium, including oxytocin itself (Ludwig et al. 2002). Hence, while plasticity in oxytocin neurons, their surrounding astrocytes, and their afferent inputs over the course of pregnancy favors the emergence of bursting (Augustine et al. 2018), these changes are not necessary for bursting to occur. Rather, it appears that the core component of the system necessary for bursts is somato-dendritic oxytocin secretion (Fig. 4.5). Indeed, in anaesthetized lactating rats, central oxytocin receptor antagonist administration inhibits burst firing during suckling. Nevertheless, somato-dendritic oxytocin secretion is likely not sufficient to induce bursts in oxytocin neurons because simple administration of oxytocin does not induce bursting in virgin rats.

The role of endocannabinoids in burst firing of oxytocin neurons is not known but if bursts liberate large amounts of endocannabinoids, these might contribute to burst

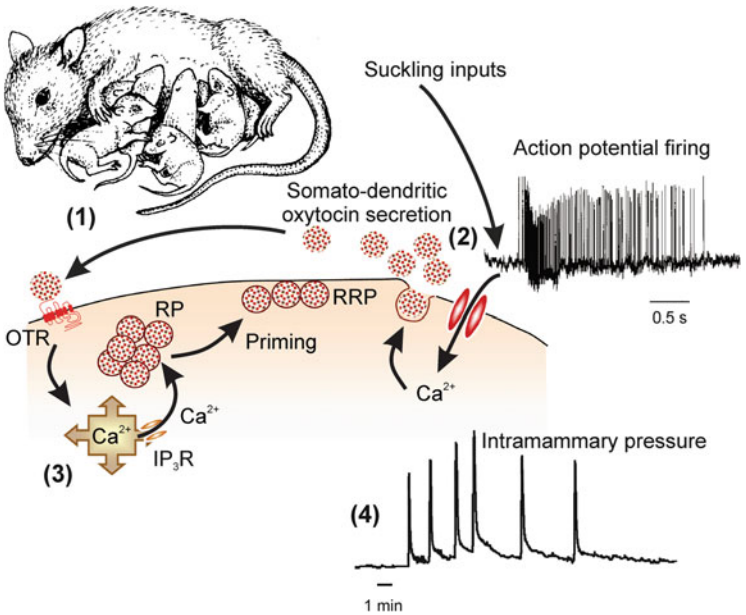

Fig. 4.5 Autocrine excitation of oxytocin neurons during suckling. Suckling during lactation (1) activates a relay of afferent inputs from the mammary glands that ultimately stimulates bursts of action potentials in oxytocin neurons as well as calcium influx (2) that triggers somato-dendritic oxytocin secretion that primes further oxytocin release by activating oxytocin receptors (OTR) to increase intracellular calcium by activating inositol triphosphate receptors (IP_3R), which mobilizes somato-dendritic dense core vesicles from the reserve pool (RP) to the readily releasable pool (RRP) near the cell surface (3). The released oxytocin might act as a paracrine signal that coordinates bursts across the population of oxytocin neurons to release large pulses that cause episodic milk let-down (4) in response to a continuous stimulus. Modified from Leng et al. (2012), with permission

termination and perhaps also the short silent period that often follows oxytocin neuron bursts.

4.4.3.2 Morphine Dependence in Oxytocin Neurons

In addition to its endocrine regulation of reproductive function, oxytocin modulates a wide range of behaviors, including addictive behaviors, and is emerging as a potential treatment for drug addiction, including opiate addiction (McGregor and Bowen 2012). Remarkably, oxytocin neurons develop dependence during chronic administration of the μ-opioid receptor agonist, morphine (Brown and Russell 2004), which is revealed by a long-lasting hyper-excitation upon removal of chronic morphine treatment.

Both norepinephrine and oxytocin levels are increased in the supraoptic nucleus during morphine withdrawal and acute antagonism of supraoptic nucleus α_1-adrenoceptors or oxytocin receptors reverses morphine-withdrawal excitation of oxytocin neurons (Brown et al. 1997), consistent with noradrenergic stimulation of somato-dendritic oxytocin secretion driving increased activity during withdrawal through autocrine (and perhaps paracrine) communication (Fig. 4.6). Oxytocin neurons are under tonic inhibition by endogenous opioid peptides during pregnancy, and this inhibition is relaxed at the end of pregnancy. However, this is likely not the trigger for birth because oxytocin neurons do not develop dependence on endogenous μ-opioid peptides (Doi et al. 2001). Furthermore, while morphine-withdrawal excitation evokes somato-dendritic oxytocin secretion as occurs during birth and suckling, it does not result in bursts of action potentials in oxytocin neurons. Rather, morphine-withdrawal excitation is a pharmacological phenomenon that precipitates a sustained increase in oxytocin neuron firing rate and of oxytocin secretion into the circulation. Hence, while somato-dendritic oxytocin secretion might be the core component of the system necessary for bursts to occur, there must be modifying elements, probably in the timing of interactions between each element in the system, as revealed by the emergence of burst firing during coordinated activation of neighboring oxytocin neurons (Ludwig et al. 2002); i.e., morphine withdrawal leads to sustained increases in somato-dendritic oxytocin secretion to underpin a sustained increase in firing rate across the population (Brown et al. 1997), whereas uterine contraction and suckling lead to fluctuations in somato-dendritic oxytocin secretion to underpin coordinated burst firing across the population.

4.4.3.3 Co-expressed Neuropeptides

Similarly to vasopressin neurons, oxytocin neurons also synthesize other neuropeptides, principally the endogenous opioid peptides, the enkephalins and dynorphin. However, it appears unlikely that these have a substantive role in orchestrating oxytocin neuron activity because administration of the broad-spectrum opioid receptor antagonist, naloxone, does not affect oxytocin neuron activity under basal conditions (Brown and Russell 2004). Rather, it appears that these co-released opioid peptides might restrain oxytocin secretion at the level of the posterior pituitary gland because opioid receptor antagonist administration increases oxytocin

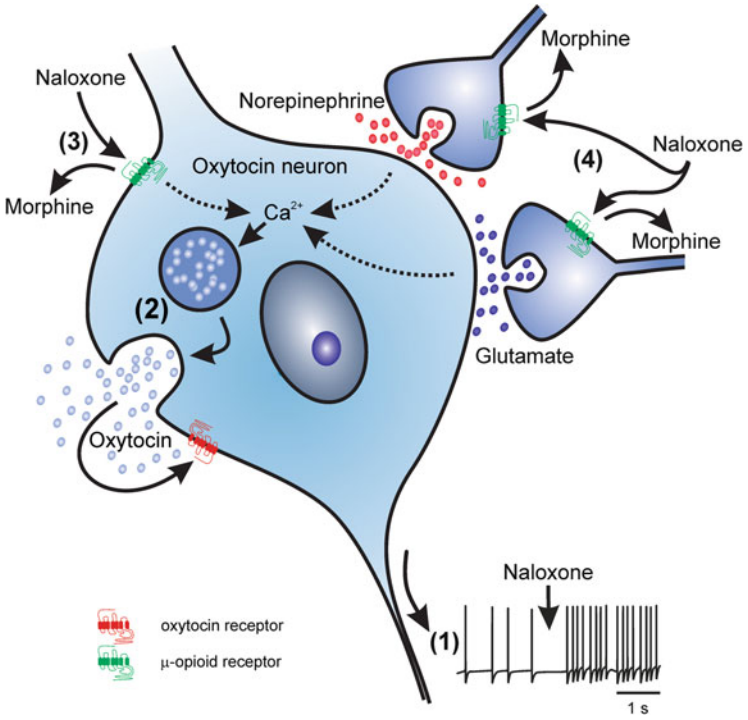

Fig. 4.6 Autocrine excitation of oxytocin neurons during morphine withdrawal. Administration of the broad-spectrum opioid receptor antagonist, naloxone, displaces morphine from chronic occupancy of μ-opioid receptors, which results in an immediate and sustained increase in oxytocin neuron firing rate (1) due, in part, to increased somato-dendritic secretion of oxytocin (2). Increased somato-dendritic oxytocin secretion during morphine withdrawal presumably results from increased intracellular calcium because excitation is prevented by administration of a calcium channel blocker (Blackburn-Munro et al. 2000). However, it is currently unknown whether calcium influx is directly triggered by naloxone antagonism of μ-opioid receptors on oxytocin neurons (3) or their principal excitatory afferent inputs, norepinephrine and glutamate, which also express μ-opioid receptors (4)

secretion under basal conditions without changing oxytocin neuron firing rate (Brown et al. 1998).

4.4.4 Paracrine Regulation of Behavior by Somato-Dendritic Oxytocin Secretion

In addition to its endocrine regulation of reproductive function, central oxytocin modulates a wide variety of behaviors (Ross and Young 2009). Some of this behavioral modulation by oxytocin is likely through axonal projections to the nucleus accumbens and central amygdala, which include axon collaterals from magnocellular oxytocin neurons (Knobloch et al. 2012). However, central oxytocin

also appears to modulate some behaviors via actions in brain areas that receive little or no axonal projections from oxytocin neurons, suggesting that these areas might respond to somato-dendritic secretion of oxytocin.

4.4.4.1 Regulation of Energy Balance by Somato-Dendritic Oxytocin

Centrally released oxytocin inhibits food intake and there is emerging evidence that oxytocin mediates the central effects of the primary anorexigenic hormone, leptin, which is secreted by adipocytes (Leng and Sabatier 2017). Leptin is sensed by pro-opiomelanocortin neurons in the arcuate nucleus of the hypothalamus that project to the supraoptic and paraventricular nuclei where they secrete *α-melanocyte stimulating hormone* (α-MSH) to activate melanocortin-3 and -4 receptors.

The effects of α-MSH on oxytocin neurons are complex; while α-MSH inhibits the activity of oxytocin neurons to reduce secretion into the circulation, it mobilizes intracellular calcium to increase somato-dendritic oxytocin secretion. The dissociation of somato-dendritic and peripheral secretion of oxytocin results from the actions of endocannabinoids, which mediate the inhibition of activity without impacting somato-dendritic oxytocin secretion (Sabatier and Leng 2006).

The effects of somato-dendritic oxytocin secretion on food intake are likely mediated by actions within the ventromedial nucleus of the hypothalamus, in addition to other brain areas where there is high expression of oxytocin receptors but essentially no oxytocin neuron axons (Leng and Sabatier 2017). Given the close proximity of the ventromedial nucleus to the supraoptic and paraventricular nuclei, it appears likely that somato-dendritic oxytocin from magnocellular neurons could diffuse through the extracellular space in sufficient quantities to activate oxytocin receptors, which have nanomolar affinity for oxytocin.

4.4.4.2 Regulation of Social Behavior by Somato-Dendritic Oxytocin

Central oxytocin impacts many behaviors, but there is little clear evidence in most cases as to whether this results from oxytocin secretion from axon terminals, or somato-dendritic secretion. There is strong evidence that the effects of oxytocin on fear conditioning are mediated via synaptic activation of central amygdala neurons by magnocellular neuron axon collaterals (Knobloch et al. 2012). While the central amygdala contains oxytocin neuron axons, the neighboring medial amygdala (which lies immediately lateral to the supraoptic nucleus) has few, if any, oxytocin neuron axons but does contain some oxytocin neuron dendrites. Oxytocin receptor antagonist injection into the medial amygdala attenuates preference for a stranger induced by activation of the supraoptic nucleus (Takayanagi et al. 2017). Hence, it appears likely that it is somato-dendritic oxytocin secretion from supraoptic nucleus neurons that enhances social recognition.

4.5 Perspectives

The autocrine effects of somato-dendritic secretion from magnocellular neurons are well established, as are the local paracrine effects on their afferent inputs. Similarly, there is strong evidence to suggest that nearby neuronal populations, specifically those in the paraventricular nucleus, ventromedial nucleus, and medial amygdala, are regulated by somato-dendritic neuropeptide secretion from magnocellular neurons. However, there is still debate as to whether vasopressin and oxytocin act as hormone-like signals on distant targets in the brain after diffusion through the extracellular space. Certainly, the neuropeptides are present in the cerebrospinal fluid (CSF), but the levels measured in various brain areas do not always parallel CSF levels (Landgraf et al. 1988). Furthermore, while vasopressin and oxytocin have half-lives of ~20 min in the CSF, extracellular peptidases likely break down the neuropeptides more rapidly in the parenchyma, and the tortuosity of the parenchyma likely limits diffusion, either from the site of release or from the ventricles (e.g., the paracrine effects of somato-dendritic vasopressin on preautonomic neurons that are only ~100–200 μm away are delayed by ~2–5 s). A further confounding factor is that many of the distant brain areas on which the neuropeptides act (such as the nucleus accumbens and nucleus tractus solitarius) receive afferent projections from magnocellular neuron axon collaterals or paraventricular nucleus parvocellular neurons. Nevertheless, the possibility remains that there is long-distance hormone-like signaling by vasopressin and oxytocin in the brain over a much longer timescale, particularly in brain regions in which there are neuropeptide receptors but no neuropeptide axons, such as the olfactory bulb. In addition, somato-dendritic secretion of vasopressin and oxytocin could modulate excitability of the same target neurons to which they (or parvocellular neurons) send axonal projections to modulate excitability on a population level on which the short-term point-to-point modulation achieved by synaptic transmission is superimposed. Resolving this long-standing debate remains an ongoing challenge for the field.

Key References: See Main List for Reference Details

Knobloch et al. (2012) Demonstration of axon collaterals from magnocellular neurons that project to the central amygdala and nucleus accumbens; oxytocin (and glutamate) release from the collaterals in the central amygdala were shown to modulate fear conditioning and the collaterals to the nucleus accumbens presumably modulate the brain reward pathway.

Ludwig and Leng (1997) First demonstration of somato-dendritic secretion of vasopressin inhibiting action potential firing in magnocellular neurons. Intasupraoptic nucleus administration of a V_1-receptor antagonist increased the firing rate of phasic vasopressin neurons, showing that endogenous vasopressin is autoinhibitory.

Pow and Morris (1989) First demonstration somato-dendritic exocytosis of dense core vesicles from magnocellular neurons.

Son et al. (2013) First unequivocal demonstration that somato-dendritic neuropeptide secretion from magnocellular neurons have direct paracrine effects to modulate action potential firing of neighboring non-magnocellular neurons.

Takayanagi et al. (2017) First direct evidence showing oxytocin release from magnocellular neuron dendrites (some of which were shown to course near/into the medial amygdala) affects neuronal populations outside the supraoptic and paraventricular nuclei.

References

Augustine RA, Seymour AJ, Campbell RE, Grattan DR, Brown CH (2018) Integrative neurohumoral regulation of oxytocin neuron activity in pregnancy and lactation. J Neuroendocrinol 30:e12569. https://doi.org/10.1111/jne.12569

Bains JS, Ferguson AV (1999) Activation of N-methyl-D-aspartate receptors evokes calcium spikes in the dendrites of rat hypothalamic paraventricular nucleus neurons. Neuroscience 90:885–891

Belin V, Moos F, Richard P (1984) Synchronization of oxytocin cells in the hypothalamic paraventricular and supraoptic nuclei in suckled rats: direct proof with paired extracellular recordings. Exp Brain Res 57:201–203

Blackburn-Munro G, Brown CH, Neumann ID, Landgraf R, Russell JA (2000) Verapamil prevents withdrawal excitation of oxytocin neurones in morphine-dependent rats. Neuropharmacology 39:1596–1607

Brown CH (2016) Magnocellular neurons and posterior pituitary function. Compr Physiol 6:1701–1741

Brown CH, Bourque CW (2004) Autocrine feedback inhibition of plateau potentials terminates phasic bursts in magnocellular neurosecretory cells of the rat supraoptic nucleus. J Physiol 557:949–960

Brown CH, Russell JA (2004) Cellular mechanisms underlying neuronal excitability during morphine withdrawal in physical dependence: lessons from the magnocellular oxytocin system. Stress 7:97–107

Brown CH, Munro G, Johnstone LE, Robson AC, Landgraf R, Russell JA (1997) Oxytocin neurone autoexcitation during morphine withdrawal in anaesthetized rats. Neuroreport 8:951–955

Brown CH, Murphy NP, Munro G, Ludwig M, Bull PM, Leng G, Russell JA (1998) Interruption of central noradrenergic pathways and morphine withdrawal excitation of oxytocin neurones in the rat. J Physiol 507:831–842

Brown CH, Scott V, Ludwig M, Leng G, Bourque CW (2007) Somatodendritic dynorphin release: orchestrating activity patterns of vasopressin neurons. Biochem Soc Trans 35:1236–1242

Brown CH, Ruan M, Scott V, Tobin VA, Ludwig M (2008) Multi-factorial somato-dendritic regulation of phasic spike discharge in vasopressin neurons. Prog Brain Res 170:219–228

Brown CH, Bains JS, Ludwig M, Stern JE (2013) Physiological regulation of magnocellular neurosecretory cell activity: integration of intrinsic, local and afferent mechanisms. J Neuroendocrinol 25:678–710

Dayanithi G, Sabatier N, Widmer H (2000) Intracellular calcium signalling in magnocellular neurones of the rat supraoptic nucleus: understanding the autoregulatory mechanisms. Exp Physiol 85(Spec No):75S

Dayanithi G, Forostyak O, Ueta Y, Verkhratsky A, Toescu EC (2012) Segregation of calcium signalling mechanisms in magnocellular neurones and terminals. Cell Calcium 51:293–299

de Kock CP, Wierda KD, Bosman LW, Min R, Koksma JJ, Mansvelder HD, Verhage M, Brussaard AB (2003) Somatodendritic secretion in oxytocin neurons is upregulated during the female reproductive cycle. J Neurosci 23:2726–2734

de Kock CP, Burnashev N, Lodder JC, Mansvelder HD, Brussaard AB (2004) NMDA receptors induce somatodendritic secretion in hypothalamic neurones of lactating female rats. J Physiol 561:53–64

Doi N, Brown CH, Cohen HD, Leng G, Russell JA (2001) Effects of the endogenous opioid peptide, endomorphin 1, on supraoptic nucleus oxytocin and vasopressin neurones *in vivo* and *in vitro*. Br J Pharmacol 132:1136–1144

Gouzenes L, Desarmenien MG, Hussy N, Richard P, Moos FC (1998) Vasopressin regularizes the phasic firing pattern of rat hypothalamic magnocellular vasopressin neurons. J Neurosci 18:1879–1885

Hermes ML, Ruijter JM, Klop A, Buijs RM, Renaud LP (2000) Vasopressin increases GABAergic inhibition of rat hypothalamic paraventricular nucleus neurons *in vitro*. J Neurophysiol 83:705–711

Hirasawa M, Schwab Y, Natah S, Hillard CJ, Mackie K, Sharkey KA, Pittman QJ (2004) Dendritically released transmitters cooperate via autocrine and retrograde actions to inhibit afferent excitation in rat brain. J Physiol 559:611–624

Hurbin A, Orcel H, Alonso G, Moos F, Rabie A (2002) The vasopressin receptors colocalize with vasopressin in the magnocellular neurons of the rat supraoptic nucleus and are modulated by water balance. Endocrinology 143:456–466

Iremonger KJ, Bains JS (2009) Retrograde opioid signaling regulates glutamatergic transmission in the hypothalamus. J Neurosci 29:7349–7358

Knobloch HS, Charlet A, Hoffmann LC, Eliava M, Khrulev S, Cetin AH, Osten P, Schwarz MK, Seeburg PH, Stoop R, Grinevich V (2012) Evoked axonal oxytocin release in the central amygdala attenuates fear response. Neuron 73:553–566

Kombian SB, Mouginot D, Hirasawa M, Pittman QJ (2000) Vasopressin preferentially depresses excitatory over inhibitory synaptic transmission in the rat supraoptic nucleus *in vitro*. J Neuroendocrinol 12:361–367

Landgraf R, Neumann I, Schwarzberg H (1988) Central and peripheral release of vasopressin and oxytocin in the conscious rat after osmotic stimulation. Brain Res 457:219

Landry M, Vila-Porcile E, Hokfelt T, Calas A (2003) Differential routing of coexisting neuropeptides in vasopressin neurons. Eur J Neurosci 17:579–589

Leng G, Sabatier N (2017) Oxytocin—the sweet hormone? Trends Endocrinol Metab 28:365–376

Leng G, Ludwig M, Douglas AJ (2012) Neural control of the posterior pituitary gland (neurohypophysis). In: Fink G, Pfaff DW, Levine JE (eds) Handbook of Neuroendocrinology. Academic, London

Ludwig M, Leng G (1997) Autoinhibition of supraoptic nucleus vasopressin neurons *in vivo*: a combined retrodialysis/electrophysiological study in rats. Eur J Neurosci 9:2532–2540

Ludwig M, Leng G (2006) Dendritic peptide release and peptide-dependent behaviours. Nat Rev Neurosci 7:126–136

Ludwig M, Callahan MF, Neumann I, Landgraf R, Morris M (1994) Systemic osmotic stimulation increases vasopressin and oxytocin release within the supraoptic nucleus. J Neuroendocrinol 6:369–373

Ludwig M, Sabatier N, Bull PM, Landgraf R, Dayanithi G, Leng G (2002) Intracellular calcium stores regulate activity-dependent neuropeptide release from dendrites. Nature 418:85–89

Ludwig M, Bull PM, Tobin VA, Sabatier N, Landgraf R, Dayanithi G, Leng G (2005) Regulation of activity-dependent dendritic vasopressin release from rat supraoptic neurones. J Physiol 564:515–522

Ludwig M, Apps D, Menzies J, Patel JC, Rice ME (2017) Dendritic release of neurotransmitters. Compr Physiol 7:235–252

Mcgregor IS, Bowen MT (2012) Breaking the loop: oxytocin as a potential treatment for drug addiction. Horm Behav 61:331–339

Moos F, Poulain DA, Rodriguez F, Guerne Y, Vincent JD, Richard P (1989) Release of oxytocin within the supraoptic nucleus during the milk ejection reflex in rats. Exp Brain Res 76:593–602
Morris JF, Pow DV (1991) Widespread release of peptides in the central nervous system: quantitation of tannic acid-captured exocytoses. Anat Rec 231:437–445
Pow DV, Morris JF (1989) Dendrites of hypothalamic magnocellular neurons release neurohypophysial peptides by exocytosis. Neuroscience 32:435–439
Ross HE, Young LJ (2009) Oxytocin and the neural mechanisms regulating social cognition and affiliative behavior. Front Neuroendocrinol 30:534–547
Sabatier N, Leng G (2006) Presynaptic actions of endocannabinoids mediate alpha-MSH-induced inhibition of oxytocin cells. Am J Physiol Regul Integr Comp Physiol 290:R577–R584
Sabatier N, Caquineau C, Dayanithi G, Bull P, Douglas AJ, Guan XM, Jiang M, Van der Ploeg L, Leng G (2003) Alpha-melanocyte-stimulating hormone stimulates oxytocin release from the dendrites of hypothalamic neurons while inhibiting oxytocin release from their terminals in the neurohypophysis. J Neurosci 23:10351–10358
Scott V, Brown CH (2010) State-dependent plasticity in vasopressin neurones: dehydration-induced changes in activity patterning. J Neuroendocrinol 22:343–354
Scott V, Bishop VR, Leng G, Brown CH (2009) Dehydration-induced modulation of kappa-opioid inhibition of vasopressin neurone activity. J Physiol 587:5679–5689
Shuster SJ, Riedl M, Li X, Vulchanova L, Elde R (2000) The kappa opioid receptor and dynorphin co-localize in vasopressin magnocellular neurosecretory neurons in guinea-pig hypothalamus. Neuroscience 96:373–383
Son SJ, Filosa JA, Potapenko ES, Biancardi VC, Zheng H, Patel KP, Tobin VA, Ludwig M, Stern JE (2013) Dendritic peptide release mediates interpopulation crosstalk between neurosecretory and preautonomic networks. Neuron 78:1036–1049
Stern JE (2015) Neuroendocrine-autonomic integration in the paraventricular nucleus: novel roles for dendritically released neuropeptides. J Neuroendocrinol 27:487–497
Sykova E (2004) Extrasynaptic volume transmission and diffusion parameters of the extracellular space. Neuroscience 129:861–876
Takayanagi Y, Yoshida M, Takashima A, Takanami K, Yoshida S, Nishimori K, Nishijima I, Sakamoto H, Yamagata T, Onaka T (2017) Activation of supraoptic oxytocin neurons by secretin facilitates social recognition. Biol Psychiatry 81:243–251
Tobin VA, Ludwig M (2007) The role of the actin cytoskeleton in oxytocin and vasopressin release from rat supraoptic nucleus neurons. J Physiol 582:1337–1348
Tobin VA, Hurst G, Norrie L, Dal Rio FP, Bull PM, Ludwig M (2004) Thapsigargin-induced mobilization of dendritic dense-cored vesicles in rat supraoptic neurons. Eur J Neurosci 19:2909–2912
Tobin VA, Douglas AJ, Leng G, Ludwig M (2011) The involvement of voltage-operated calcium channels in somato-dendritic oxytocin release. PLoS One 6:e25366
Tobin V, Schwab Y, Lelos N, Onaka T, Pittman QJ, Ludwig M (2012) Expression of exocytosis proteins in rat supraoptic nucleus neurones. J Neuroendocrinol 24:629–641
Wang YF, Hatton GI (2005) Burst firing of oxytocin neurons in male rat hypothalamic slices. Brain Res 1032:36–43

Further Recommended Reading

Somato-Dendritic Secretion

Dendritic Neurotransmitter Release (2004) ed. Ludwig, M. pp xvi + 334, Springer, New York. ISBN 10: 0387229337 ISBN 13: 9780387229331
Ludwig M, Apps D, Menzies J, Patel JC, Rice ME (2016) Dendritic release of neurotransmitters. Compr Physiol 7:235–252

Phasic Activity Patterning in Vasopressin Neurons

Brown CH, Bourque CW (2006) Mechanisms of rhythmogenesis: insights from hypothalamic vasopressin neurons. Trends Neurosci 29:108–115

Morphine Dependence in Oxytocin Neurons

Brown CH, Russell JA (2004) Cellular mechanisms underlying neuronal excitability during morphine withdrawal in physical dependence: lessons from the magnocellular oxytocin system. Stress 7:97–107

Inter-Population Signaling

Stern JE (2015) Neuroendocrine-autonomic integration in the paraventricular nucleus: novel roles for dendritically released neuropeptides. J Neuroendocrinol 27:487–497

Reproductive Regulation of Oxytocin Neuron Activity

Augustine RA, Seymour AJ, Campbell RE, Grattan DR, Brown CH (2018) Integrative neuro-humoral regulation of oxytocin neuron activity in pregnancy and lactation. J Neuroendocrinol 30:e12569. https://doi.org/10.1111/jne.12569

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Leng G, Sabatier N (2017) Oxytocin—the sweet hormone? Trends Endocrinol Metab 28:365–376

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Ross HE, Young LJ (2009) Oxytocin and the neural mechanisms regulating social cognition and affiliative behavior. Front Neuroendocrinol 30:534–547

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