6 Neuroanatomical and Functional Relationship Between Parvocellular and Magnocellular Oxytocin and Vasopressin Neurons

Ferdinand Althammer, Javier E. Stern, and Valery Grinevich

Abstract

Hypothalamic neuroendocrine cells that synthesize oxytocin (OT) and vasopressin (AVP) can be categorized into two major cell types, namely magnocellular and parvocellular neurons. In addition to the previously known differences in morphology, connectivity, and electrophysiological properties, recent studies highlight fundamentally different functions and genetic compositions of these cells. Parvocellular OT neurons have recently been implicated in pain perception and processing, regulation of OT release during fear, and promotion of social behavior in female rats following gentle touch. Despite the vast knowledge of parvocellular OT neurons, surprisingly little is known about parvocellular AVP cells. The activity of AVP receptor-expressing presympathetic cells in the paraventricular nucleus of the hypothalamus is regulated by somato-dendritically released AVP from nearby magnocellular AVP cells. However, the contribution of actual parvocellular AVP neurons to this phenomenon remains questionable. Here we summarize the current body of knowledge about the neuroanatomy and functional relationship of the magnocellular and parvocellular OT and AVP systems. In addition, we discuss several controversial topics including the post-synaptic location of OT receptors, various modes of OT release, and

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misconceptions/fallacies that might have led to oversimplified models of the OT system.

Keywords

Parvocellular · Magnocellular · Oxytocin · Vasopressin · Somato-dendritic release · Anatomy · Projections

Abbreviations

AC	Auditory cortex
AN	Accessory nuclei
AON	Anterior olfactory nucleus
Arc	Arcuate hypothalamic nucleus
AVP	Arginine-vasopressin
BLA	Basolateral amygdala
BNST	Bed nucleus of stria terminalis
BS	Brainstem
CB	Cerebellum
CeA	Central amygdala
CRH	Corticotropin-releasing hormone
HC	Hippocampus
HDB	Horizontal limb of diagonal band nucleus
iCj	Island of Calleja
LC	Locus coeruleus
LS	Lateral septum
magnAVP neuron	magnocellular vasopressin neuron
magnOT neuron	magnocellular oxytocin neuron
MC	Motor cortex
MeA	Medial amygdala
NAcc	Nucleus accumbens
OB	Olfactory bulb
OT	oxytocin
parvAVP neuron	parvocellular vasopressin neuron
parvOT neuron	parvocellular oxytocin neuron
PC	Piriform cortex
PFC	Prefrontal cortex
PLC	Prelimbic cortex
PV	Paraventricular thalamus
PVN	Paraventricular nucleus of the hypothalamus
RGC	Retina ganglion cells
RMg	Raphe magnus nucleus
RVLM	Rostral ventrolateral medulla
SC	Spinal cord

SCN	Suprachiasmatic nucleus
SON	Supraoptic nucleus
SSC	Somatosensory cortex
Tu	Olfactory tubercele
vDB	Ventral diagonal band of Broca

6.1 The Rodent Oxytocin System: Cell Types, Function, and Mode of Release

6.1.1 Oxytocinergic Cell Types

Oxytocin (OT)-ergic neurons can be categorized into two major types: magnocellular (magnOT) and parvocellular (parvOT) cells (Althammer and Grinevich 2017; Swanson and Sawchenko 1980, 1983). They differ in size, shape, anatomical location, function, projection sites, mode of release, and electrophysiological properties. While there has been recent speculation about the potential existence of additional oxytocinergic cell types based on genetic cluster analysis (Romanov et al. 2017), thus far no concrete functional evidence has been provided to corroborate these findings. Moreover, due to the fact that concrete genetic profiles for magnOT and parvOT neurons are currently missing, it is not possible to genetically target and reliably manipulate these two OT-ergic cell types.

Currently available techniques aimed to discriminate between the two cell types make use of cell-type-specific projections sites (i.e., parvOT neurons projection to the supraoptic nucleus (SON)), which can be exploited via virus-based approaches; patch clamp recordings and analysis of afterhyperpolarization/LTD and Flourogold-labeling of magnOT neurons. For a comprehensive description of available techniques see (Althammer and Grinevich 2017).

MagnOT cells are large neuroendocrine cells with a diameter of somas of 20–30 μm, which can be found in the supraoptic (SON), paraventricular (PVN), and accessory (AN) nuclei of reptilian, avian and mammalian hypothalamus (Grinevich and Polenov 1994; Knobloch and Grinevich 2014). The rat hypothalamus comprises approximately 7600 OT cells (Althammer and Grinevich 2017), while the vast majority (>99%) are magnOT neurons. MagnOT neurons release OT into the peripheral circulation (blood stream) and therefore—by definition—all magnOT cells send one axon to the posterior lobe of the pituitary. In addition to peripheral release, most—if not all—magnOT neurons project collaterals from axons of the hypothalamic-neurohypophysial tract to various forebrain regions (Zhang et al. 2021). To this day, more than 50 forebrain regions have been identified as targets for magnOT neurons (Knobloch et al. 2012; Mitre et al. 2016).

ParvOT cells are smaller neurons with a diameter of somas of 10–20 μm and are located mainly in selective subdivisions of the caudal PVN ((Swanson and Kuypers 1980; Swanson and Sawchenko 1983). ParvOT neurons project to the brainstem and

spinal cord and are involved in food intake regulation (Blevins et al. 2004), autonomic functions, such as breathing (Mack et al. 2002), erection and copulation (Melis et al. 1986), cardiovascular reactions (Petersson 2002), gastric reflexes (Sabatier et al. 2013) and pain perception (Rash et al. 2014). All of these projections arise from a small population of parvOT neurons residing within the PVN. While it is well established that parvOT neurons synapse onto magnOT neurons located in the SON to control activity-dependent release of OT into the systemic circulation (Eliava et al. 2016; Hasan et al. 2019), it was recently demonstrated that parvOT neurons tightly control magnOT activity within the PVN as well. While parvOT neurons have been underappreciated for most of the twentieth century, they recently emerged as key regulators of the OT system. In fact, the latest research suggests that somatosensory information first converges on parvOT neurons, which, upon activation, subsequently activate the much larger population of magnOT neurons. This mode of action allows a fine-tuned and effective global activation of the OT system, with coordinated release and context-dependent activity patterns of magnOT subdivisions.

Within the past 5 years, parvOT neurons emerged as new players in modulation of the OT system and it became evident that this small subpopulation of cells plays a vital role in somatosensory signal integration during social interaction (Tang et al. 2020), coordination of nociceptive response both on a central and a peripheral level (Eliava et al. 2016) as well as context-dependent activation of fear-sensitive OT-ergic engram cells in the hypothalamus (Hasan et al. 2019). In fact, these studies suggest that parvOT neurons might be master regulators that tightly control and orchestrate magnOT neuron activity under various conditions. Given the types of scenarios described (fear, pain, and social interaction), it seems reasonable to suspect that the coordination of magnOT release by parvOT neurons might be the general rule rather than the exception. The different projection sites of parvOT and magnOT are depicted in Fig. 6.1.

6.1.2 Functional Relationship and Mode of Release of parvOT and magnOT Neurons

The role of PVN → SON projecting parvOT neurons has been studied extensively (Althammer and Grinevich 2017; Eliava et al. 2016; Hasan et al. 2019; Tang et al. 2020). However, it is far from clear whether all parvOT neurons synapse onto magnOT neurons to coordinate their activity (i), whether all magnOT neurons receive synaptic innervation by parvOT neurons (ii), whether PVN → SON and PVN → PVN projecting parvOT neurons represent overlapping or distinct entities (iii) and how somatodendritic release of OT within the SON and PVN contributes to the activation of magnOT neurons that might or might not receive innervation by parvOT neurons (iv).

To better understand the functional relationship of magnOT and parvOT neurons it is required to have a close look at their electrophysiological characteristics and modes of neuropeptide release, as summarized below.

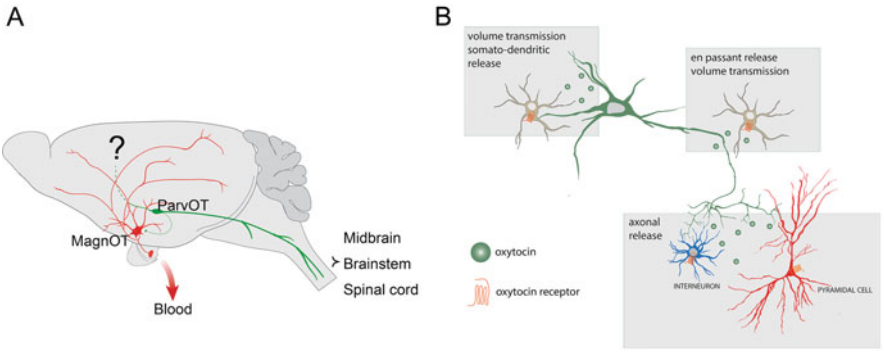

Fig. 6.1 Projection sites and modes of the release of magnOT and parvOT. (**a**) Different projection sites of magnOT and parvOT neurons. (**b**) Magnocellular neurons release OT and AVP from somas and dendrites, from axons passing by (*en passant*) and from long-range axons. OTRs have been found in various neuronal cell types, including GABAergic interneurons (Huber et al. 2005) and pyramidal cells (Lin et al. 2017). The precise pre- and postsynaptic mechanisms, as well as the location of OTRs remain elusive. The brain scheme depicts the currently known magnOT (red) and parvOT (green) neuron interconnectivity within the PVN and SON and their distinct projections to the pituitary, forebrain, midbrain, brainstem, and spinal cord. The green dashed line and the question mark highlight potential, but not yet confirmed, parvOT projections to the forebrain. Modified from Grinevich and Ludwig 2021

6.1.3 Electrophysiological Properties of magnOT and parvOT Neurons

By measuring the electrophysiological properties of blindly recorded cells in the PVN, Tasker and Dudek (1991) first identified two clearly distinct types of neuron by their distinct membrane properties and anatomical peculiarities. Given their blind approach, these cells most likely comprised both AVP and OT cells. Each of these types displayed unique, characteristic features, which allowed precise discrimination. Neurons named type I were characterized by the absence of low-threshold depolarizing potentials, which was found in type II cells. In contrast, type II neurons generally showed relatively small low-threshold depolarizations, which generated one to two action potentials. Furthermore, type I neurons had a significantly shorter membrane time constant (the time it takes the membrane to repolarize after a small current injection of fixed amplitude and duration) than those of type II. Based on the finding that type I neurons were found both in the SON and PVN, the authors concluded that they are most likely magnocellular neurons. Distinctly, type II neurons were found only in the PVN (especially in the caudal part) and therefore most probably belonged to parvocellular neurons, which was recently confirmed (Eliava et al. 2016). Usually, neurons receive an injection of an −100 pA current to hyperpolarize the neuron membrane (reaching −100 mV) before each step. These steps start at 0 pA and increase by 20 pA, reaching +60 pA. To discriminate between parvOT and magnOT, the hyperpolarizing notch and the T-outward rectification (membrane allowing outward current to flow more easily) are measured. Finally,

based on these values and the shape of the action potential it is possible to clearly identify magnOT and parvOT neurons. This protocol is well-established and has been used by several groups (Chu et al. 2013; Luther et al. 2002; Luther and Tasker 2000; Stern et al. 2000; Tang et al. 2020; Yuill et al. 2007). While the original studies by Tasker and Dudek were conducted blind, seminal works by William E. Armstrong and Javier E. Stern provided insights about individual properties of OT and AVP neurons and described various regulatory mechanisms (Du et al. 2015; Roper et al. 2003; Shevchenko et al. 2004; Stern and Armstrong 1995; Stern and Zhang 2005; Teruyama and Armstrong 2007).

6.1.4 The Different Modes of OT Release

There is very little evidence that magnOT neurons form true, functionally relevant synapses with other neurons. Although magnOT neurons project axons to almost the entire rodent forebrain, there has been no report about actual synapse formation from magnOT axons, except the synaptic contact found in the central nucleus of amygdala (Knobloch et al. 2012). In addition to the well-described somatodendritic release of OT and AVP (Landgraf and Neumann 2004; Ludwig and Leng 2006; Tobin et al. 2012), which takes place in the PVN and SON, magnOT neurons engage in volume transmission or *en passant* release (although not confirmed functionally), which is likely the synapse-independent, diffuse release of a small number of large dense core vesicles (LDCVs, please see below), containing OT, within a target region (Chini et al. 2017). For this mode of release, no synapse formation is required and the bulk of release neuropeptide diffuses to its target site with a clear concentration gradient. This phenomenon partly explains the occasionally observed delays (up to 90 s) of OT-ergic action after evoking instantaneous release via optogenetics (Hasan et al. 2019; Knobloch et al. 2012). On the other hand, parvOT neurons have been reported to form true synapses in various structures including the SON, PVN, brainstem and spinal cord (Buijs 1983; Buijs and Van Heerikhuize 1982; Swanson and Sawchenko 1983). This issue has been addressed in more detail in our recent review (Grinevich and Neumann 2021). However, it seems that the function of these synapses is the facilitation not of OT release, but rather of glutamate, which is co-released with OT (Knobloch et al. 2012; Hasan et al. 2019). Whether or not parvOT neurons engage in volume transmission is currently unknown. The potential forms of OT release within the central nervous system (CNS) are summarized in Fig. 6.1.

6.1.5 Controversy Over OTR Activation at Pre- and Postsynaptic Sites

For several decades, it seemed clear that OT-ergic activation of neuronal circuits follows the classical cascade of Ca^{2+}-mediated exocytosis and downstream OT signaling (Burbach et al. 2001). Briefly, OT is packed into large-dense core vesicles (LDCVs)—each of which can hold up to 85,000 molecules of OT (Morris 1976;

Nordmann and Morris 1984). LDCVs are transported to the readily releasable pool of vesicles along the axonal terminals and synaptic vesicle fusion and SNARE-mediated exocytosis takes place in a Ca^{2+}-dependent manner. It was assumed that secreted OT binds to postsynaptic OTRs, triggering a postsynaptic G-protein-dependent signaling cascade involving various G-protein subtypes/pathways (Gaq, Ga11, Gi/o, and β-arrestin) (Chini et al. 2017).

Despite the vast knowledge about synthesis and release, precise mechanisms by which OT targets and activates cells still remain largely elusive. Several seminal papers showed that OT can act on oxytocin neurons themselves (both in the SON and PVN), in a postsynaptic manner. Already in the 1980s several groups showed that OT acts in an autocrine manner (Freund-Mercier and Richard 1984; Moos et al. 1984; Moos et al. 1989; Moos and Richard 1989) and that this process involves calcium release from intracellular thapsigargin-sensitive calcium stores. Finally, Brussaard showed that within OT neurons, OT can also postsynaptically modulate the potency of GABAergic synapses (Brussaard et al. 1996). Although some groups demonstrated the presence of OTR-immunoreactivity at extra-hypothalamic postsynapses (Mitre et al. 2016), there are currently no reports supporting their functional role. Thus, beyond known postsynaptic actions of OT on OT neurons themselves as a mechanism to autoregulate their activity, there are currently no convincing reports further supporting postsynaptic actions in extra-hypothalamic regions.

On the contrary, some papers have been published that suggest presynaptic expression of OTRs (Dolen et al. 2013; Hung et al. 2017; Mairesse et al. 2015). The proposed mechanism includes activation of OTRs on presynaptic neurons by neighboring (or the same) cells, which may lead a subsequent release of conventional neurotransmitters or neuromodulators (such as glutamate or serotonin), which in turns activate the postsynaptic cell in addition or instead of direct "postsynaptic" OT action on OT-sensitive neurons.

6.1.6 The Rodent AVP System: Receptor Subtypes and Islands of AVP Expression

The total number of AVP neurons in the rodent brain (~7500) (Rhodes et al. 1981) is comparable to the number of OT neurons (~7600) (Althammer and Grinevich 2017). While OT neurons in the rodent brain are almost exclusively located in the PVN, SON, and accessory nuclei of the hypothalamus, AVP neurons are also found in various extra-hypothalamic forebrain nuclei, including the bed nucleus of stria terminalis (BNST) and medial nucleus of the amygdala (De Vries et al. 1984). In addition, scattered OT neurons have been found within neighboring areas, such as the BNST of mice (Duque-Wilckens et al. 2020) (Fig. 6.2). While OT acts on only one G-protein coupled receptor, AVP targets three distinct AVP receptor subtypes. These three subtypes of vasopressin receptors are known as V_1, V_2, and V_3 (or V_{1b}). V_2 receptors are present in the renal collecting duct, where AVP regulates water excretion through the insertion of Aquaporin-2 channels into the apical plasma

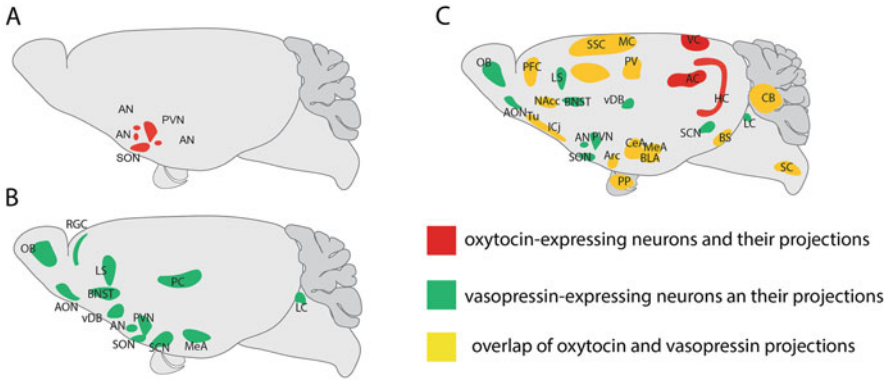

Fig. 6.2 OT and VP systems in the rodent brain—synthesizing nuclei and distinct/overlapping projection sites. Brain schemes highlight the location of OT-synthesizing nuclei (**a**), AVP-synthesizing nuclei (**b**), as well as their projection sites (**c**). All abbreviations of brain structures can be found in the list of abbreviations. Modified from Grinevich and Ludwig 2021

membrane of the principal cells of renal collecting ducts. V_1 receptors are located in the vascular bed, kidney, bladder, spleen, and hepatocytes, as well as the brain (Holmes et al. 2003). The difference between OT and AVP-synthesizing nuclei in the brain as well as their overlapping and distinct projection sites are shown in Fig. 6.2.

In transgenic rats that express the AVP-GFP fused protein under the control of the AVP promoter (Ueta et al. 2005), a GFP signal was also found in neurons of the olfactory bulb, where it modulates the processing of olfactory social signals (Tobin et al. 2010). Very recently, the same group also showed that a small fraction of ganglionic cells in the retina expresses AVP and, through its projections to the suprachiasmatic nucleus (which also contains AVP cells), modulates circadian rhythmicity (Tsuji et al. 2017). The low density and sparse innervation of axonal AVP projections in many brain regions make it technically difficult to dissect the origin of respective axons. A study by Scott Young III and colleagues showed that magnocellular AVP (magnAVP) neurons of the PVN project to CA2 of the dorsal hippocampus (Smith et al. 2016). Moreover, an elegant study of Hernandez and colleagues (Hernandez et al. 2015) combined extracellular recording of CA2, juxtacellular labeling and anatomical reconstructions demonstrated various extrahypothalamic AVP projections of magnAVP cells to numerous forebrain regions, including the preoptic area, suprachiasmatic nucleus, lateral habenula, and the amygdala (for details, please see respective chapter of Limei Zhang and co-authors in this book).

Notably, the forebrain projections of magnOT and magnAVP neurons largely overlap, suggesting simultaneous action of both neuropeptides on the same brain regions and probably on the same cells, which require further investigations (Dumais and Veenema 2016; Grinevich and Stoop 2018; Stoop 2012), especially taking into

consideration the affinity of each neuropeptide for the other receptor (Chini et al. 2008).

6.1.7 Parvocellular AVP Neurons: An Overlooked Cell Type?

While the projections, properties, and functions of parvOT neurons have been extensively studied, very little is known about the respective role of parvocellular AVP (parvAVP) neurons. Early studies identified AVP as a regulator of the hypothalamic-pituitary-adrenocortical axis and showed that AVP can potentiate the stimulatory effect of corticotropin-releasing hormone (CRH) on adrenocorticotropin (ACTH) cells of the anterior pituitary (Whitnall 1993). Later, Greti Aguilera and her colleagues showed that the synthesis of AVP in CRH neurons is triggered by chronic stress, which coincided with the downregulation of CRH expression in these cells. It was proposed that AVP substitutes CRH as the main factor in maintaining the release of adrenal corticosteroids under chronic stress and inflammatory conditions (Grinevich et al. 2001, 2002, 2003). A similar mechanism has been also observed in lactating rats, which exhibit a blunted CRH response that is partly compensated by enhanced synthesis of AVP in CRH neurons, which results in increased neuronal sensitivity (Walker et al. 2001). While it seems possible that parvAVP cells are involved in the stress-induced regulation of the CRH system, especially under chronic inflammatory stress, no concrete evidence confirming this theory has been presented yet. In addition, this particular line of research has been discontinued and thus the role of AVP in CRH neurons should be re-visited with the implementation of novel genetic and functional techniques developed during the last two decades. A good example of re-visiting an old research question with new methods is the recent study led by Yoichi Ueta that investigated the role of cisplatin in the activation of AVP neurons (Akiyama et al. 2020).

In contrast, the intricate interaction between neurosecretory magnAVP networks and preautonomic neurons in the PVN has been intensively studied. The seminal work of Javier Stern lab (Son et al. 2013) has convincingly demonstrated that activity-dependent AVP release from magnocellular neurosecretory neurons stimulated neighboring presympathetic neurons (within the range of 100 μm), thereby mediating interpopulation crosstalk. Moreover, the described mechanisms seem to play a pivotal role in the AVP-dependent polymodal neurohumoral response to a hyperosmotic challenge. This mechanism seems to be distinct to parvOT neurons, which synaptically innervate magnOT neurons in the SON (Eliava et al. 2016). On contrary, magnocellular AVP neurons extend their dendrites to the parvocellular compartments of the PVN containing various parvocellular cells, and this interpopulation crosstalk is mediated by the dendritic release of AVP from magnAVP neurons. In contrast to the conventional synaptic release of a signaling molecule from axonal terminals that act in a temporally and spatially constrained manner, dendritically released AVP acts in a "volume transmission" manner (Son et al. 2013), and the underlying mechanisms regulating release from the somatodendritic compartment differ significantly from those mediating axonal

release of the same peptide (Pitra et al. 2019). This involves diffusion of the neuropeptide in the extracellular space in a rather non-specific manner, "bathing" a mixed population of functionally distinct neighboring neurons within the PVN. In this signaling modality, the specificity of communication is determined by the presence/absence of specific receptors for the released signaling molecule. As demonstrated by Son et al. (2013) a specific population of neurons enriched with V2a receptors is parvocellular presympathetic neurons that project to the neurons of the rostral ventrolateral medulla (RVLM), a structure intimately associated with sympathetic regulation of the cardiovascular system (Guyenet 2006). Using dual-patch recordings and photolytic uncaging, the authors demonstrated that dendritically released AVP acts on V1a receptors located on neighboring parvocellular presympathetic PVN neurons. The V1aR-mediated depolarization and firing discharge of presympathetic neurons was shown to directly influence sympathetic outflow to the cardiovascular system and to specifically participate in the coordination of sympathetic and neurosecretory responses to a systemic osmotic challenge (Son et al. 2013). Importantly, the interpopulation crosstalk between magnAVP and parvo-presympathetic-V1a receptor-expressing neurons may also play an important role in prevalent cardiometabolic diseases, including hypertension, heart failure, and diabetes, in which an exacerbated neurohumoral activation state, which is characterized by elevated neurosecretory and sympathetic outflows, is known to influence prognosis, morbidity and mortality in these conditions (Althammer et al. 2020; Biancardi et al. 2011; Potapenko et al. 2011).

Taken together, the current body of knowledge does not provide evidence for a clear magno/parvo distinction based on projections, functions, and input for AVP neurons. In fact, the unique interaction of parvOT and magnOT neurons seems to be a unique feature of the OT system. Figure 6.3 provides an overview of the limited insight on the interaction between magnAVP, parvAVP, and presympathetic neurons.

6.1.8 Conclusion and Outlook

Recent publications on OT-ergic transmission in the CNS suggest that the classical projections from parvOT and magnOT as well as the presumed modes of release from these axons may be outdated and may have to be overthrown. The lack of clear evidence for postsynaptic receptors, the absence of true synapses in magnOT axonal terminals, the contribution of glial cells in the modulation of OT's effect on neuronal circuits and the discrepancy between magnOT and parvOT projection suggest an intricate interaction of OTergic circuits. Figure 6.4 summarizes the latest findings on OTergic modulation of neuronal and glial circuits and provides an overview of the respective modes of action and release from parvOT and magnOT neurons.

A reliable discrimination of parvOT and magnOT neurons based on their genetic profiles has not yet been achieved. Genetic analysis of OT neurons resulted in four different clusters, although it is not clear if parvOT and magnOT neurons are exclusively represented within those genetic subgroups of OT neurons. In a recent

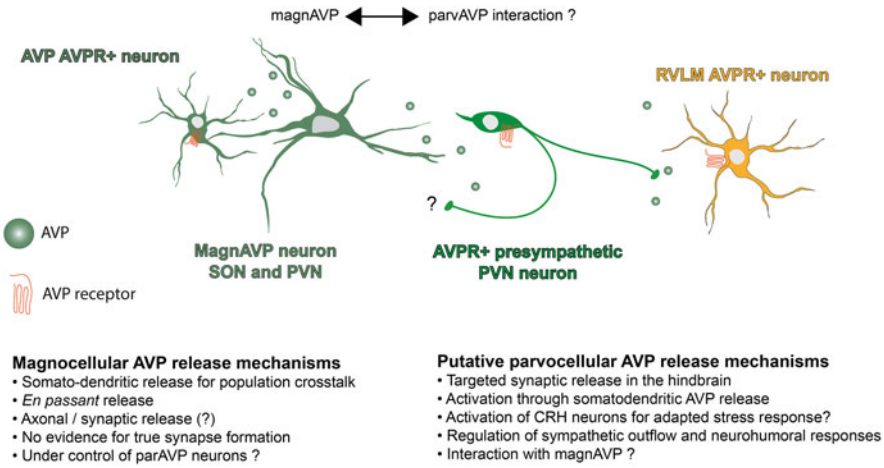

Fig. 6.3 Modes of release and interaction between parvAVP and magnAVP cells. Somatodendritically released AVP from SON and PVN magnAVP cells activates nearby AVPR-positive neurons. Within the PVN, somatodendritic release coordinates interpopulation crosstalk by activation of presympathetic neurons that project to the RVLM to coordinate cardiovascular responses

study (Lewis et al. 2020), the lab of Gul Dölen reports autism risk genes to be enriched in parvOT neurons, which have been genetically dissected based on anatomical location and Flourogold (FG) labeling. Intriguingly, the group reported that 34% of all OT neurons were parvocellular, which is in stark contrast (1–5%) to what has been previously reported in rats. While this discrepancy can partially be attributed to a species-dependent difference in the composition of the OT-ergic system and technical limitations with the use of Flourogold as a marker of magnocellular (neuroendocrine) neurons, further identification of genetic markers discriminating OT cell types will be essential to dissect phenotypes of OT neurons, which can be not limited to only parvocellular or magnocellular cells.

Within the last few years, it has become evident that the classical view on magnOT and parvOT projections is outdated. It seems that magnOT do not project exclusively to the pituitary and forebrain regions and that innervation by parvOT neurons is not confined to hindbrain structures. We now know that parvOT neurons project to OT neurons within the PVN (Tang et al. 2020) and SON (Eliava et al. 2016) and that magnOT neurons innervate the VTA (Hung et al. 2017). Furthermore, a very recent study (Oti et al. 2021) proposes that magnOT neurons also project to the spinal cord, based on the size of LDCVs (75–100 nm), typical of magnOT cells, although no research contradicts the possibility of LDVC presence in axonal terminals of parvOT neurons. Although all of these new findings argue for the long-held dogma on non-overlapping projection sites of parvOT and magnOT neurons, they stimulate further studies focused on compartmentalized subdivisions

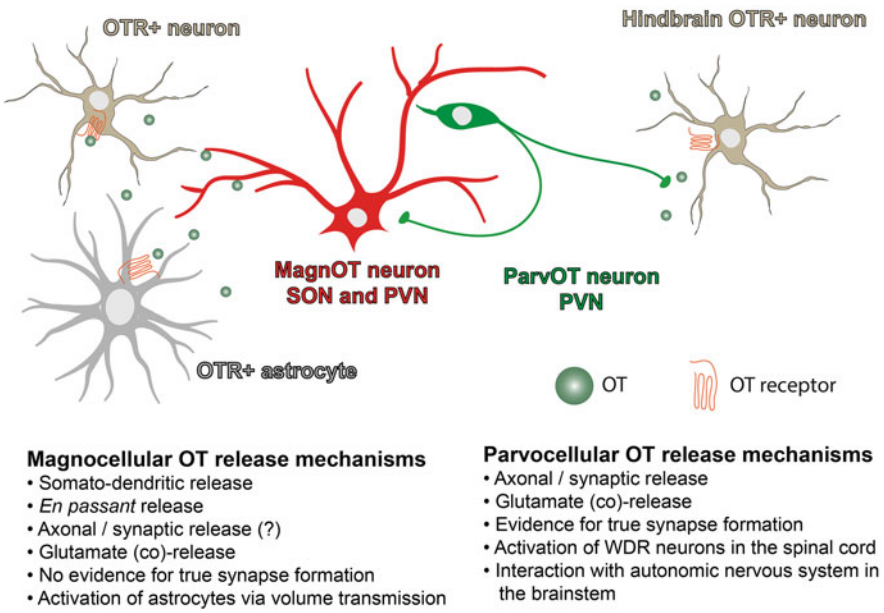

Fig. 6.4 Modes of release and interaction between parvOT and magnOT cells. ParvOT neurons act as hypothalamic master cells and project onto magnOT neurons in the PVN and SON to coordinate their activity. Somato-dendritic release from magnOT neurons provides a feedback mechanism between magnOT neurons. ParvOT neurons form clear synapses with other neurons in the PVN and spinal cord, while secretion from magnOT via volume transmission or *en passant* release activates nearby astrocytes and neurons. WDR: Wide dynamic range neurons

of each OT cell type linked to the specific regulation of distinct brain regions and respective behaviors.

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