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Citation for published version:

Brown, CH, Ludwig, M, Tasker, JG & Stern, JE 2020, 'Somato-dendritic vasopressin and oxytocin secretion in endocrine and autonomic regulation', *Journal of Endocrinology*. <https://doi.org/oi.org/10.1111/jne.12856>

Digital Object Identifier (DOI):

[oi.org/10.1111/jne.12856](https://doi.org/oi.org/10.1111/jne.12856)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Journal of Endocrinology

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Journal of Neuroendocrinology**Somato-dendritic vasopressin and oxytocin secretion in endocrine and autonomic regulation**

Journal:	<i>Journal of Neuroendocrinology</i>
Manuscript ID	JNE-20-0008-RA.R1
Manuscript Type:	Review Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Brown, Colin; University of Otago, Department of Physiology Ludwig, Mike; University of Edinburgh, Centre for Discovery Brain Sciences Tasker, Jeffrey G.; Tulane University, Cell and Molecular Biology Stern, Javier; Georgia State University, Neuroscience
Keywords:	Somato-dendritic secretion, Paraventricular nucleus, Supraoptic nucleus, Oxytocin, Vasopressin

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3 1 **Somato-dendritic vasopressin and oxytocin secretion in endocrine and autonomic regulation**
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8 3 Colin H. Brown ¹, Mike Ludwig ^{2,3}, Jeffrey G. Tasker ⁴ and Javier E. Stern ⁵
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11
12 5 *¹ Brain Health Research Centre, Centre for Neuroendocrinology and Department of Physiology,*
13 *University of Otago, Dunedin, New Zealand*

14 6
15
16 7 *² Centre for Discovery Brain Sciences, University of Edinburgh, Edinburgh, UK*

17 8
18 9 *³ Centre for Neuroendocrinology, Department of Immunology, University of Pretoria, Pretoria, South*
19 *Africa*

20 10
21 11 *⁴ Brain Institute and Department of Cell and Molecular Biology, Tulane University, New Orleans, LA,*
22 *USA*

23 12
24 13 *⁵ Neuroscience Institute, Georgia State University, Atlanta, GA, USA*
25
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27 14 **Running title:** Somato-dendritic VP and OT secretion
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33 15
34 16 **Key words:** Somato-dendritic secretion, paraventricular nucleus, supraoptic nucleus, oxytocin,
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38 17 vasopressin
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43 19 **Corresponding author:** Colin H. Brown, Department of Physiology, University of Otago, Dunedin
44 20 9054, New Zealand. Tel.: +64-3-479-7354, Fax.: +64-3-479-7323, E-mail: colin.brown@otago.ac.nz
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22 **Abstract**

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

41 **Information transfer in the central nervous system**

42 The classical understanding of communication in the nervous system is of synaptic transmission in a
43 unidirectional manner within networks from presynaptic neurones to postsynaptic neurones. However,
44 it has become clear that information transfer in the central nervous system is more complex than
45 simple point-to-point, unidirectional transmission between neurones at synapses. Among the
46 additional mechanisms that contribute to information transfer in the nervous system is somato-

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3 47 dendritic secretion. Unlike classical synaptic transmission by neurotransmitters such as glutamate and
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5 48 GABA, which signals between pre- and postsynaptic neurones with spatial precision and high
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7 49 temporal resolution, somato-dendritic secretion causes longer-term changes than synaptic
8
9 50 transmission that alters the overall excitability of neurones by modulating the strength of synaptic
10
11 51 inputs and/or by modulating the baseline membrane potential. These effects can be autocrine or
12
13 52 paracrine, on the neurone from which somato-dendritic secretion occurs or on nearby neurones, and
14
15 53 might spread over relatively long distances to modulate the activity of neurones in brain areas distant
16
17 54 from the site of secretion.

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19
20
21 55 Somato-dendritic secretion occurs in many types of neurone and can involve many types of
22
23 56 transmitter molecule (1). Magnocellular neurosecretory cells (MNCs) of the hypothalamic supraoptic
24
25 57 nucleus (SON) and paraventricular nucleus (PVN) are among those for which the mechanisms and
26
27 58 consequences of somato-dendritic secretion are best characterised. This review focusses on studies
28
29 59 from the authors' laboratories, some of which were presented at the 22nd International Symposium on
30
31 60 Regulatory Peptides, which have contributed to our understanding of how somato-dendritic secretion
32
33 61 from MNCs contributes to endocrine and autonomic regulation of peripheral physiology in health and
34
35 62 disease.

36 37 38 39 63 **The magnocellular neurosecretory system**

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41
42 64 The magnocellular neurosecretory system comprises MNCs that predominantly secrete either
43
44 65 vasopressin (the antidiuretic hormone) or oxytocin into the general circulation from the posterior
45
46 66 pituitary gland (neurohypophysis). The principal function of vasopressin is to maintain body fluid
47
48 67 balance and blood pressure by activation of renal V₂-receptors to increase water reabsorption from the
49
50 68 urine and, when blood pressure/volume is decreased, by activation of vascular V_{1a}-receptors (V_{1a}Rs)
51
52 69 to cause vasoconstriction (2). The best-characterised physiological functions of oxytocin are to trigger
53
54 70 uterine contractions during birth and milk ejection during lactation (2). However, oxytocin also
55
56 71 contributes to body fluid balance by promoting natriuresis in the kidney (3) and by stimulating atrial
57
58 72 natriuretic peptide secretion (4).

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2
3 73 The human hypothalamus contains over 100,000 MNCs (5), with ~10,000 in the rat, that are
4
5 74 principally located in the SON and PVN as well as in several accessory nuclei (6). MNCs each project
6
7 75 a single axon to the posterior pituitary gland (Figure 1) and each axon branches extensively to form
8
9 76 several thousand neurosecretory axon swellings and terminals (7) that are each tightly packed with
10
11 77 dense core vesicles containing ~85,000 molecules of vasopressin or oxytocin in rats (8). Hormone
12
13 78 secretion is triggered by action potential invasion of the neurosecretory swellings and terminals. It has
14
15 79 been estimated that each MNC contains about 10 million dense core vesicles and secretes between
16
17 80 100 and 10,000 dense core vesicles from the posterior pituitary gland every minute to maintain basal
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19 81 hormone concentrations in the circulation (9). Hence, the sustained output of the hormones, and the
20
21 82 consequent regulation of peripheral physiology, depends on the average action potential discharge
22
23 83 from the population (2, 10).

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25
26
27 84 MNCs also synthesise lesser amounts of other neurotransmitters and neuromodulators that can be
28
29 85 contained in the same dense core vesicles as vasopressin or oxytocin (11), as well as glutamate-
30
31 86 containing microvesicles (12). To date, the only evidence of effects of these other neurotransmitters
32
33 87 and neuromodulators on peripheral physiology is for secretin, which increases renal antidiuresis (13).
34
35 88 Rather, their principal function appears to be modulation of hormone secretion at the level of the
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37 89 posterior pituitary gland, which is comprehensively reviewed elsewhere (14), and at the level of the
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39 90 somata and dendrites, as we describe here.

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43 91 Some MNCs project axon collaterals to other brain areas. Originally, these were thought to remain
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45 92 proximal to the SON (15) and PVN (16), projecting to local interneurons as part of a proposed local
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47 93 feedback loop. More recently, it was shown that some MNC axon collaterals project more broadly
48
49 94 throughout the brain, with oxytocin MNCs projecting to the medial amygdala (MeA), central
50
51 95 amygdala (CeA), nucleus accumbens (17) and the lateral septum (18), and vasopressin MNCs to the
52
53 96 medial and lateral preoptic area, suprachiasmatic nucleus, lateral habenula, CeA, MeA (19, 20), locus
54
55 97 coeruleus (21) and arcuate nucleus (ARC) (22). These axon collaterals have been implicated in the
56
57 98 modulation of different behaviours, but it remains to be established how secretion from axon
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3 99 collaterals to modulate behaviour relates to secretion from the posterior pituitary gland to modulate
4
5 100 peripheral physiology.

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7
8 101 MNCs possess 1 – 3 thick, varicose, aspiny dendrites of a few hundred micrometres in length. MNCs
9
10 102 of the SON extend their dendrites to the ventral surface of the nucleus, where the dendrites bundle
11
12 103 together within the ventral glial lamina (a layer of astrocytes on the ventral surface of the brain within
13
14 104 the SON) (23) and MNCs of the PVN extend their dendrites towards the subependymal region of the
15
16 105 third ventricle (24). In addition to being the site of afferent synaptic input, MNC dendrites are active
17
18 106 players in shaping MNC activity through exocytosis of vasopressin and oxytocin (as well as other
19
20 107 neurotransmitters/neuromodulators) into the extracellular space of the SON and PVN.

21 108 **Somato-dendritic secretion from magnocellular neurosecretory cells**

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26
27 109 The somata and dendrites of MNCs are tightly packed with dense core vesicles containing either
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29 110 vasopressin or oxytocin (Figure 2), which undergo exocytosis to secrete their major neuropeptides
30
31 111 (25, 26) along with lesser amounts of other co-packaged neurotransmitters and neuromodulators (11).
32
33 112 Tannic acid capture of somato-dendritic secretion reveals that the entire vesicle content is released
34
35 113 from MNCs (25).

36
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38
39 114 Unlike synaptic transmission by classical neurotransmitters, dense core vesicle exocytosis from the
40
41 115 somata and dendrites of MNCs requires a sustained increase in intracellular calcium (27, 28,) and
42
43 116 calcium buffering limits increases in cytoplasmic calcium to restrain the activation of somato-
44
45 117 dendritic secretion from MNCs (29). MNCs express different arrays of voltage-gated calcium
46
47 118 channels in their somata and axon terminals (30). Relative to other voltage-gated calcium channels,
48
49 119 N-type calcium channels ($Ca_{v2.2}$) carry a comparatively small current in MNC somata, but
50
51 120 nevertheless contribute most significantly to somato-dendritic oxytocin secretion (31). While the
52
53 121 primary trigger for somato-dendritic secretion is the influx of extracellular calcium, intracellular
54
55 122 calcium release also contributes to somato-dendritic secretion from MNCs (27, 28).

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3 123 Action potential invasion triggers exocytosis from axon terminals and MNC dendrites and appears to
4
5 124 support depolarisation-induced calcium spikes (32). Capacitance measurements from isolated MNCs
6
7 125 suggest that single action potentials trigger somato-dendritic secretion (33). However, functional
8
9 126 studies suggest that sustained intracellular calcium release is required to trigger somato-dendritic
10
11 127 secretion (27, 28). Furthermore, if every action potential fired by each MNC triggered somato-
12
13 128 dendritic secretion of a single dense core vesicle, the brain would be awash with vasopressin and
14
15 129 oxytocin (34). Exocytosis of ~6,000 dense core vesicles per second has been calculated to be
16
17 130 sufficient to maintain the concentrations of vasopressin and oxytocin measured in the rat
18
19 131 hypothalamus (34). There are ~10,000 MNCs in the rat hypothalamus (6). While ~25% of MNCs are
20
21 132 silent under basal conditions, active MNCs display a mean firing rate of ~5 Hz under basal conditions
22
23 133 (35). Hence, up to 37,500 action potentials are fired by MNCs every second, which is almost 10-fold
24
25 134 more than the number of dense core vesicles secreted. Hence, it is likely that trains of action potentials
26
27 135 that cause a more sustained depolarisation and calcium influx are required to trigger somato-dendritic
28
29 136 secretion from MNCs. Indeed, under basal conditions, some stimuli reduce the oxytocin MNC action
30
31 137 potential firing rate but increase somato-dendritic oxytocin secretion (36, 37), and it was shown
32
33 138 recently that action potential firing alone at physiological firing rates is insufficient to trigger
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35 139 measurable somato-dendritic secretion from individual vasopressin MNCs (38).

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40 140 In addition to permeation through voltage-gated calcium channels, calcium influx also occurs through
41
42 141 N-methyl-D-aspartate (NMDA) receptors (NMDARs), and synaptic NMDA receptors would be
43
44 142 expected to further increase cytoplasmic calcium concentrations during action potential firing.
45
46 143 Furthermore, MNCs express extrasynaptic NMDARs (39-41). While these extrasynaptic NMDARs
47
48 144 are activated by basal glutamate levels *in vitro* (39), they are not activated under basal conditions *in*
49
50 145 *vivo*, but are activated under stimulated conditions (35) and trigger somato-dendritic peptide secretion
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52 146 (38).

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54
55 147 In addition to triggering somato-dendritic secretion, increased cytoplasmic calcium also promotes
56
57 148 movement of dense core vesicles from the reserve pool toward the cell surface (42), where they are

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3 149 ready for secretion in response to subsequent stimuli that raise cytoplasmic calcium. In parallel,
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5 150 increased intracellular calcium also promotes recruitment of N-type calcium channels (31) to make
6
7 151 the system more sensitive to subsequent cytoplasmic calcium increases. Hence, this 'priming'
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9 152 increases somato-dendritic secretion triggered by subsequent signals that increase cytoplasmic
10
11 153 calcium.

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15 154 Action potential-mediated depolarisation is not the only trigger for somato-dendritic secretion from
16
17 155 MNCs. Vasopressin and oxytocin MNCs express their respective receptors (43, 44) and activation of
18
19 156 these receptors increases cytoplasmic calcium concentrations (45) to trigger somato-dendritic
20
21 157 secretion (27, 28). While vasopressin and oxytocin trigger somato-dendritic secretion from
22
23 158 vasopressin and oxytocin MNCs without a prior stimulus to prime the system, once the MNCs are
24
25 159 primed, the peptides can trigger a much greater somato-dendritic secretion (27, 28).

26
27
28 160 There is an elaborate network of actin and microtubules in MNC somata and dendrites (46, 47).
29
30 161 Cortical F-actin regulates somato-dendritic exocytosis; F-actin polymerization inhibits and F-actin
31
32 162 depolymerisation increases somato-dendritic secretion from MNCs (48). Presumably, F-actin
33
34 163 depolymerisation increases access to the plasma membrane and this process might account for the
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36 164 requirement for a sustained increase in intracellular calcium to trigger somato-dendritic secretion,
37
38 165 since calcium causes F-actin depolymerisation. Unlike synaptic transmission, there does not appear to
39
40 166 be any specific structure on the soma or dendrites that is specialised for somato-dendritic secretion
41
42 167 (49), although it remains to be determined whether there are regions of the cortical F-actin network
43
44 168 that are more readily depolymerised to allow dense core vesicles preferential access to the plasma
45
46 169 membrane at specific sites for secretion.

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50 170 Exocytosis can occur once the dense core vesicles reach the plasma membrane, which requires
51
52 171 exocytotic machinery. The involvement of the soluble N-ethylmaleimide-sensitive factor attachment
53
54 172 receptor (SNARE) complex in exocytosis from axon terminals is well established (50). While less
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56 173 well characterised, it appears that somato-dendritic secretion is also mediated by SNARE proteins.
57
58 174 MNCs express SNARE proteins (51), however, while vesicle-associated membrane protein-2

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3 175 (VAMP-2) and synaptosomal-associated protein 25 (SNAP-25) are both expressed in the axon
4
5 176 terminals (52, 53), they are not expressed in the somata or dendrites of MNCs (54). Hence, the suite
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7 177 of SNARE complex proteins for somato-dendritic exocytosis likely differs from that for axon terminal
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9 178 secretion from MNCs.

12 179 **Stimulation of somato-dendritic secretion by neurotransmitters, peptides and hormones**

15 180 Noradrenergic afferents from the ventrolateral medulla (VLM) A1 cell group and the nucleus of the
16
17 181 tractus solitarius (NTS) A2 cell group make prominent projections to MNCs (2). NTS noradrenergic
18
19 182 afferents are activated during birth and lactation (55) as part of the Ferguson reflex (56), and
20
21 183 noradrenaline facilitates somato-dendritic oxytocin secretion in late pregnancy and lactation (57-59).
22
23 184 Oxytocin also increases noradrenaline secretion within the SON (60), which presumably establishes a
24
25 185 local positive feedback loop that reinforces oxytocin MNC excitation and promotes oxytocin secretion
26
27 186 into the circulation to trigger uterine contractions during birth and milk ejection during lactation
28
29 187 (Figure 3).

32 188 Proopiomelanocortin (POMC) afferents from the ARC project to the SON and PVN, particularly to
33
34 189 regions of the SON and PVN that are enriched in oxytocin MNCs (61). POMC neurones secrete α -
35
36 190 melanocyte stimulating hormone (α -MSH), which acts on melanocortin-4 (MC4-R) receptors in the
37
38 191 SON and PVN (62). While α -MSH inhibits oxytocin secretion into the circulation, it increases
39
40 192 somato-dendritic oxytocin secretion (37, 63). MC4-R activation increases intracellular calcium in
41
42 193 oxytocin MNCs to trigger somato-dendritic oxytocin secretion as well as endocannabinoid secretion,
43
44 194 which inhibits the activity of the MNCs to reduce axonal oxytocin secretion into the blood (37, 63).
45
46 195 Remarkably, α -MSH inhibition of oxytocin MNC activity is lost in mid-pregnancy (62), but it has yet
47
48 196 to be determined whether this represents a switch from pre-pregnancy inhibition to stimulation during
49
50 197 lactation, as is seen for prolactin effects on oxytocin MNCs (64). Furthermore, it is not known
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52 198 whether α -MSH effects on somato-dendritic oxytocin secretion change in pregnancy and lactation.
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3 199 **In addition to neurotransmitters, other hormones can also** trigger somato-dendritic secretion from
4
5 200 MNCs. The orexigenic hormone, ghrelin is synthesised by oxyntic cells in the gastric mucosa, but not
6
7 201 in the brain (65). Central ghrelin administration increases vasopressin secretion into the circulation via
8
9 202 activation of neuropeptide Y neurones (66). In addition, ghrelin stimulates somato-dendritic
10
11 203 vasopressin secretion, which increases adenosine triphosphate (ATP) release from astrocytes to
12
13 204 increase presynaptic GABA release onto the vasopressin MNCs (67) (Figure 4).

205 **Autocrine/paracrine modulation of vasopressin magnocellular neurosecretory cell activity**

206 The effects of vasopressin, oxytocin and other neurotransmitters and neuromodulators secreted from
21
22 207 the somata and dendrites of MNCs can be broadly categorised as **autocrine, regulating the activity of**
23
24 208 **the MNC from which secretion occurs, and paracrine, regulating the activity of neighbouring neurons,**
25
26 209 **including other neuronal populations.**

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29 210 $V_{1a}R$ and V_{1b} receptors (**V1bR**) are expressed in the membranes of vasopressin-containing dense core
30
31 211 vesicles (68) and are presumably inserted into the plasma membrane during somato-dendritic
32
33 212 vasopressin secretion. Hence, vasopressin receptors newly trafficked to the plasma membrane will be
34
35 213 exposed to high concentrations of vasopressin to underpin activity-dependent autocrine feedback
36
37 214 regulation of vasopressin MNC activity.

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39
40 215 Vasopressin MNCs express a range of activity patterns under basal conditions; some are silent
41
42 216 throughout recordings, some display irregular activity, some are continuously-active (typically at
43
44 217 ~ 6 spikes s^{-1}), and some display rhythmic 'phasic' firing (69). Phasic firing is characterised by
45
46 218 bursts of activity that last more than 15 s, after which bursts stop randomly (70). Each burst is
47
48 219 followed by inactivity for at least 10 s, after which the next burst starts randomly (70). At burst
49
50 220 onset, vasopressin MNCs can reach firing rates of $\sim 15 - 25$ spikes s^{-1} for the first 5 - 10 s, before
51
52 221 spike frequency adaptation occurs to a steady-state firing rate of ~ 6 spikes s^{-1} for the remainder of
53
54 222 the burst (71, 72).

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3 223 Of the different activity patterns recorded in vasopressin MNCs, phasic bursting is the most efficient
4
5 224 pattern for vasopressin secretion into the circulation because vasopressin secretion is maximal at ~13
6
7 225 spikes s⁻¹ (73, 74), which is typically only achieved by phasically firing MNCs and only during the
8
9 226 first 5 – 10 s of each phasic burst. Vasopressin secretion from the posterior pituitary gland rapidly
10
11 227 fatigues during continuous stimulation, but this fatigue is reversed when stimulation is stopped for a
12
13 228 few tens of seconds (75). Hence, vasopressin MNCs firing continuously at high frequency do not
14
15 229 secrete as much vasopressin into the circulation as do phasic MNCs firing at the same frequency
16
17 230 because the silent periods between bursts in phasic MNCs reset the system for efficient vasopressin
18
19 231 secretion at the onset of the next burst, when the typical firing frequency is again in the range that is
20
21 232 most efficient for vasopressin secretion. The importance of phasic activity for efficient vasopressin
22
23 233 secretion into the circulation is highlighted by the changes in activity patterning that occur under
24
25 234 chronically stimulated conditions, such as prolonged osmotic stimulation. While burst duration does
26
27 235 increase during shorter periods of stimulation, prolonged osmotic stimulation leads to an increase in
28
29 236 firing rate within bursts while the burst duration and inter-burst interval remain similar to those seen
30
31 237 under basal conditions (76-79).
32
33
34
35 238 V1aR antagonists consistently increase the activity of phasic MNCs when administered into the
36
37 239 SON (80), suggesting that somato-dendritic vasopressin mediates feedback inhibition of
38
39 240 vasopressin MNCs via V1aR activation (Figure 5). This feedback inhibition likely involves direct
40
41 241 autocrine actions on the MNC that secretes vasopressin because V1aR activation reduces excitatory
42
43 242 postsynaptic potential amplitude in vasopressin MNCs (81). However, autocrine activation of
44
45 243 V1aRs does not mediate autoregulation of vasopressin MNC activity alone because vasopressin
46
47 244 also increases inhibitory postsynaptic potential frequency (82) via stimulation of astrocytic
48
49 245 adenosine triphosphate (ATP) release, which acts as a gliotransmitter at P2X receptors on
50
51 246 presynaptic GABA neurones to increase GABA release (67). Hence, somato-dendritic vasopressin
52
53 247 secretion appears to contribute to the generation of phasic activity in vasopressin MNCs via a
54
55 248 combination of autocrine actions on the MNC from which secretion occurs and paracrine actions
56
57 249 on nearby cells that modulate the activity of the MNC from which secretion occurs.
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3 250 While V1aR activation mediates autocrine and paracrine inhibition of phasic activity, local
4
5 251 application of exogenous vasopressin was first reported to inhibit highly active phasic MNCs and
6
7 252 stimulate weakly active phasic MNCs (83). Vasopressin MNCs also express V1bR (68), and while
8
9 253 it has yet to be determined whether V1bR activation also contributes to autocrine regulation of
10
11 254 vasopressin MNCs, it might underpin the excitatory effects of vasopressin evident in weakly active
12
13 255 vasopressin MNCs. Regardless of the vasopressin excitation of weakly active phasic MNCs
14
15 256 (perhaps via V1bR), such an action of endogenous vasopressin would presumably increase
16
17 257 peripheral vasopressin secretion to cause robust vasoconstriction that is not present under basal
18
19 258 conditions (84). Hence, it seems likely that any contribution of somato-dendritic vasopressin
20
21 259 secretion to peripheral vasopressin secretion by feedback excitation is overridden by the V1aR-
22
23 260 mediated feedback inhibition.

24
25
26
27 261 While, somato-dendritic vasopressin secretion functions as a negative feedback regulator of
28
29 262 vasopressin MNC activity at the single cell level, the important output of the system is overall
30
31 263 hormone secretion, which depends on the integrated activity of the MNCs at a population level
32
33 264 (10). Some of the earliest work on somato-dendritic secretion showed that osmotic stimulation of
34
35 265 vasopressin MNCs increases vasopressin levels in the circulation before levels increase in the SON
36
37 266 (85), which is consistent with somato-dendritic vasopressin secretion acting as a negative feedback
38
39 267 regulator of vasopressin MNC activity at a population level to modulate overall vasopressin
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41 268 secretion into the circulation.

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45 269 **Autocrine/paracrine modulation of vasopressin magnocellular neurosecretory cell activity by**
46
47 270 **co-secreted transmitters**

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49
50 271 Vasopressin MNCs also synthesise and secrete a number of other neurotransmitters and
51
52 272 neuromodulators, including apelin (86), ATP (87), carbon monoxide (CO) (88), dynorphin (89),
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54 273 endocannabinoids (90-92), galanin (93), neuroendocrine regulatory peptides (NERPs) (94, 95),
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56 274 nitric oxide (NO) (96), PACAP (97) and secretin (13).

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3 275 Most neuropeptides synthesised by MNCs are packaged within the same dense core vesicles as
4
5 276 either vasopressin or oxytocin. However, apelin and galanin are differentially packaged in
6
7 277 vasopressin MNCs. Apelin is packaged in dense core vesicles that do not contain vasopressin (98).
8
9 278 While galanin is also packaged in some dense core vesicles that also contain vasopressin, it is also
10
11 279 packaged in others that do not contain vasopressin and some dense core vesicles contain
12
13 280 vasopressin but no galanin. Presumably, differential packaging in dense core vesicles might allow
14
15 281 for secretion of separate pools that contain vasopressin or their co-expressed neuropeptides. Indeed,
16
17 282 dense core vesicles containing galanin alone are trafficked to the dendrites while those that contain
18
19 283 only vasopressin are trafficked to the axon terminals in the posterior pituitary gland (93).
20
21
22 284 Vasopressin MNCs express apelin receptors (APJ receptors) (99) and centrally-administered apelin
23
24 285 inhibits vasopressin MNCs (86) to decrease basal vasopressin secretion (86, 100). However, systemic
25
26 286 apelin administration increases vasopressin secretion (101) and chronic infusion of apelin into the
27
28 287 PVN also increases vasopressin secretion (102). Furthermore, administration of apelin directly into
29
30 288 the SON increases the activity of phasic MNCs (and presumably vasopressin secretion into the
31
32 289 circulation) via non-specific cation channel activation, but reduces somato-dendritic vasopressin
33
34 290 secretion (99), which presumably weakens vasopressin-mediated autoregulation to disinhibit and thus
35
36 291 further excite vasopressin MNCs.
37
38
39 292 Vasopressin MNCs express galanin receptor-1 (Gal-R1) on their somata and dendrites (103). While
40
41 293 centrally-administered galanin increases vasopressin secretion into the circulation *in vivo* (104, 105),
42
43 294 it inhibits vasopressin secretion from isolated neurohypophyses or hypothalamo-neurohypophysial
44
45 295 explants *in vitro* (106), suggesting that the direct effects of galanin are inhibitory, despite the reduced
46
47 296 somato-dendritic vasopressin secretion. Indeed, galanin directly inhibits vasopressin MNCs *in vitro* by
48
49 297 inducing hyperpolarization and reducing the slow afterdepolarisation (sADP) (107), which is a
50
51 298 prominent excitatory post-spike potential in vasopressin MNCs (108). Galanin also reduces EPSC
52
53 299 frequency (109), suggesting that it might also have paracrine effects after somato-dendritic secretion
54
55 300 by retrograde inhibition of excitatory synaptic transmission.
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3 301 Similarly to vasopressin receptors, κ -opioid receptors (KORs) are expressed in the membranes of
4
5 302 vasopressin-containing dense core vesicles (110) and unlike apelin and galanin, the endogenous
6
7 303 opioid peptide (EOP) ligand for KORs, dynorphin, is packaged with vasopressin in the same dense
8
9 304 core vesicles (111). Hence, KORs newly-trafficked to the vasopressin MNC plasma membrane will be
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11 305 exposed to high concentrations of dynorphin upon somato-dendritic secretion of dense core vesicles.
12
13
14 306 KOR agonists inhibit vasopressin MNCs *in vivo* (69, 112) and *in vitro* (113, 114). More importantly,
15
16 307 antagonism of SON KORs increases burst duration in phasic MNCs under basal conditions *in vivo*
17
18 308 (69, 70, 115) and *in vitro* (70, 116), showing that an endogenous KOR agonist inhibits phasic bursts.
19
20 309 Phasic bursts are underpinned by the summation of sADPs to form a plateau potential that maintains a
21
22 310 depolarised membrane potential to sustain further firing during bursts, and KOR activation causes
23
24 311 activity-dependent sADP inhibition (116) to progressively decrease the plateau potential amplitude,
25
26 312 which eventually leads to burst termination (70). Furthermore, KOR desensitisation prevents phasic
27
28 313 activity in vasopressin MNCs, even when intensely stimulated (69). Hence, an endogenous KOR
29
30 314 agonist inhibits phasic MNCs by autocrine inhibition of the sADP in the MNC from which dynorphin
31
32 315 is secreted and this inhibition appears to be necessary for the expression of phasic activity by
33
34 316 vasopressin MNCs.
35
36
37
38 317 In addition to sADP inhibition, KOR agonists reduce EPSP and IPSP amplitude (114, 117) and the
39
40 318 delayed rectifier potassium current (118), while increasing the transient A-type potassium current
41
42 319 (118) in vasopressin MNCs, although it has yet to be established whether these effects also contribute
43
44 320 to the generation of phasic activity.
45
46
47 321 While KOR activation inhibits continuously-active vasopressin MNCs, KOR antagonism does not
48
49 322 affect continuously-active vasopressin MNCs, even when they are strongly excited (76). Hence it
50
51 323 appears that continuously-active vasopressin MNCs express KORs but do not release sufficient
52
53 324 dynorphin to affect activity. Some vasopressin MNCs display irregular activity and these MNCs
54
55 325 appear to be even more strongly excited by KOR antagonism than phasic MNCs (76). Taken together,
56
57 326 this pattern-dependent sensitivity to KOR inhibition suggests that somato-dendritic dynorphin
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3 327 secretion might determine the firing pattern of vasopressin MNCs and that transitions between firing
4
5 328 patterns in individual vasopressin MNCs might result from changes in somato-dendritic dynorphin
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7 329 secretion (119)
8
9
10 330 MNCs also express receptors for pituitary adenylate cyclase-activating polypeptide (PACAP), which
11
12 331 they also synthesise and secrete (97). PACAP increases somato-dendritic vasopressin secretion (120)
13
14 332 by a direct depolarisation through activation of non-specific cation channels (121).
15
16
17 333 Neuroendocrine regulatory peptides (NERPs) 1 – 3 are packaged with vasopressin in the SON and
18
19 334 PVN (94, 95). NERP-1 has paracrine effects on vasopressin MNC activity by retrograde inhibition of
20
21 335 excitatory synaptic transmission whereas paracrine inhibition of vasopressin MNCs by NERP-2 is
22
23 336 mediated by activation of upstream GABAergic interneurons that inhibit glutamatergic neurons that
24
25 337 project to vasopressin MNCs (122). In contrast to NERPs 1 and 2, NERP-3 stimulates vasopressin
26
27 338 secretion from the isolated posterior pituitary gland (95).
28
29
30 339 Vasopressin MNCs express secretin receptors and central secretin administration increases plasma
31
32 340 vasopressin concentrations (13), suggesting that somato-dendritic secretin might stimulate systemic
33
34 341 vasopressin secretion. However, secretin is also released from afferent inputs to the SON (123) and
35
36 342 systemic secretin administration excites vasopressin (and oxytocin) MNCs via noradrenergic
37
38 343 afferent inputs (124), suggesting that its actions might be mediated by afferent inputs rather than
39
40 344 somato-dendritic secretion. While its role as a neurohypophysial hormone has not yet been
41
42 345 definitively established, secretin is expressed in the posterior pituitary gland (13) and increases
43
44 346 insertion of aquaporin-2 into the luminal membrane of the kidney to increase water reabsorption
45
46 347 (125). Hence, secretin synthesised by vasopressin MNCs might act as a neurohypophysial hormone
47
48 348 after secretion from the posterior pituitary gland rather than as an autoregulatory factor secreted
49
50 349 from the somata and dendrites.
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53
54 350 Vasopressin MNCs express P2X and P2Y receptors (126 , 127) and injection of ATP into the SON
55
56 351 induces antidiuresis (128). ATP is packaged in vasopressin dense core vesicles (87). ATP depolarises
57
58 352 MNCs (129) and increases vasopressin secretion from hypothalamo-neurohypophysial explants (130).
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3 353 ATP also increases glutamate and GABA release at synapses on MNCs (131). Hence, somato-
4
5 354 dendritic ATP secretion might excite vasopressin MNCs by autocrine actions on the MNC from
6
7 355 which it is secreted and paracrine actions on afferent inputs to the MNC from which it is secreted.

8
9 356 However, MNCs are also excited by ATP released by astrocytes as a gliotransmitter (67, 132) as well
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11 357 as by ATP released from noradrenergic afferent inputs (133).

12
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14 358 While somato-dendritic ATP secretion might modulate vasopressin MNC activity, ATP is rapidly
15
16 359 catabolised to adenosine in the extracellular space (134). Vasopressin MNCs express adenosine A1
17
18 360 and A2A receptors (135) and A1 receptor antagonism excites phasic MNCs *in vivo*, but does not
19
20 361 affect the firing rate of continuously-active vasopressin MNCs (136). A1 receptor antagonism reduces
21
22 362 activity-dependent inhibition of EPSCs and IPSCs (137) as well as activity-dependent enhancement of
23
24 363 the medium afterhyperpolarisation (mAHP) in vasopressin MNCs (138). mAHP activation induces
25
26 364 spike frequency adaptation at the onset of phasic bursts (139) and so endogenous adenosine
27
28 365 enhancement of the mAHP increases spike frequency adaptation, thereby shortening bursts in phasic
29
30 366 MNCs (136). While A2 receptor activation depolarises MNCs to increase firing rate (135),
31
32 367 vasopressin MNCs are inhibited when adenosine uptake is blocked. Hence, the overall effect of
33
34 368 endogenous adenosine appears to be vasopressin MNC inhibition (140).

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38 369 In addition to somato-dendritic exocytosis, vasopressin MNCs also release the gaseous transmitters,
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40 370 NO and carbon monoxide (CO), by diffusion after synthesis by NO synthase (NOS) and haem-
41
42 371 oxygenase I, respectively. NO inhibits vasopressin MNCs (141, 142) by increasing IPSC amplitude
43
44 372 and frequency (142, 143), whereas CO excites vasopressin MNCs (88).

45
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47 373 Somato-dendritic modulation of vasopressin MNC activity appears to impact hormone secretion
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49 374 into the circulation through a complex interplay of excitatory (apelin, PACAP, ATP, NO and
50
51 375 perhaps secretin) and inhibitory (galanin, dynorphin, NERPs, adenosine and CO) feedback that
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53 376 might fine tune the activity of individual MNCs to prevent any one MNC bearing too much of the
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55 377 secretory load for too long under basal conditions. It seems counter-intuitive that the autoregulatory
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57 378 effects of (at least some) co-secreted transmitters appear greater than that of vasopressin itself,
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3 379 which is secreted in vastly greater quantities. Perhaps the autoregulatory effects of co-secreted
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5 380 transmitters are magnified by activation of both paracrine and autocrine mechanisms. In addition, it
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7 381 is possible that vasopressin's major role is paracrine inhibition of the population as a whole to
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9 382 prevent over-secretion of vasopressin into the circulation in response to perturbations of body fluid
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11 383 balance and/or blood pressure/volume.

14 384 **Autocrine/paracrine modulation of oxytocin magnocellular neurosecretory cell activity**

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17 385 Similar to somato-dendritic vasopressin secretion, somato-dendritic oxytocin secretion also has
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19 386 autocrine and paracrine actions that modulate oxytocin MNC activity. In contrast to vasopressin, the
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21 387 autocrine and paracrine effects of oxytocin are arranged in series rather than in parallel; somato-
22
23 388 dendritic oxytocin secretion activates oxytocin receptors (OTRs) on oxytocin MNCs to increase
24
25 389 intracellular calcium, which has various actions including the release of endocannabinoids that cause
26
27 390 retrograde inhibition of excitatory synaptic transmission under basal conditions (90). While the
28
29 391 oxytocin-stimulated retrograde endocannabinoid suppression of excitatory synaptic input is expected
30
31 392 to inhibit oxytocin MNCs (Figure 6), the best characterised effects of somato-dendritic oxytocin
32
33 393 secretion is excitation, but only under specific (patho)physiological conditions. Hence, it has been
34
35 394 proposed that endocannabinoid inhibition might occur over a longer timescale than autocrine effects
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37 395 of oxytocin to shape activity patterning in oxytocin MNCs during birth and lactation (144), but it has
38
39 396 yet to be established whether this occurs in vivo. Alternatively, the excitatory effects of oxytocin
40
41 397 might involve a switch from endocannabinoid inhibition to excitation during pregnancy, perhaps by
42
43 398 enhanced expression/activation of excitatory transient receptor potential vanilloid-1 channels (145)
44
45 399 for which the endocannabinoid, anandamide, is an endogenous ligand (146). Additionally, spillover of
46
47 400 the endocannabinoid 2-arachidonoylglycerol from glutamate onto GABA synapses and a resulting
48
49 401 suppression of inhibitory synaptic input has been observed in MNCs following glial retraction
50
51 402 induced by salt loading (91). This endocannabinoid spillover could also occur with glial retraction
52
53 403 during parturition and lactation to reduce inhibitory synaptic transmission, although this remains to be
54
55 404 determined. Finally, it is also possible that oxytocin-stimulated endocannabinoid retrograde
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3 405 modulation of excitatory and inhibitory synapses might be overridden by changes in the postsynaptic
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5 406 properties of oxytocin MNCs (147, 148), increased excitatory afferent inputs (149-153), or a switch in
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7 407 GABA signalling from inhibitory to excitatory, or less inhibitory, during pregnancy (64, 154).
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10 408 Oxytocin MNCs typically exhibit continuous activity at $\sim 1 - 5$ spikes s^{-1} under basal conditions to
11
12 409 maintain circulating oxytocin concentrations of $\sim 1 - 3$ pg ml^{-1} , with higher concentrations during
13
14 410 sleep (2). However, oxytocin is best known for its stimulation of rhythmic uterine contraction
15
16 411 during birth and of episodic milk ejection during suckling. Uterine contractions and mammary duct
17
18 412 contraction each occur at intervals of several minutes and each contraction is triggered by a
19
20 413 coordinated, high frequency burst of activity across the population of oxytocin MNCs (155) to
21
22 414 secrete a discrete pulse of oxytocin into the circulation, which transiently increases intrauterine
23
24 415 pressure during birth (156) and intramammary pressure during suckling (157).
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28 416 Somato-dendritic oxytocin secretion increases immediately preceding each burst of activity in
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30 417 lactating rats (158) and bursts are blocked by OTR antagonist administration (159), as is the rise in
31
32 418 somato-dendritic oxytocin secretion (160), suggesting that somato-dendritic oxytocin secretion is
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34 419 required for bursts to occur. However, the mechanisms by which somato-dendritic oxytocin
35
36 420 secretion promotes burst firing in oxytocin MNCs are not fully understood and it is likely not the
37
38 421 only contributor; synchronised volleys of EPSPs (161), rebound depolarization after bursts of
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40 422 IPSPs (162) and enhancement of the sADP (147, 163) have all been proposed to trigger or sustain
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42 423 firing during bursts in oxytocin MNCs.
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46 424 In brain slices from male rats that do not normally fire bursts, α_1 -adrenoceptor activation in low
47
48 425 calcium can induce bursts in oxytocin MNCs reminiscent of those seen during birth and milk ejection
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50 426 (164). Hence, noradrenergic inputs might trigger bursts. Consistent with this hypothesis,
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52 427 noradrenergic innervation of oxytocin MNCs is increased in late pregnancy (152) and these afferent
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54 428 inputs are activated during birth (55) to increase noradrenaline release into the SON (165).
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3 429 Noradrenergic stimulation of bursts in oxytocin MNCs might be mediated by somato-dendritic
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5 430 oxytocin release because noradrenergic receptor stimulation is required for suckling-induced somato-
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7 431 dendritic oxytocin release (58), which might be part of a positive feedback loop that builds towards
8
9 432 bursts during continuous suckling. Indeed, burst-like activity can also be induced in virgin rats *in vivo*
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11 433 by coordinated activation of neighbouring oxytocin MNCs, which induces priming of somato-
12
13 434 dendritic dense core vesicles for subsequent secretion (28). Once primed, high-frequency electrical
14
15 435 stimulation induces bursting in oxytocin MNCs of virgin rats (28). Hence, continuous suckling might
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17 436 trigger tonic noradrenaline release onto oxytocin MNCs that triggers increasing somato-dendritic
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19 437 oxytocin secretion, which could prime further somato-dendritic oxytocin secretion until a tipping-
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21 438 point is reached to induce each burst.

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23
24 439 In addition to facilitating burst firing in individual oxytocin MNCs, somato-dendritic oxytocin
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26 440 secretion might also help coordinate the timing of bursts across the population of oxytocin MNCs.
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28 441 Oxytocin injection into one SON increases the frequency of milk ejection bursts in the contralateral
29
30 442 SON (166). Oxytocin MNCs have 1 – 3 dendrites (148) that are normally separated from
31
32 443 neighbouring dendrites by astrocytic processes. However, in late pregnancy and lactation, astrocytes
33
34 444 withdraw their processes from between oxytocin MNC dendrites, which then form bundles of ~ 10
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36 445 closely apposed dendrites (167, 168). A mathematical model in which oxytocin MNCs send each
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38 446 dendrite to different dendritic bundles to form a sparse network of interactions emulates burst firing in
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40 447 which each burst is initiated randomly at any of the dendritic bundles and spreads rapidly through the
41
42 448 oxytocin MNC population (144).

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44
45 449 However, this model does not account for coordination of bursts across the bilateral SONs and PVNs
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47 450 which might be mediated by noradrenergic inputs that project bilaterally to the SON (169). Indeed,
48
49 451 sectioning the optic chiasm or mammillary body disrupts co-ordination of bursts between oxytocin
50
51 452 MNCs in the left and right SON, suggesting that burst coordination across the magnocellular nuclei
52
53 453 involves projections through these areas (169, 170). Furthermore, the perinuclear zone that lies
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55 454 immediately dorsal to the SON sends prominent projections to the SON (171) and PVN (172, 173)
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57 455 that might also contribute to coordination of bursts across the four main magnocellular nuclei.
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3 456 **Autocrine/paracrine modulation of oxytocin magnocellular neurosecretory cell activity by co-**
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5 457 **secreted transmitters**

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8 458 Oxytocin MNCs also synthesise other transmitters that are likely secreted from their somata and
9
10 459 dendrites, but the effects of these co-transmitters are not as well characterised as for those released
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12 460 from vasopressin MNCs.

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14
15 461 Oxytocin MNCs express μ -opioid receptors (MORs) and KORs (174, 175), and MOR or KOR
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17 462 activation inhibits oxytocin MNCs (69, 176). While oxytocin MNCs synthesise μ - and κ -EOPs
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19 463 (177, 178), neither MOR nor KOR antagonists affect the activity of oxytocin MNCs *in vivo* (69,
20
21 464 179). Hence it appears that if EOPs undergo somato-dendritic secretion with oxytocin, they do not
22
23 465 modulate oxytocin MNC activity to any appreciable extent under basal conditions. MOR-mediated
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25 466 EOP inhibition of somato-dendritic oxytocin secretion and oxytocin MNC activity is increased in
26
27 467 late pregnancy (180), but this modulation is likely to be mediated by afferent inputs (181).

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31 468 By contrast to the central actions of MOR activation, KOR activation appears to restrain secretion
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33 469 into the bloodstream at the posterior pituitary gland (182) and this effect also increases in late
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35 470 pregnancy (183). KOR restraint of oxytocin secretion might build up stores of oxytocin for birth
36
37 471 and lactation and might potentiate secretion during bursts because KORs are desensitised on the
38
39 472 day of birth (184, 185).

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43 473 Oxytocin MNC dense core vesicles also contain ATP, which is presumably secreted along with
44
45 474 oxytocin from the somata and dendrites. Co-secreted ATP does not modulate oxytocin MNC
46
47 475 activity via adenosine receptor activation (136), it might excite oxytocin MNC via P2X receptor
48
49 476 activation (130, 131).

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52 477 Oxytocin MNCs also express NOS (96) and NO appears to restrain the activity of oxytocin MNCs,
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54 478 particularly under stimulated conditions (186, 187), suggesting that NO is an inhibitory
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56 479 autocrine/paracrine modulator of oxytocin MNC activity.

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3 480 Remarkably, chronic MOR activation by the opioid alkaloid agonist, morphine, (but not EOPs
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5 481 (188)) induces tolerance and dependence in oxytocin MNCs (189). Tolerance is revealed as loss of
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7 482 inhibition to acute administration of morphine (176) and dependence is revealed by a sustained
8
9 483 hyperexcitation upon withdrawal of chronic morphine administration (112). Somato-dendritic
10
11 484 oxytocin secretion is increased during morphine withdrawal and OTR antagonism reduces
12
13 485 morphine withdrawal-induced excitation of oxytocin MNCs (190). Hence, somato-dendritic
14
15 486 oxytocin secretion appears to contribute to morphine withdrawal-induced excitation of oxytocin
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17 487 MNCs, although the mechanism by which it does so has yet to be identified.

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21 488 **Paracrine modulation of parvocellular paraventricular nucleus neurone activity by somato-**
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23 489 **dendritic secretion from magnocellular neurosecretory cells**

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26 490 While the SON essentially contains only MNCs (and glia and cells of the vasculature), the PVN also
27
28 491 contains parvocellular neurones. Parvocellular neurones are sub-divided by their projections and
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30 492 functions: neurosecretory parvocellular neurones project to the hypothalamic median eminence, where
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32 493 they secrete hormones into the hypophysial portal blood vessels to control hormone secretion from the
33
34 494 anterior pituitary gland; preautonomic parvocellular neurones project to the brainstem and spinal cord
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36 495 to modulate parasympathetic and sympathetic nervous system activity (191, 192); the remaining
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38 496 parvocellular neurones project to various brain areas to modulate behaviour.

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42 497 It has long been hypothesised that somato-dendritic secretion from MNCs modulates the activity of
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44 498 parvocellular neurones but only recently has definitive evidence to support this hypothesis been
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46 499 generated for somato-dendritic vasopressin (38, 193, 194). For paracrine effects on other neuronal
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48 500 phenotypes to occur, first vasopressin (or oxytocin) must diffuse through the parenchyma to reach
49
50 501 other neurones. The effective diffusion distance for somato-dendritic vasopressin was determined
51
52 502 under basal conditions using Chinese hamster ovary cells transfected with human V1aRs and a
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54 503 calcium indicator to generate biosensor 'sniffer' cells with a threshold detection level of 0.5 nM and
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56 504 an EC_{50} of 7.2 nM for vasopressin (38). Using sniffer cells that were dispersed over the PVN in
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58 505 hypothalamic slices, it was shown that activation of an individual MNC induces sufficient somato-

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3 506 dendritic vasopressin secretion to induce intracellular calcium increases for tens of seconds in sniffer
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5 507 cells over 100 μm from the soma of the activated MNC (38). Similar results were seen using HEK-
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7 508 293 sniffer cells in the SON (194). Hence, somato-dendritic vasopressin release from an individual
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9 509 MNC diffuses through the PVN at sufficient concentration to activate V1aRs expressed on
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11 510 parvocellular neurone somata or dendrites under basal conditions (38, 193). Remarkably, astrocytes
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13 511 withdraw their processes from between MNCs when chronically stimulated (167, 168, 195, 196),
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15 512 which reduces the tortuosity of the extracellular space and likely increases the effective diffusion
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17 513 distance for somato-dendritic vasopressin and oxytocin through the parenchyma (197).
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21 514 Some preautonomic parvocellular neurones project to the rostral ventrolateral medulla (RVLM) in the
22
23 515 brainstem, which projects to sympathetic ganglia to regulate sympathetic nerve activity (198).
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25 516 RVLM-projecting parvocellular neurones express V1aRs and their dendrites are intermingled with
26
27 517 vasopressin MNC somata and dendrites in the PVN (193). Hence, the architecture is in place to
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29 518 provide for somato-dendritic vasopressin modulation of autonomic function by paracrine modulation
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31 519 of preautonomic neurones within the PVN (Figure 7). Activation of individual vasopressin MNCs by
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33 520 uncaging NMDA increases action potential firing in RVLM-projecting parvocellular neurones beyond
34
35 521 100 μm from the activated MNC (193) and this activation is much more potent than that elicited by
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37 522 action potential firing alone (38), suggesting that dendritic NMDARs might be a main driver of
38
39 523 somato-dendritic secretion. The responses of RVLM-projecting parvocellular neurones to vasopressin
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41 524 MNC activation occur after a delay of several seconds, are blocked by superfusion of a V1aR
42
43 525 antagonist and are enhanced by a peptidase inhibitor (193). Most importantly, the depolarisation of
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45 526 RVLM-projecting parvocellular neurones in response to vasopressin MNC activation is not affected
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47 527 by blockade of action potential firing with tetrodotoxin. Taken together, the data demonstrate that the
48
49 528 excitation of RVLM-projecting parvocellular neurones is mediated by diffusion of somato-dendritic
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51 529 vasopressin through the extracellular space of the PVN.
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55 530 Given that activation of an individual vasopressin MNC can excite preautonomic neurones within a
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57 531 radius of at least 100 μm , it appears likely that somato-dendritic secretion from the population of
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3 532 MNCs, as occurs *in vivo*, could function as a population-to-population signal to recruit preautonomic
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5 533 neurones as a whole. Indeed, administration of a V1aR antagonist alone reduces preautonomic
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7 534 neurone activity and the more active the MNC, the more effective is the antagonist at reducing
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9 535 preautonomic neurone activity (193), suggesting that preautonomic neurones are under tonic
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11 536 modulation by vasopressin MNCs to coordinate the humoral (circulating vasopressin) and neuronal
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13 537 (sympathetic nerve activity) responses to changes in body fluid balance and to pathophysiological
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15 538 conditions, such as hypertension, myocardial infarction and chronic heart failure.

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19 539 Hyperosmolality increases vasopressin secretion into the circulation by MNCs and increases renal
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21 540 sympathetic nerve activity, both of which increase water retention to protect body fluid balance. The
22
23 541 mechanisms that underpin these responses to hyperosmolality are thoroughly reviewed elsewhere
24
25 542 (199, 200). While these mechanisms occur in parallel, somato-dendritic vasopressin secretion likely
26
27 543 coordinates the responses because intracarotid infusion of hyperosmotic saline causes a dose-
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29 544 dependent increase in renal sympathetic nerve activity that is accompanied by increased somato-
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31 545 dendritic vasopressin secretion, and bilateral injection of a V1aR antagonist into the PVN abolishes
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33 546 the renal sympathetic nerve activation (193). Hence, it appears that somato-dendritic vasopressin
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35 547 secretion coordinates the humoral and neuronal responses to increased osmolality.

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39 548 PVN-driven sympathoexcitation is a key pathophysiological mechanism in hypertension (201, 202),
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41 549 acute myocardial infarction (192, 203) and heart failure (204, 205) that contributes to morbidity and
42
43 550 mortality (206). Vasopressin MNCs are activated in hypertension (207, 208), acute myocardial
44
45 551 infarction (209) and heart failure (210, 211). While the increased circulating vasopressin levels
46
47 552 contribute directly to detrimental myocardial effects (212, 213), increased vasopressin MNC activity
48
49 553 probably also increases somato-dendritic vasopressin secretion to contribute to the pathophysiological
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51 554 sympathoexcitation via activation of PVN preautonomic neurones.

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55 555 While less well established than for vasopressin effects on preautonomic neurones, it appears that
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57 556 somato-dendritic oxytocin secretion might also modulate the activity of a neighbouring population of
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59 557 neurones within the PVN, corticotrophin-releasing hormone (CRH) neurones. Stress-induced CRH
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3 558 secretion stimulates adrenocorticotrophic hormone secretion from the anterior pituitary gland (214)
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5 559 that, in turn, increases adrenal corticosteroid secretion to mediate the body's response to the stressor.
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7 560 CRH neurones express mRNA for OTRs (215) and oxytocin inhibits EPSC frequency, but not
8
9 561 amplitude, in CRH neurones (216). Oxytocin MNC and CRH neurone dendrites are intermingled
10
11 562 within the PVN (216), allowing for dendro-dendritic interactions between the two populations. Hence,
12
13 563 somato-dendritic oxytocin might suppress CRH neurone excitability by presynaptic inhibition of
14
15 564 excitatory synaptic inputs to reduce activation of the stress axis. However, OTR antagonism has no
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17 565 effect on CRH neurones in brain slices (216), suggesting that, unlike vasopressin modulation of
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19 566 preautonomic neurone activity, there is no OTR tone on CRH neurones, at least under *in vitro* basal
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21 567 conditions.
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25 568 **Paracrine modulation of arteriolar vasoconstriction in the supraoptic nucleus by somato-**
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27 569 **dendritic secretion from magnocellular neurosecretory cells**
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30 570 Classically, neuronal activity is thought to dilate arterioles and thereby increase local cerebral
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32 571 blood flow to meet the metabolic demands of active brain areas; this 'neurovascular coupling' is
33
34 572 generally accepted to result from glutamatergic synaptic transmission that evokes release of
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36 573 vasoactive substances from neurones and astrocytes to relax vascular smooth muscle cells (217).
37
38 574 However, vascular smooth muscle cells express V1aRs, providing a target for somato-dendritic
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40 575 vasopressin, at least within the SON and PVN. Vasoconstriction can be elicited in SON arterioles
41
42 576 by stimulation of an individual vasopressin MNC, an effect that is blocked by V1aR antagonism
43
44 577 (218) (Figure 7). Consistent with its effects on preautonomic neurones, somato-dendritic
45
46 578 vasopressin can induce responses in arterioles beyond 100 μm from the activated MNC under basal
47
48 579 conditions (218). Importantly, this V1aR-mediated vasoconstriction is over-ridden in hyperosmotic
49
50 580 conditions by parallel release of NO, which causes vasodilation of local arterioles (218).
51
52 581 Presumably the NO-induced vasodilation increases blood flow through the SON when increased
53
54 582 vasopressin MNC activity is required to protect from further fluid loss and maintain blood pressure
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56 583 in the general circulation through vasopressin secretion from the posterior pituitary gland.
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3 584 **Paracrine modulation of neuronal activity beyond the paraventricular nucleus by somato-**
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5 585 **dendritic secretion from magnocellular neurosecretory cells**
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8 586 While paracrine modulation of parvocellular neurones within the PVN by somato-dendritic secretion
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10 587 from MNCs is now well characterised, it has yet to be definitively established whether neuropeptides
11
12 588 secreted from MNC somata and dendrites can affect the activity of neurones outside the PVN.

13
14 589 Nevertheless, there is some evidence that somato-dendritic oxytocin might act on neurones in brain
15
16 590 areas relatively close to the SON and/or PVN, particularly for brain areas that receive little or no
17
18 591 axonal projections from MNCs or from vasopressin or oxytocin parvocellular neurones.

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20
21 592 The central effects of the primary anorexigenic hormone, leptin, are mediated by oxytocin, at least in
22
23 593 part (219). Leptin is sensed by ARC POMC neurones that, as described above, project to the SON and
24
25 594 PVN (61), where they secrete α -MSH to activate MC4-Rs (62) and thereby increase somato-dendritic
26
27 595 oxytocin secretion (63, 220). Oxytocin inhibition of food intake is mediated, in part, by the
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29 596 ventromedial hypothalamus (VMH) because oxytocin injection into the VMH decreases food intake
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31 597 that is driven by energy balance rather than palatability (221). While OTRs are highly expressed in the
32
33 598 VMH (222), there are essentially no oxytocin MNC axons in the VMH (219). Given that vasopressin
34
35 599 released from a single MNC can activate cells over 100 μ m from the MNC soma from which it is
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37 600 secreted (38, 193) and the VMH is situated roughly between the SON and PVN, it is possible that
38
39 601 somato-dendritic oxytocin release from MNCs could diffuse through the parenchyma in sufficient
40
41 602 quantities to activate OTRs in the VMH, which have nanomolar affinity for oxytocin (223). It is also
42
43 603 possible that OTR-expressing astrocytes in the SON and PVN could expand the spatial domain of the
44
45 604 dendritically released oxytocin signalling by relaying the signals through astrocytic networks, as has
46
47 605 been reported for vasopressin release from vasopressin MNC dendrites (67) and CRH neurone
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49 606 dendrites (224).

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54 607 While oxytocin MNCs inhibit fear responses via axon collaterals to the CeA (17), it appears likely
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56 608 that SON somato-dendritic oxytocin secretion enhances social recognition via actions in the MeA.

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58 609 The CeA contains oxytocin MNC axons collaterals but there are no oxytocin (MNC or parvocellular)
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3 610 neurone axons in the MeA (17). OTRs are highly expressed in the MeA (222) and OTR antagonist
4
5 611 injection into the MeA reduces social recognition induced by SON activation (225). However, MeA
6
7 612 OTRs are not directly activated by oxytocin secreted into the CeA from MNC axon collaterals (17).
8
9 613 The MeA lies immediately lateral to the SON and, even if somato-dendritic oxytocin secreted within
10
11 614 the SON does not reach the MeA, some oxytocin MNC dendrites project to the MeA (225), which
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13 615 might deliver sufficient oxytocin to the MeA to promote social recognition. Alternatively, OTRs
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15 616 might be **activated** by vasopressin MNC axon collaterals in the MeA (19) because vasopressin has
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17 617 appreciable activity at OTRs (223).

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21 618 **Hormone-like modulation of neuronal activity in distant brain areas by somato-dendritic**
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23 619 **secretion from magnocellular neurosecretory cells**

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26 620 It has been hypothesised that somato-dendritic vasopressin and oxytocin from MNCs are a hormone-
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28 621 like signal in the brain with widespread effects on distant populations of neurones (226). However,
29
30 622 accumulating evidence of the functional impact of MNC axon collaterals on behaviour via direct
31
32 623 projections to distant brain areas (17-21) have led to this hypothesis being challenged (227).

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35 624 The half-lives of vasopressin and oxytocin are ~20 min in the cerebrospinal fluid (CSF) (228), giving
36
37 625 time for diffusion through the ventricular system, particularly downstream. However, vasopressin (at
38
39 626 least) has a half-life of less than 1 min in the parenchyma (229). Given that the paracrine effects of
40
41 627 somato-dendritic vasopressin on preautonomic neurones that are only ~100 μm away is delayed by ~2
42
43 628 – 5 s (193), it appears unlikely that the neuropeptides could diffuse long distances through the brain to
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45 629 act as a hormone-like signal. However, dense core vesicle exocytosis is a slow process compared to
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47 630 microvesicle fusion at the synapse, with latencies of several seconds in hippocampal neurones (230),
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49 631 which could account for much of the latency of the preautonomic neurone response to somato-
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51 632 dendritic vasopressin secreted by MNCs in the PVN. Furthermore, vasopressin and oxytocin are
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53 633 secreted in sufficient quantities to be measured in dialysates collected from the SON and PVN (231),
54
55 634 as well as in other brain areas (232-234) and in the cerebrospinal fluid (CSF) (235), suggesting that
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57 635 they diffuse through the parenchyma sufficiently to reach the CSF. Indeed, the microdialysis probes
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3 636 used to measure vasopressin and oxytocin in many experiments have a recovery rate of <10% for
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5 637 vasopressin in the SON and PVN (236). Hence, it is likely that the actual concentrations of
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7 638 vasopressin and oxytocin present in the parenchyma and CSF are appreciably higher than those
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9 639 measured in dialysates. A further factor to be considered is retraction of astrocytic processes from
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11 640 around MNCs in dehydration and pregnancy (167, 168, 195, 196), which decreases tortuosity in the
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13 641 extracellular space, presumably allowing more ready escape of somato-dendritic vasopressin and
14
15 642 oxytocin from the SON and PVN. It is difficult to imagine that the relatively sparse terminal fields of
16
17 643 MNC axon collaterals and parvocellular vasopressin and oxytocin MNCs could release sufficient
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19 644 vasopressin and oxytocin to maintain the ambient levels of the neuropeptides found in the brain and
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21 645 CSF.
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25 646 While there are clear examples of axon collaterals from sub-populations of MNCs affecting neuronal
26
27 647 activity beyond the SON and PVN (237), this does not preclude the possibility that there is also long-
28
29 648 distance inter-population signalling mediated by somato-dendritic volume transmission of vasopressin
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31 649 and oxytocin over a longer timescale, particularly in brain regions in which there are neuropeptide
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33 650 receptors but no neuropeptide axons, such as in the olfactory bulb. Nevertheless, there is still no
34
35 651 compelling evidence for, or against, distal hormone-like signalling by somato-dendritic vasopressin
36
37 652 and oxytocin transmission, although the levels of oxytocin and vasopressin present in the
38
39 653 cerebrospinal fluid and in brain areas devoid of oxytocin and vasopressin axon terminals appear to be
40
41 654 much higher than could be achieved from axon terminal release from MNC and parvocellular axon
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43 655 collaterals. The resolution of this debate remains an ongoing challenge for the field.
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47 656 **Concluding remarks**

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50 657 Autocrine/paracrine modulation of MNC activity by somato-dendritic vasopressin and oxytocin
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52 658 release has been extensively studied and is broadly accepted as a major function of somato-dendritic
53
54 659 secretion from MNCs (238). While it is clear that co-secreted transmitters also modulate MNC
55
56 660 activity, there is no evidence of paracrine actions on other neurones, even other MNCs. Indeed,
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58 661 somato-dendritic dynorphin terminates bursts in the MNC from which it is secreted (70), but there is
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3 662 no correlation between burst termination in phasic MNCs in paired recordings using a single electrode
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5 663 in which the recorded MNCs would be at most tens of micrometres apart (71), which is well within
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7 664 the range of somato-dendritic vasopressin but evidently beyond the range of somato-dendritic
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9 665 dynorphin. Hence, it is possible that co-secreted transmitters act as autocrine/paracrine modulators of
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11 666 the individual MNC from which they are secreted, whereas the much higher levels of vasopressin or
12
13 667 oxytocin secreted modulate the activity of the population as a whole to regulate peripheral physiology.

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15
16 668 Recently, compelling evidence has emerged that somato-dendritic secretion from MNCs modulates
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18 669 arteriole diameter in the SON (218) as well as the activity of neurones, particularly RVLM-projecting
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20 670 preautonomic neurones in the parvocellular PVN (193) (and perhaps also CRH neurones (216)). This
21
22 671 inter-population cross-talk between MNCs and preautonomic neurones likely coordinates the
23
24 672 hormonal (vasopressin secretion into the circulation) and neural (sympathetic nerve activation)
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26 673 response to perturbations of body fluid balance and blood pressure/volume (239).

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29
30 674 To date, there is no definitive evidence that somato-dendritic vasopressin and oxytocin have actions
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32 675 beyond the SON and PVN and it remains to be determined whether these neuropeptides act as
33
34 676 hormone-like signals after secretion from MNC somata and dendrites. Nevertheless, while much of
35
36 677 the data are circumstantial, it appears likely that somato-dendritic oxytocin release modulates the
37
38 678 activity of neurones in some nearby brain areas that express OTRs but do not contain oxytocin (MNC
39
40 679 or parvocellular) neurone projections, specifically the VMH (219, 222) and MeA (222, 225). The
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42 680 confirmation (or refutation) of the effects of somato-dendritic oxytocin on the VMH and/or MeA is
43
44 681 required to resolve this ongoing debate within the field.

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4 1307 **Figure legends**

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7 1308 **Figure 1. Magnocellular neurosecretory cells.** Magnocellular neurosecretory cells (MNCs) of the
8
9 1309 hypothalamic supraoptic nucleus and paraventricular nucleus each possess 1 – 3 dendrites and project
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11 1310 a single axon to the posterior pituitary gland where they secrete either oxytocin or vasopressin into the
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13 1311 circulation. Some MNC axons project axon collaterals to other brains areas.

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16 1312 **Figure 2. Mechanisms of somato-dendritic release of oxytocin from magnocellular**
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18 1313 **neurosecretory cells.** Neuropeptides are synthesized and packaged in the soma and stored in
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20 1314 dendrites in a reserve pool containing large numbers of large dense core vesicles (LDCVs).
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22 1315 Depolarization-induced calcium entry through voltage-gated calcium channels (VGCCs) stimulates
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24 1316 peptide release by exocytosis of LDCVs. This requires the depolymerization of F-actin to G-actin.
25
26 1317 Furthermore, the stimulation of G-protein coupled receptors (GPR), such as the oxytocin receptor,
27
28 1318 stimulates the mobilization of Ca^{2+} from IP₃-dependent intracellular stores of the rough endoplasmic
29
30 1319 reticulum (ER) and an increase in the number of LDCVs at the plasma membrane, thus priming the
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32 1320 exocytosis machinery for subsequent activity-dependent release. Although some members of the
33
34 1321 SNARE family are detectable by immunocytochemistry, there appears to be a lack of VAMP, SNAP-
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36 1322 25 and synaptotagmin-1 in the somata and dendrites, with their function presumably being replaced
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38 1323 by other SNARE proteins.

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42 1324 **Figure 3. Autocrine modulation of burst firing in oxytocin magnocellular neurosecretory cells.**
43
44 1325 Cervical stretch during birth activates stretch receptors to activate **A2 noradrenergic neurones in the**
45
46 1326 **nucleus tractus solitarius** (NTS) that, in turn, activates somato-dendritic oxytocin secretion from
47
48 1327 oxytocin magnocellular neurosecretory cells (MNCs). Oxytocin feeds back on oxytocin MNCs to
49
50 1328 increase excitability. Oxytocin also increases noradrenaline secretion within the SON to establishes a
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52 1329 local positive feedback loop that reinforces oxytocin MNC excitation and promotes oxytocin secretion
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54 1330 into the circulation to trigger uterine contractions during birth.

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3 1331 **Figure 4. Ghrelin stimulation of somato-dendritic vasopressin secretion.** Ghrelin activation of
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5 1332 growth hormone secretagogue receptors (GHSR) on vasopressin magnocellular neurosecretory cells
6
7 1333 (MNCs) induces somato-dendritic vasopressin secretion, which activates V_{1a} receptors (V1aRs) on
8
9 1334 neighbouring astrocytes to increase intracellular calcium. Increased astrocytic calcium triggers release
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11 1335 of the gliotransmitter, ATP, which activates ionotropic P2X receptors on GABA interneurons that
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13 1336 project back to vasopressin MNCs.

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17 1337 **Figure 5. Autocrine modulation of vasopressin magnocellular neurosecretory cell activity.**
18
19 1338 Vasopressin magnocellular neurosecretory cells (MNCs) secrete vasopressin, ATP and dynorphin
20
21 1339 (and other transmitters) from their somata and dendrites. Endogenous AVP (2) inhibits spike
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23 1340 discharge throughout bursts via inhibition of EPSC amplitude. Endogenous ATP is rapidly converted
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25 1341 to adenosine (3), which enhances the medium afterhyperpolarisation (mAHP) amplitude over the first
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27 1342 few seconds of bursts to contribute to spike frequency adaptation. Endogenous dynorphin (4)
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29 1343 inhibition of the afterdepolarisation (ADP) increases progressively over the course of bursts,
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31 1344 eventually resulting in burst termination. Combined, these autocrine feedback effects of somato-
32
33 1345 dendritic vasopressin and co-secreted transmitters shape phasic activity for efficient secretion
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35 1346 vasopressin into the circulation from the posterior pituitary gland.

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39 1347 **Figure 6. Endocannabinoid modulation of excitatory and inhibitory synapses on MNCs.**
40
41 1348 Oxytocin activation of autocrine oxytocin receptors (OTR) on oxytocin neurons leads to a
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43 1349 tonic basal release of the endocannabinoid anandamide (AEA) at GABA synapses, which
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45 1350 tonically suppresses synaptic inhibitory input to oxytocin neurons by activating presynaptic
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47 1351 CB1 receptors. Depolarization (e.g., via action potential generation) or corticosteroid (Cort)
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49 1352 exposure (e.g., during stress) leads to a calcium-dependent release of the other main
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51 1353 endocannabinoid, 2-arachidonoylglycerol (2-AG), at glutamate synapses, which suppresses
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53 1354 synaptic excitation of both oxytocin and vasopressin MNCs by activating presynaptic CB1
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55 1355 receptors. Glial retraction induced by salt loading allows the 2-AG released at glutamate
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3 1356 synapses to spill over onto GABA synapses and suppress synaptic inhibition via CB1
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5 1357 receptor activation. Tonic AEA occupation of CB1 receptors at GABA synapses is non-
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7 1358 saturating, allowing additional suppression of GABA release following phasic 2-AG release
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10 1359 and synaptic spillover.

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13 1360 **Figure 7. Paracrine actions of somato-dendritic vasopressin secretion.** Activation of
14
15 1361 neurosecretory vasopressin magnocellular neurosecretory cells (MNCs) (1) triggers action potential
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17 1362 firing (2) to release vasopressin into the circulation from the posterior pituitary gland (3). In parallel,
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19 1363 action potentials back-propagate into the dendrites (4) to trigger somato-dendritic vasopressin
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21 1364 secretion (5). In addition to autocrine feedback inhibition of vasopressin MNC activity via V_{1a}
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23 1365 receptors ($V_{1a}Rs$) (6), somato-dendritic vasopressin diffuses through the extracellular space to bind to
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25 1366 $V_{1a}Rs$ on presympathetic paraventricular nucleus neurones (7) to increase action potential firing (8)
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27 1367 and therefore increase sympathetic outflow to peripheral organs. Somato-dendritic vasopressin also
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29 1368 activates $V_{1a}Rs$ on local blood vessels (9) to cause vasoconstriction, which is predicted to inhibit
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31 1369 vasopressin MNCs at a population level (10) by restricting the availability of oxygen and nutrients.
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33
34 1370 Hence, somato-dendritic vasopressin secretion coordinates neurohumoral responses to
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36 1371 (patho)physiological activation (11).

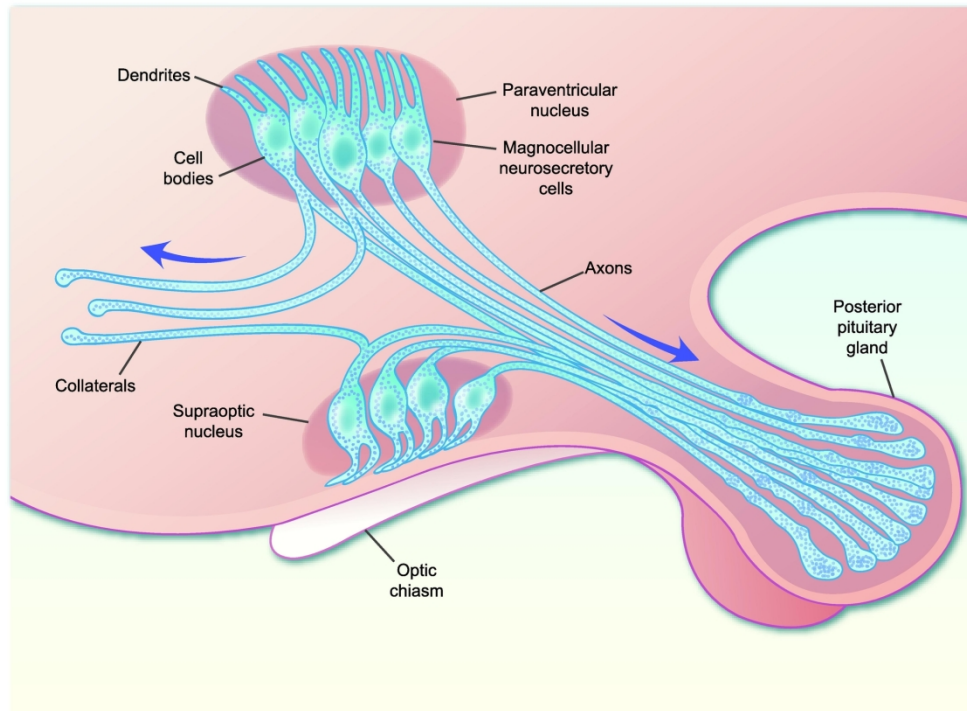


Figure 1. Magnocellular neurosecretory cells. Magnocellular neurosecretory cells (MNCs) of the hypothalamic supraoptic nucleus and paraventricular nucleus each possess 1 – 3 dendrites and project a single axon to the posterior pituitary gland where they secrete either oxytocin or vasopressin into the circulation. Some MNC axons project axon collaterals to other brains areas.

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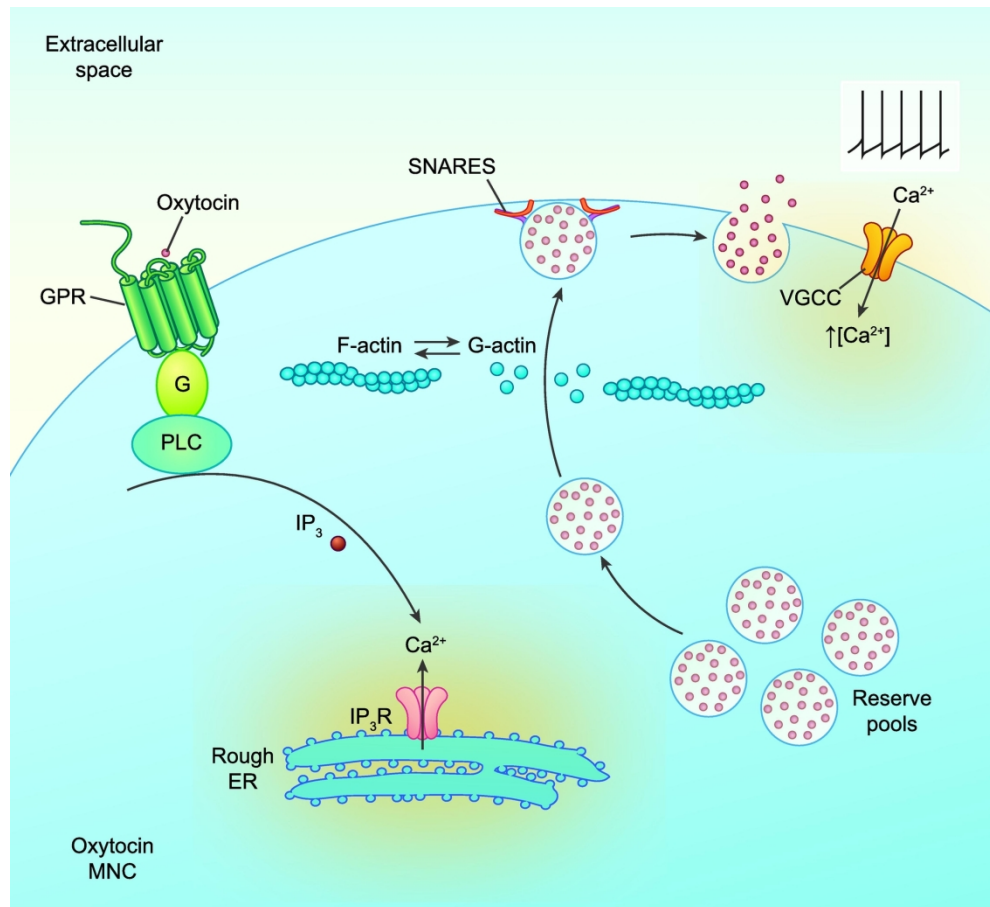


Figure 2. Mechanisms of somato-dendritic release of oxytocin from magnocellular neurosecretory cells.

Neuropeptides are synthesized and packaged in the soma and stored in dendrites in a reserve pool containing large numbers of large dense core vesicles (LDCVs). Depolarization-induced calcium entry through voltage-gated calcium channels (VGCCs) stimulates peptide release by exocytosis of LDCVs. This requires the depolymerization of F-actin to G-actin. Furthermore, the stimulation of G-protein coupled receptors (GPR), such as the oxytocin receptor, stimulates the mobilization of Ca^{2+} from 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 SNARE family are detectable by immunocytochemistry, there appears to be a lack of VAMP, SNAP-25 and synaptotagmin-1 in the somata and dendrites, with their function presumably being replaced by other SNARE proteins.

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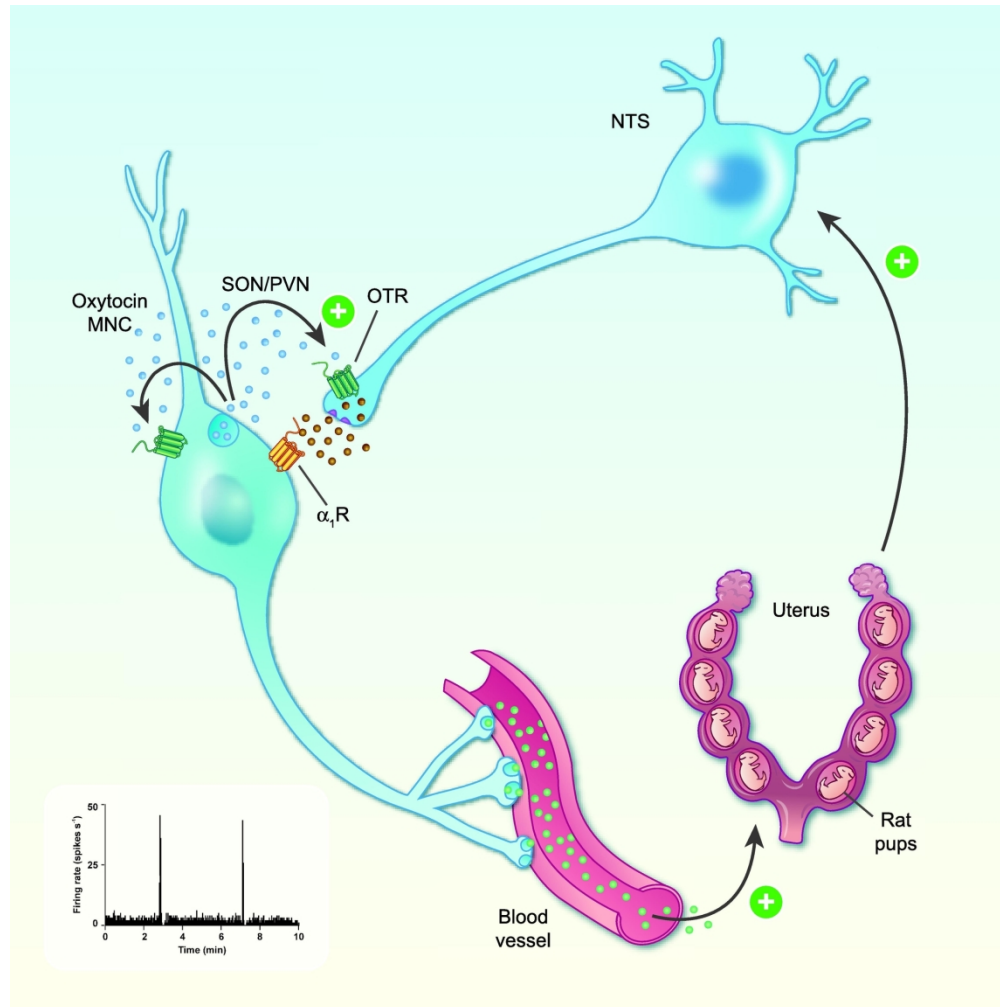


Figure 3. Autocrine modulation of burst firing in oxytocin magnocellular neurosecretory cells. Cervical stretch during birth activates stretch receptors to activate A2 noradrenergic neurones in the nucleus tractus solitarius (NTS) that, in turn, activates somato-dendritic oxytocin secretion from oxytocin magnocellular neurosecretory cells (MNCs). Oxytocin feeds back on oxytocin MNCs to increase excitability. Oxytocin also increases noradrenaline secretion within the 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.

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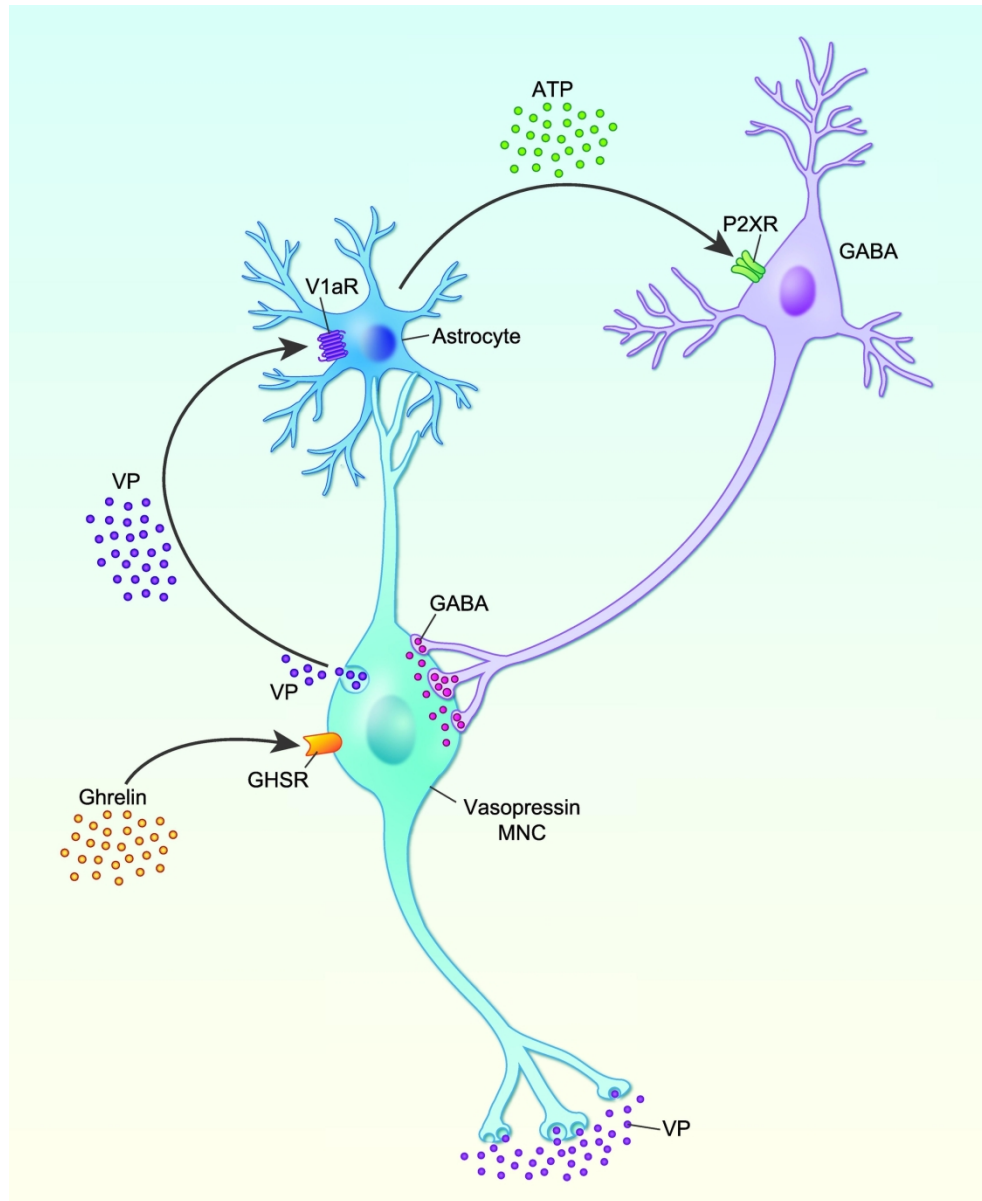


Figure 4. Ghrelin stimulation of somato-dendritic vasopressin secretion. Ghrelin activation of growth hormone secretagogue receptors (GHSR) on vasopressin magnocellular neurosecretory cells (MNCs) induces somato-dendritic vasopressin secretion, which activates V1a receptors (V1aRs) on neighbouring astrocytes to increase intracellular calcium. Increased astrocytic calcium triggers release of the gliotransmitter, ATP, which activates ionotropic P2X receptors on GABA interneurons that project back to vasopressin MNCs.

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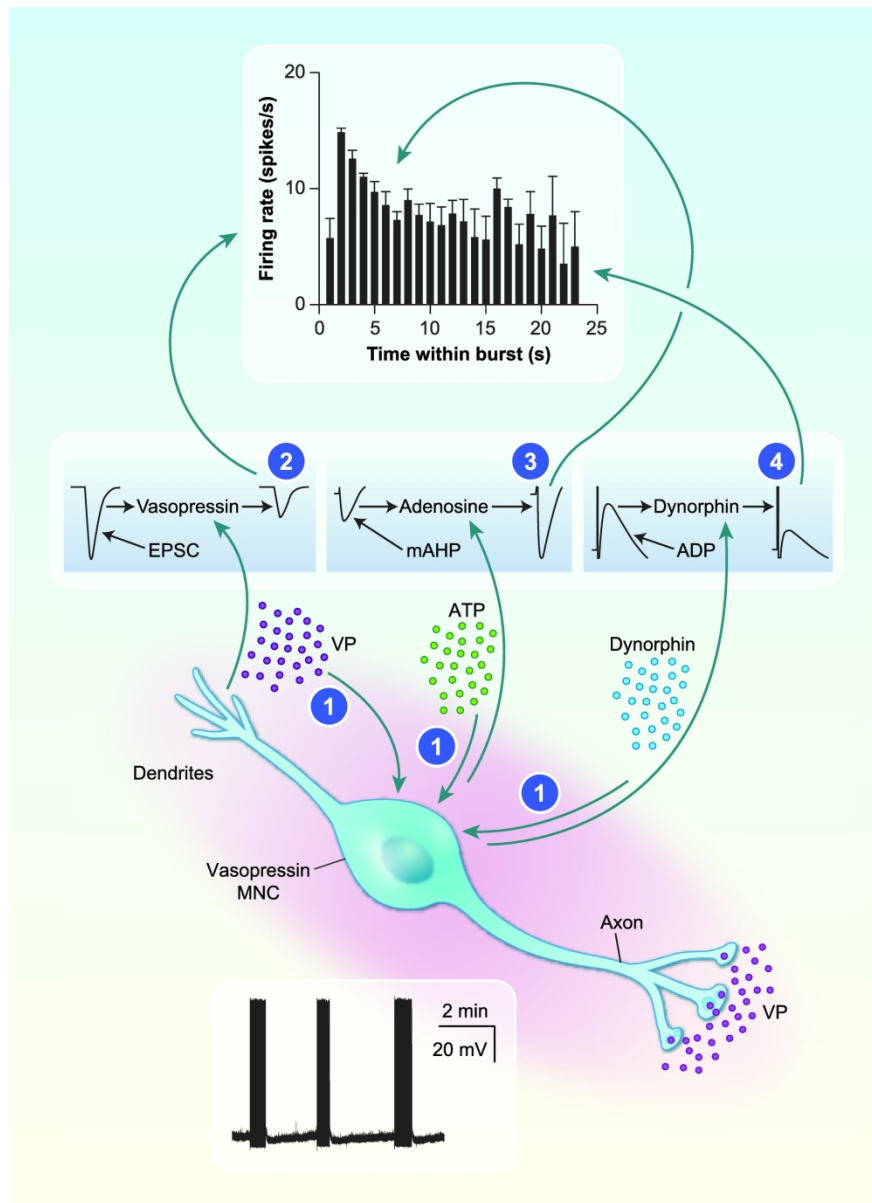


Figure 5. Autocrine modulation of vasopressin magnocellular neurosecretory cell activity. Vasopressin magnocellular neurosecretory cells (MNCs) secrete vasopressin, ATP and dynorphin (and other transmitters) from their somata and dendrites. Endogenous AVP (2) inhibits spike discharge throughout bursts via inhibition of 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.

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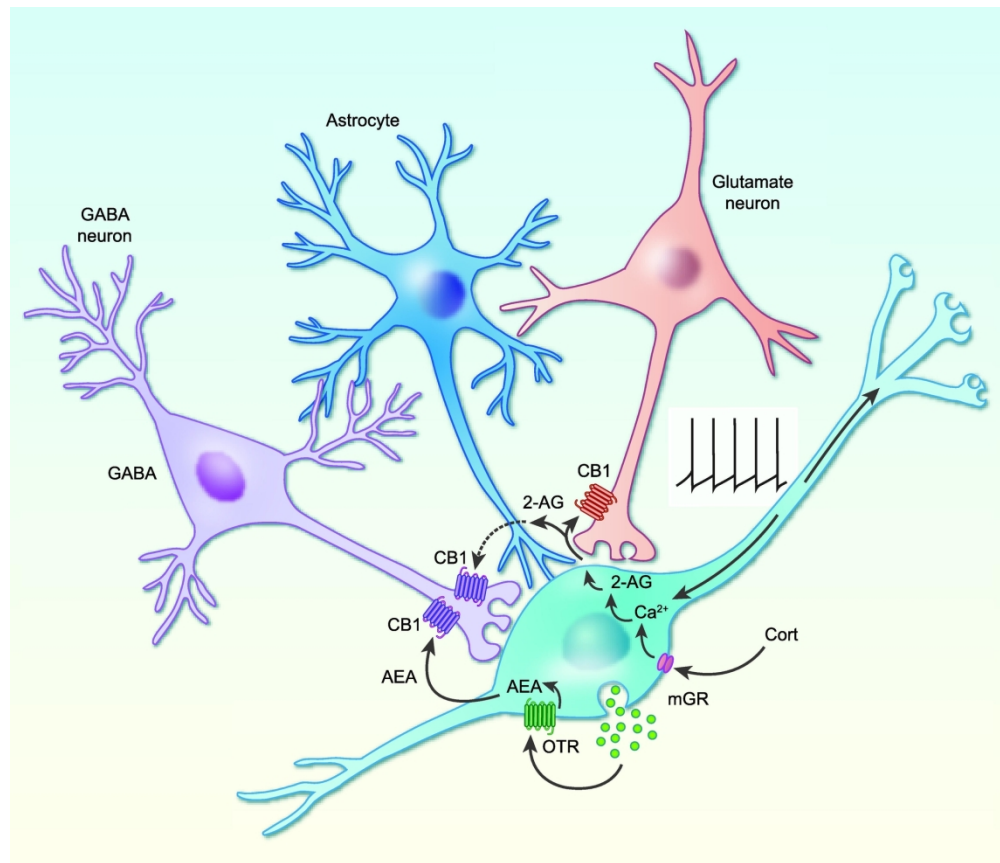


Figure 6. Endocannabinoid modulation of excitatory and inhibitory synapses on MNCs. Oxytocin activation of autocrine oxytocin receptors (OTR) on oxytocin neurons leads to a tonic basal release of the endocannabinoid anandamide (AEA) at GABA synapses, which tonically suppresses synaptic inhibitory input to oxytocin neurons by activating presynaptic CB1 receptors. Depolarization (e.g., via action potential generation) or corticosteroid (Cort) exposure (e.g., 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.

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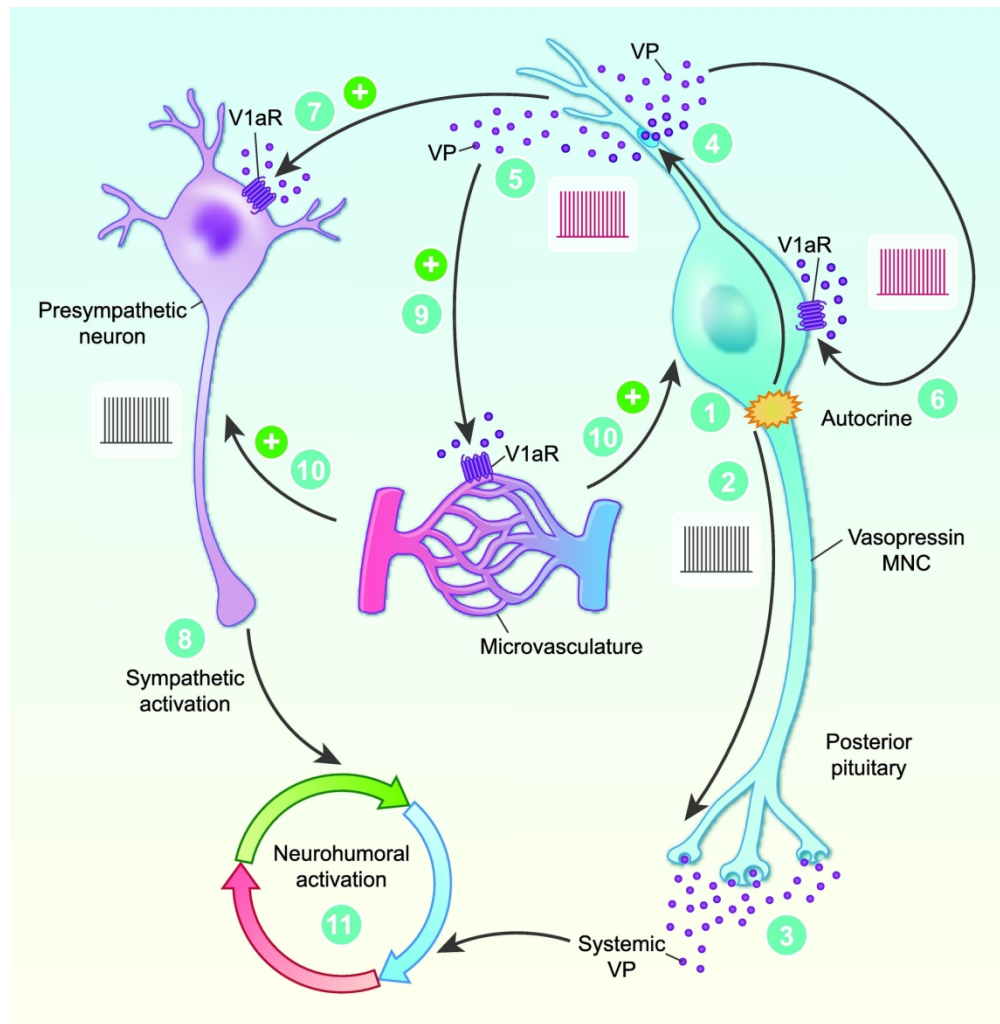


Figure 7. Paracrine actions of somato-dendritic vasopressin secretion. Activation of neurosecretory vasopressin magnocellular neurosecretory cells (MNCs) (1) triggers action potential firing (2) to release vasopressin into the circulation from the posterior pituitary gland (3). In parallel, action potentials back-propagate into the dendrites (4) to trigger somato-dendritic vasopressin secretion (5). In addition to autocrine feedback inhibition of vasopressin MNC activity via V1a receptors (V1aRs) (6), somato-dendritic vasopressin diffuses through the extracellular space to bind to V1aRs 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).

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