



Published in final edited form as:

J Neuroendocrinol. 2020 June ; 32(6): e12856. doi:10.1111/jne.12856.

Somato-dendritic vasopressin and oxytocin secretion in endocrine and autonomic regulation

Colin H. Brown¹, Mike Ludwig^{2,3}, Jeffrey G. Tasker⁴, Javier E. Stern⁵

¹Department of Physiology, Brain Health Research Centre, Centre for Neuroendocrinology, University of Otago, Dunedin, New Zealand

²Centre for Discovery Brain Sciences, University of Edinburgh, Edinburgh, UK

³Department of Immunology, Centre for Neuroendocrinology, University of Pretoria, Pretoria, South Africa

⁴Department of Cell and Molecular Biology, Brain Institute, Tulane University, New Orleans, LA, USA

⁵Neuroscience Institute, Georgia State University, Atlanta, GA, USA

Abstract

Somato-dendritic secretion was first demonstrated over 30 years ago. However, although its existence has become widely accepted, the function of somato-dendritic secretion is still not completely understood. Hypothalamic magnocellular neurosecretory cells were among the first neuronal phenotypes in which somato-dendritic secretion was demonstrated and are among the neurones for which the functions of somato-dendritic secretion are best characterised. These neurones secrete the neuropeptides, vasopressin and oxytocin, in an orthograde manner from their axons in the posterior pituitary gland into the blood circulation to regulate body fluid balance and reproductive physiology. Retrograde somato-dendritic secretion of vasopressin and oxytocin modulates the activity of the neurones from which they are secreted, as well as the activity of neighbouring populations of neurones, to provide intra- and inter-population signals that coordinate the endocrine and autonomic responses for the control of peripheral physiology. Somato-dendritic vasopressin and oxytocin have also been proposed to act as hormone-like signals in the brain. There is some evidence that somato-dendritic secretion from magnocellular neurosecretory cells modulates the activity of neurones beyond their local environment where there are no vasopressin- or oxytocin-containing axons but, to date, there is no conclusive evidence for, or against, hormone-like signalling throughout the brain, although it is difficult to imagine that the levels of vasopressin found throughout the brain could be underpinned by release from relatively sparse axon terminal fields. The generation of data to resolve this issue remains a priority for the field.

Keywords

oxytocin; paraventricular nucleus; somato-dendritic secretion; supraoptic nucleus; vasopressin

1 | INFORMATION TRANSFER IN THE CENTRAL NERVOUS SYSTEM

The classical understanding of communication in the nervous system is of synaptic transmission in a unidirectional manner within networks from presynaptic neurones to postsynaptic neurones. However, it has become clear that information transfer in the central nervous system is more complex than simple point-to-point, unidirectional transmission between neurones at synapses. Among the additional mechanisms that contribute to information transfer in the nervous system is somato-dendritic secretion. Unlike classical synaptic transmission by neurotransmitters such as glutamate and GABA, which signal between pre- and postsynaptic neurones with spatial precision and high temporal resolution, somato-dendritic secretion causes longer-term changes that alter the overall excitability of neurones by modulating the strength of synaptic inputs and/or by modulating the baseline membrane potential. These effects can be autocrine or paracrine, on the neurone from which somato-dendritic secretion occurs or on nearby neurones, and might spread over relatively long distances to modulate the activity of neurones in brain areas distant from the site of secretion.

Somato-dendritic secretion occurs in many types of neurone and can involve many types of transmitter molecule.¹ Magnocellular neurosecretory cells (MNCs) of the hypothalamic supraoptic nucleus (SON) and paraventricular nucleus (PVN) are among those for which the mechanisms and consequences of somato-dendritic secretion are best characterised. This review focusses on studies from the authors' laboratories, some of which were presented at the 22nd International Symposium on Regulatory Peptides, which have contributed to our understanding of how somato-dendritic secretion from MNCs contributes to endocrine and autonomic regulation of peripheral physiology in health and disease.

2 | THE MAGNOCELLULAR NEUROSECRETORY SYSTEM

The magnocellular neurosecretory system comprises MNCs that predominantly secrete either vasopressin (antidiuretic hormone, ADH) or oxytocin into the general circulation from the posterior pituitary gland (neurohypophysis). The principal function of vasopressin is to maintain body fluid balance and blood pressure by activation of renal V₂-receptors to increase water reabsorption from the urine and, when blood pressure/volume is decreased, by activation of vascular V_{1a}-receptors (V_{1a}Rs) to cause vasoconstriction.² The best-characterised physiological functions of oxytocin are to trigger uterine contractions during birth and milk ejection during lactation.² However, oxytocin also contributes to body fluid balance by promoting natriuresis in the kidney³ and by stimulating atrial natriuretic peptide secretion.⁴

The human hypothalamus contains over 100 000 MNCs,⁵ with approximately 10 000 in the rat, that are principally located in the SON and PVN, as well as in several accessory nuclei.⁶ MNCs each project a single axon to the posterior pituitary gland (Figure 1) and each axon branches extensively to form several thousand neurosecretory axon swellings and terminals⁷ that are each tightly packed with dense-core vesicles containing approximately 85 000 molecules of vasopressin or oxytocin in rats.⁸ Hormone secretion is triggered by action potential invasion of the neurosecretory swellings and terminals. It has been estimated

that each MNC contains approximately 10 million dense-core vesicles and secretes between 100 and 10 000 dense-core vesicles from the posterior pituitary gland every minute to maintain basal hormone concentrations in the circulation.⁹ Hence, the sustained output of the hormones, and the consequent regulation of peripheral physiology, depends on the average action potential discharge from the population.^{2,10}

MNCs also synthesise lesser amounts of other neurotransmitters and neuromodulators that can be contained in the same dense-core vesicles as vasopressin or oxytocin,¹¹ as well as glutamate-containing microvesicles.¹² To date, the only evidence of effects of these other neurotransmitters and neuromodulators on peripheral physiology is for secretin, which increases renal antidiuresis.¹³ Rather, their principal function appears to be modulation of hormone secretion at the level of the posterior pituitary gland, which has been comprehensively reviewed elsewhere,¹⁴ and at the level of the somata and dendrites, as we describe in the present review.

Some MNCs project axon collaterals to other brain areas. Originally, these were assumed to remain proximal to the SON¹⁵ and PVN,¹⁶ projecting to local interneurons as part of a proposed local feedback loop. More recently, it was shown that some MNC axon collaterals project more broadly throughout the brain, with oxytocin MNCs projecting to the medial amygdala (MeA), central amygdala (CeA), nucleus accumbens¹⁷ and the lateral septum,¹⁸ and vasopressin MNCs to the medial and lateral preoptic area, supra-chiasmatic nucleus, lateral habenula, CeA, MeA,^{19,20} locus coeruleus²¹ and arcuate nucleus (ARC).²² These axon collaterals have been implicated in the modulation of different behaviours, although it remains to be established how secretion from axon collaterals to modulate behaviour relates to secretion from the posterior pituitary gland to modulate peripheral physiology.

MNCs possess one to three thick, varicose, aspiny dendrites of a few hundred micrometres in length. MNCs of the SON extend their dendrites to the ventral surface of the nucleus, where the dendrites bundle together within the ventral glial lamina (a layer of astrocytes on the ventral surface of the brain within the SON)²³ and MNCs of the PVN extend their dendrites towards the subependymal region of the third ventricle.²⁴ In addition to being the site of afferent synaptic input, MNC dendrites are active players in shaping MNC activity through exocytosis of vasopressin and oxytocin (as well as other neurotransmitters/neuromodulators) into the extracellular space of the SON and PVN.

3 | SOMATO-DENDRITIC SECRETION FROM MAGNOCELLULAR NEUROSECRETORY CELLS

The somata and dendrites of MNCs are tightly packed with dense-core vesicles containing either vasopressin or oxytocin (Figure 2), which undergo exocytosis to secrete their major neuropeptides^{25,26} along with lesser amounts of other co-packaged neurotransmitters and neuromodulators.¹¹ Tannic acid capture of somato-dendritic secretion reveals that the entire vesicle content is released from MNCs.²⁵

Unlike synaptic transmission by classical neurotransmitters, dense-core vesicle exocytosis from the somata and dendrites of MNCs requires a sustained increase in intracellular

calcium^{27,28} and calcium buffering limits increases in cytoplasmic calcium to restrain the activation of somato-dendritic secretion from MNCs.²⁹ MNCs express different arrays of voltage-gated calcium channels in their somata and axon terminals.³⁰ Relative to other voltage-gated calcium channels, N-type calcium channels ($Ca_v2.2$) carry a comparatively small current in MNC somata, although they nevertheless contribute most significantly to somato-dendritic oxytocin secretion.³¹ Although the primary trigger for somato-dendritic secretion is the influx of extracellular calcium, intracellular calcium release also contributes to somato-dendritic secretion from MNCs.^{27,28}

Action potential invasion triggers exocytosis from axon terminals and MNC dendrites and appears to support depolarisation-induced calcium spikes.³² Capacitance measurements from isolated MNCs suggest that single action potentials trigger somato-dendritic secretion.³³ However, functional studies suggest that sustained intracellular calcium release is required to trigger somato-dendritic secretion.^{27,28} Furthermore, if every action potential fired by each MNC triggered somato-dendritic secretion of a single dense-core vesicle, the brain would be awash with vasopressin and oxytocin.³⁴ Exocytosis of approximately 6000 dense-core vesicles per second has been calculated to be sufficient to maintain the concentrations of vasopressin and oxytocin measured in the rat hypothalamus.³⁴ There are approximately 10 000 MNCs in the rat hypothalamus.⁶ Although approximately 25% of MNCs are silent under basal conditions, active MNCs display a mean firing rate of approximately 5 Hz under basal conditions.³⁵ Hence, up to 37 500 action potentials are fired by MNCs every second, which is almost 10-fold more than the number of dense-core vesicles secreted. Hence, trains of action potentials that cause a more sustained depolarisation and calcium influx are probably required to trigger somato-dendritic secretion from MNCs. Indeed, under basal conditions, some stimuli reduce the oxytocin MNC action potential firing rate but increase somato-dendritic oxytocin secretion,^{36,37} and it was shown recently that action potential firing alone at physiological firing rates is insufficient to trigger measurable somato-dendritic secretion from individual vasopressin MNCs.³⁸

In addition to permeation through voltage-gated calcium channels, calcium influx also occurs through NMDA receptors (NMDARs), and synaptic NMDA receptors would be expected to further increase cytoplasmic calcium concentrations during action potential firing. Furthermore, MNCs express extrasynaptic NMDARs.^{39–41} Although these extrasynaptic NMDARs are activated by basal glutamate levels *in vitro*,³⁹ they are not activated under basal conditions *in vivo* but they are activated under stimulated conditions³⁵ and trigger somato-dendritic peptide secretion.³⁸

In addition to triggering somato-dendritic secretion, increased cytoplasmic calcium also promotes movement of dense-core vesicles from the reserve pool toward the cell surface,⁴² where they are ready for secretion in response to subsequent stimuli that raise cytoplasmic calcium. In parallel, increased intracellular calcium also promotes the recruitment of N-type calcium channels³¹ to make the system more sensitive to subsequent cytoplasmic calcium increases. Hence, this ‘priming’ increases somato-dendritic secretion triggered by subsequent signals that increase cytoplasmic calcium.

Action potential-mediated depolarisation is not the only trigger for somato-dendritic secretion from MNCs. Vasopressin and oxytocin MNCs express their respective receptors^{43,44} and activation of these receptors increases cytoplasmic calcium concentrations⁴⁵ to trigger somato-dendritic secretion.^{27,28} Although vasopressin and oxytocin trigger somato-dendritic secretion from vasopressin and oxytocin MNCs without a prior stimulus to prime the system, once the MNCs are primed, the peptides can trigger a much greater somato-dendritic secretion.^{27,28}

There is an elaborate network of actin and microtubules in MNC somata and dendrites.^{46,47} Cortical F-actin regulates somato-dendritic exocytosis; F-actin polymerisation inhibits and F-actin depolymerisation increases somato-dendritic secretion from MNCs.⁴⁸ Presumably, F-actin depolymerisation increases access to the plasma membrane and this process might account for the requirement for a sustained increase in intracellular calcium to trigger somato-dendritic secretion because calcium causes F-actin depolymerisation. Unlike synaptic transmission, there does not appear to be any specific structure on the soma or dendrites that is specialised for somato-dendritic secretion,⁴⁹ although it remains to be determined whether there are regions of the cortical F-actin network that are more readily depolymerised to allow dense-core vesicles preferential access to the plasma membrane at specific sites for secretion.

Exocytosis can occur once the dense-core vesicles reach the plasma membrane, which requires exocytotic machinery. The involvement of the soluble N-ethylmaleimide-sensitive factor attachment receptor (SNARE) complex in exocytosis from axon terminals is well established.⁵⁰ Although less well characterised, it appears that somato-dendritic secretion is also mediated by SNARE proteins. MNCs express SNARE proteins⁵¹; however, although vesicle-associated membrane protein-2 (VAMP-2) and synaptosomal-associated protein 25 (SNAP-25) are both expressed in the axon terminals,^{52,53} they are not expressed in the somata or dendrites of MNCs.⁵⁴ Hence, the suite of SNARE complex proteins for somato-dendritic exocytosis probably differs from that for axon terminal secretion from MNCs.

4 | STIMULATION OF SOMATO-DENDRITIC SECRETION BY NEUROTRANSMITTERS, PEPTIDES AND HORMONES

Noradrenergic afferents from the ventrolateral medulla (VLM) A1 cell group and the nucleus of the tractus solitarius (NTS) A2 cell group make prominent projections to MNCs.² NTS noradrenergic afferents are activated during birth and lactation⁵⁵ as part of the Ferguson reflex,⁵⁶ and noradrenaline facilitates somato-dendritic oxytocin secretion in late pregnancy and lactation.⁵⁷⁻⁵⁹ Oxytocin also increases noradrenaline secretion within the SON,⁶⁰ which presumably establishes a local positive-feedback loop that reinforces oxytocin MNC excitation and promotes oxytocin secretion into the circulation to trigger uterine contractions during birth and milk ejection during lactation (Figure 3).

Pro-opiomelanocortin (POMC) afferents from the ARC project to the SON and PVN, particularly to regions of the SON and PVN that are enriched in oxytocin MNCs.⁶¹ POMC neurones secrete α -melanocyte stimulating hormone (α -MSH), which acts on melanocortin-4 (MC4-R) receptors in the SON and PVN.⁶² Although α -MSH inhibits

oxytocin secretion into the circulation, it increases somato-dendritic oxytocin secretion.^{37,63} MC4-R activation increases intracellular calcium in oxytocin MNCs to trigger somato-dendritic oxytocin secretion, as well as endocannabinoid secretion, which inhibits the activity of the MNCs to reduce axonal oxytocin secretion into the blood.^{37,63} Remarkably, α -MSH inhibition of oxytocin MNC activity is lost in mid-pregnancy,⁶² although it has yet to be determined whether this represents a switch from pre-pregnancy inhibition to stimulation during lactation, as is seen for the effects of prolactin on oxytocin MNCs.⁶⁴ Furthermore, it is not known whether α -MSH effects on somato-dendritic oxytocin secretion change in pregnancy and lactation.

In addition to neurotransmitters, other hormones can also trigger somato-dendritic secretion from MNCs. The orexigenic hormone ghrelin is synthesised by oxyntic cells in the gastric mucosa, although not in the brain.⁶⁵ Central ghrelin administration increases vasopressin secretion into the circulation via activation of neuropeptide Y neurones.⁶⁶ In addition, ghrelin stimulates somato-dendritic vasopressin secretion, which increases ATP release from astrocytes to increase presynaptic GABA release onto the vasopressin MNCs⁶⁷ (Figure 4).

5 | AUTOCRINE/PARACRINE MODULATION OF VASOPRESSIN MAGNOCELLULAR NEUROSECRETORY CELL ACTIVITY

The effects of vasopressin, oxytocin and other neurotransmitters and neuromodulators secreted from the somata and dendrites of MNCs can be broadly categorised as autocrine, regulating the activity of the MNC from which secretion occurs, and paracrine, regulating the activity of neighbouring neurones, including other neuronal populations.

V_{1a}R and V_{1b} receptors (V_{1b}R) are expressed in the membranes of vasopressin-containing dense-core vesicles⁶⁸ and are presumably inserted into the plasma membrane during somato-dendritic vasopressin secretion. Hence, vasopressin receptors newly trafficked to the plasma membrane will be exposed to high concentrations of vasopressin to underpin activity-dependent autocrine feedback regulation of vasopressin MNC activity.

Vasopressin MNCs express a range of activity patterns under basal conditions; some are silent throughout recordings, some display irregular activity, some are continuously active (typically at approximately 6 spikes s⁻¹) and some display rhythmic ‘phasic’ firing.⁶⁹ Phasic firing is characterised by bursts of activity that last more than 15 seconds, after which bursts stop randomly.⁷⁰ Each burst is followed by inactivity for at least 10 seconds, after which the next burst starts randomly.⁷⁰ At burst onset, vasopressin MNCs can reach firing rates of approximately 15–25 spikes s⁻¹ for the first 5–10 seconds, before spike frequency adaptation occurs to a steady-state firing rate of approximately 6 spikes s⁻¹ for the remainder of the burst.^{71,72}

Of the different activity patterns recorded in vasopressin MNCs, phasic bursting is the most efficient pattern for vasopressin secretion into the circulation because vasopressin secretion is maximal at approximately 13 spikes s⁻¹,^{73,74} which is typically only achieved by phasically firing MNCs and only during the first 5–10 seconds of each phasic burst. Vasopressin secretion from the posterior pituitary gland rapidly fatigues during continuous

stimulation, although this fatigue is reversed when stimulation is stopped for a few tens of seconds.⁷⁵ Hence, vasopressin MNCs firing continuously at high frequency do not secrete as much vasopressin into the circulation as do phasic MNCs firing at the same frequency because the silent periods between bursts in phasic MNCs reset the system for efficient vasopressin secretion at the onset of the next burst, when the typical firing frequency is again in the range that is most efficient for vasopressin secretion. The importance of phasic activity for efficient vasopressin secretion into the circulation is highlighted by the changes in activity patterning that occur under chronically stimulated conditions, such as prolonged osmotic stimulation. Although burst duration does increase during shorter periods of stimulation, prolonged osmotic stimulation leads to an increase in firing rate within bursts, whereas the burst duration and inter-burst interval remain similar to those seen under basal conditions.^{76–79}

V1aR antagonists consistently increase the activity of phasic MNCs when administered into the SON,⁸⁰ suggesting that somato-dendritic vasopressin mediates feedback inhibition of vasopressin MNCs via V1aR activation (Figure 5). This feedback inhibition probably involves direct autocrine actions on the MNC that secretes vasopressin because V1aR activation reduces excitatory postsynaptic potential amplitude in vasopressin MNCs.⁸¹ However, autocrine activation of V1aRs does not mediate autoregulation of vasopressin MNC activity alone because vasopressin also increases inhibitory postsynaptic potential frequency⁸² via stimulation of astrocytic ATP release, which acts as a gliotransmitter at P2X receptors on presynaptic GABA neurones to increase GABA release.⁶⁷ Hence, somato-dendritic vasopressin secretion appears to contribute to the generation of phasic activity in vasopressin MNCs via a combination of autocrine actions on the MNC from which secretion occurs and paracrine actions on nearby cells that modulate the activity of the MNC from which secretion occurs.

Although V1aR activation mediates autocrine and paracrine inhibition of phasic activity, local application of exogenous vasopressin was first reported to inhibit highly active phasic MNCs and stimulate weakly active phasic MNCs.⁸³ Vasopressin MNCs also express V1bR⁶⁸ and, although it has yet to be determined whether V1bR activation also contributes to autocrine regulation of vasopressin MNCs, it might underpin the excitatory effects of vasopressin evident in weakly active vasopressin MNCs. Regardless of the vasopressin excitation of weakly active phasic MNCs (perhaps via V1bR), such an action of endogenous vasopressin would presumably increase peripheral vasopressin secretion to cause robust vasoconstriction that is not present under basal conditions.⁸⁴ Hence, it appears that any contribution of somato-dendritic vasopressin secretion to peripheral vasopressin secretion by feedback excitation is probably overridden by the V1aR-mediated feedback inhibition.

Although somato-dendritic vasopressin secretion functions as a negative-feedback regulator of vasopressin MNC activity at the single cell level, the important output of the system is overall hormone secretion, which depends on the integrated activity of the MNCs at a population level.¹⁰ Some of the earliest work on somato-dendritic secretion showed that osmotic stimulation of vasopressin MNCs increases vasopressin levels in the circulation before levels increase in the SON,⁸⁵ which is consistent with somato-dendritic vasopressin

secretion acting as a negative-feedback regulator of vasopressin MNC activity at a population level to modulate overall vasopressin secretion into the circulation.

6 | AUTOCRINE/PARACRINE MODULATION OF VASOPRESSIN MAGNOCELLULAR NEUROSECRETORY CELL ACTIVITY BY CO-SECRETED TRANSMITTERS

Vasopressin MNCs also synthesise and secrete a number of other neurotransmitters and neuromodulators, including apelin,⁸⁶ ATP,⁸⁷ carbon monoxide (CO),⁸⁸ dynorphin,⁸⁹ endocannabinoids,^{90–92} galanin,⁹³ neuroendocrine regulatory peptides (NERPs),^{94,95} nitric oxide (NO),⁹⁶ pituitary adenylate cyclase-activating polypeptide (PACAP)⁹⁷ and secretin.¹³

Most neuropeptides synthesised by MNCs are packaged within the same dense-core vesicles as either vasopressin or oxytocin. However, apelin and galanin are differentially packaged in vasopressin MNCs. Apelin is packaged in dense-core vesicles that do not contain vasopressin.⁹⁸ Although galanin is packaged in some dense-core vesicles that contain vasopressin, it is also packaged in others that do not contain vasopressin and some dense-core vesicles contain vasopressin but no galanin. Presumably, differential packaging in dense-core vesicles might allow for secretion of separate pools that contain vasopressin or their co-expressed neuropeptides. Indeed, dense-core vesicles containing galanin alone are trafficked to the dendrites, whereas those that contain only vasopressin are trafficked to the axon terminals in the posterior pituitary gland.⁹³

Vasopressin MNCs express apelin receptors (APJ receptors)⁹⁹ and centrally administered apelin inhibits vasopressin MNCs⁸⁶ to decrease basal vasopressin secretion.^{86,100} However, systemic apelin administration increases vasopressin secretion¹⁰¹ and chronic infusion of apelin into the PVN also increases vasopressin secretion.¹⁰² Furthermore, administration of apelin directly into the SON increases the activity of phasic MNCs (and presumably vasopressin secretion into the circulation) via non-specific cation channel activation, although it reduces somato-dendritic vasopressin secretion,⁹⁹ which presumably weakens vasopressin-mediated autoregulation to disinhibit and thus further excite vasopressin MNCs.

Vasopressin MNCs express galanin receptor-1 on their somata and dendrites.¹⁰³ Although centrally administered galanin increases vasopressin secretion into the circulation *in vivo*,^{104,105} it inhibits vasopressin secretion from isolated neurohypophyses or hypothalamic-neurohypophysial explants *in vitro*,¹⁰⁶ suggesting that the direct effects of galanin are inhibitory, despite the reduced somato-dendritic vasopressin secretion. Indeed, galanin directly inhibits vasopressin MNCs *in vitro* by inducing hyperpolarisation and reducing the slow afterdepolarisation (sADP),¹⁰⁷ which is a prominent excitatory post-spike potential in vasopressin MNCs.¹⁰⁸ Galanin also reduces excitatory post-synaptic current (EPSC) frequency,¹⁰⁹ suggesting that it might also have paracrine effects after somato-dendritic secretion by retrograde inhibition of excitatory synaptic transmission.

Similarly to vasopressin receptors, κ -opioid receptors (KORs) are expressed in the membranes of vasopressin-containing dense-core vesicles¹¹⁰ and, unlike apelin and galanin, the endogenous opioid peptide (EOP) ligand for KORs, dynorphin, is packaged with

vasopressin in the same dense-core vesicles.¹¹¹ Hence, KORs newly trafficked to the vasopressin MNC plasma membrane will be exposed to high concentrations of dynorphin upon somato-dendritic secretion of dense-core vesicles.

KOR agonists inhibit vasopressin MNCs *in vivo*^{69,112} and *in vitro*.^{113,114} More importantly, antagonism of SON KORs increases burst duration in phasic MNCs under basal conditions *in vivo*^{69,70,115} and *in vitro*,^{70,116} showing that an endogenous KOR agonist inhibits phasic bursts. Phasic bursts are underpinned by the summation of sADPs to form a plateau potential that maintains a depolarised membrane potential to sustain further firing during bursts, and KOR activation causes activity-dependent sADP inhibition¹¹⁶ to progressively decrease the plateau potential amplitude, which eventually leads to burst termination.⁷⁰ Furthermore, KOR desensitisation prevents phasic activity in vasopressin MNCs, even when intensely stimulated.⁶⁹ Hence, an endogenous KOR agonist inhibits phasic MNCs by autocrine inhibition of the sADP in the MNC from which dynorphin is secreted and this inhibition appears to be necessary for the expression of phasic activity by vasopressin MNCs.

In addition to sADP inhibition, KOR agonists reduce excitatory postsynaptic potential (EPSP) and inhibitory postsynaptic potential (IPSP) amplitude^{114,117} and the delayed rectifier potassium current,¹¹⁸ at the same time as increasing the transient A-type potassium current¹¹⁸ in vasopressin MNCs, although it has yet to be established whether these effects also contribute to the generation of phasic activity.

Although KOR activation inhibits continuously active vasopressin MNCs, KOR antagonism does not affect continuously active vasopressin MNCs, even when they are strongly excited.⁷⁶ Hence, it appears that continuously active vasopressin MNCs express KORs but do not release sufficient dynorphin to affect activity. Some vasopressin MNCs display irregular activity and these MNCs appear to be even more strongly excited by KOR antagonism than phasic MNCs.⁷⁶ Taken together, this pattern-dependent sensitivity to KOR inhibition suggests that somato-dendritic dynorphin secretion might determine the firing pattern of vasopressin MNCs and that transitions between firing patterns in individual vasopressin MNCs might result from changes in somato-dendritic dynorphin secretion.¹¹⁹

MNCs also express receptors for PACAP, which they also synthesise and secrete.⁹⁷ PACAP increases somato-dendritic vasopressin secretion¹²⁰ by a direct depolarisation through activation of non-specific cation channels.¹²¹

NERP-1–3 are packaged with vasopressin in the SON and PVN.^{94,95} NERP-1 has paracrine effects on vasopressin MNC activity by retrograde inhibition of excitatory synaptic transmission, whereas paracrine inhibition of vasopressin MNCs by NERP-2 is mediated by activation of upstream GABAergic interneurons that inhibit glutamatergic neurons that project to vasopressin MNCs.¹²² By contrast to NERP-1 and –2, NERP-3 stimulates vasopressin secretion from the isolated posterior pituitary gland.⁹⁵

Vasopressin MNCs express secretin receptors and central secretin administration increases plasma vasopressin concentrations,¹³ suggesting that somato-dendritic secretin might stimulate systemic vasopressin secretion. However, secretin is also released from afferent inputs to the SON¹²³ and systemic secretin administration excites vasopressin (and

oxytocin) MNCs via noradrenergic afferent inputs,¹²⁴ suggesting that its actions might be mediated by afferent inputs rather than somato-dendritic secretion. Although its role as a neurohypophysial hormone has not yet been definitively established, secretin is expressed in the posterior pituitary gland¹³ and increases insertion of aquaporin-2 into the luminal membrane of the kidney to increase water reabsorption.¹²⁵ Hence, secretin synthesised by vasopressin MNCs might act as a neurohypophysial hormone after secretion from the posterior pituitary gland rather than as an autoregulatory factor secreted from the somata and dendrites.

Vasopressin MNCs express P2X and P2Y receptors^{126,127} and injection of ATP into the SON induces antidiuresis.¹²⁸ ATP is packaged in vasopressin dense-core vesicles.⁸⁷ ATP depolarises MNCs¹²⁹ and increases vasopressin secretion from hypothalamic-neurohypophysial explants.¹³⁰ ATP also increases glutamate and GABA release at synapses on MNCs.¹³¹ Hence, somato-dendritic ATP secretion might excite vasopressin MNCs by autocrine actions on the MNC from which it is secreted and paracrine actions on afferent inputs to the MNC from which it is secreted. However, MNCs are also excited by ATP released by astrocytes as a gliotransmitter,^{67,132} as well as by ATP released from noradrenergic afferent inputs.¹³³

Although somato-dendritic ATP secretion might modulate vasopressin MNC activity, ATP is rapidly catabolised to adenosine in the extracellular space.¹³⁴ Vasopressin MNCs express adenosine A1 and A2A receptors¹³⁵ and A1 receptor antagonism excites phasic MNCs in vivo, although it does not affect the firing rate of continuously active vasopressin MNCs.¹³⁶ A1 receptor antagonism reduces activity-dependent inhibition of EPSCs and inhibitory post-synaptic currents (IPSCs),¹³⁷ as well as activity-dependent enhancement of the medium afterhyperpolarisation (mAHP) in vasopressin MNCs.¹³⁸ mAHP activation induces spike frequency adaptation at the onset of phasic bursts¹³⁹ and so endogenous adenosine enhancement of the mAHP increases spike frequency adaptation, thereby shortening bursts in phasic MNCs.¹³⁶ Although A2 receptor activation depolarises MNCs to increase firing rate,¹³⁵ vasopressin MNCs are inhibited when adenosine uptake is blocked. Hence, the overall effect of endogenous adenosine appears to be vasopressin MNC inhibition.¹⁴⁰

In addition to somato-dendritic exocytosis, vasopressin MNCs also release the gaseous transmitters, NO and CO, by diffusion after synthesis by NO synthase and haem-oxygenase I, respectively. NO inhibits vasopressin MNCs^{141,142} by increasing IPSC amplitude and frequency,^{142,143} whereas CO excites vasopressin MNCs.⁸⁸

Somato-dendritic modulation of vasopressin MNC activity appears to impact hormone secretion into the circulation through a complex interplay of excitatory- (apelin, PACAP, ATP, NO and perhaps secretin) and inhibitory- (galanin, dynorphin, NERPs, adenosine and CO) feedback that might fine tune the activity of individual MNCs to prevent any one MNC bearing too much of the secretory load for too long under basal conditions. It appears to be counter-intuitive that the autoregulatory effects of (at least some) co-secreted transmitters appear greater than that of vasopressin itself, which is secreted in vastly greater quantities. Perhaps the autoregulatory effects of co-secreted transmitters are magnified by activation of both paracrine and autocrine mechanisms. In addition, it is possible that the major role of

vasopressin is paracrine inhibition of the population as a whole to prevent over-secretion of vasopressin into the circulation in response to perturbations of body fluid balance and/or blood pressure/volume.

7 | AUTOCRINE/PARACRINE MODULATION OF OXYTOCIN MAGNOCELLULAR NEUROSECRETORY CELL ACTIVITY

Similar to somato-dendritic vasopressin secretion, somato-dendritic oxytocin secretion also has autocrine and paracrine actions that modulate oxytocin MNC activity. By contrast to vasopressin, the autocrine and paracrine effects of oxytocin are arranged in series rather than in parallel; somato-dendritic oxytocin secretion activates oxytocin receptors (OTRs) on oxytocin MNCs to increase intracellular calcium, which has various actions, including the release of endocannabinoids that cause retrograde inhibition of excitatory synaptic transmission under basal conditions.⁹⁰ Although the oxytocin-stimulated retrograde endocannabinoid suppression of excitatory synaptic input is expected to inhibit oxytocin MNCs (Figure 6), the best characterised effect of somato-dendritic oxytocin secretion is excitation, although only under specific (patho)physiological conditions. Hence, it has been proposed that endocannabinoid inhibition might occur over a longer timescale than autocrine effects of oxytocin to shape activity patterning in oxytocin MNCs during birth and lactation,¹⁴⁴ although it has yet to be established whether this occurs in vivo. Alternatively, the excitatory effects of oxytocin might involve a switch from endocannabinoid inhibition to excitation during pregnancy, perhaps by enhanced expression/activation of excitatory transient receptor potential vanilloid-1 channels¹⁴⁵ for which the endocannabinoid, anandamide, is an endogenous ligand.¹⁴⁶ Additionally, spillover of the endocannabinoid 2-arachi-donoyleglycerol from glutamate onto GABA synapses and a resulting suppression of inhibitory synaptic input has been observed in MNCs following glial retraction induced by salt loading.⁹¹ This endocannabinoid spillover could also occur with glial retraction during parturition and lactation to reduce inhibitory synaptic transmission, although this remains to be determined. Finally, it is also possible that oxytocin-stimulated endocannabinoid retrograde modulation of excitatory and inhibitory synapses might be overridden by changes in the postsynaptic properties of oxytocin MNCs,^{147,148} increased excitatory afferent inputs,^{149–153} or a switch in GABA signalling from inhibitory to excitatory, or less inhibitory, during pregnancy.^{64,154}

Oxytocin MNCs typically exhibit continuous activity at approximately 1–5 spikes s^{-1} under basal conditions to maintain circulating oxytocin concentrations of approximately 1–3 pg mL^{-1} , with higher concentrations during sleep.² However, oxytocin is best known for its stimulation of rhythmic uterine contraction during birth and of episodic milk ejection during suckling. Uterine contractions and mammary duct contraction each occur at intervals of several minutes and each contraction is triggered by a coordinated, high frequency burst of activity across the population of oxytocin MNCs¹⁵⁵ to secrete a discrete pulse of oxytocin into the circulation, which transiently increases intrauterine pressure during birth¹⁵⁶ and intra-mammary pressure during suckling.¹⁵⁷

Somato-dendritic oxytocin secretion increases immediately preceding each burst of activity in lactating rats¹⁵⁸ and bursts are blocked by OTR antagonist administration,¹⁵⁹ as is the rise in somato-dendritic oxytocin secretion,¹⁶⁰ suggesting that somato-dendritic oxytocin secretion is required for bursts to occur. However, the mechanisms by which somato-dendritic oxytocin secretion promotes burst firing in oxytocin MNCs are not fully understood and it is probably not the only contributor; synchronised volleys of EPSPs,¹⁶¹ rebound depolarisation after bursts of IPSPs¹⁶² and enhancement of the sADP^{147,163} have all been proposed to trigger or sustain firing during bursts in oxytocin MNCs.

In brain slices from male rats that do not normally fire bursts, α_1 -adrenoceptor activation in low calcium can induce bursts in oxytocin MNCs reminiscent of those seen during birth and milk ejection.¹⁶⁴ Hence, noradrenergic inputs might trigger bursts. Consistent with this hypothesis, noradrenergic innervation of oxytocin MNCs is increased in late pregnancy¹⁵² and these afferent inputs are activated during birth⁵⁵ to increase noradrenaline release into the SON.¹⁶⁵

Noradrenergic stimulation of bursts in oxytocin MNCs might be mediated by somato-dendritic oxytocin release because noradrenergic receptor stimulation is required for suckling-induced somato-dendritic oxytocin release,⁵⁸ which might be part of a positive-feedback loop that builds towards bursts during continuous suckling. Indeed, burst-like activity can also be induced in virgin rats in vivo by coordinated activation of neighbouring oxytocin MNCs, which induces priming of somato-dendritic dense-core vesicles for subsequent secretion.²⁸ Once primed, high-frequency electrical stimulation induces bursting in oxytocin MNCs of virgin rats.²⁸ Hence, continuous suckling might trigger tonic noradrenaline release onto oxytocin MNCs that triggers increasing somato-dendritic oxytocin secretion, which could prime further somato-dendritic oxytocin secretion until a tipping-point is reached to induce each burst.

In addition to facilitating burst firing in individual oxytocin MNCs, somato-dendritic oxytocin secretion might also help coordinate the timing of bursts across the population of oxytocin MNCs. Oxytocin injection into one SON increases the frequency of milk ejection bursts in the contralateral SON.¹⁶⁶ Oxytocin MNCs have one to three dendrites¹⁴⁸ that are normally separated from neighbouring dendrites by astrocytic processes. However, in late pregnancy and lactation, astrocytes withdraw their processes from between oxytocin MNC dendrites, which then form bundles of approximately 10 closely apposed dendrites.^{167,168} A mathematical model in which oxytocin MNCs send each dendrite to different dendritic bundles to form a sparse network of interactions emulates burst firing in which each burst is initiated randomly at any of the dendritic bundles and spreads rapidly through the oxytocin MNC population.¹⁴⁴

However, this model does not account for coordination of bursts across the bilateral SONs and PVNs, which might be mediated by noradrenergic inputs that project bilaterally to the SON.¹⁶⁹ Indeed, sectioning the optic chiasm or mammillary body disrupts coordination of bursts between oxytocin MNCs in the left and right SON, suggesting that burst coordination across the magnocellular nuclei involves projections through these areas.^{169,170} Furthermore, the perinuclear zone that lies immediately dorsal to the SON sends prominent

projections to the SON¹⁷¹ and PVN^{172,173} that might also contribute to coordination of bursts across the four main magnocellular nuclei.

8 | AUTOCRINE/PARACRINE MODULATION OF OXYTOCIN MAGNOCELLULAR NEUROSECRETORY CELL ACTIVITY BY CO-SECRETED TRANSMITTERS

Oxytocin MNCs also synthesise other transmitters that are probably secreted from their somata and dendrites, although the effects of these co-transmitters are not as well characterised as for those released from vasopressin MNCs.

Oxytocin MNCs express μ -opioid receptors (MORs) and KORs,^{174,175} and MOR or KOR activation inhibits oxytocin MNCs.^{69,176} Although oxytocin MNCs synthesise μ - and κ -EOPs,^{177,178} neither MOR, nor KOR antagonists affect the activity of oxytocin MNCs in vivo.^{69,179} Hence, it appears that, if EOPs undergo somato-dendritic secretion with oxytocin, they do not modulate oxytocin MNC activity to any appreciable extent under basal conditions. MOR-mediated EOP inhibition of somato-dendritic oxytocin secretion and oxytocin MNC activity is increased in late pregnancy,¹⁸⁰ although this modulation is probably mediated by afferent inputs.¹⁸¹

By contrast to the central actions of MOR activation, KOR activation appears to restrain secretion into the bloodstream at the posterior pituitary gland¹⁸² and this effect also increases in late pregnancy.¹⁸³ KOR restraint of oxytocin secretion might build up stores of oxytocin for birth and lactation and might potentiate secretion during bursts because KORs are desensitised on the day of birth.^{184,185}

Oxytocin MNC dense-core vesicles also contain ATP, which is presumably secreted along with oxytocin from the somata and dendrites. Co-secreted ATP does not modulate oxytocin MNC activity via adenosine receptor activation,¹³⁶ but it might excite oxytocin MNC via P2X receptor activation.^{130,131}

Oxytocin MNCs also express NO synthase⁹⁶ and NO appears to restrain the activity of oxytocin MNCs, particularly under stimulated conditions,^{186,187} suggesting that NO is an inhibitory autocrine/paracrine modulator of oxytocin MNC activity.

Remarkably, chronic MOR activation by the opioid alkaloid agonist, morphine (but not EOPs¹⁸⁸), induces tolerance and dependence in oxytocin MNCs.¹⁸⁹ Tolerance is revealed as loss of inhibition to acute administration of morphine¹⁷⁶ and dependence is revealed by a sustained hyperexcitation upon withdrawal of chronic morphine administration.¹¹² Somato-dendritic oxytocin secretion is increased during morphine withdrawal and OTR antagonism reduces morphine withdrawal-induced excitation of oxytocin MNCs.¹⁹⁰ Hence, somato-dendritic oxytocin secretion appears to contribute to morphine withdrawal-induced excitation of oxytocin MNCs, although the mechanism by which it does so has yet to be identified.

9 | PARACRINE MODULATION OF PARVOCELLULAR PARAVENTRICULAR NUCLEUS NEURONE ACTIVITY BY SOMATO-DENDRITIC SECRETION FROM MAGNOCELLULAR NEUROSECRETORY CELLS

Although the SON essentially contains only MNCs (as well as glia and cells of the vasculature), the PVN also contains parvocellular neurones. Parvocellular neurones are subdivided by their projections and functions: neurosecretory parvocellular neurones project to the hypothalamic median eminence, where they secrete hormones into the hypophysial portal blood vessels to control hormone secretion from the anterior pituitary gland; preautonomic parvocellular neurones project to the brainstem and spinal cord to modulate parasympathetic and sympathetic nervous system activity^{191,192}; the remaining parvocellular neurones project to various brain areas to modulate behaviour.

It has long been hypothesised that somato-dendritic secretion from MNCs modulates the activity of parvocellular neurones but only recently has definitive evidence to support this hypothesis been generated for somato-dendritic vasopressin.^{38,193,194} For paracrine effects on other neuronal phenotypes to occur, vasopressin (or oxytocin) must first diffuse through the parenchyma to reach other neurones. The effective diffusion distance for somato-dendritic vasopressin was determined under basal conditions using Chinese hamster ovary cells transfected with human V1aRs and a calcium indicator to generate biosensor 'sniffer' cells with a threshold detection level of 0.5 nmol L⁻¹ and an EC₅₀ of 7.2 nmol L⁻¹ for vasopressin.³⁸ Using sniffer cells that were dispersed over the PVN in hypothalamic slices, it was shown that activation of an individual MNC induces sufficient somato-dendritic vasopressin secretion to induce intracellular calcium increases for tens of seconds in sniffer cells over 100 µm from the soma of the activated MNC.³⁸ Similar results were seen using HEK-293 sniffer cells in the SON.¹⁹⁴ Hence, somato-dendritic vasopressin release from an individual MNC diffuses through the PVN at sufficient concentration to activate V1aRs expressed on parvocellular neurone somata or dendrites under basal conditions.^{38,193} Remarkably, astrocytes withdraw their processes from between MNCs when chronically stimulated,^{167,168,195,196} which reduces the tortuosity of the extracellular space and probably increases the effective diffusion distance for somato-dendritic vasopressin and oxytocin through the parenchyma.¹⁹⁷

Some preautonomic parvocellular neurones project to the rostral ventrolateral medulla (RVLM) in the brainstem, which projects to sympathetic ganglia to regulate sympathetic nerve activity.¹⁹⁸ RVLM-projecting parvocellular neurones express V1aRs and their dendrites are intermingled with vasopressin MNC somata and dendrites in the PVN.¹⁹³ Hence, the architecture is in place to provide for somato-dendritic vasopressin modulation of autonomic function by paracrine modulation of preautonomic neurones within the PVN (Figure 7). Activation of individual vasopressin MNCs by uncaging NMDA increases action potential firing in RVLM-projecting parvocellular neurones beyond 100 µm from the activated MNC¹⁹³ and this activation is much more potent than that elicited by action potential firing alone,³⁸ suggesting that dendritic NMDARs might be a main driver of somato-dendritic secretion. The responses of RVLM-projecting parvocellular neurones to vasopressin MNC activation occur after a delay of several seconds, are blocked by

superfusion of a V1aR antagonist and are enhanced by a peptidase inhibitor.¹⁹³ Most importantly, the depolarisation of RVLN-projecting parvocellular neurones in response to vasopressin MNC activation is not affected by blockade of action potential firing with tetrodotoxin. Taken together, the data demonstrate that the excitation of RVLN-projecting parvocellular neurones is mediated by diffusion of somato-dendritic vasopressin through the extracellular space of the PVN.

Given that activation of an individual vasopressin MNC can excite preautonomic neurones within a radius of at least 100 μm , somato-dendritic secretion from the population of MNCs could function as a population-to-population signal to recruit preautonomic neurones as a whole. Indeed, administration of a V1aR antagonist alone reduces preautonomic neurone activity and the more active the MNC, the more effective is the antagonist at reducing preautonomic neurone activity,¹⁹³ suggesting that preautonomic neurones are under tonic modulation by vasopressin MNCs to coordinate the humoral (circulating vasopressin) and neuronal (sympathetic nerve activity) responses to changes in body fluid balance and to pathophysiological conditions, such as hypertension, myocardial infarction and chronic heart failure.

Hyperosmolality increases vasopressin secretion into the circulation by MNCs and increases renal sympathetic nerve activity, both of which increase water retention to protect body fluid balance. The mechanisms that underpin these responses to hyperosmolality have been reviewed in detail elsewhere.^{199,200} Although these mechanisms occur in parallel, somato-dendritic vasopressin secretion probably coordinates the responses because intracarotid infusion of hyperosmotic saline causes a dose-dependent increase in renal sympathetic nerve activity that is accompanied by increased somato-dendritic vasopressin secretion, and bilateral injection of a V1aR antagonist into the PVN abolishes the renal sympathetic nerve activation.¹⁹³ Hence, it appears that somato-dendritic vasopressin secretion coordinates the humoral and neuronal responses to increased osmolality.

PVN-driven sympathoexcitation is a key pathophysiological mechanism in hypertension,^{201,202} acute myocardial infarction^{192,203} and heart failure^{204,205} that contributes to morbidity and mortality.²⁰⁶ Vasopressin MNCs are activated in hypertension,^{207,208} acute myocardial infarction²⁰⁹ and heart failure.^{210,211} Although the increased circulating vasopressin levels contribute directly to detrimental myocardial effects,^{212,213} increased vasopressin MNC activity probably also increases somato-dendritic vasopressin secretion to contribute to the pathophysiological sympathoexcitation via activation of PVN preautonomic neurones.

Although less well established than for vasopressin effects on preautonomic neurones, it appears that somato-dendritic oxytocin secretion might also modulate the activity of a neighbouring population of neurones within the PVN, corticotrophin-releasing hormone (CRH) neurones. Stress-induced CRH secretion stimulates adrenocorticotrophic hormone secretion from the anterior pituitary gland,²¹⁴ which, in turn, increases adrenal corticosteroid secretion to mediate the response to the stressor. CRH neurones express mRNA for OTRs²¹⁵ and oxytocin inhibits EPSC frequency (but not amplitude) in CRH neurones.²¹⁶ Oxytocin MNC and CRH neurone dendrites are intermingled within the PVN,²¹⁶ allowing for den-

dro-dendritic interactions between the two populations. Hence, somato-dendritic oxytocin might suppress CRH neurone excitability by presynaptic inhibition of excitatory synaptic inputs to reduce activation of the stress axis. However, OTR antagonism has no effect on CRH neurones in brain slices,²¹⁶ suggesting that, unlike vasopressin modulation of preautonomic neurone activity, there is no OTR tone on CRH neurones, at least under in vitro basal conditions.

10 | PARACRINE MODULATION OF ARTERIOLAR VASOCONSTRICTION IN THE SUPRAOPTIC NUCLEUS BY SOMATO-DENDRITIC SECRETION FROM MAGNOCELLULAR NEUROSECRETORY CELLS

Classically, neuronal activity is considered to dilate arterioles and thereby increase local cerebral blood flow to meet the metabolic demands of active brain areas; this ‘neurovascular coupling’ is generally accepted to result from glutamatergic synaptic transmission that evokes the release of vasoactive substances from neurones and astrocytes to relax vascular smooth muscle cells.²¹⁷ However, vascular smooth muscle cells express V1aRs, providing a target for somato-dendritic vasopressin, at least within the SON and PVN. Vasoconstriction can be elicited in SON arterioles by stimulation of an individual vasopressin MNC, an effect that is blocked by V1aR antagonism²¹⁸ (Figure 7). Consistent with its effects on preautonomic neurones, somato-dendritic vasopressin can induce responses in arterioles beyond 100 µm from the activated MNC under basal conditions.²¹⁸ Importantly, this V1aR-mediated vasoconstriction is overridden in hyperosmotic conditions by parallel release of NO, which causes vasodilation of local arterioles.²¹⁸ Presumably, the NO-induced vasodilation increases blood flow through the SON when increased vasopressin MNC activity is required to protect from further fluid loss and maintain blood pressure in the general circulation through vasopressin secretion from the posterior pituitary gland.

11 | PARACRINE MODULATION OF NEURONAL ACTIVITY BEYOND THE PARAVENTRICULAR NUCLEUS BY SOMATO-DENDRITIC SECRETION FROM MAGNOCELLULAR NEUROSECRETORY CELLS

Although paracrine modulation of parvocellular neurones within the PVN by somato-dendritic secretion from MNCs is now well characterised, it has yet to be definitively established whether neuropeptides secreted from MNC somata and dendrites can affect the activity of neurones outside the PVN. Nevertheless, there is some evidence that somato-dendritic oxytocin might act on neurones in brain areas relatively close to the SON and/or PVN, particularly for brain areas that receive little or no axonal projections from MNCs or from vasopressin or oxytocin parvocellular neurones.

The central effects of the primary anorexigenic hormone, leptin, are mediated by oxytocin, at least in part.²¹⁹ Leptin is sensed by ARC POMC neurones that, as described above, project to the SON and PVN,⁶¹ where they secrete α -MSH to activate MC4-Rs⁶² and thereby increase somato-dendritic oxytocin secretion.^{63,220} Oxytocin inhibition of food intake is mediated, in part, by the ventromedial hypothalamus (VMH) because oxytocin

injection into the VMH decreases food intake that is driven by energy balance rather than palatability.²²¹ Although OTRs are highly expressed in the VMH,²²² there are essentially no oxytocin MNC axons in the VMH.²¹⁹ Given that vasopressin released from a single MNC can activate cells over 100 μm from the MNC soma from which it is secreted^{38,193} and the VMH is situated roughly between the SON and PVN, it is possible that somato-dendritic oxytocin release from MNCs could diffuse through the parenchyma in sufficient quantities to activate OTRs in the VMH, which have nanomolar affinity for oxytocin.²²³ It is also possible that OTR-expressing astrocytes in the SON and PVN could expand the spatial domain of the dendritically released oxytocin signalling by relaying the signals through astrocytic networks, as has been reported for vasopressin release from vasopressin MNC dendrites⁶⁷ and CRH neurone dendrites.²²⁴

Although oxytocin MNCs inhibit fear responses via axon collaterals to the CeA,¹⁷ SON somato-dendritic oxytocin secretion probably enhances social recognition via actions in the MeA. The CeA contains oxytocin MNC axon collaterals, although there are no oxytocin (MNC or parvocellular) neurone axons in the MeA.¹⁷ OTRs are highly expressed in the MeA²²² and OTR antagonist injection into the MeA reduces social recognition induced by SON activation.²²⁵ However, MeA OTRs are not directly activated by oxytocin secreted into the CeA from MNC axon collaterals.¹⁷ The MeA lies immediately lateral to the SON and, even if somato-dendritic oxytocin secreted within the SON does not reach the MeA, some oxytocin MNC dendrites project to the MeA,²²⁵ which might deliver sufficient oxytocin to the MeA to promote social recognition. Alternatively, OTRs might be activated by vasopressin MNC axon collaterals in the MeA¹⁹ because vasopressin has appreciable activity at OTRs.²²³

12 | HORMONE-LIKE MODULATION OF NEURONAL ACTIVITY IN DISTANT BRAIN AREAS BY SOMATO-DENDRITIC SECRETION FROM MAGNOCELLULAR NEUROSECRETORY CELLS

It has been hypothesised that somato-dendritic vasopressin and oxytocin from MNCs comprise a hormone-like signal in the brain with widespread effects on distant populations of neurones.²²⁶ However, accumulating evidence of the functional impact of MNC axon collaterals on behaviour via direct projections to distant brain areas^{17–21} have led to this hypothesis being challenged.²²⁷

The half-lives of vasopressin and oxytocin are approximately 20 minutes in the cerebrospinal fluid (CSF),²²⁸ giving time for diffusion through the ventricular system, particularly downstream. However, vasopressin (at least) has a half-life of less than 1 minute in the parenchyma.²²⁹ Given that the paracrine effects of somato-dendritic vasopressin on preautonomic neurones that are only approximately 100 μm away is delayed by 2–5 seconds,¹⁹³ it is improbable that the neuropeptides could diffuse long distances through the brain to act as a hormone-like signal. However, dense-core vesicle exocytosis is a slow process compared to microvesicle fusion at the synapse, with latencies of several seconds in hippocampal neurones,²³⁰ which could account for much of the latency of the preautonomic neurone response to somato-dendritic vasopressin secreted by MNCs

in the PVN. Furthermore, vasopressin and oxytocin are secreted in sufficient quantities to be measured in dialysates collected from the SON and PVN,²³¹ as well as in other brain areas^{232–234} and in the CSF,²³⁵ suggesting that they diffuse through the parenchyma sufficiently to reach the CSF. Indeed, the microdialysis probes used to measure vasopressin and oxytocin in many experiments have a recovery rate of <10% for vasopressin in the SON and PVN.²³⁶ Hence, the actual concentrations of vasopressin and oxytocin present in the parenchyma and CSF are probably appreciably higher than those measured in dialysates. A further factor to be considered is retraction of astrocytic processes from around MNCs in dehydration and pregnancy,^{167,168,195,196} which decreases tortuosity in the extracellular space, presumably allowing more ready escape of somato-dendritic vasopressin and oxytocin from the SON and PVN. It is difficult to imagine that the relatively sparse terminal fields of MNC axon collaterals and parvocellular vasopressin and oxytocin MNCs could release sufficient vasopressin and oxytocin to maintain the ambient levels of the neuropeptides found in the brain and CSF.

Although there are clear examples of axon collaterals from sub-populations of MNCs affecting neuronal activity beyond the SON and PVN,²³⁷ this does not preclude the possibility that there is also long-distance inter-population signalling mediated by somato-dendritic volume transmission of vasopressin and oxytocin over a longer timescale, particularly in brain regions in which there are neuropeptide receptors but no neuropeptide axons, such as in the olfactory bulb. Nevertheless, there is still no compelling evidence for (or against) distal hormone-like signalling by somato-dendritic vasopressin and oxytocin transmission, although the levels of oxytocin and vasopressin present in the cerebrospinal fluid and in brain areas devoid of oxytocin and vasopressin axon terminals appear to be much higher than could be achieved from axon terminal release from MNC and parvocellular axon collaterals. The resolution of this debate remains an ongoing challenge for the field.

13 | CONCLUDING REMARKS

Autocrine/paracrine modulation of MNC activity by somato-dendritic vasopressin and oxytocin release has been extensively studied and is broadly accepted as a major function of somato-dendritic secretion from MNCs.²³⁸ Although it is clear that co-secreted transmitters also modulate MNC activity, there is no evidence of paracrine actions on other neurones, even other MNCs. Indeed, somato-dendritic dynorphin terminates bursts in the MNC from which it is secreted,⁷⁰ although there is no correlation between burst termination in phasic MNCs in paired recordings using a single electrode in which the recorded MNCs would be at most tens of micrometres apart,⁷¹ which is well within the range of somato-dendritic vasopressin but evidently beyond the range of somato-dendritic dynorphin. Hence, it is possible that co-secreted transmitters act as autocrine/paracrine modulators of the individual MNC from which they are secreted, whereas the much higher levels of vasopressin or oxytocin secreted modulate the activity of the population as a whole to regulate peripheral physiology.

Recently, compelling evidence has emerged indicating that somato-dendritic secretion from MNCs modulates the arteriole diameter in the SON,²¹⁸ as well as the activity of neurones,

particularly RVLN-projecting preautonomic neurones in the parvocellular PVN¹⁹³ (and perhaps also CRH neurones²¹⁶). This inter-population cross-talk between MNCs and preautonomic neurones probably coordinates the hormonal (vasopressin secretion into the circulation) and neural (sympathetic nerve activation) response to perturbations of body fluid balance and blood pressure/volume.²³⁹

To date, there is no definitive evidence that somato-dendritic vasopressin and oxytocin have actions beyond the SON and PVN and it remains to be determined whether these neuropeptides act as hormone-like signals after secretion from MNC somata and dendrites. Nevertheless, although much of the data remains circumstantial, somato-dendritic oxytocin release probably modulates the activity of neurones in some nearby brain areas that express OTRs but do not contain oxytocin (MNC or parvocellular) neurone projections, specifically the VMH^{219,222} and MeA.^{222,225} The confirmation (or refutation) of the effects of somato-dendritic oxytocin on the VMH and/or MeA is required to resolve the ongoing debate within this field.

REFERENCES

1. Ludwig M Dendritic Neurotransmitter Release. New York: Kluwer Academic Publishers; 2004.
2. Brown CH. Magnocellular neurons and posterior pituitary function. *Compr Physiol.* 2016;6:1701–1741. [PubMed: 27783857]
3. Verbalis JG, Mangione MP, Stricker EM. Oxytocin produces natriuresis in rats at physiological plasma concentrations. *Endocrinology.* 1991;128:1317–1322. [PubMed: 1847854]
4. Haanwinckel MA, Elias LK, Favaretto AL, Gutkowska J, McCann SM, Antunes-Rodrigues J. Oxytocin mediates atrial natriuretic peptide release and natriuresis after volume expansion in the rat. *Proc Natl Acad Sci USA.* 1995;92:7902–7906. [PubMed: 7644511]
5. Manaye KF, Lei DL, Tizabi Y, Davila-Garcia MI, Mouton PR, Kelly PH. Selective neuron loss in the paraventricular nucleus of hypothalamus in patients suffering from major depression and bipolar disorder. *J Neuropathol Exp Neurol.* 2005;64:224–229. [PubMed: 15804054]
6. Rhodes CH, Morrell JI, Pfaff DW. Immunohistochemical analysis of magnocellular elements in rat hypothalamus: distribution and numbers of cells containing neurophysin, oxytocin, and vasopressin. *J Comp Neurol.* 1981;198:45–64. [PubMed: 7014660]
7. Tweedle CD, Smithson KG, Hatton GI. Neurosecretory endings in the rat neurohypophysis are en passant. *Exp Neurol.* 1989;106:20–26. [PubMed: 2792295]
8. Nordmann JJ, Morris JF. Method for quantitating the molecular content of a subcellular organelle: hormone and neurophysin content of newly formed and aged neurosecretory granules. *Proc Natl Acad Sci USA.* 1984;81:180–184. [PubMed: 6582475]
9. Leng G, Ludwig M. Neurotransmitters and peptides: whispered secrets and public announcements. *J Physiol.* 2008;586:5625–5632. [PubMed: 18845614]
10. Leng G, Brown C, Sabatier N, Scott V. Population dynamics in vasopressin cells. *Neuroendocrinology.* 2008;88:160–172. [PubMed: 18667805]
11. Brown CH, Ruan M, Scott V, Tobin VA, Ludwig M. Multi-factorial somato-dendritic regulation of phasic spike discharge in vasopressin neurons. *Prog Brain Res.* 2008;170:219–228. [PubMed: 18655885]
12. Meeker RB, Swanson DJ, Greenwood RS, Hayward JN. Ultrastructural distribution of glutamate immunoreactivity within neurosecretory endings and pituicytes of the rat neurohypophysis. *Brain Res.* 1991;564:181–193. [PubMed: 1687373]
13. Chu JY, Lee LTO, Lai CH et al. Secretin as a neurohypophysial factor regulating body water homeostasis. *Proc Natl Acad Sci USA.* 2009;106:15961–15966. [PubMed: 19805236]
14. Lemos JR, Ortiz-Miranda SI, Cuadra AE et al. Modulation/physiology of calcium channel subtypes in neurosecretory terminals. *Cell Calcium.* 2012;51:284–292. [PubMed: 22341671]

15. Mason WT, Ho YW, Hatton GI. Axon collaterals of supraoptic neurones: anatomical and electrophysiological evidence for their existence in the lateral hypothalamus. *Neuroscience*. 1984;11:169–182. [PubMed: 6324027]
16. Hatton GI, Cobbett P, Salm AK. Extranuclear axon collaterals of paraventricular neurons in the rat hypothalamus: intracellular staining, immunocytochemistry and electrophysiology. *Brain Res Bull*. 1985;14:123–132. [PubMed: 2986791]
17. Knobloch HS, Charlet A, Hoffmann LC et al. Evoked axonal oxytocin release in the central amygdala attenuates fear response. *Neuron*. 2012;73:553–566. [PubMed: 22325206]
18. Menon R, Grund T, Zoclas I et al. Oxytocin signaling in the lateral septum prevents social fear during lactation. *Curr Biol*. 2018;28:1066–78.e6. [PubMed: 29551417]
19. Hernandez VS, Vazquez-Juarez E, Marquez MM, Jauregui-Huerta F, Barrio RA, Zhang L. Extra-neurohypophyseal axonal projections from individual vasopressin-containing magnocellular neurons in rat hypothalamus. *Front Neuroanat*. 2015;9:130. [PubMed: 26500509]
20. Hernandez VS, Hernandez OR, de la Mora M Perez et al. Hypothalamic vasopressinergic projections innervate central amygdala GABAergic neurons: Implications for anxiety and stress coping. *Front Neural Circuits*. 2016;10:92. [PubMed: 27932956]
21. Hernandez-Perez OR, Hernandez VS, Nava-Kopp AT et al. A synaptically connected hypothalamic magnocellular vasopressin-locus coeruleus neuronal circuit and its plasticity in response to emotional and physiological stress. *Front Neurosci*. 2019;13:196. [PubMed: 30949017]
22. Yeo SH, Kyle V, Blouet C, Jones S, Colledge WH. Mapping neuronal inputs to Kiss1 neurons in the arcuate nucleus of the mouse. *PLoS ONE*. 2019;14:e0213927. [PubMed: 30917148]
23. Armstrong WE, Scholer J, McNeill TH. Immunocytochemical, golgi and electron microscopic characterization of putative dendrites in the ventral glial lamina of the rat supraoptic nucleus. *Neuroscience*. 1982;7:679–694. [PubMed: 6175923]
24. Hatton GI. Emerging concepts of structure-function dynamics in adult brain: the hypothalamo-neurohypophysial system. *Prog Neurobiol*. 1990;34:437–504.
25. Pow DV, Morris JF. Dendrites of hypothalamic magnocellular neurons release neurohypophysial peptides by exocytosis. *Neuroscience*. 1989;32:435–439. [PubMed: 2586758]
26. Ludwig M, Apps D, Menzies J, Patel JC, Rice ME. Dendritic release of neurotransmitters. *Compr Physiol*. 2017;7:235–252.
27. Ludwig M, Bull PM, Tobin VA et al. Regulation of activity-dependent dendritic vasopressin release from rat supraoptic neurones. *J Physiol*. 2005;564:515–522. [PubMed: 15731188]
28. Ludwig M, Sabatier N, Bull PM, Landgraf R, Dayanithi G, Leng G. Intracellular calcium stores regulate activity-dependent neuropeptide release from dendrites. *Nature*. 2002;418:85–89. [PubMed: 12097911]
29. Dayanithi G, Forostyak O, Ueta Y, Verkhratsky A, Toescu EC. Segregation of calcium signalling mechanisms in magnocellular neurones and terminals. *Cell Calcium*. 2012;51:293–299. [PubMed: 22386684]
30. Fisher TE, Bourque CW. Calcium-channel subtypes in the somata and axon terminals of magnocellular neurosecretory cells. *Trends Neurosci*. 1996;19:440–444. [PubMed: 8888522]
31. Tobin VA, Douglas AJ, Leng G, Ludwig M. The involvement of voltage-operated calcium channels in somato-dendritic oxytocin release. *PLoS ONE*. 2011;6:e25366. [PubMed: 22028774]
32. Bains JS, Ferguson AV. Activation of N-methyl-D-aspartate receptors evokes calcium spikes in the dendrites of rat hypothalamic paraventricular nucleus neurons. *Neuroscience*. 1999;90:885–891. [PubMed: 10218788]
33. de Kock CP, Wierda KD, Bosman LW et al. Somatodendritic secretion in oxytocin neurons is upregulated during the female reproductive cycle. *J Neurosci*. 2003;23:2726–2734. [PubMed: 12684458]
34. Brown CH, Scott V, Ludwig M, Leng G, Bourque CW. Somatodendritic dynorphin release: orchestrating activity patterns of vasopressin neurons. *Biochem Soc Trans*. 2007;35:1236–1242. [PubMed: 17956321]
35. Joe N, Scott V, Brown CH. Glial regulation of extrasynaptic NMDA receptor-mediated excitation of supraoptic nucleus neurons during dehydration. *J Neuroendocrinol*. 2014;26:35–42. [PubMed: 24267175]

36. Sabatier N alpha-Melanocyte-stimulating hormone and oxytocin: a peptide signalling cascade in the hypothalamus. *J Neuroendocrinol.* 2006;18:703–710. [PubMed: 16879169]
37. Sabatier N, Caqueneau C, Dayanithi G et al. 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.* 2003;23:10351–10358. [PubMed: 14614094]
38. Pitra S, Zhang M, Cauley E, Stern JE. NMDA receptors potentiate activity-dependent dendritic release of neuropeptides from hypothalamic neurons. *J Physiol.* 2019;597:1735–1756. [PubMed: 30629746]
39. Fleming TM, Scott V, Naskar K, Joe N, Brown CH, Stern JE. State-dependent changes in astrocyte regulation of extrasynaptic NMDA receptor signalling in neurosecretory neurons. *J Physiol.* 2011;589:3929–3941. [PubMed: 21690192]
40. Naskar K, Stern JE. A functional coupling between extrasynaptic NMDA receptors and A-type K^+ channels under astrocyte control regulates hypothalamic neurosecretory neuronal activity. *J Physiol.* 2014;592:2813–2827. [PubMed: 24835172]
41. Zhang M, Biancardi VC, Stern JE. An increased extrasynaptic NMDA tone inhibits A-type $K(+)$ current and increases excitability of hypothalamic neurosecretory neurons in hypertensive rats. *J Physiol.* 2017;595:4647–4661. [PubMed: 28378360]
42. Tobin VA, Hurst G, Norrie L, Dal Rio FP, Bull PM, Ludwig M. Thapsigargin-induced mobilization of dendritic dense-cored vesicles in rat supraoptic neurons. *Eur J Neurosci.* 2004;19:2909–2912. [PubMed: 15147325]
43. Hurbin A, Boissin-Agasse L, Orcel H et al. The V_{1a} and V_{1b} , but not V_2 , vasopressin receptor genes are expressed in the supraoptic nucleus of the rat hypothalamus, and the transcripts are essentially colocalized in the vasopressinergic magnocellular neurons. *Endocrinology.* 1998;139:4701–4707. [PubMed: 9794482]
44. Meddle SL, Bishop VR, Gkoumassi E, van Leeuwen FW, Douglas AJ. Dynamic changes in oxytocin receptor expression and activation at parturition in the rat brain. *Endocrinology.* 2007;148:5095–5104. [PubMed: 17628000]
45. Dayanithi G, Sabatier N, Widmer H. Intracellular calcium signalling in magnocellular neurones of the rat supraoptic nucleus: understanding the autoregulatory mechanisms. *ExpPhysiol.* 2000;85:75S.
46. Zhang Z, Kindrat AN, Sharif-Naeini R, Bourque CW. Actin filaments mediate mechanical gating during osmosensory transduction in rat supraoptic nucleus neurons. *J Neurosci.* 2007;27:4008–4013. [PubMed: 17428977]
47. Prager-Khoutorsky M, Khoutorsky A, Bourque CW. Unique interweaved microtubule scaffold mediates osmosensory transduction via physical interaction with TRPV1. *Neuron.* 2014;83:866–878. [PubMed: 25123313]
48. Tobin VA, Ludwig M. The role of the actin cytoskeleton in oxytocin and vasopressin release from rat supraoptic nucleus neurons. *J Physiol.* 2007;582:1337–1348. [PubMed: 17478532]
49. Morris JF, Pow DV. Widespread release of peptides in the central nervous system: quantitation of tannic acid-captured exocytoses. *AnatRec.* 1991;231:437.
50. Zhou Q, Zhou P, Wang AL et al. The primed SNARE-complexin-synaptotagmin complex for neuronal exocytosis. *Nature.* 2017;548:420–425. [PubMed: 28813412]
51. Jurgutis P, Shuang R, Fletcher A, Stuenkel EL. Characterization and distribution of SNARE proteins at neuroendocrine nerve endings. *Neuroendocrinology.* 1996;64:379–392. [PubMed: 8930938]
52. Pupier S, Leveque C, Marqueze B, Kataoka M, Takahashi M, Seagar MJ. Cysteine string proteins associated with secretory granules of the rat neurohypophysis. *J Neurosci.* 1997;17:2722–2727. [PubMed: 9092593]
53. Miyata S, Takamatsu H, Maekawa S et al. Plasticity of neurohypophysial terminals with increased hormonal release during dehydration: ultrastructural and biochemical analyses. *J Comp Neurol.* 2001;434:413–427. [PubMed: 11343290]
54. Tobin V, Schwab Y, Lelos N, Onaka T, Pittman QJ, Ludwig M. Expression of exocytosis proteins in rat supraoptic nucleus neurones. *J Neuroendocrinol.* 2012;24:629–641. [PubMed: 21988098]

55. Meddle SL, Leng G, Selvarajah JR, Bicknell RJ, Russell JA. Direct pathways to the supraoptic nucleus from the brainstem and the main olfactory bulb are activated at parturition in the rat. *Neuroscience*. 2000;101:1013–1021. [PubMed: 11113350]
56. Brunton PJ, Russell JA. The expectant brain: adapting for motherhood. *Nat Rev Neurosci*. 2008;9:11–25. [PubMed: 18073776]
57. Lipschitz DL, Crowley WR, Bealer SL. Differential sensitivity of intranuclear and systemic oxytocin release to central noradrenergic receptor stimulation during mid- and late gestation in rats. *Am J Physiol Endocrinol Metab*. 2004;287:E523–E528. [PubMed: 15149956]
58. Bealer SL, Crowley WR. Noradrenergic control of central oxytocin release during lactation in rats. *Am J Physiol*. 1998;274:E453–E458. [PubMed: 9530128]
59. Bealer SL, Armstrong WE, Crowley WR. Oxytocin release in magnocellular nuclei: neurochemical mediators and functional significance during gestation. *Am J Physiol Regul Integr Comp Physiol*. 2010;299:R452–R528. [PubMed: 20554931]
60. Onaka T, Ikeda K, Yamashita T, Honda K. Facilitative role of endogenous oxytocin in noradrenaline release in the rat supraoptic nucleus. *Eur J Neurosci*. 2003;18:3018–3026. [PubMed: 14656297]
61. Bagnol D, Lu XY, Kaelin CB et al. Anatomy of an endogenous antagonist: Relationship between Agouti-related protein and proopiomelanocortin in brain. *J Neurosci*. 1999;19:Rc26. [PubMed: 10479719]
62. Ladyman SR, Augustine RA, Scherf E, Phillipps HR, Brown CH, Grattan DR. Attenuated hypothalamic responses to alpha-melanocyte stimulating hormone during pregnancy in the rat. *J Physiol*. 2016;594:1087–1101. [PubMed: 26613967]
63. Sabatier N, Leng G. Presynaptic actions of endocannabinoids mediate alpha-MSH-induced inhibition of oxytocin cells. *Am J Physiol Regul Integr Comp Physiol*. 2006;290:R577–R584. [PubMed: 16269571]
64. Augustine RA, Ladyman SR, Bouwer GT et al. Prolactin regulation of oxytocin neurone activity in pregnancy and lactation. *J Physiol*. 2017;595:3591–3605. [PubMed: 28211122]
65. Sakata I, Nakano Y, Osborne-Lawrence S et al. Characterization of a novel ghrelin cell reporter mouse. *Regul Pept*. 2009;155:91–98. [PubMed: 19361544]
66. Ishizaki S, Murase T, Sugimura Y et al. Role of ghrelin in the regulation of vasopressin release in conscious rats. *Endocrinology*. 2002;143:1589–1593. [PubMed: 11956139]
67. Haam J, Halmos KC, Di S, Tasker JG. Nutritional state-dependent ghrelin activation of vasopressin neurons via retrograde trans-neuronal-gliatal stimulation of excitatory GABA circuits. *J Neurosci*. 2014;34:6201–6213. [PubMed: 24790191]
68. Hurbin A, Orcel H, Alonso G, Moos F, Rabie A. The vasopressin receptors colocalize with vasopressin in the magnocellular neurons of the rat supraoptic nucleus and are modulated by water balance. *Endocrinology*. 2002;143:456–466. [PubMed: 11796498]
69. Brown CH, Ludwig M, Leng G. Kappa-opioid regulation of neuronal activity in the rat supraoptic nucleus *in vivo*. *J Neurosci*. 1998;18:9480–9488. [PubMed: 9801385]
70. Brown CH, Leng G, Ludwig M, Bourque CW. Endogenous activation of supraoptic nucleus kappa-opioid receptors terminates spontaneous phasic bursts in rat magnocellular neurosecretory cells. *J Neurophysiol*. 2006;95:3235–3244. [PubMed: 16495366]
71. Brown CH. Rhythmogenesis in vasopressin cells. *J Neuroendocrinol*. 2004;16:727–739. [PubMed: 15344911]
72. Brown CH, Bourque CW. Mechanisms of rhythmogenesis: insights from hypothalamic vasopressin neurons. *Trends Neurosci*. 2006;29:108–115. [PubMed: 16330104]
73. Bicknell RJ. Optimizing release from peptide hormone secretory nerve terminals. *J Exp Biol*. 1988;139:51–65. [PubMed: 2850339]
74. Dutton A, Dyball RE. Phasic firing enhances vasopressin release from the rat neurohypophysis. *J Physiol*. 1979;290:433–440. [PubMed: 469785]
75. Bicknell RJ, Brown D, Chapman C, Hancock PD, Leng G. Reversible fatigue of stimulus-secretion coupling in the rat neurohypophysis. *J Physiol*. 1984;348:601–613. [PubMed: 6716296]
76. Scott V, Bishop VR, Leng G, Brown CH. Dehydration-induced modulation of kappa-opioid inhibition of vasopressin neurone activity. *J Physiol*. 2009;587:5679–5689. [PubMed: 19822541]

77. Wakerley JB, Poulain DA, Brown D. Comparison of firing patterns in oxytocin- and vasopressin-releasing neurones during progressive dehydration. *Brain Res.* 1978;148:425–440. [PubMed: 656941]
78. Dyball RE, Pountney PS. Discharge patterns of supraoptic and paraventricular neurones in rats given a 2 per cent NaCl solution instead of drinking water. *J Endocrinol.* 1973;56:91–98. [PubMed: 4683417]
79. Walters JK, Hatton GI. Supraoptic neuronal activity in rats during five days of water deprivation. *Physiol Behav.* 1974;13:661–667. [PubMed: 4610604]
80. Ludwig M, Leng G. Autoinhibition of supraoptic nucleus vasopressin neurons *in vivo*: a combined retrodialysis/electrophysiological study in rats. *Eur J Neurosci.* 1997;9:2532–2540. [PubMed: 9517458]
81. Kombian SB, Mougnot D, Hirasawa M, Pittman QJ. Vasopressin preferentially depresses excitatory over inhibitory synaptic transmission in the rat supraoptic nucleus *in vitro*. *J Neuroendocrinol.* 2000;12:361–367. [PubMed: 10718934]
82. Hermes ML, Ruijter JM, Klop A, Buijs RM, Renaud LP. Vasopressin increases GABAergic inhibition of rat hypothalamic paraventricular nucleus neurons *in vitro*. *J Neurophysiol.* 2000;83:705–711. [PubMed: 10669486]
83. Gouzenes L, Desarmenien MG, Hussy N, Richard P, Moos FC. Vasopressin regularizes the phasic firing pattern of rat hypothalamic magnocellular vasopressin neurons. *J Neurosci.* 1998;18:1879–1885. [PubMed: 9465012]
84. Yosten GL, Samson WK. Pressor doses of vasopressin result in only transient elevations in plasma peptide levels. *Peptides.* 2012;33:342–345. [PubMed: 22227112]
85. Ludwig M, Callahan MF, Neumann I, Landgraf R, Morris M. Systemic osmotic stimulation increases vasopressin and oxytocin release within the supraoptic nucleus. *J Neuroendocrinol.* 1994;6:369–373. [PubMed: 7987366]
86. De Mota N, Reaux-Le Goazigo A, El Messari S et al. Apelin, a potent diuretic neuropeptide counteracting vasopressin actions through inhibition of vasopressin neuron activity and vasopressin release. *Proc Natl Acad Sci USA.* 2004;101:10464–10469. [PubMed: 15231996]
87. Poisner AM, Douglas WW. Adenosine triphosphate and adenosine triphosphatase in hormone-containing granules of posterior pituitary gland. *Science.* 1968;160:203–204. [PubMed: 4230606]
88. Reis WL, Biancardi VC, Son S, Antunes-Rodrigues J, Stern JE. Enhanced expression of heme oxygenase-1 and carbon monoxide excitatory effects in oxytocin and vasopressin neurones during water deprivation. *J Neuroendocrinol.* 2012;24:653–663. [PubMed: 22060896]
89. Watson SJ, Akil H, Fischli W et al. Dynorphin and vasopressin: common localization in magnocellular neurons. *Science.* 1982;216:85–87. [PubMed: 6121376]
90. Hirasawa M, Schwab Y, Natah S et al. Dendritically released transmitters cooperate via autocrine and retrograde actions to inhibit afferent excitation in rat brain. *J Physiol.* 2004;559:611–624. [PubMed: 15254151]
91. Di S, Popescu IR, Tasker JG. Glial control of endocannabinoid heterosynaptic modulation in hypothalamic magnocellular neuroendocrine cells. *J Neurosci.* 2013;33:18331–18342. [PubMed: 24227742]
92. Iremonger KJ, Kuzmiski JB, Baimoukhametova DV, Bains JS. Dual regulation of anterograde and retrograde transmission by endocannabinoids. *J Neurosci.* 2011;31:12011–12020. [PubMed: 21849561]
93. Landry M, Vila-Porcile E, Hokfelt T, Calas A. Differential routing of coexisting neuropeptides in vasopressin neurons. *Eur J Neurosci.* 2003;17:579–589.
94. Yamaguchi H, Sasaki K, Satomi Y et al. Peptidomic identification and biological validation of neuroendocrine regulatory peptide-1 and -2. *J Biol Chem.* 2007;282:26354–26360. [PubMed: 17609209]
95. Fujihara H, Sasaki K, Mishiro-Sato E et al. Molecular characterization and biological function of neuroendocrine regulatory peptide-3 in the rat. *Endocrinology.* 2012;153:1377–1386. [PubMed: 22253422]
96. Kadowaki K, Kishimoto J, Leng G, Emson PC. Up-regulation of nitric oxide synthase (NOS) gene expression together with NOS activity in the rat hypothalamo-hypophysial system after

- chronic salt loading: evidence of a neuromodulatory role of nitric oxide in arginine vasopressin and oxytocin secretion. *Endocrinology*. 1994;134:1011–1017. [PubMed: 7509733]
97. Gillard ER, Leon-Olea M, Mucio-Ramirez S et al. A novel role for endogenous pituitary adenylate cyclase activating polypeptide in the magnocellular neuroendocrine system. *Endocrinology*. 2006;147:791–803. [PubMed: 16282358]
98. Reaux-Le Goazigo A, Morinville A, Burlet A, Llorens-Cortes C, Beaudet A. Dehydration-induced cross-regulation of apelin and vasopressin immunoreactivity levels in magnocellular hypothalamic neurons. *Endocrinology*. 2004;145:4392–4400. [PubMed: 15166125]
99. Tobin VA, Bull PM, Arunachalam S, O'Carroll AM, Ueta Y, Ludwig M. The effects of apelin on the electrical activity of hypothalamic magnocellular vasopressin and oxytocin neurons and somatodendritic peptide release. *Endocrinology*. 2008;149:6136–6145. [PubMed: 18703633]
100. Reaux A, De Mota N, Skultetyova I et al. Physiological role of a novel neuropeptide, apelin, and its receptor in the rat brain. *J Neurochem*. 2001;77:1085–1096. [PubMed: 11359874]
101. Hus-Citharel A, Bodineau L, Frugiere A, Joubert F, Bouby N, Llorens-Cortes C. Apelin counteracts vasopressin-induced water reabsorption via cross talk between apelin and vasopressin receptor signaling pathways in the rat collecting duct. *Endocrinology*. 2014;155:4483–4493. [PubMed: 25157454]
102. Zhang F, Sun HJ, Xiong XQ et al. Apelin-13 and APJ in paraventricular nucleus contribute to hypertension via sympathetic activation and vasopressin release in spontaneously hypertensive rats. *Acta Physiol (Oxf)*. 2014;212:17–27. [PubMed: 24995933]
103. Burazin TC, Larm JA, Gundlach AL. Regulation by osmotic stimuli of galanin-R1 receptor expression in magnocellular neurones of the paraventricular and supraoptic nuclei of the rat. *J Neuroendocrinol*. 2001;13:358–370. [PubMed: 11264724]
104. Ciosek J, Cisowska A. Centrally administered galanin modifies vasopressin and oxytocin release from the hypothalamo-neurohypophysial system of euhydrated and dehydrated rats. *J Physiol Pharmacol*. 2003;54:625–641. [PubMed: 14726616]
105. Cisowska-Maciejewska A, Ciosek J. Galanin influences vasopressin and oxytocin release from the hypothalamo-neurohypophysial system of salt loaded rats. *J Physiol Pharmacol*. 2005;56:673–688. [PubMed: 16391423]
106. Wodowska J, Ciosek J. Galanin and galanin-like peptide modulate vasopressin and oxytocin release in vitro: the role of galanin receptors. *Neuropeptides*. 2014;48:387–397. [PubMed: 25464889]
107. Papas S, Bourque CW. Galanin inhibits continuous and phasic firing in rat hypothalamic magnocellular neurosecretory cells. *J Neurosci*. 1997;17:6048–6056. [PubMed: 9236216]
108. Andrew RD, Dudek FE. Burst discharge in mammalian neuroendocrine cells involves an intrinsic regenerative mechanism. *Science*. 1983;221:1050–1052. [PubMed: 6879204]
109. Kozoriz MG, Kuzmiski JB, Hirasawa M, Pittman QJ. Galanin modulates neuronal and synaptic properties in the rat supraoptic nucleus in a use and state dependent manner. *J Neurophysiol*. 2006;96:154–164. [PubMed: 16611841]
110. Shuster SJ, Riedl M, Li X, Vulchanova L, Elde R. The kappa opioid receptor and dynorphin co-localize in vasopressin magnocellular neurosecretory neurons in guinea-pig hypothalamus. *Neuroscience*. 2000;96:373–383. [PubMed: 10683577]
111. Whitnall MH, Gainer H, Cox BM, Molineaux CJ. Dynorphin-A-(1–8) is contained within vasopressin neurosecretory vesicles in rat pituitary. *Science*. 1983;222:1137–1139. [PubMed: 6648526]
112. Ludwig M, Brown CH, Russell JA, Leng G. Local opioid inhibition and morphine dependence of supraoptic nucleus oxytocin neurones in the rat in vivo. *J Physiol*. 1997;505:145–152. [PubMed: 9409478]
113. Inenaga K, Imura H, Yanaihara N, Yamashita H. Kappa-selective opioid receptor agonists leuorphan and dynorphin inhibit supraoptic neurons in rat hypothalamic slice preparations. *J Neuroendocrinol*. 1990;2:389–395. [PubMed: 19215365]
114. Inenaga K, Nagatomo T, Nakao K, Yanaihara N, Yamashita H. Kappa-selective agonists decrease postsynaptic potentials and calcium components of action potentials in the supraoptic nucleus of rat hypothalamus *in vitro*. *Neuroscience*. 1994;58:331–340. [PubMed: 7908725]

115. Brown CH, Ludwig M, Leng G. Temporal dissociation of the feedback effects of dendritically co-released peptides on rhythmogenesis in vasopressin cells. *Neuroscience*. 2004;124:105–111. [PubMed: 14960343]
116. Brown CH, Bourque CW. Autocrine feedback inhibition of plateau potentials terminates phasic bursts in magnocellular neurosecretory cells of the rat supraoptic nucleus. *J Physiol*. 2004;557:949–960. [PubMed: 15107473]
117. Iremonger KJ, Bains JS. Retrograde opioid signaling regulates glutamatergic transmission in the hypothalamus. *J Neurosci*. 2009;29:7349–7358. [PubMed: 19494156]
118. Muller W, Hallermann S, Swandulla D. Opioidergic modulation of voltage-activated K⁺ currents in magnocellular neurons of the supraoptic nucleus in rat. *J Neurophysiol*. 1999;81:1617. [PubMed: 10200198]
119. Scott V, Brown CH. State-dependent plasticity in vasopressin neurones: dehydration-induced changes in activity patterning. *J Neuroendocrinol*. 2010;22:343–354. [PubMed: 20088912]
120. Shibuya I, Noguchi J, Tanaka K et al. PACAP increases the cytosolic Ca²⁺ concentration and stimulates somatodendritic vasopressin release in rat supraoptic neurons. *J Neuroendocrinol*. 1998;10:31–42. [PubMed: 9510056]
121. Shibuya I, Kabashima N, Tanaka K et al. Patch-clamp analysis of the mechanism of PACAP-induced excitation in rat supraoptic neurones. *J Neuroendocrinol*. 1998;10:759–768. [PubMed: 9792327]
122. Toshinai K, Saito T, Yamaguchi H et al. Neuroendocrine regulatory peptide-1 and -2 (NERPs) inhibit the excitability of magnocellular neurosecretory cells in the hypothalamus. *Brain Res*. 2014;1563:52–60. [PubMed: 24704271]
123. Lee VH, Lee LT, Chu JY et al. An indispensable role of secretin in mediating the osmoregulatory functions of angiotensin II. *FASEB J*. 2010;24:5024–5032. [PubMed: 20739612]
124. Velmurugan S, Brunton PJ, Leng G, Russell JA. Circulating secretin activates supraoptic nucleus oxytocin and vasopressin neurons via noradrenergic pathways in the rat. *Endocrinology*. 2010;151:2681–2688. [PubMed: 20332196]
125. Chu JY, Chung SC, Lam AK, Tam S, Chung SK, Chow BK. Phenotypes developed in secretin receptor-null mice indicated a role for secretin in regulating renal water reabsorption. *Mol Cell Biol*. 2007;27:2499–2511. [PubMed: 17283064]
126. Xiang Z, Bo X, Oglesby I, Ford A, Burnstock G. Localization of ATP-gated P2X2 receptor immunoreactivity in the rat hypothalamus. *Brain Res*. 1998;813:390–397. [PubMed: 9838201]
127. Song Z, Vijayaraghavan S, Sladek CD. ATP increases intracellular calcium in supraoptic neurons by activation of both P2X and P2Y purinergic receptors. *Am J Physiol Regul Integr Comp Physiol*. 2007;292:R423–R431. [PubMed: 16973929]
128. Mori M, Tsushima H, Matsuda T. Antidiuretic effects of ATP induced by microinjection into the hypothalamic supraoptic nucleus in water-loaded and ethanol-anesthetized rats. *Jpn J Pharmacol*. 1994;66:445–450. [PubMed: 7723221]
129. Hiruma H, Bourque CW. P2 purinoceptor-mediated depolarization of rat supraoptic neurosecretory cells in vitro. *J Physiol*. 1995;489:805–811. [PubMed: 8788944]
130. Song Z, Gomes DA, Stevens W, Sladek CD. Multiple alpha1-adrenergic receptor subtypes support synergistic stimulation of vasopressin and oxytocin release by ATP and phenylephrine. *Am J Physiol Regul Integr Comp Physiol*. 2010;299:R1529–R1537. [PubMed: 20881098]
131. Vavra V, Bhattacharya A, Zemkova H. Facilitation of glutamate and GABA release by P2X receptor activation in supraoptic neurons from freshly isolated rat brain slices. *Neuroscience*. 2011;188:1–12. [PubMed: 21575687]
132. Gordon GR, Baimoukhametova DV, Hewitt SA, Rajapaksha WR, Fisher TE, Bains JS. Norepinephrine triggers release of glial ATP to increase postsynaptic efficacy. *Nat Neurosci*. 2005;8:1078–1086. [PubMed: 15995701]
133. Day TA, Sibbald JR, Khanna S. ATP mediates an excitatory noradrenergic neuron input to supraoptic vasopressin cells. *Brain Res*. 1993;607:341–344. [PubMed: 8481811]
134. Song Z, Sladek CD. Does conversion of ATP to adenosine terminate ATP-stimulated vasopressin release from hypothalamo-neurohypophyseal explants? *Brain Res*. 2005;1047:105–111. [PubMed: 15893296]

135. Ponzio TA, Wang YF, Hatton GI. Activation of adenosine A2A receptors alters postsynaptic currents and depolarizes neurons of the supraoptic nucleus. *Am J Physiol Regul Integr Comp Physiol.* 2006;291:R359–R366. [PubMed: 16644907]
136. Bull PM, Brown CH, Russell JA, Ludwig M. Activity-dependent feedback modulation of spike patterning of supraoptic nucleus neurons by endogenous adenosine. *Am J Physiol Regul Integr Comp Physiol.* 2006;291:R83–R90. [PubMed: 16497815]
137. Oliet SH, Poulain DA. Adenosine-induced presynaptic inhibition of IPSCs and EPSCs in rat hypothalamic supraoptic nucleus neurones. *J Physiol.* 1999;520:815–825. [PubMed: 10545146]
138. Ruan M, Brown CH. Feedback inhibition of action potential discharge by endogenous adenosine enhancement of the medium afterhyperpolarization. *J Physiol.* 2009;587:1043–1056. [PubMed: 19139041]
139. Kirkpatrick K, Bourque CW. Activity dependence and functional role of the apamin-sensitive K^+ current in rat supraoptic neurones *in vitro*. *J Physiol.* 1996;494:389–398. [PubMed: 8841999]
140. Ponzio TA, Hatton GI. Adenosine postsynaptically modulates supraoptic neuronal excitability. *J Neurophysiol.* 2005;93:535–547. [PubMed: 15356187]
141. Liu QS, Jia YS, Ju G. Nitric oxide inhibits neuronal activity in the supraoptic nucleus of the rat hypothalamic slices. *Brain Res Bull.* 1997;43:121–125. [PubMed: 9222524]
142. Stern JE, Ludwig M. NO inhibits supraoptic oxytocin and vasopressin neurons via activation of GABAergic synaptic inputs. *Am J Physiol.* 2001;280:R1815–R1822.
143. Ozaki M, Shibuya I, Kabashima N et al. Preferential potentiation by nitric oxide of spontaneous inhibitory postsynaptic currents in rat supraoptic neurones. *J Neuroendocrinol.* 2000;12:273–281. [PubMed: 10718923]
144. Rossoni E, Feng J, Tirozzi B, Brown D, Leng G, Moos F. Emergent synchronous bursting of oxytocin neuronal network. *PLoS Comput Biol.* 2008;4:e1000123. [PubMed: 18636098]
145. Sharif Naeini R, Witty MF, Seguela P, Bourque CW. An N-terminal variant of Trpv1 channel is required for osmosensory transduction. *Nat Neurosci.* 2006;9:93–98. [PubMed: 16327782]
146. Zygmunt PM, Petersson J, Andersson DA et al. Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. *Nature.* 1999;400:452–457. [PubMed: 10440374]
147. Stern JE, Armstrong WE. Changes in the electrical properties of supraoptic nucleus oxytocin and vasopressin neurons during lactation. *J Neurosci.* 1996;16:4861–4871. [PubMed: 8756418]
148. Stern JE, Armstrong WE. Reorganization of the dendritic trees of oxytocin and vasopressin neurons of the rat supraoptic nucleus during lactation. *J Neurosci.* 1998;18:841–853. [PubMed: 9437006]
149. El Majdoubi M, Poulain DA, Theodosios DT. The glutamatergic innervation of oxytocin- and vasopressin-secreting neurons in the rat supraoptic nucleus and its contribution to lactation-induced synaptic plasticity. *Eur J Neurosci.* 1996;8:1377–1389.
150. Gies U, Theodosios DT. Synaptic plasticity in the rat supraoptic nucleus during lactation involves GABA innervation and oxytocin neurons: a quantitative immunocytochemical analysis. *J Neurosci.* 1994;14:2861–2869. [PubMed: 8182444]
151. Stern JE, Hestrin S, Armstrong WE. Enhanced neurotransmitter release at glutamatergic synapses on oxytocin neurones during lactation in the rat. *J Physiol.* 2000;526:109–114. [PubMed: 10878104]
152. Michaloudi HC, El Majdoubi M, Poulain DA, Papadopoulos GC, Theodosios DT. The noradrenergic innervation of identified hypothalamic magnocellular somata and its contribution to lactation-induced synaptic plasticity. *J Neuroendocrinol.* 1997;9:17–23. [PubMed: 9023735]
153. Seymour AJ, Scott V, Augustine RA, Bouwer GT, Campbell RE, Brown CH. Development of an excitatory kisspeptin projection to the oxytocin system in late pregnancy. *J Physiol.* 2017;595:825–838. [PubMed: 27589336]
154. Lee SW, Kim YB, Kim JS et al. GABAergic inhibition is weakened or converted into excitation in the oxytocin and vasopressin neurons of the lactating rat. *Mol Brain.* 2015;8:34. [PubMed: 26017151]
155. Belin V, Moos F, Richard P. Synchronization of oxytocin cells in the hypothalamic paraventricular and supraoptic nuclei in suckled rats: direct proof with paired extracellular recordings. *Exp Brain Res.* 1984;57:201–203. [PubMed: 6542868]

156. Douglas A, Scullion S, Antonijevic I, Brown D, Russell J, Leng G. Uterine contractile activity stimulates supraoptic neurons in term pregnant rats via a noradrenergic pathway. *Endocrinology*. 2001;142:633–644. [PubMed: 11159834]
157. Augustine RA, Seymour AJ, Campbell RE, Grattan DR, Brown CH. Integrative neuro-humoral regulation of oxytocin neuron activity in pregnancy and lactation. *J Neuroendocrinol*. 2018;30:e12569.
158. Moos F, Poulain DA, Rodriguez F, Guerne Y, Vincent JD, Richard P. Release of oxytocin within the supraoptic nucleus during the milk ejection reflex in rats. *Exp Brain Res*. 1989;76:593–602. [PubMed: 2792248]
159. Freund-Mercier MJ, Richard P. Electrophysiological evidence for facilitatory control of oxytocin neurones by oxytocin during suckling in the rat. *J Physiol*. 1984;352:447–466. [PubMed: 6747898]
160. Neumann I, Douglas AJ, Pittman QJ, Russell JA, Landgraf R. Oxytocin released within the supraoptic nucleus of the rat brain by positive feedback action is involved in parturition-related events. *J Neuroendocrinol*. 1996;8:227–233. [PubMed: 8730656]
161. Israel JM, Le Masson G, Theodosis DT, Poulain DA. Glutamatergic input governs periodicity and synchronization of bursting activity in oxytocin neurons in hypothalamic organotypic cultures. *Eur J Neurosci*. 2003;17:2619–2629. [PubMed: 12823469]
162. Popescu IR, Buraei Z, Haam J, Weng FJ, Tasker JG. Lactation induces increased IPSC bursting in oxytocinergic neurons. *Physiol Rep*. 2019;7:e14047. [PubMed: 31008554]
163. Teruyama R, Armstrong WE. Changes in the active membrane properties of rat supraoptic neurones during pregnancy and lactation. *J Neuroendocrinol*. 2002;14:933–944. [PubMed: 12472874]
164. Wang YF, Hatton GI. Burst firing of oxytocin neurons in male rat hypothalamic slices. *Brain Res*. 2005;1032:36–43. [PubMed: 15680939]
165. Herbison AE, Voisin DL, Douglas AJ, Chapman C. Profile of monoamine and excitatory amino acid release in rat supraoptic nucleus over parturition. *Endocrinology*. 1997;138:33–40. [PubMed: 8977382]
166. Moos F, Richard P. Paraventricular and supraoptic bursting oxytocin cells in rat are locally regulated by oxytocin and functionally related. *J Physiol*. 1989;408:1–18. [PubMed: 2778722]
167. Hatton GI. Astroglial modulation of neurotransmitter/peptide release from the neurohypophysis: present status. *J Chem Neuroanat*. 1999;16:203–221. [PubMed: 10422739]
168. Perlmutter LS, Tweedle CD, Hatton GI. Neuronal/glial plasticity in the supraoptic dendritic zone: dendritic bundling and double synapse formation at parturition. *Neuroscience*. 1984;13:769–779. [PubMed: 6527778]
169. Moos F, Marganec A, Fontanaud P, Guillou-Duvoid A, Alonso G. Synchronization of oxytocin neurons in suckled rats: possible role of bilateral innervation of hypothalamic supraoptic nuclei by single medullary neurons. *Eur J Neurosci*. 2004;20:66–78. [PubMed: 15245480]
170. Wang YF, Negoro H, Higuchi T. Lesions of hypothalamic mammillary body desynchronise milk-ejection bursts of rat bilateral supraoptic oxytocin neurones. *J Neuroendocrinol*. 2012;25:67–75.
171. Boudaba C, Di S, Tasker JG. Presynaptic noradrenergic regulation of glutamate inputs to hypothalamic magnocellular neurones. *J Neuroendocrinol*. 2003;15:803–810. [PubMed: 12834442]
172. Roland BL, Sawchenko PE. Local origins of some GABAergic projections to the paraventricular and supraoptic nuclei of the hypothalamus in the rat. *J Comp Neurol*. 1993;332:123–143. [PubMed: 7685780]
173. Boudaba C, Tasker JG. Internuclear coupling of hypothalamic magnocellular nuclei by glutamate synaptic circuits. *Am J Physiol Regul Integr Comp Physiol*. 2006;291:R102–R111. [PubMed: 16469835]
174. Sumner BE, Coombes JE, Pumford KM, Russell JA. Opioid receptor subtypes in the supraoptic nucleus and posterior pituitary gland of morphine-tolerant rats. *Neuroscience*. 1990;37:635–645. [PubMed: 2174133]
175. Smith MJ, Wise PM. Localization of kappa opioid receptors in oxytocin magnocellular neurons in the paraventricular and supraoptic nuclei. *Brain Res*. 2001;898:162–165. [PubMed: 11292460]

176. Kim JS, Brown CH, Anderson GM. Anti-opioid effects of RFRP-3 on magnocellular neuron activity in morphine-naive and morphine-treated female rats. *Endocrinology*. 2016;157: 4003–4011. [PubMed: 27533886]
177. Martin R, Moll U, Voigt KH. An attempt to characterize by immunocytochemical methods the enkephalin-like material in oxytocin endings of the rat neurohypophysis. *Life Sci*. 1983;33(Suppl. 1):69–72. [PubMed: 6664245]
178. Eriksson M, Ceccatelli S, Uvnas-Moberg K, Iadarola M, Hokfelt T. Expression of Fos-related antigens, oxytocin, dynorphin and galanin in the paraventricular and supraoptic nuclei of lactating rats. *Neuroendocrinology*. 1996;63:356–367. [PubMed: 8739891]
179. Brown CH, Murphy NP, Munro G et al. Interruption of central noradrenergic pathways and morphine withdrawal excitation of oxytocin neurones in the rat. *J Physiol*. 1998;507:831–842. [PubMed: 9508843]
180. Douglas AJ, Neumann I, Meeren HK et al. Central endogenous opioid inhibition of supraoptic oxytocin neurons in pregnant rats. *J Neurosci*. 1995;15:5049–5057. [PubMed: 7623133]
181. Douglas AJ, Bicknell RJ, Leng G, Russell JA, Meddle SL. Beta-endorphin cells in the arcuate nucleus: Projections to the supraoptic nucleus and changes in expression during pregnancy and parturition. *J Neuroendocrinol*. 2002;14:768–777. [PubMed: 12372001]
182. Zhao BG, Chapman C, Bicknell RJ. Functional kappa-opioid receptors on oxytocin and vasopressin nerve terminals isolated from the rat neurohypophysis. *Brain Res*. 1988;462:62–66. [PubMed: 2902908]
183. Leng G, Dye S, Bicknell RJ. Kappa-opioid restraint of oxytocin secretion: plasticity through pregnancy. *Neuroendocrinology*. 1997;66:378–383. [PubMed: 9430443]
184. Douglas AJ, Bicknell RJ. Oxytocin nerve terminal desensitization to kappa-opioids at the end of pregnancy. *Ann NY Acad Sci*. 1993;689:589–592. [PubMed: 8396878]
185. Douglas AJ, Dye S, Leng G, Russell JA, Bicknell RJ. Endogenous opioid regulation of oxytocin secretion through pregnancy in the rat. *J Neuroendocrinol*. 1993;5:307–314. [PubMed: 8100468]
186. Srisawat R, Ludwig M, Bull PM, Douglas AJ, Russell JA, Leng G. Nitric oxide and the oxytocin system in pregnancy. *J Neurosci*. 2000;20:6721–6737. [PubMed: 10964978]
187. Bull PM, Ludwig M, Blackburn-Munro GJ, Delgado-Cohen H, Brown CH, Russell JA. The role of nitric oxide in morphine dependence and withdrawal excitation of rat oxytocin neurons. *Eur J Neurosci*. 2003;18:2545–2551. [PubMed: 14622155]
188. Doi N, Brown CH, Cohen HD, Leng G, Russell JA. Effects of the endogenous opioid peptide, endomorphin 1, on supraoptic nucleus oxytocin and vasopressin neurones *in vivo* and *in vitro*. *Br J Pharmacol*. 2001;132:1136–1144. [PubMed: 11226145]
189. Brown CH, Russell JA. Cellular mechanisms underlying neuronal excitability during morphine withdrawal in physical dependence: lessons from the magnocellular oxytocin system. *Stress*. 2004;7:97–107. [PubMed: 15512853]
190. Brown CH, Munro G, Johnstone LE, Robson AC, Landgraf R, Russell JA. Oxytocin neurone autoexcitation during morphine withdrawal in anaesthetized rats. *NeuroReport*. 1997;8:951–955. [PubMed: 9141071]
191. Pinol RA, Jameson H, Popratiloff A, Lee NH, Mendelowitz D. Visualization of oxytocin release that mediates paired pulse facilitation in hypothalamic pathways to brainstem autonomic neurons. *PLoS ONE*. 2014;9:e112138. [PubMed: 25379676]
192. Roy RK, Augustine RA, Brown CH, Schwenke DO. Activation of oxytocin neurons in the paraventricular nucleus drives cardiac sympathetic nerve activation following myocardial infarction in rats. *Commun Biol*. 2018;1:160. [PubMed: 30320228]
193. Son SJ, Filosa JA, Potapenko ES et al. Dendritic peptide release mediates interpopulation crosstalk between neurosecretory and preautonomic networks. *Neuron*. 2013;78:1036–1049. [PubMed: 23791197]
194. Zaelzer C, Gizowski C, Salmon CK, Murai KK, Bourque CW. Detection of activity-dependent vasopressin release from neuronal dendrites and axon terminals using sniffer cells. *J Neurophysiol*. 2018;120:1386–1396. [PubMed: 29975164]

195. Theodosios DT, Poulain DA. Evidence that oxytocin-secreting neurones are involved in the ultrastructural reorganisation of the rat supraoptic nucleus apparent at lactation. *Cell Tissue Res.* 1984;235:217–219. [PubMed: 6365328]
196. Tweedle CD, Hatton GI. Ultrastructural changes in rat hypothalamic neurosecretory cells and their associated glia during minimal dehydration and rehydration. *Cell Tissue Res.* 1977;181:59–72. [PubMed: 880623]
197. Piet R, Vargova L, Sykova E, Poulain DA, Oliet SH. Physiological contribution of the astrocytic environment of neurons to intersynaptic crosstalk. *Proc Natl Acad Sci USA.* 2004;101:2151–2155. [PubMed: 14766975]
198. Strack AM, Sawyer WB, Hughes JH, Platt KB, Loewy AD. A general pattern of CNS innervation of the sympathetic outflow demonstrated by transneuronal pseudorabies viral infections. *Brain Res.* 1989;491:156–162. [PubMed: 2569907]
199. Bourque CW. Central mechanisms of osmosensation and systemic osmoregulation. *Nat Rev Neurosci.* 2008;9:519–531. [PubMed: 18509340]
200. Toney GM, Chen QH, Cato MJ, Stocker SD. Central osmotic regulation of sympathetic nerve activity. *Acta Physiol Scand.* 2003;177:43–55. [PubMed: 12492778]
201. Gabor A, Leenen FH. Central neuromodulatory pathways regulating sympathetic activity in hypertension. *J Appl Physiol.* 2012;113:1294–1303. [PubMed: 22773773]
202. Han SY, Gray E, Hughes G, Brown CH, Schwenke DO. Increased sympathetic drive during the onset of hypertension in conscious Cyp1a1-Ren2 rats. *Pflugers Arch Eur J Physiol.* 2014;466:459–466. [PubMed: 23979225]
203. Jardine DL, Charles CJ, Ashton RK et al. Increased cardiac sympathetic nerve activity following acute myocardial infarction in a sheep model. *J Physiol.* 2005;565:325–333. [PubMed: 15774526]
204. Leenen FH. Brain mechanisms contributing to sympathetic hyperactivity and heart failure. *Circ Res.* 2007;101:221–223. [PubMed: 17673679]
205. Biancardi VC, Son SJ, Sonner PM, Zheng H, Patel KP, Stern JE. Contribution of central nervous system endothelial nitric oxide synthase to neurohumoral activation in heart failure rats. *Hypertension.* 2011;58:454–463. [PubMed: 21825233]
206. Cohn JN, Levine TB, Olivari MT et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med.* 1984;311:819–823. [PubMed: 6382011]
207. Han SY, Bouwer GT, Seymour AJ, Korpak AK, Schwenke DO, Brown CH. Induction of hypertension blunts baroreflex inhibition of vasopressin neurons in the rat. *Eur J Neurosci.* 2015;42:2690–2698. [PubMed: 26342194]
208. Korpak AK, Han SY, Schwenke DO, Brown CH. A switch from GABA inhibition to excitation of vasopressin neurons exacerbates the development of angiotensin II-dependent hypertension. *J Neuroendocrinol.* 2018;30:e12564.
209. Roy RK, Augustine RA, Brown CH, Schwenke DO. Acute myocardial infarction activates magnocellular vasopressin and oxytocin neurons. *J Neuroendocrinol.* 2019;31:e12808. [PubMed: 31715034]
210. Potapenko ES, Biancardi VC, Zhou Y, Stern JE. Altered astrocyte glutamate transporter regulation of hypothalamic neurosecretory neurons in heart failure rats. *Am J Physiol Regul Integr Comp Physiol.* 2012;303:R291–R300. [PubMed: 22696576]
211. Stern JE, Potapenko ES. Enhanced NMDA receptor-mediated intracellular calcium signaling in magnocellular neurosecretory neurons in heart failure rats. *Am J Physiol Regul Integr Comp Physiol.* 2013;305:R414–R422.
212. Goldsmith SR, Francis GS, Cowley AW Jr, Levine TB, Cohn JN. Increased plasma arginine vasopressin levels in patients with congestive heart failure. *J Am Coll Cardiol.* 1983;1:1385–1390. [PubMed: 6343460]
213. Goldsmith SR, Gheorghide M. Vasopressin antagonism in heart failure. *J Am Coll Cardiol.* 2005;46:1785–1791. [PubMed: 16286160]
214. Murakami K, Akana S, Dallman MF, Ganong WF. Correlation between the stress-induced transient increase in corticotropin-releasing hormone content of the median eminence of the

- hypothalamus and adrenocorticotrophic hormone secretion. *Neuroendocrinology*. 1989;49:233–241. [PubMed: 2541356]
215. Dabrowska J, Hazra R, Ahern TH et al. Neuroanatomical evidence for reciprocal regulation of the corticotrophin-releasing factor and oxytocin systems in the hypothalamus and the bed nucleus of the stria terminalis of the rat: Implications for balancing stress and affect. *Psychoneuroendocrinology*. 2011;36:1312–1326. [PubMed: 21481539]
216. Jamieson BB, Nair BB, Iremonger KJ. Regulation of hypothalamic corticotropin-releasing hormone neurone excitability by oxytocin. *J Neuroendocrinol*. 2017;29:e12532.
217. Atwell D, Buchan AM, Charpak S, Lauritzen M, Macvicar BA, Newman EA. Glial and neuronal control of brain blood flow. *Nature*. 2010;468:232–243. [PubMed: 21068832]
218. Du W, Stern JE, Filosa JA. Neuronal-derived nitric oxide and somatodendritically released vasopressin regulate neurovascular coupling in the rat hypothalamic supraoptic nucleus. *J Neurosci*. 2015;35:5330–5341. [PubMed: 25834057]
219. Leng G, Sabatier N. Oxytocin - the sweet hormone? *Trends Endocrinol Metab*. 2017;28:365–376. [PubMed: 28283319]
220. Sabatier N, Caquineau C, Douglas AJ, Leng G. Oxytocin released from magnocellular dendrites: a potential modulator of alpha-melanocyte-stimulating hormone behavioral actions? *Ann N Y Acad Sci*. 2003;994:218–224. [PubMed: 12851319]
221. Klockars OA, Waas JR, Klockars A, Levine AS, Olszewski PK. Neural basis of ventromedial hypothalamic oxytocin-driven decrease in appetite. *Neuroscience*. 2017;366:54–61. [PubMed: 29037599]
222. Patisaul HB, Scordalakes EM, Young LJ, Rissman EF. Oxytocin, but not oxytocin receptor, is regulated by oestrogen receptor beta in the female mouse hypothalamus. *J Neuroendocrinol*. 2003;15:787–793. [PubMed: 12834440]
223. Manning M, Misicka A, Olma A et al. Oxytocin and vasopressin agonists and antagonists as research tools and potential therapeutics. *J Neuroendocrinol*. 2012;24:609–628. [PubMed: 22375852]
224. Chen C, Jiang Z, Fu X, Yu D, Huang H, Tasker JG. Astrocytes amplify neuronal dendritic volume transmission stimulated by norepinephrine. *Cell Rep*. 2019;29:4349–4361.e4. [PubMed: 31875545]
225. Takayanagi Y, Yoshida M, Takashima A et al. Activation of supraoptic oxytocin neurons by secretin facilitates social recognition. *Biol Psychiatry*. 2017;81:243–251. [PubMed: 26803341]
226. Ludwig M, Leng G. Dendritic peptide release and peptide-dependent behaviours. *Nat Rev Neurosci*. 2006;7:126–136. [PubMed: 16429122]
227. Chini B, Verhage M, Grinevich V. The action radius of oxytocin release in the mammalian CNS: from single vesicles to behavior. *Trends Pharmacol Sci*. 2017;38:982–991. [PubMed: 28899620]
228. Mens WB, Witter A, van Wimersma Greidanus TB. Penetration of neurohypophyseal hormones from plasma into cerebrospinal fluid (CSF): half-times of disappearance of these neuropeptides from CSF. *Brain Res*. 1983;262:143–149. [PubMed: 6831225]
229. Stark H, Burbach JP, Van der Kleij AA, De Wied D. In vivo conversion of vasopressin after microinjection into limbic brain areas of rats. *Peptides*. 1989;10:717–720. [PubMed: 2587414]
230. Xia X, Lessmann V, Martin TF. Imaging of evoked dense-core-vesicle exocytosis in hippocampal neurons reveals long latencies and kiss-and-run fusion events. *J Cell Sci*. 2009;122:75–82. [PubMed: 19066284]
231. Engelmann M, Ebner K, Landgraf R, Wotjak CT. Effects of Morris water maze testing on the neuroendocrine stress response and intrahypothalamic release of vasopressin and oxytocin in the rat. *Horm Behav*. 2006;50:496–501. [PubMed: 16875693]
232. Ebner K, Wotjak CT, Landgraf R, Engelmann M. Forced swimming triggers vasopressin release within the amygdala to modulate stress-coping strategies in rats. *Eur J Neurosci*. 2002;15:384–388. [PubMed: 11849304]
233. Ebner K, Wotjak CT, Landgraf R, Engelmann M. A single social defeat experience selectively stimulates the release of oxytocin, but not vasopressin, within the septal brain area of male rats. *Brain Res*. 2000;872:87–92. [PubMed: 10924679]

234. Engelmann M, Ebner K, Landgraf R, Wotjak CT. Swim stress triggers the release of vasopressin within the suprachiasmatic nucleus of male rats. *Brain Res.* 1998;792:343–347. [PubMed: 9593985]
235. Ebner K, Wotjak CT, Holsboer F, Landgraf R, Engelmann M. Vasopressin released within the septal brain area during swim stress modulates the behavioural stress response in rats. *EurJNeurosci.* 1999;11:997–1002.
236. Landgraf R, Ludwig M. Vasopressin release within the supraoptic and paraventricular nuclei of the rat brain: osmotic stimulation via microdialysis. *Brain Res.* 1991;558:191–196. [PubMed: 1782541]
237. Althammer F, Grinevich V. Diversity of oxytocin neurons: beyond magno- and parvocellular cell types? *J Neuroendocrinol.* 2017; 30:e12549.
238. Ludwig M, Sabatier N, Dayanithi G, Russell JA, Leng G. The active role of dendrites in the regulation of magnocellular neurosecretory cell behavior. *Prog Brain Res.* 2002;139:247. [PubMed: 12436940]
239. Stern JE. Neuroendocrine-autonomic integration in the paraventricular nucleus: novel roles for dendritically released neuropeptides. *J Neuroendocrinol.* 2015;27:487–497. [PubMed: 25546497]

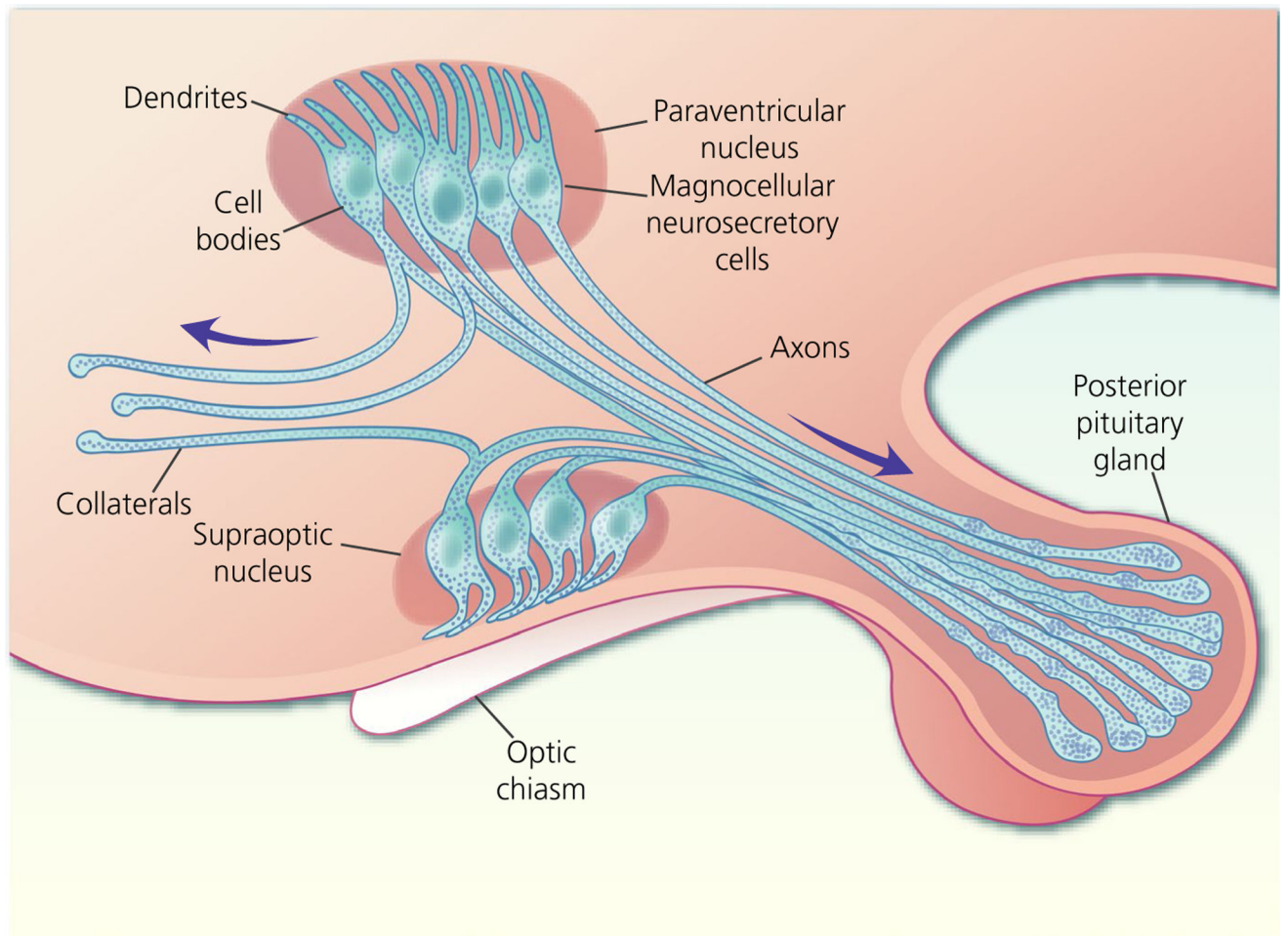


FIGURE 1. Magnocellular neurosecretory cells (MNCs) of the hypothalamic supraoptic nucleus and paraventricular nucleus each possess one to three dendrites and project a single axon to the posterior pituitary gland where they secrete either oxytocin or vasopressin into the circulation. Some MNC axons project axon collaterals to other brains areas

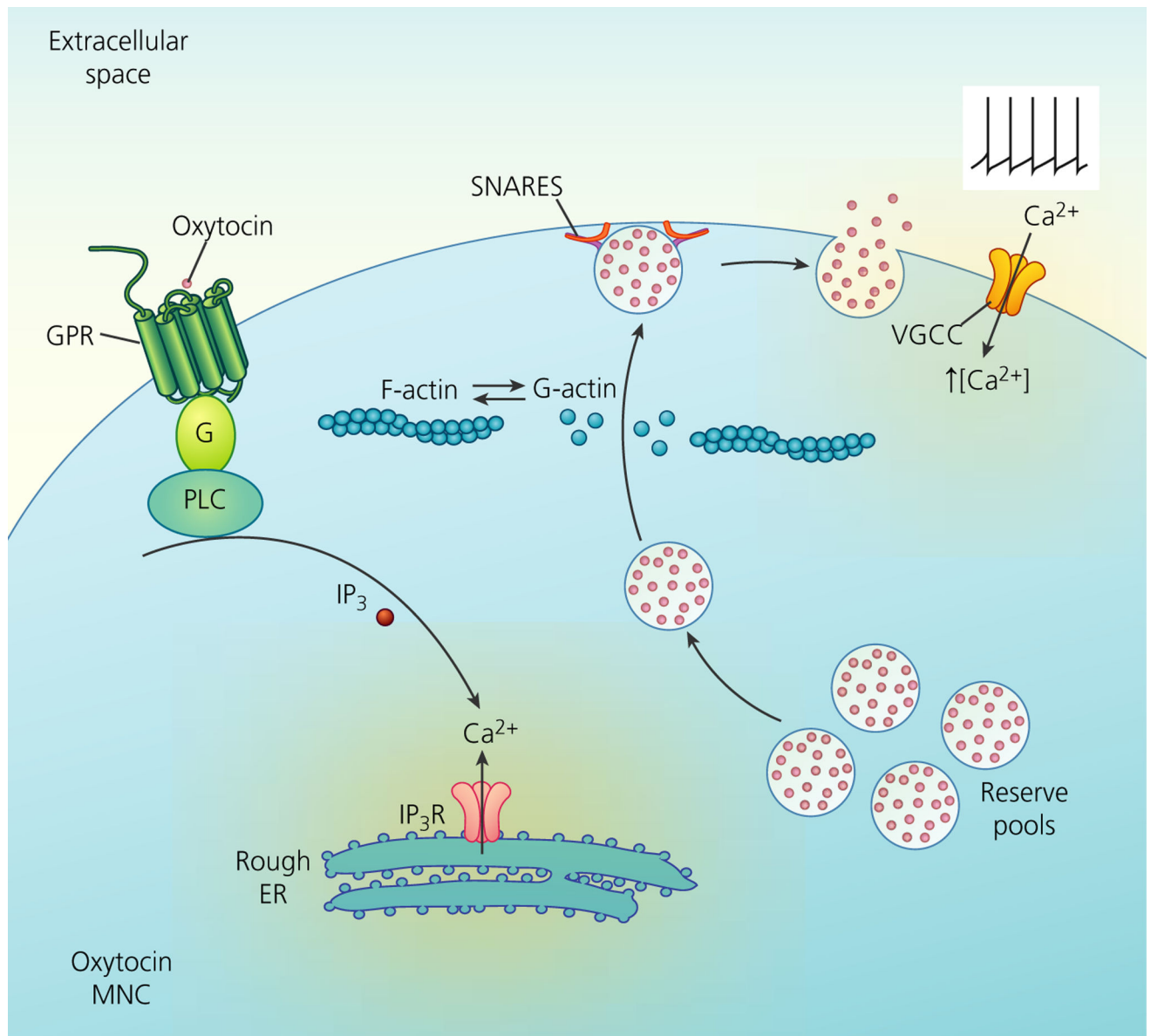


FIGURE 2.

Mechanisms of somato-dendritic release of oxytocin from magnocellular neurosecretory cells (MNCs). Neuropeptides are synthesised and packaged in the soma and stored in dendrites in a reserve pool containing large numbers of large dense-core vesicles (LDCVs). Depolarisation-induced calcium entry through voltage-gated calcium channels (VGCCs) stimulates peptide release by exocytosis of LDCVs. This requires the depolymerisation of F-actin to G-actin. Furthermore, the stimulation of G-protein coupled receptors (GPR), such as the oxytocin receptor, stimulates the mobilisation of Ca^{2+} from inositol trisphosphate (IP_3)-dependent intracellular stores of the rough endoplasmic reticulum (ER) and an increase in the number of LDCVs at the plasma membrane, thus priming the exocytosis machinery for subsequent activity-dependent release. Although some members of the soluble N-ethylmaleimide-sensitive factor attachment receptor (SNARE) family are detectable by

immunocytochemistry, there appears to be a lack of vesicle-associated membrane protein-2, synaptosomal-associated protein 25 and synaptotagmin-1 in the somata and dendrites, with their function presumably being replaced by other SNARE proteins. IP₃R, inositol trisphosphate receptor; PLC, phospholipase C

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

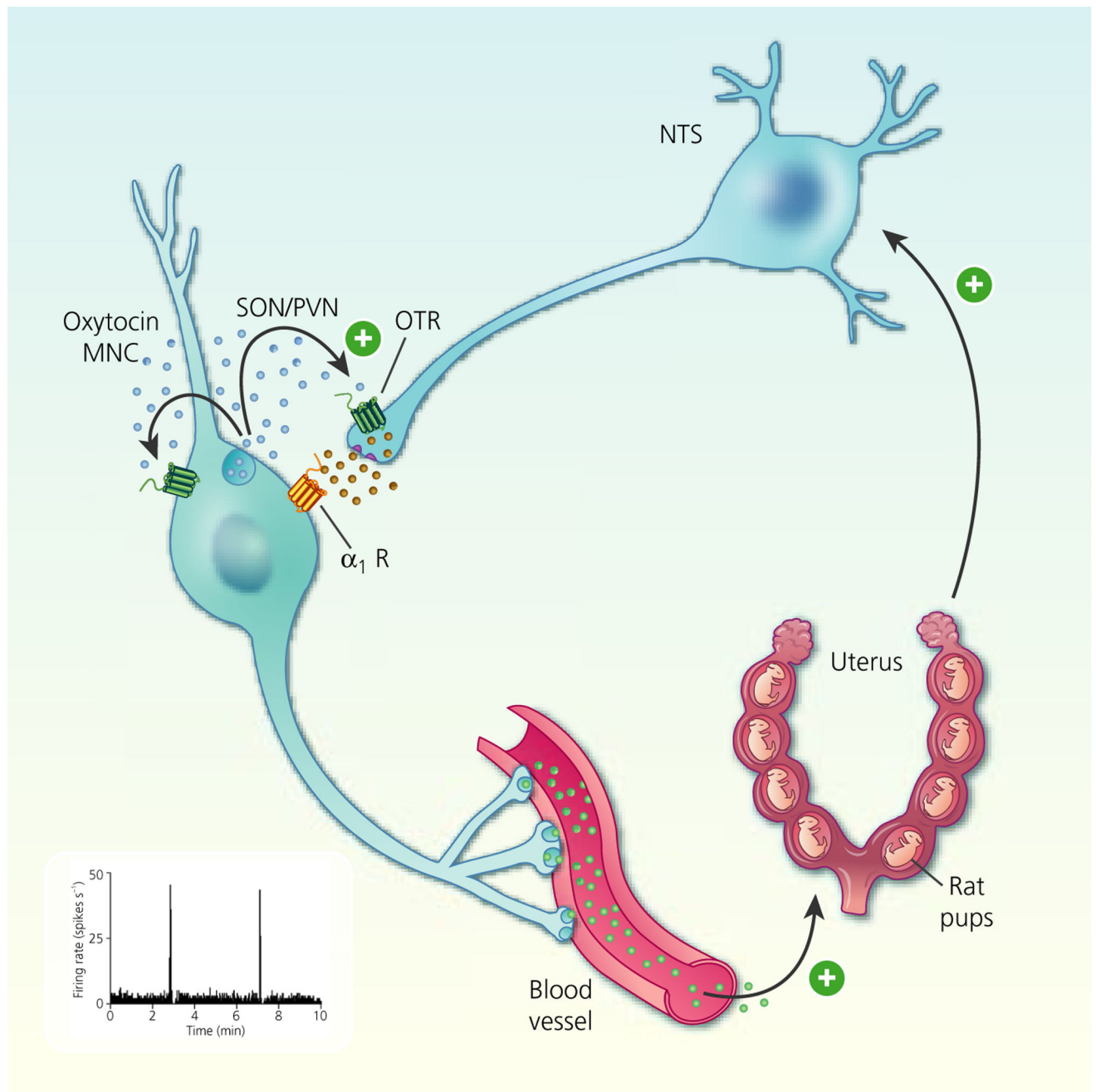
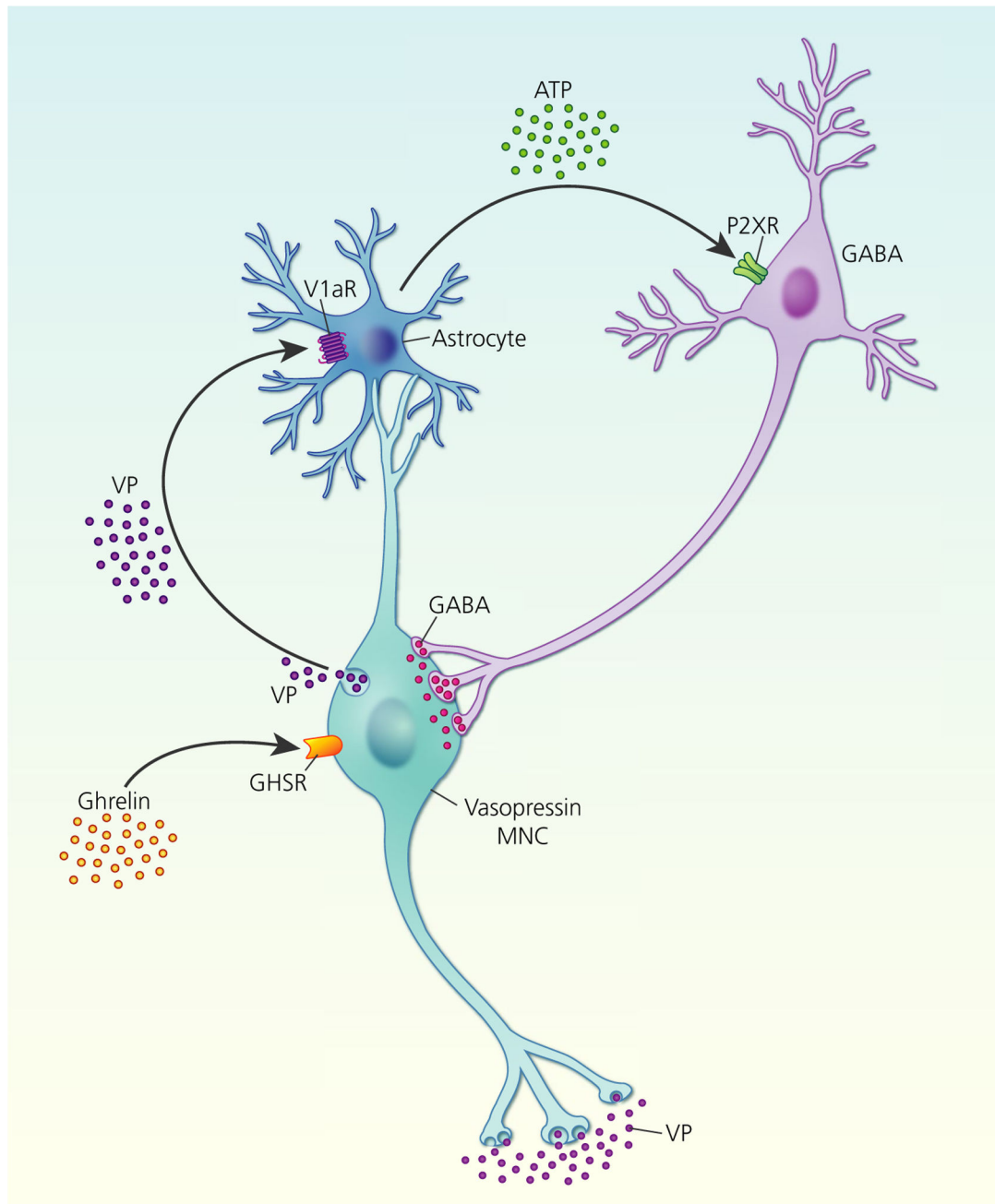


FIGURE 3.

Autocrine modulation of burst firing in oxytocin magnocellular neurosecretory cells (MNCs). Cervical stretch during birth activates stretch receptors to activate A2 noradrenergic neurones in the nucleus tractus solitarius (NTS) that, in turn, activate somato-dendritic oxytocin secretion from oxytocin MNCs. Oxytocin feeds back on oxytocin MNCs to increase excitability. Oxytocin also increases noradrenaline secretion within the supraoptic nucleus (SON) to establish a local positive feedback loop that reinforces oxytocin MNC excitation and promotes oxytocin secretion into the circulation to trigger uterine contractions during birth. OTR, oxytocin receptor; PVN, paraventricular nucleus

**FIGURE 4.**

Ghrelin stimulation of somato-dendritic vasopressin (VP) secretion. Ghrelin activation of growth hormone secretagogue receptors (GHSR) on vasopressin magnocellular neurosecretory cells (MNCs) induces somato-dendritic vasopressin secretion, which activates V_{1a} receptors (V_{1a}R) on neighbouring astrocytes to increase intracellular calcium. Increased astrocytic calcium triggers release of the gliotransmitter, ATP, which activates ionotropic P_{2X} receptors (P_{2X}R) on GABA interneurons that project back to vasopressin MNCs

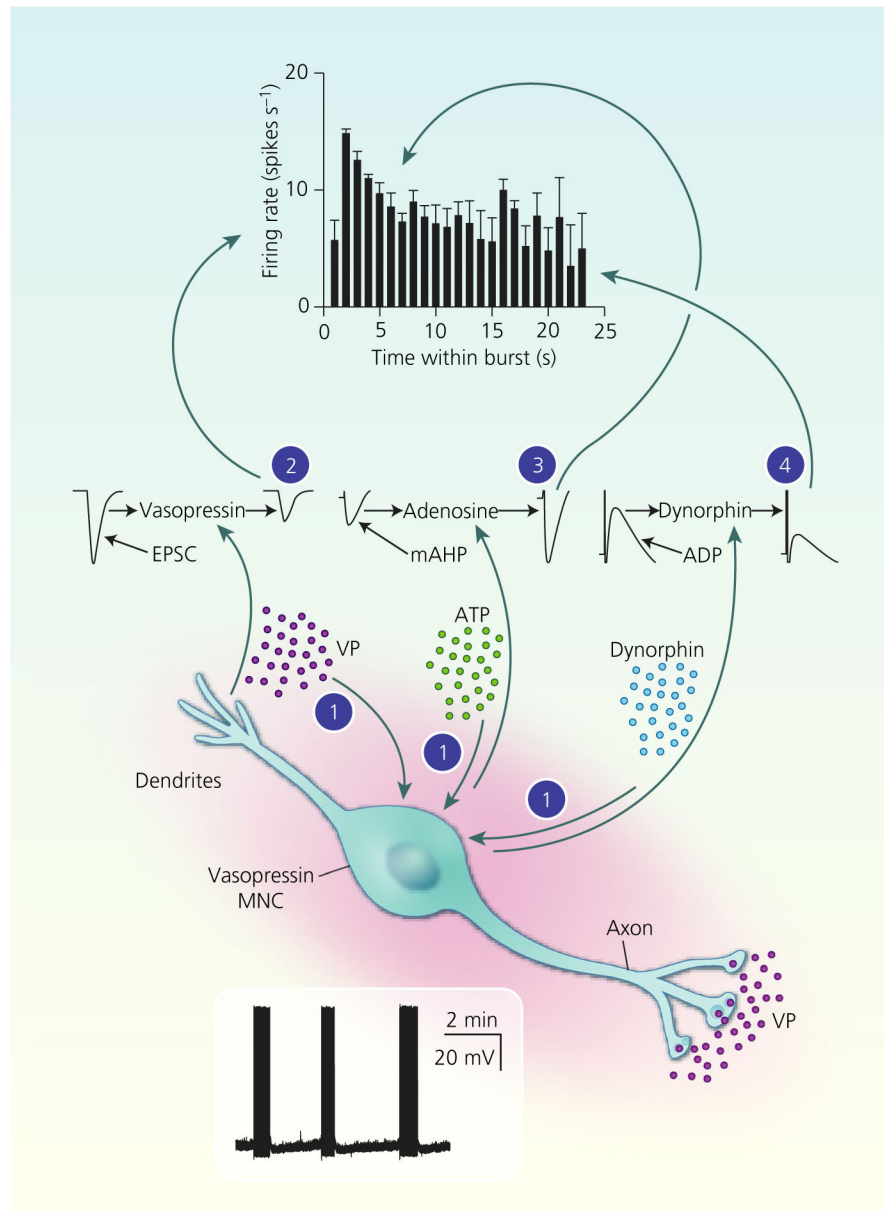


FIGURE 5.

Autocrine modulation of vasopressin magnocellular neurosecretory cell (MNC) activity. Vasopressin (VP) MNCs secrete vasopressin, ATP and dynorphin (and other transmitters) from their somata and dendrites. Endogenous arginine vasopressin (AVP) (2) inhibits spike discharge throughout bursts via inhibition of the excitatory post-synaptic current (EPSC) amplitude. Endogenous ATP is rapidly converted to adenosine (3), which enhances the medium afterhyperpolarisation (mAHP) amplitude over the first few seconds of bursts to contribute to spike frequency adaptation. Endogenous dynorphin (4) inhibition of the afterdepolarisation (ADP) increases progressively over the course of bursts, eventually resulting in burst termination. Combined, these autocrine feedback effects of somato-dendritic vasopressin and co-secreted transmitters shape phasic activity for efficient secretion vasopressin into the circulation from the posterior pituitary gland

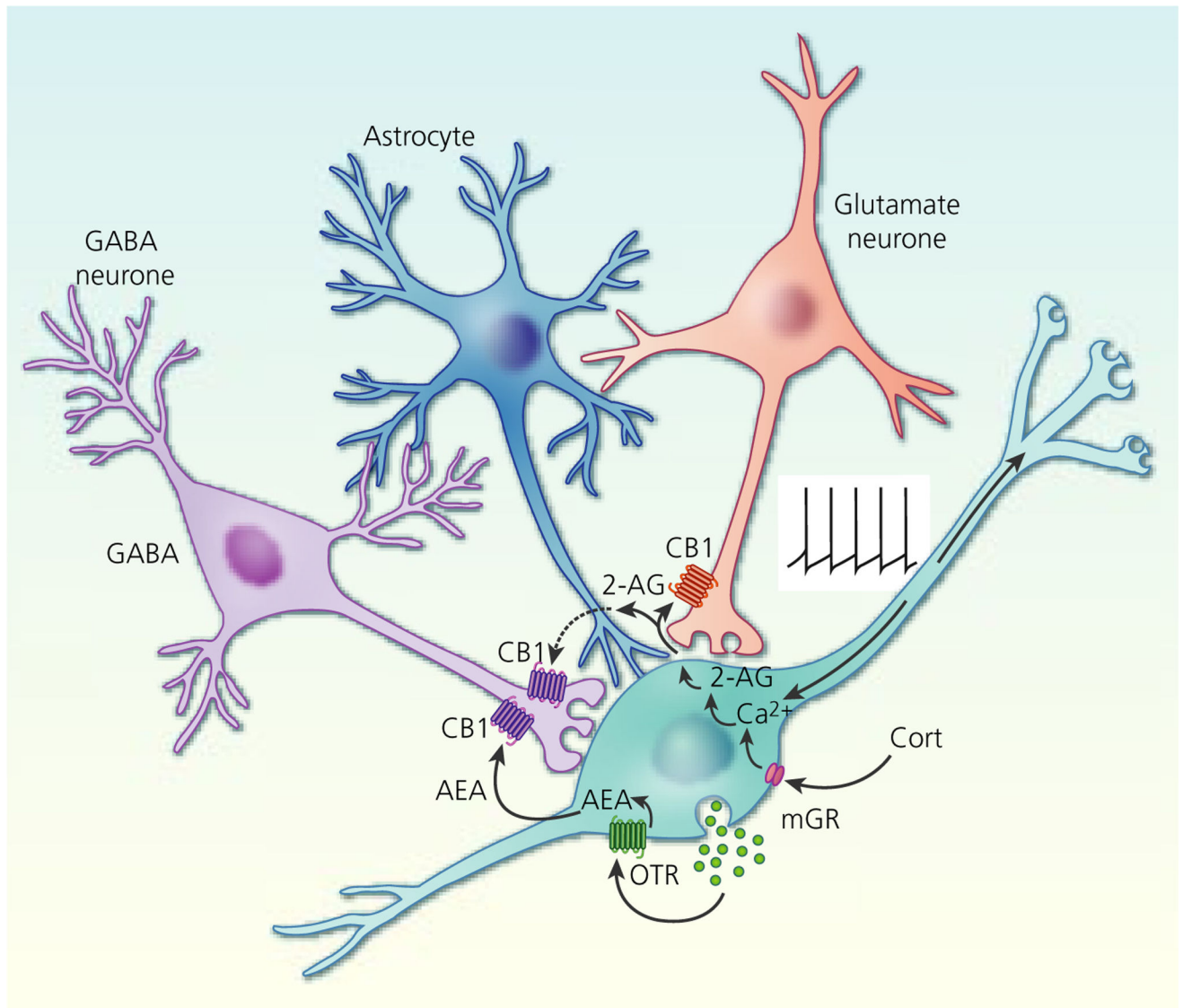


FIGURE 6.

Endocannabinoid modulation of excitatory and inhibitory synapses on magnocellular neurosecretory cells (MNCs). Oxytocin activation of autocrine oxytocin receptors (OTR) on oxytocin neurones leads to a tonic basal release of the endocannabinoid anandamide (AEA) at GABA synapses, which tonically suppresses synaptic inhibitory input to oxytocin neurones by activating presynaptic CB1 receptors. Depolarisation (eg, via action potential generation) or corticosteroid (Cort) activation of membrane glucocorticoid receptors (mGR) (eg, during stress) leads to a calcium-dependent release of the other main endocannabinoid, 2-arachidonoylglycerol (2-AG), at glutamate synapses, which suppresses synaptic excitation of both oxytocin and vasopressin MNCs by activating presynaptic CB1 receptors. Glial retraction induced by salt loading allows the 2-AG released at glutamate synapses to spill over onto GABA synapses and suppress synaptic inhibition via CB1 receptor activation. Tonic AEA occupation of CB1 receptors at GABA synapses is non-saturating, allowing

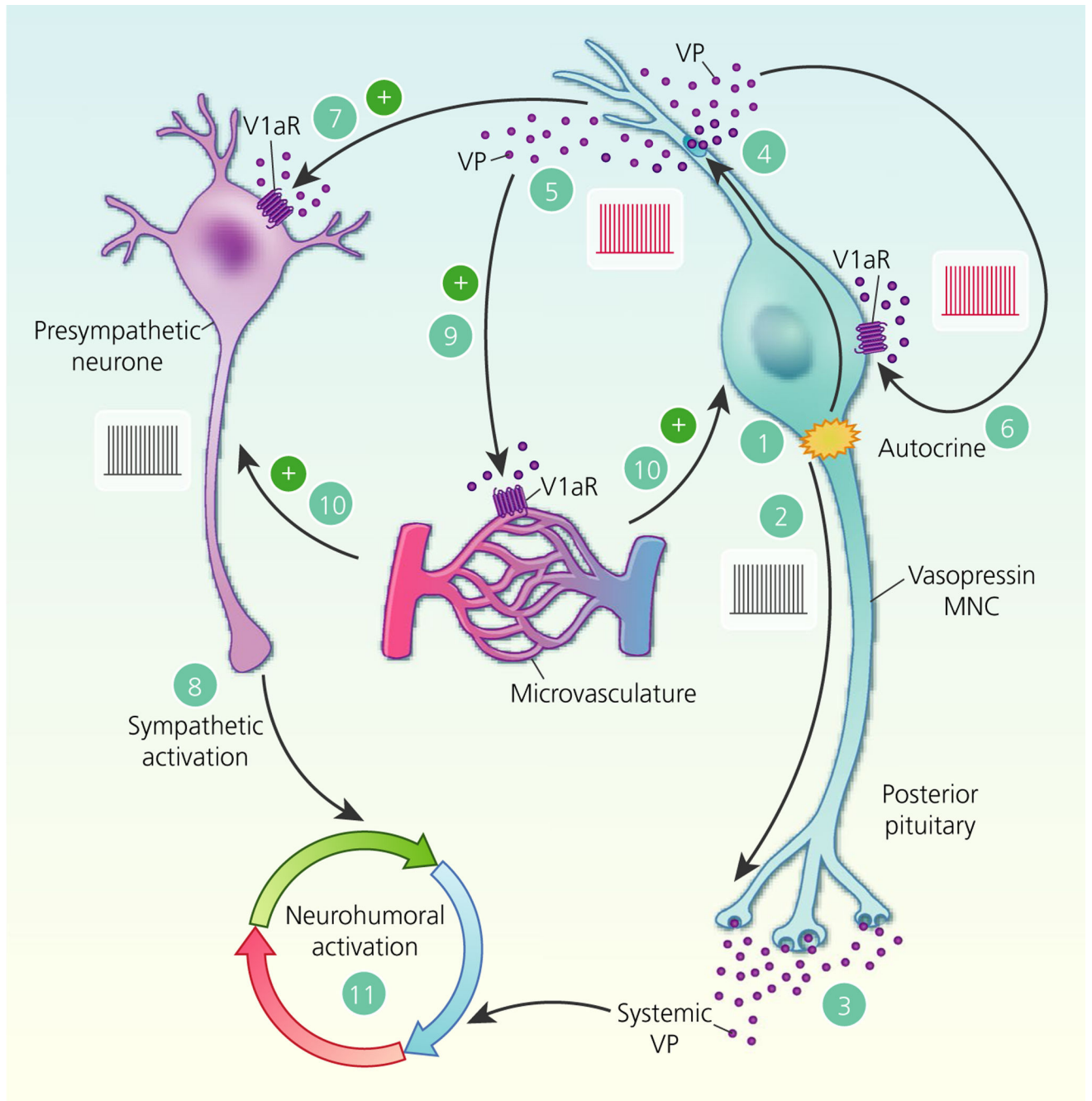
additional suppression of GABA release following phasic 2-AG release and synaptic spillover

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

**FIGURE 7.**

Paracrine actions of somato-dendritic vasopressin (VP) secretion. Activation of neurosecretory vasopressin magnocellular neurosecretory cells (MNCs) (1) triggers action potential firing (2) to release vasopressin into the circulation from the posterior pituitary gland (3). In parallel, action potentials back-propagate into the dendrites (4) to trigger somato-dendritic vasopressin secretion (5). In addition to autocrine feedback inhibition of vasopressin MNC activity via V_{1a} receptors ($V_{1a}Rs$) (6), somato-dendritic vasopressin diffuses through the extracellular space to bind to $V_{1a}Rs$ on presympathetic paraventricular nucleus neurons (7) to increase action potential firing (8) and therefore increase

sympathetic outflow to peripheral organs. Somato-dendritic vasopressin also activates V1aRs on local blood vessels (9) to cause vasoconstriction, which is predicted to inhibit vasopressin MNCs at a population level (10) by restricting the availability of oxygen and nutrients. Hence, somato-dendritic vasopressin secretion coordinates neurohumoral responses to (patho)physiological activation (11)

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript