Cell and Tissue Research (2019) 375:41–48
https://doi.org/10.1007/s00441-018-2960-5

REVIEW

Diversity of central oxytocinergic projections

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Received: 21 September 2018 / Accepted: 6 November 2018 / Published online: 29 November 2018

Abstract

Localization and distribution of hypothalamic neurons expressing the nonapeptide oxytocin has been extensively studied. Their projections to the neurohypophyseal system release oxytocin into the systemic circulation thus controlling endocrine events associated with reproduction in males and females. Oxytocinergic neurons seem to be confined to the ventral hypothalamus in all mammals. Groups of such cells located outside the supraoptic and the paraventricular nuclei are summarized as "accessory neurons." Although evolutionary probably associated with the classical magocellular nuclei, accessory oxytocin neurons seem to consist of rather heterogenous groups: Periventricular oxytocin neurons may gain contact to the third ventricle to secrete the peptide into the cerebrospinal fluid. Perivascular neurons may be involved in control of cerebral blood flow. They may also gain access to the portal circulation of the anterior pituitary lobe. Central projections of oxytocinergic neurons extend to portions of the limbic system, to the mesencephalon and to the brain stem. Such projections have been associated with control of behaviors, central stress response as well as motor and vegetative functions. Activity of the different oxytocinergic systems seems to be malleable to functional status, strongly influenced by systemic levels of steroid hormones.

Keywords Hypothalamo neurohypophyseal system · Circumventricular organs · Liquor contacting neurons · Perivascular system · Limbic system

Introduction

Numerous studies have been performed on the hypothalamic nonapeptide oxytocin (OT). Its importance as a neurohypophyseal hormone for the induction of labor and milk ejection led to clinical applications, its ability to enhance sperm motility has found practical use in veterinary medicine (Fuchs et al. 1989). In addition, OT has been known for a long time to act as a central neurotransmitter throughout the limbic system to control reproductive and social behaviors (review: Pedersen et al. 1988) as well as central and systemic stress response (Winter and Jurek 2018). OT positive projections to the brain stem seem to be involved in some functions of the autonomic nervous system (Freeman et al. 2017). OT receptors have been characterized and localized in different brain areas (Boccia et al. 2013; Devost et al. 2008; Gould and Zingg 2003; Marlin and Froemke 2017) and in numerous peripheral tissues (review: Ivell et al. 2001). While peripheral OT expression has been shown to occur in prostate, gonads, or skin, OT expression in the brain seems to be confined to the hypothalamus. It is synthesized predominantly in the magnocellular hypothalamic supraoptic (SON) and paraventricular (PVN) nuclei as well as in some of the parvocellular neurons within the PVN (Figs. 1, 2, 3 and 4, Jirikowski et al. 1989). OT is also expressed in single cells or groups of neurons outside these nuclei normally referred to as "accessory neurons" (Møller et al. 2018). Cerebral OT is synthesized as part of a precursor protein "prooxytophysin" together with its associated neurophysin I (NP1). This is in analogy to the closely related "propressophysin" which is transcribed in other populations of hypothalamic neurons within SON and PVN and which is processed to the antidiuretic hormone arginin vasopressin (AVP), neurophysin II, and a glycoprotein (which is missing in the OT precursor, review: Sofroniew 1983). The functional importance of neurophysins is still a matter of discussion. According to the textbook OT expression occurs in magnocellular and in parvocellular hypothalamic nuclei. Clearly the physiological properties of peptidergic neurons cannot be assessed by their mere size. Recently, four different genomic clusters of oxytocinergic hypothalamus neurons have been described (Althammer and Grinevich 2017). OT and AVP are normally expressed in distinct populations of neurons. This,

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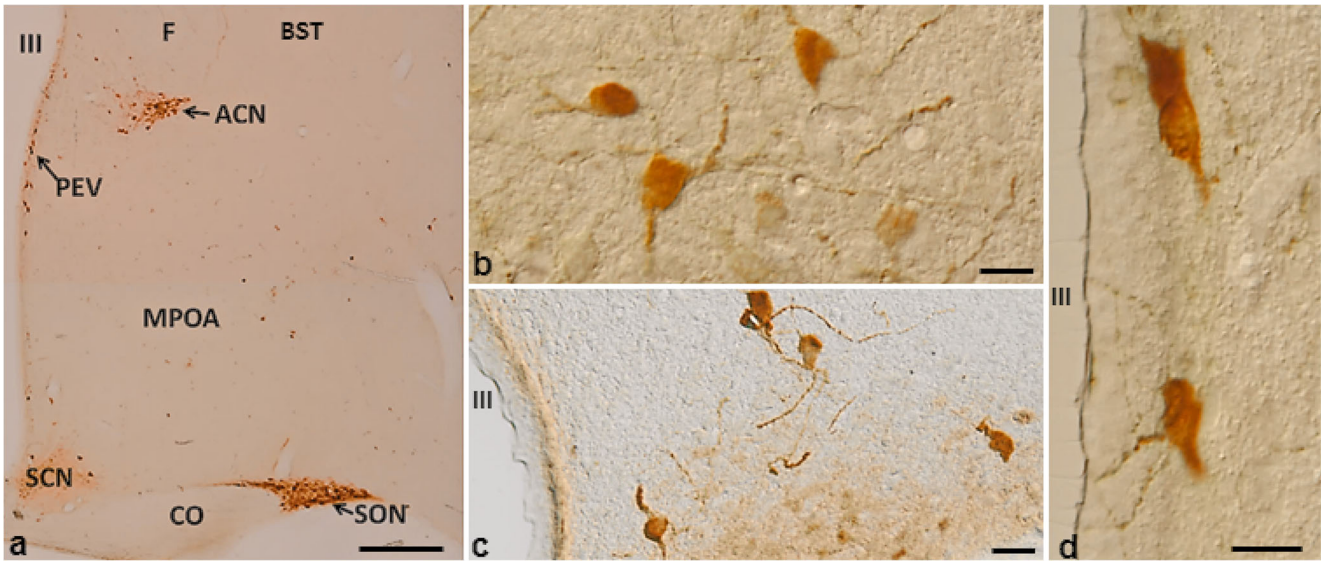

Fig. 1 **a** Frontal vibratome section through the rat hypothalamus 0.8 mm caudal from Bregma, immunostained for OT. Groups of OT neurons occur in the supraoptic nucleus (SON) with predominantly neurohypophyseal projections. OT positive perikarya are visible in the anterior commissural nucleus (ACN, **b**) ventral to the Fornix (F). Their projections stretch towards the bed nucleus of the stria terminalis (BST). Single magnocelluar OT positive perikarya occur in the suprachiasmatic nucleus (SCN, **c**). OT neurons in the periventricular nucleus (PEV) extend processes through the ependymal layer towards the third ventricle (III, **d**). OT positive perikarya in the medial preoptic area (MPOA) seem to have projections within the anterior hypothalamus and the preoptic region (**c**). CO = optic chiasma. Scale bar **a** = 300 μm, scale bars **b**–**d** = 10 μm

however, seems to be malleable to functional status to some extent since both nonapeptides are coexpressed in some of the hypothalamic neurons upon chronic stress (Dief et al. 2018), during parturition (Jirikowski et al. 1991a) or under septic shock (Sendemir et al. 2013). The total number of OT/AVP coexpressing neurons can increase up to 5% during lactation (Kiyama and Emson 1990; Gainer 2012). OT expression and terminal secretion depends in part on steroid hormones: OT-induced behavioral changes are enhanced by estrogens (Caldwell et al. 1989), OT actions on stress response depend on glucocorticoids (Jirikowski et al. 1993). Steroids are capable of crossing the blood brain barrier, so they are likely to be peripheral mediators of central oxytocinergic functions. On the other hand, OT secreted from peripheral organs is unlikely to enter the brain.

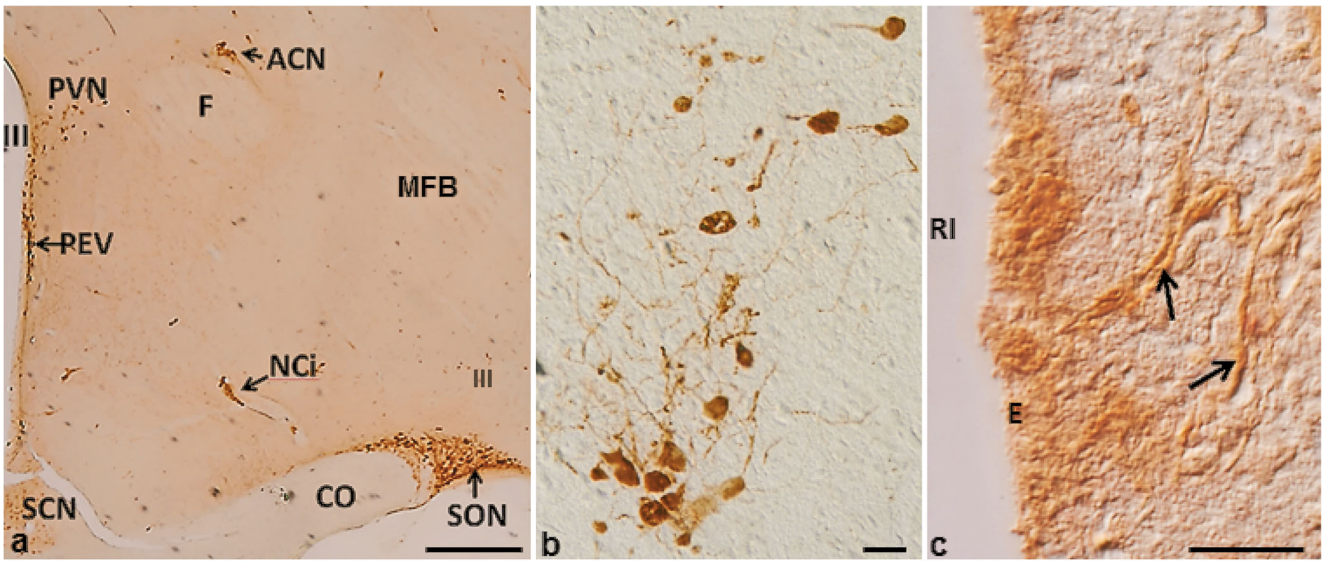

Fig. 2 **a** Cross section through the rat hypothalamus 1.3 mm caudal from Bregma: OT neurons appear in the rostral portion of the paraventricular nucleus (PVN) and in the nucleus circularis (NCi). OT positive cell bodies in the ACN **b** seem to extend their projections towards the median forebrain bundle (MFB) and to the bed nucleus of the BST. The recessus infundibularis (RI, **c**) in the posterior pituitary lobe is lined with OT immunostained ependymal cells (E) which receive OT positive nerve terminals (arrows). Scale bar **a** = 300 μm, scale bars **b**, **c** = 10 μm

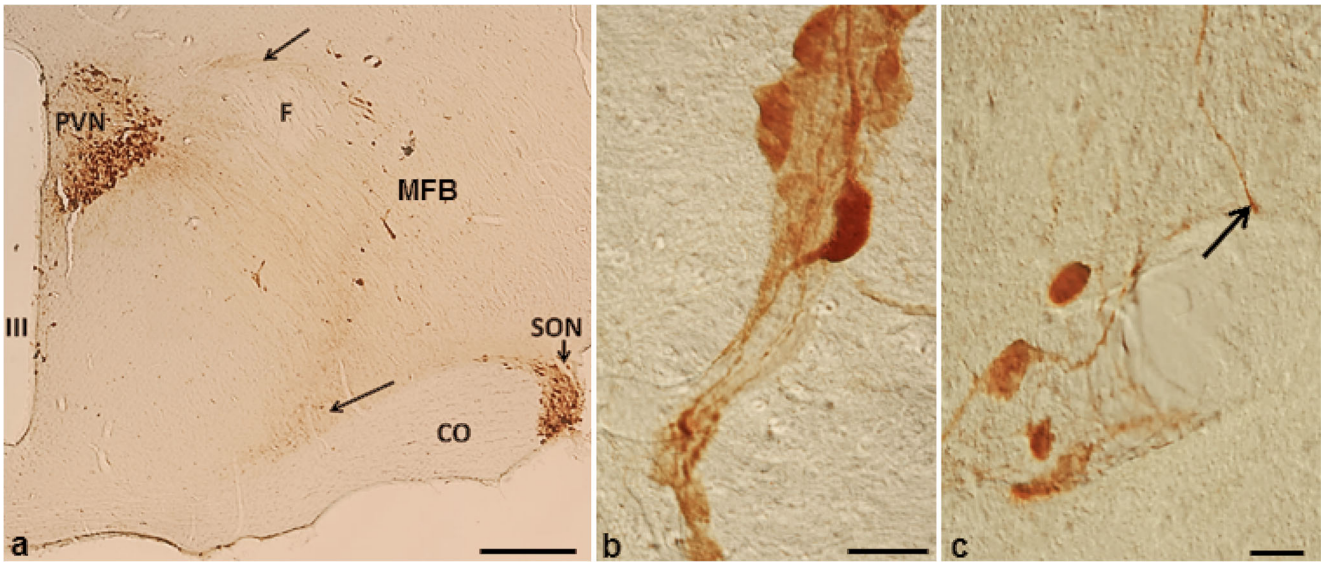

Fig. 3 **a** OT immunostained hypothalamus section 1.6 mm caudal from Bregma: numerous OT neurons in the PVN extend their projections dorsally and ventrally from F (arrows) and merge with SON projections towards the median eminence. Groups of OT positive perikarya are attached to blood vessels to form the nuclei circulares **b**. OT positive processes with varicosities are associated with the vascular wall **c**. Scale bar **a** = 300 μm, scale bars **b**,**c** = 10 μm

While there is a huge (and steadily increasing) body of literature on the molecular physiological, pharmacological, and behavioral significance of OT, the underlying neuroanatomical and neurochemical basis has been studied to a much lesser extent and it seems that this topic has mostly escaped researchers' attention in the recent years. This is especially true for oxytocinergic projections within various brain areas. While there is ultrastructural evidence for oxytocinergic synapses indicating that OT may act as a neurotransmitter (Sofroniew 1983), axonal swellings in neurohemal organs suggest paracrine secretion (Morris et al. 1998). Close apposition of OT positive projections to blood vessels (Møller et al. 2018) or to the ventricular system (Vigh-Teichmann et al. 1970) may be indications

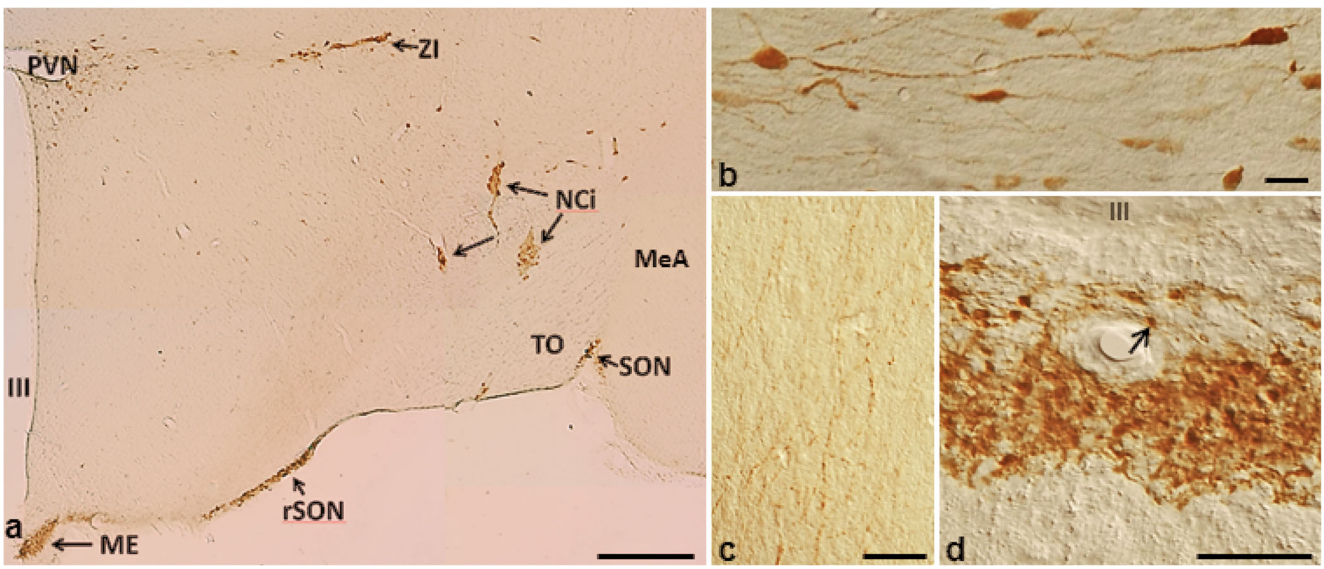

Fig. 4 **a** OT immunostained hypothalamus section 2.3 mm caudal from Bregma: OT positive neurons in the caudal portion of the PVN project parallel to the ventricular system towards the mesencephalon and the brain stem. Groups of immunostained perikarya occur in the zona incerta (ZI, **b**). They extend projections towards the reticular thalamic nucleus (Rt). OT neurons in the retrochiasmatic portion of the SON (rSON) seem to project to the median eminence (ME) while SON neurons lateral from the optic tract (TO) appear to have projections to the medial amygdala (MeA, **c**). OT positive neuronal projections in the internal zone of the ME form the neurohypophyseal tract (NT, **d**). They occasionally show close apposition to blood vessels (arrow). Scale bar **a** = 300 μm, scale bars **b**–**d** = 10 μm. Stereotaxic coordinates according to Paxinos and Watson (1986). Immunoperoxidase staining for oxytocin (Peroxidase-anti-peroxidase method) of 100 μm thick serial vibratome sections of formaldehyde-fixed rat brains. For details on the immunocytochemical methods see Jirikowski et al. (1988).

for further functional properties of the nonapeptide within the brain.

Neurohypophyseal projections

OT neurons in the PVN extend long axons with numerous varicosities through the lateral hypothalamus towards the SON where they meet supraoptic projections to form the neurohypophyseal tract. These fibers stretch on top of the optic chiasm into the internal zone of the median eminence, the infundibular stalk and to the posterior pituitary lobe where they end as Herring bodies in close association with blood vessels (Figs. 2, 3, and 4). Pituicytes are astrocyte-related glial cells that mediate a functional blood brain barrier within this neurohemal organ. This is known as hypothalamo neurohypophyseal system (HNS). Given the axonal length, the numbers of varicosities and the size of a Herring body, the axonal volume of a magnocellular OT neuron that projects to the posterior lobe is likely to exceed the volume of the perinuclear cytoplasm by 500×–1000×. This OT storage packed with secretory vesicles may be of great functional importance for stimulus secretion coupling (Morris et al. 1998). Axonal OT pools may efficiently replenish OT that had been released into the systemic circulation. This way, immediate physiological demand for OT can be met independently from de novo transcription and processing of the hormone. With in situ hybridization, we could demonstrate that mRNA encoding prooxytophysin is located in hypothalamo neurohypophyseal axons (Jirikowski 1992). Hybridization product was located within secretory vesicles indicating that OT-encoding transcripts may be subject to rapid axonal transport (Jirikowski et al. 1990a). It has been proposed that mRNA compartmentalized in axonal varicosities may be the source of immediate prooxytophysin translation upon certain stimuli prior to de novo transcription. A similar mechanism seems to exist in the HNS for the immediate early gene c fos (Giovannelli et al. 1990).

Both expression and terminal secretion of OT depend on estrogens. OT neurons express in part nuclear estrogen receptors; estradiol treatment alters numbers and distribution of OT immunoreactive neurons (Jirikowski et al. 1990b) as well as levels of mRNA encoding OT precursor (Caldwell et al. 1988). Estradiol treatment also changes systemic OT levels indicating that biosynthesis and terminal secretion are malleable to systemic steroid concentrations. Similar observations have been made in parturient animals (Jirikowski et al. 1991a). Interestingly, there is no linear relationship between steroid concentrations and OT expression since low estrogen doses given once seem to active OT expressing hypothalamus neurons while chronic treatment with high estrogen doses seems to down regulate SON and PVN (Jirikowski et al. 1988).

Hypophyseal secretion of OT seems to be influenced in a similar fashion by glucocorticoids and by vitamin D (Jirikowski et al. 2009). While nuclear steroid receptors are present only in a portion of the oxytocinergic perikarya (Jirikowski et al. 1993), the related steroid binding globulins are expressed in most of the OT neurons (Sivukhina and Jirikowski 2014). Sex hormone-binding globulin (SHBG), corticosteroid-binding globulin (CBG), and vitamin D-binding protein (DBP) were all found in OT positive magnocellular neurons (review: Caldwell et al. 2017). It has been discussed that these steroid-binding proteins may be linked to non-genomic effects of steroid hormones. Steroid dependent release of a neuropeptide from axon terminals is most likely not mediated through genomic effects and nuclear steroid receptors. Instead, this involves most likely rapid, membrane actions. The underlying cellular and molecular mechanisms are unclear to date. Membrane associated estrogen receptor GPR30 has been described in oxytocinergic neurons (Sakamoto et al. 2007). Its functional interaction with the binding globulins and nuclear receptors ERα and ERß has yet to be characterized. Clearly, neurohypophyseal functions of OT, e.g., in parturition, lactation of in stress response, require fast release ion of OT from the posterior lobe. Posterior lobe OT can be completely drained upon extreme challenge, e.g., during septic shock (Sendemir et al. 2013; Da Silva et al. 2014).

Hypophyseotropic OT system

Axons of OT neurons in SON, PVN, and perhaps the perivascular groups pass through the internal zone of the median eminence (ME). Some of these OT positive varicosities appear in close apposition to ME blood vessels (Fig. 4d). The external zone of the ME is a neurohemal organ that hosts blood vessels of the hypophyseal portal system as part of the hypothalamo adenohypophyseal system (HAS). Hypothalamic releasing and inhibiting factors enter the portal circulation to regulate endocrine cells of the anterior lobe. Tanycytes, which are specialized ependymal cells on the base of the third ventricle, interconnected by tight junctions provide a functional blood brain barrier in this circumventricular organ. So far, the internal zone of the ME was thought to exclusively host axons of the magnocellular hypothalamic nuclei as part to the HNS. However, the presence of blood vessels with fenestrated endothelia (Wittkowski 1969) and with large perivascular spaces in this region suggests a functional relationship also with the adenohypophyseal portal system. It has been proposed that OT is the long sought after prolactin releasing factor (Villegas-Gabutti et al. 2018) and the perivascular spaces in the internal portion of the ME may be the port of entry for OT to the HAS. So the milk ejecting neurohypophyseal hormone may also be capable of stimulation milk production in the mammary glands through adenohypophyseal prolactin.

Perivascular OT neurons

Clusters of OT positive neurons have been described in close apposition to blood vessels that connect SON and PVN (Fig. 3b,c). Such groups of neurons form small nuclei. They are particularly abundant in human brain. Due to their crescent-like shape along the large hypothalamic blood vessels, they have been termed Ncll. circulares (NCi, Møller et al. 2018). The functional properties of these neurons are still a matter of controversy. Some of these neurons may contribute to the HNS since their long processes with typical varicosities seem to merge into the neurohypophyseal tract. They also may contact the perivascular area, known as Virchow Robin space that contains cerebrospinal fluid (CSF) and that is connected with the ventricular system. OT liberated from these neurons in a paracrine fashion (Morris et al. 1998) may therefore contribute to CSF OT levels. Perivascular groups of OT neurons are mostly found associated with larger blood vessels. It has been proposed that neurosecretory nerve endings may be capable of releasing OT into the vasculature, making the NCi a further neurohemal organ (Møller et al. 2018). It is unclear why an additional release site of OT into the systemic circulation should be necessary. Considering that intrahypothalamic blood vessels are most likely part of the blood brain barrier, systemic release of OT should be rather unlikely from the NCi. It is known however that the blood brain barrier is subject to some functional dynamics: Diabetes insipidus caused by disruption of the infundibular stalk and loss of systemic AVP is in many cases only transitory although neurohypophyseal projections are unlikely to regenerate. Posterior lobe hormones released from perivascular intrahypothalamic groups may indeed supplement or even replace neurohypophyseal functions (Blanco et al. 1992). A similar situation may exist for OT during late pregnancy, parturition, and lactation: We observed with immunohistochemical electron microscopy plasticity of the interface between perivascular OT neurons and the vasculature, suggesting functional dynamics of the blood brain barrier in the NCi (Blanco et al. 1990).

Perivascular OT and AVP may also have vasoactive properties by affecting smooth muscle cells of arterial walls. So both nonapeptides could be involved in control of intracerebral blood pressure.

Periventricular OT neurons

The periventricular nucleus (PEV) hosts a large number of bi- and multipolar neurons that show intense immunostaining for OT. They are positioned below the ependymal layer of the third ventricle and extend processes through the ependyma towards the ventricular space (Fig. 1d). Some of these cells even seem to be located inside the ventricular lumen. They have been termed liquor contracting neurons (Vigh-Teichmann et al. 1970) and are thought to be among the sources of OT in the CSF. The functional properties of liquor OT is far from being understood to date. It has been shown that OT levels in CSF are dramatically reduced in patients afflicted with severe chronic depression (Frasch et al. 1996). It has been proposed that intranasal application of OT could be used as an antidepressant remedy (Leppanen et al. 2017). Uptake of OT by the olfactory mucosa has been shown to result in rapid increase of CSF OT levels which led to clinical use of OT nasal spray for conditions including impaired lactation, chronic pain, or male sexual dysfunctions (Syntocinon®, BGP Products GmbH, CH 6341 Baar). The olfactory mucosa is known to be a pharmacological access to the brain since it allows for bypassing the blood brain barrier (Scantamburlo et al. 2015). However, the actual physiological basis of intranasal uptake of OT is not completely understood today.

Neurohypophyseal projections of hypothalamic nuclei are known to terminate as Herring bodies in the posterior lobe. Some of these nerve endings appear in close apposition to portions of the third ventricle within the infundibulum and the neurohypophysis, termed recessus infundibularis (RI). This structure is particularly well developed in larger mammals including humans. The ependymal lining within the RI has been shown to contain gaps that provide direct contact of OT immunostained Herring bodies to the CSF. In conjunction with secretory ependymal cells this may be a further source of OT in the CSF (Fig. 2c). Early ultrastructural and histochemical studies observed that the ependymal cells in this region show features of secretory cells suggesting secretion of neurohormones into the CSF (Wittkowski 1969). He proposed the term “ependymokrinie.” Although direct evidence for intraventricular OT liberation within the IR is still missing, the above-mentioned light- and electron microscopical studies strongly argue in favor of this hypothesis.

Intracerebral projections of OT neurons

OT immunoreactive neurons within the classical nuclei as well as accessory OT neurons are known to extend wide spread axonal projections within the brain. Numerous tracing studies have been performed in order to detect target sites of SON and PVN OT neurons. These methods include stereotaxic in vivo injections with horseradish peroxidase (HRP, Mohamadi et al. 2015), fluoro-gold, or viral constructs (Althammer and Grinevich 2017), all combined with OT immunocytochemistry. Widespread oxytocinergic projections in portions of the limbic system and their involvement in the attenuation of fear response could be shown by viral vector-based tracing (Knobloch et al. 2012). Tracing studies on single accessory OT neurons in life animals become feasible with this innovative method. Their actual projection sites are yet

to be determined. Sofar immunocytochemistry of 100 μm thick vibratome sections was one of the options for an approximation of peptidergic target regions. In consecutive series of such thick sections it was possible to follow OT projections for some distance.

Immuno-electron microscopy revealed oxytocinergic synapses in parts of the limbic system suggesting that the neurohormone also has neurotransmitter properties throughout the brain (Bakos et al. 2018, Buijs and Swaab 1979, Buijs and Van Heerikhuize 1982). Oxytocinergic projections within the brain have been linked to behavioral changes including sexual arousal, maternal behavior, and stress response (Jirikowski et al. 1988; Dief et al. 2018). Brain regions known to control such behaviors express OT receptors (OTR, Clipperton-Allen et al. 2012) as determined by immunocytochemistry, in situ hybridization, radio ligand assays and RT-PCR (Review: Devost et al. 2008). Stereotaxic injections with OT in presumed target areas have been shown to affect behaviors (Pedersen et al. 1988), supporting the idea of receptor-mediated OT effects. Different regions seem to be involved in different behavioral functions.

Paraventricular nuclei

OT neurons in the posterio-lateral portion of the PVN project to the median forebrain bundle and to the striatum (Fig. 2a). These projections may either be collaterals of the neurohypophyseal tract or independent projections. Although the functions of most of the centrally projecting OT neurons are yet to be characterized, their great diversity suggests that there may be multiple functional properties, ranging from influence of the limbic system and behavioral changes, affections of the brain stem to influence vegetative functions and intra hypothalamic projections to exert neuroendocrine properties (László et al. 2016).

Supraoptic nuclei

Single OT neurons in the caudal portion of the SON project in part to nuclei of the medial and central amygdala. They seem to modulate anxiety behavior to some extent (Gorka et al. 2015). Microinjections with OT into the central nuclei of the amygdala result in positive reinforcement of reproductive and social behaviors. Although the number of oxytocinergic afferences from hypothalamic nuclei throughout the amygdala is rather small, the expression of OTR is extensive in this part of the limbic system (Jurek and Neumann 2018). It could well be that single-defined SON neurons are important for oxytocinergic innervation of specific portions of the amygdala.

OT neurons in the retrochiasmatic portion of the SON (rSON) form groups of cells that line the lateral basis of the diencephalon (Fig. 4a). Their projections contribute to the internal and external zones of the ME. In addition, they are closely associated with the pia mater. It seems possible that these neurons release OT into the external spaces of the CSF.

Periventricular nucleus

In addition to their above mentioned relationship to the third ventricle, PEV neurons extend long axonal projections subependymally parallel to the ventricular system (Fig. 1d) through the mesencephalon and to the brain stem. These are likely to be among the oxytocinergic projections (together with the OT neurons in the caudal portion of the PVN) that control various vegetative functions in mesencephalon and brain stem: For example, OT-receptor-expressing neurons in the parabrachial nucleus have been shown to regulate fluid intake (Ryan et al. 2017).

Medial preoptic area

Single OT neurons have been observed in the medial preoptic area (MPOA). Their importance for the control of sexual and maternal behaviors is well established (Pedersen et al. 1988). OT injections into the basal forebrain of rats have been shown to have anxiolytic effects (Sabihi et al. 2014). OT effects in the MPOA clearly depend on steroid hormones. Interestingly, OT neurons in the MPOA rarely show nuclear uptake of radiolabelled estradiol indicating absence of classical estrogen receptors (Jirikowski et al. 2018). The MPOA is among the brain regions with the highest density of estrogen target neurons (Jirikowski et al. 1990a). So estrogen actions on OT neurons in the MPOA may be mediated either through OT negative estrogen target interneurons or through non-genomic estrogen actions.

Zona incerta

Laterally to the posterior PVN is the zona incerta (ZI) which also hosts numerous OT-stained neurons. They extend their axons through the capsula interna, presumably to neocortical regions (Figs. 4a,b). The functional importance of OT neurons in the ZI is unknown so far. However, their numbers have been shown to increase in male mice during mating, indicating that they may play a role in this physiological state (Jirikowski et al. 1991b).

Anterior commissural nucleus

A group of OT neurons is found ventro laterally to the anterior commissure. These cells have been termed anterior commissural nucleus (ACN) or lateral subcommissural nucleus (LSN, Jirikowski et al. 1990a,b). These neurons seem to project in part to the nucleus accumbens. These neurons also extend projections to the lateral septum which is known to be an

extensive OT target region. It has been shown that OT in the lateral septum prevents social fear during lactation (Menon et al. 2018).

Suprachiasmatic nucleus

Single magnocellular OT neurons have been detected in the suprachiasmatic nucleus (SCN, Fig. 1a). The morphology of the SCN has been shown to have gender differences although OT positive neurons in the SCN occur in both males and females. The SCN has been linked to endocrine events related to circadian rhythm, light cyclus, and feeding behavior (Santoso et al. 2017). The SCN is predominantly parvocellular most of these cells express AVP. It is unclear whether the single magnocellular OT neurons visible in the dorsal portion of the SCN (Fig. 1c) are actually part of this nucleus or dispersed from the MPOA. This question has to be addressed to genotyping and viral vector tracing.

Conclusions

OT neurons are confined to the hypothalamus although there seems to be a huge functional diversity. On the other hand, OTR is quite abundant throughout the brain. The current opinion that oxytocinergic neurons are exclusively magnocellular had to be revised some time ago. In addition to parvocellular OT systems there may be more types of OT neurons which cannot be characterized just by their size (Althammer and Grinevich 2017). It should be emphasized that the different oxytocinergic systems may not so much be structural as they are functional (Lefevre et al. 2018). First of all, one oxytocinergic neuron may have multiple functional properties: It may extend a dendrite to the wall of a blood vessel, another one across the ependyma and an axon to the posterior lobe with a collateral to the limbic system. Furthermore, there seems to be some malleability to functional status. Estrogen treatment greatly enhances numbers of OT positive neurons. Interestingly, there is no linear relationship between steroid concentrations and OT expression since moderate estrogen concentrations seem to stimulate while chronic and high concentrations seem to deplete OT.

References

Althammer F, Grinevich V (2017) Diversity of oxytocin neurons: beyond magno- and parvocellular cell types? J Neuroendocrinol. https://doi.org/10.1111/jne.12549

Bakos J, Srancikova A, Havranek T, Bacova Z (2018) Molecular mechanisms of oxytocin signaling at the synaptic connection. Neural Plast. https://doi.org/10.1155/2018/4864107

Blanco E, Jirikowski GF, Gonzalez R, Pilgrim C, Vazquez R (1990) Ultrastructural changes of the neuropil interposed between oxytocin-secreting neurons and blood vessels during late pregnancy and lactation in the rat. An Anat 36:30–32

Blanco E, Pilgrim C, Vazquez R, Jirikowski GF (1992) Plasticity of the interface between oxytocin neurons and the vasculature in late pregnant rats: an ultrastructural morphometric study. Acta Histochem 91: 165–170

Boccia ML, Petrusz P, Suzuki K, Marson L, Pedersen CA (2013) Immunohistochemical localization of oxytocin receptors in human brain. Neuroscience 253:155–164

Buijs RM, Swaab DF (1979) Immuno-electron microscopical demonstration of vasopressin and oxytocin synapses in the limbic system of the rat. Cell Tissue Res 204:355–365

Buijs RM, Van Heerikhuize JJ (1982) Vasopressin and oxytocin release in the brain–a synaptic event. Brain Res 252:71–76

Caldwell JD, Jirikowski GF, Greer ER, Stumpf WE, Pedersen CA (1988) Ovarian steroids and sexual interaction alter oxytocinergic content and distribution in the basal forebrain. Brain Res 446:236–244

Caldwell JD, Brooks PJ, Jirikowski GF, Barakat AS, Lund PK, Pedersen CA (1989) Estrogen alters oxytocin mRNA levels in the preoptic area. J Neuroendocrinol 1:273–278

Caldwell JD, Londe K, Ochs SD, Hajdu Z, Rodewald A, Gebhart VM, Jirikowski GF (2017) Three steroid-binding globulins, their localization in the brain and nose, and what they might be doing there. Steroids. https://doi.org/10.1016/j.steroids.2017.12.004

Clipperton-Allen AE, Lee AW, Reyes A, Devidze N, Phan A, Pfaff DW, Choleris E (2012) Oxytocin, vasopressin and estrogen receptor gene expression in relation to social recognition in female mice. Physiol Behav 105:915–924

Da Silva FP, Machado MC, Sallet PC, Zampieri FG, Goulart AC, Torggler Filho F, Barbeiro HV, Velasco IT, da Cruz Neto LM, de Souza HP (2014) Neuropeptide downregulation in sepsis. Inflammation 37:142–145

Devost D, Wrzal P, Zingg HH (2008) Oxytocin receptor signalling. Prog Brain Res 170:167–176

Dief AE, Sivukhina EV, Jirikowski GF (2018) Oxytocin and stress response. Open J Endocrine Metab Dis 8:93–104

Frasch A, Zetzsche T, Steiger A, Jirikowski GF (1996) Reduction of plasma oxytocin levels in patients suffering from major depression. In: Ivell R, Russell J (eds) Oxytocin, cellular and molecular approaches in medicine and research. Advances in Experimental Medicine and Biology, Plenum Press, New York, pp 152–155

Freeman SM, Smith AL, Goodman MM, Bales KL (2017) Selective localization of oxytocin receptors and vasopressin 1a receptors in the human brainstem. Soc Neurosci. https://doi.org/10.1080/17470919.2016.1156570

Fuchs U, Leipnitz C, Lippert TH (1989) The action of oxytocin on sperm motility. In vitro experiments with bull spermatozoa. Clin Exp Obstet Gynecol 16:95–97

Gainer H (2012) Cell-type specific expression of oxytocin and vasopressin genes: an experimental odyssey. J Neuroendocrinol 24:528–538

Giovannelli L, Shiromani P, Jirikowski GF, Bloom FE (1990) Oxytocin neurons in the rat hypothalamus exhibit c-fos immunoreactivity upon osmotic stress. Brain Res 531:299–303

Gorka SM, Fitzgerald DA, Labuschagne I, Hosanagar A, Wood AG, Nathan PJ, Phan KL (2015) Oxytocin modulation of amygdala functional connectivity to fearful faces in generalized social anxiety disorder. Neuropsychopharmacology 40:278–286

Gould BR, Zingg HH (2003) Mapping oxytocin receptor gene expression in the mouse brain and mammary gland using an oxytocin receptor-LacZ reporter mouse. Neuroscience 122:155–167

Ivell R, Kimura T, Müller D, Augustin K, Abend N, Bathgate R, Telgmann R, Balvers M, Tillmann G, Fuchs AR (2001) The structure and regulation of the oxytocin receptor. Exp Physiol 86:289–296

Jirikowski GF (1992) Oxytocinergic hypothalamic chemoarchitecture during mating, pregnancy, parturition and lactation. In: Pedersen CA, Caldwell JD, Jirikowski GF, Insel T (eds) Oxytocin in maternal, sexual and social behaviors, vol 652. Annals of the New York Academy of Sciences, New York, pp 253–270

Jirikowski GF, Caldwell JD, Stumpf WE, Pedersen CA (1988) Oxytocinergic neuronal systems in the rat hypothalamus are influenced by estrogens. Neuroscience 25:237–248

Jirikowski GF, Caldwell JD, Pilgrim C, Stumpf WE, Pedersen CA (1989) Changes in immunostaining for oxytocin in the forebrain of the female rat during late pregnancy, parturition and early lactation. Cell Tiss Res 256:411–417

Jirikowski GF, Stumpf WE, Pedersen CA (1990a) Oxytocinergic estradiol targets in the mouse hypothalamus. Fol Histochem Cytobiol 28: 3–11

Jirikowski GF, Sanna PP, Bloom FE (1990b) mRNA coding for oxytocin is present in axons of the hypothalamo-neurohypophysial tract. Proc Natl Acad Sci U S A 87:7400–7404

Jirikowski GF, Ramalho-Ortigao JF, Caldwell JD (1991a) Transitory coexistence of oxytocin and vasopressin in the hypothalamo neurohypophysial system of parturient rats. Horm Metab Res 23:476–480

Jirikowski GF, Caldwell JD, Häussler HU, Pedersen CA (1991b) Mating alters topography and content of oxytocin immunoreactivity in male mouse brain. Cell Tissue Res 266:399–403

Jirikowski GF, Mc Gimsey WC, Sar M (1993) Topography of oxytocinergic glucocorticoid target neurons in the rat hypothalamus. Horm Metab Res 25:543–544

Jirikowski GF, Kaunzner UW, Dief AE, Caldwell JD (2009) Distribution of vitamin D binding protein expressing neurons in the rat hypothalamus. Histochem Cell Biol 131:365–370

Jirikowski GF, Ochs SD, Caldwell JD (2018) Oxytocin and steroid actions. Curr Top Behav Neurosci 35:77–95

Jurek B, Neumann ID (2018) The oxytocin receptor: from intracellular signaling to behavior. Physiol Rev 98:1805–1908

Kiyama H, Emson PC (1990) Evidence for the co-expression of oxytocin and vasopressin messenger ribonucleic acids in magnocellular neurosecretory cells: simultaneous demonstration of two neurohypophysin messenger ribonucleic acids by hybridization histochemistry. J Neuroendocrinol 1:257–259

Knobloch HS, Charlet A, Hoffmann LC, Eliava M, Khrulev S, Cetin AH, Osten P, Schwarz MK, Seeburg PH, Stoop R, Grinevich V (2012) Evoked axonal oxytocin release in the central amygdala attenuates fear response. Neuron 9(73):553–566

László K, Kovács A, Zagoracz O, Ollmann T, Péczely L, Kertes E, Lacy DG, Lénárd L (2016) Positive reinforcing effect of oxytocin microinjection in the rat central nucleus of amygdala. Behav Brain Res 296:279–285

Lefevre A, Hurlemann R, Grinevich V (2018) Imaging neuropeptide effects on human brain function. Cell Tissue Res. https://doi.org/10.1007/s00441-018-2899-6

Leppanen J, Cardi V, Ng KW, Paloyelis Y, Stein D, Tchanturia K, Treasure J (2017) The effects of intranasal oxytocin on smoothie intake, cortisol and attentional bias in anorexia nervosa. Psychoneuroendocrinology. https://doi.org/10.1016/j.psyneuen.2017.01.017

Marlin BJ, Froemke RC (2017) Oxytocin modulation of neural circuits for social behavior. Dev Neurobiol 77:169–189

Menon R, Grund T, Zoicas I, Althammer F, Fiedler D, Biermeier V, Bosch OJ, Hiraoka Y, Nishimori K, Eliava M, Grinevich V, Neumann ID (2018) Oxytocin signaling in the lateral septum prevents social fear during lactation. Curr Biol 28:1066–1078

Mohamadi Y, Jameie SB, Akbari M, Staji M, Moradi F, Mokhtari T, Khanehzad M, Hassanzadeh G (2015) Hyperglycemia decreased medial amygdala projections to medial preoptic area in experimental model of diabetes mellitus. Acta Med Iran 53:1–7

Møller M, Busch JR, Jacobsen C, Lundemose SB, Lynnerup N, Rath MF, Banner J (2018) The accessory magnocellular neurosecretory system of the rostral human hypothalamus. Cell Tissue Res. https://doi.org/10.1007/s00441-018-2818-x

Morris JF, Budd TC, Epton MJ, Ma D, Pow DV, Wang H (1998) Functions of the perikaryon and dendrites in magnocellular vasopressin-secreting neurons: new insights from ultrastructural studies. Prog Brain Res 119:21–30

Paxinos G, Watson C (1986) The rat brain in stereotaxic coordinates, 2nd edn. Academic Press, San Diego

Pedersen CA, Caldwell JD, Jirikowski GF (1988) Oxytocin and reproductive behavior. In: Yoshida S, Share L (eds) Recent progress in posterior pituitary hormones. Elsevier, Amsterdam, pp 139–141

Ryan PJ, Ross SI, Campos CA, Derkach VA, Palmiter RD (2017) Oxytocin-receptor-expressing neurons in the parabrachial nucleus regulate fluid intake. Nat Neurosci 20:1722–1733

Sabihi S, Durosko NE, Dong SM, Leuner B (2014) Oxytocin in the prelimbic medial prefrontal cortex reduces anxiety-like behavior in female and male rats. Psychoneuroendocrinology 45:31–42

Sakamoto H, Matsuda K, Hosokawa K, Nishi M, Morris JF, Prossnitz ER, Kawata M (2007) Expression of G protein-coupled receptor-30, a G protein-coupled membrane estrogen receptor, in oxytocin neurons of the rat paraventricular and supraoptic nuclei. Endocrinology 148:5842–5850

Santoso P, Nakata M, Ueta Y, Yada T (2017) Suprachiasmatic vasopressin to paraventricular oxytocin neurocircuit in the hypothalamus relays light reception to inhibition of feeding behavior. Am J Physiol Endocrinol Metab. https://doi.org/10.1152/ajpendo.00338.2016

Scantamburlo G, Hansenne M, Geenen V, Legros JJ, Ansseau M (2015) Additional intranasal oxytocin to escitalopram improves depressive symptoms in resistant depression: an open trial. Eur Psychiatry 30: 65–68

Sendemir E, Kafa IM, Schäfer HH, Jirikowski GF (2013) Altered oxytocinergic hypothalamus systems in sepsis. J Chem Neuroanat 52:44–48

Sivukhina EV, Jirikowski GF (2014) Adrenal steroids in the brain: role of the intrinsic expression of corticosteroid-binding globulin (CBG) in the stress response. Steroids 81:70–73

Sofroniew MV (1983) Morphology of vasopressin and oxytocin neurones and their central and vascular projections. Prog Brain Res 60:101–114

Vigh-Teichmann I, Vigh B, Koritsánszky S (1970) Liquor contacting neurons in the paraventricular nucleus. Z Zellforsch Mikrosk Anat 103:483–501

Villegas-Gabutti CM, Pennacchio GE, Vivas L, Jahn GA, Soaje M (2018) Role of oxytocin in prolactin secretion during late pregnancy. Neuroendocrinology 106:324–334

Winter J, Jurek B (2018) The interplay between oxytocin and the CRF system: regulation of the stress response. Cell Tissue Res. https://doi.org/10.1007/s00441-018-2866-2

Wittkowski W (1969) Ependymokrinie und Rezeptoren in der Wand des Recessus infundibularis der Maus und ihre Beziehung zum kleinzeligen Hypothalamus. Z Zellforschung 93:530–546