



**HAL**  
open science

## Emerging role of astrocytes in oxytocin-mediated control of neural circuits and brain functions

Angel Baudon, Etienne Clauss Creusot, Ferdinand Althammer, Christian P Schaaf, Alexandre Charlet

► **To cite this version:**

Angel Baudon, Etienne Clauss Creusot, Ferdinand Althammer, Christian P Schaaf, Alexandre Charlet. Emerging role of astrocytes in oxytocin-mediated control of neural circuits and brain functions. Progress in Neurobiology, 2022, 217, 10.1016/j.pneurobio.2022.102328 . hal-03795847

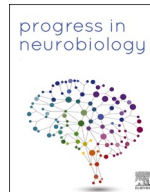
**HAL Id: hal-03795847**

**<https://hal.science/hal-03795847v1>**

Submitted on 4 Oct 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



## Review article

## Emerging role of astrocytes in oxytocin-mediated control of neural circuits and brain functions

Angel Baudon<sup>a,1</sup>, Etienne Clauss Creusot<sup>a,1</sup>, Ferdinand Althammer<sup>b</sup>, Christian P. Schaaf<sup>b</sup>, Alexandre Charlet<sup>a,\*</sup><sup>a</sup> Centre National de la Recherche Scientifique and University of Strasbourg, Institute of Cellular and Integrative Neuroscience, Strasbourg 67000 France<sup>b</sup> Institute of Human Genetics, Heidelberg University, Heidelberg, Germany

## ARTICLE INFO

## Keywords:

Astrocytes  
Oxytocin  
Amygdala  
Hypothalamus  
Neuropeptide

## ABSTRACT

The neuropeptide oxytocin has been in the focus of scientists for decades due to its profound and pleiotropic effects on physiology, activity of neuronal circuits and behaviors, among which sociality. Until recently, it was believed that oxytocinergic action exclusively occurs through direct activation of neuronal oxytocin receptors. However, several studies demonstrated the existence and functional relevance of astroglial oxytocin receptors in various brain regions in the mouse and rat brain. Astrocytic signaling and activity is critical for many important physiological processes including metabolism, neurotransmitter clearance from the synaptic cleft and integrated brain functions. While it can be speculated that oxytocinergic action on astrocytes predominantly facilitates neuromodulation via the release of specific gliotransmitters, the precise role of astrocytic oxytocin receptors remains elusive. In this review, we discuss the latest studies on the interaction between the oxytocinergic system and astrocytes, including detailed information about intracellular cascades, and speculate about future research directions on astrocytic oxytocin signaling.

## 1. Introduction

The hypothalamic neuropeptide oxytocin (OT) has been in the focus of researchers for several decades, ever since it was first described by Sir Henry H. Dale (Dale, 1906). Due to its prosocial and trust-enhancing effects, the popular press even coined the term *love hormone*. In fact, OT is involved in a plethora of social interactions and emotional processes and is pivotal for pair bonding (Young and Wang, 2004) and attachment (Insel and Young, 2001). Current data suggest that OT first emerged around 600 million years ago (Gwee et al., 2009) and evolved with its sister peptide arginine-vasopressin (AVP) from a common ancestor peptide, namely vasotocin (Gwee et al., 2009; Theofanopoulou et al., 2021). Its function is the regulation of osmolarity, one of the crucial homeostasis parameters. It is assumed that over time, the vasotocin gene duplicated and gave rise to two distinct neuropeptides with different properties and physiological functions. While the first evolutionary lineage leads to AVP, which can be found in all vertebrates and is still critical for osmoregulation and control of blood pressure, the alternate path is at the origin of oxytocin-like peptides whose structures

are dependent on the species: Isotocin can be found in fish, mesotocin is present in amphibia and reptiles, and OT is synthesized in all mammals (Gimpl and Fahrenholz, 2001; Jurek and Neumann, 2018; Theofanopoulou et al., 2021). It has been recently proposed to standardize the nomenclature of these two peptides across species to OT for all oxytocin-like peptides and VT for all AVP-like ones (Theofanopoulou et al., 2021).

In mammals, the gene encoding OT (*Oxt*) is transcribed in the hypothalamus, and its mRNA is one of the most prevalent hypothalamic-specific mRNAs (Gautvik et al., 1996; Gimpl and Fahrenholz, 2001). Like many other peptides, OT mRNA is translated into an inactive precursor, which is then cleaved into smaller fragments, ultimately resulting in the active oxytocin peptide. Following synthesis, OT is stored in large dense-core vesicles (Leng and Ludwig, 2008), released via calcium-dependent exocytosis (Leng and Ludwig, 2008; Ludwig and Stern, 2015; Maicas-Royo et al., 2018; Tobin et al., 2012) and acts on the membrane-bound, G-protein-coupled oxytocin receptor (OTR) (Jurek and Neumann, 2018). To date, two distinct intracellular signaling cascades have been identified following OTR activation:  $G\alpha_{i/o}$ - and

\* Correspondence to: Institute of Cellular and Integrative Neuroscience, INCI CNRS UPR32128, Allée du Général Rouvillois, 67000 Strasbourg, France.

E-mail address: [acharlet@unistra.fr](mailto:acharlet@unistra.fr) (A. Charlet).<sup>1</sup> Equally contributing authors.

$G\alpha_q$ -dependent pathways (Jurek and Neumann, 2018).

Different modes of OT release in the central nervous system have been described including axonal release (Grinevich et al., 2016; Knobloch et al., 2012), somato-dendritic release (Ludwig and Leng, 2006) and en passant release (Bakos et al., 2018; Fuxe et al., 2012; Ludwig and Leng, 2006). OT is also released into the portal circulation through the neurohypophysis in the posterior pituitary and reaches a variety of peripheral targets via the blood stream. Targeted, local release of OT within different brain regions that express OTR allows the peptide to act both as a neurotransmitter (Althammer et al., 2021; Buijs, 1983; Landgraf and Neumann, 2004; Leng and Ludwig, 2008; Stoop, 2012) and a neuromodulator (Mitre et al., 2018; Owen et al., 2013; Stoop, 2012; Tirko et al., 2018), thus affecting a wide range of behaviors (Froemke and Young, 2021; Grinevich and Neumann, 2020). Past research on OT was solely focused on its direct effects on neural circuits. As a result, the prevailing hypothesis was that OTR actions are exclusively mediated by neurons and this view has not been challenged until recently (Wahis et al., 2021). Moreover, a growing body of evidence suggests that oxytocin also acts directly on non-neuronal cells (Havranek et al., 2017; Mairesse et al., 2019; Tasker et al., 2012; Wang and Hatton, 2009).

Recent studies suggest that neuronal and glial cells in the brain exist in a 1:1 ratio in the human brain, albeit the individual proportions strongly depend on brain regions and species (von Bartheld et al., 2016). Glial cells are composed of several types including astrocytes, microglia or oligodendrocytes. Per definition, they are non-electrically excitable. Thus, for a long time it was believed that they are merely passive cells and do not actively participate in sensory processing and signal transduction. While, to our knowledge, there is currently no evidence suggesting OTR action on oligodendrocytes, it has been shown that oxytocin influences microglia activity (Inoue et al., 2019; Panaro et al., 2020), neural progenitor differentiation (Palanisamy et al., 2018) and pituitary cell stellation (Rosso et al., 2002). Importantly, evidence has been accumulating to demonstrate an action of oxytocin on astrocytes (Di Scala-Guenot et al., 1994; Panatier et al., 2006; Wahis et al., 2021).

Astrocytes are paramount for brain homeostasis, nutrient supply and metabolism. They account for ~20–40 % of all glial cells, depending on the species and brain region (Augusto-Oliveira et al., 2020). Within the last two decades astrocytes emerged as key players involved in neuromodulation and neuroinflammation both in the healthy and diseased brain. It is particularly intriguing how astrocytes mediate the function of local neurocircuits. Neurons and astrocytes are fundamentally different in their morphology and activity kinetics: neurons have characteristic dendrites and axons allowing the formation of long-range projections, while astrocytes possess a myriad of tiny filaments to infiltrate the local environment and can respond to many signaling cues; neurons have a millisecond-range electrical activity, whereas the duration of astrocytic calcium transients can range from minutes to hours (Bazargani and Attwell, 2016). This drastic temporal dynamic difference between the two cell types could affect the way that different neuromodulators operate within these microcircuits. Thus, it is imperative to understand the interplay of neurons and glial cells in response to neuromodulators to fully decipher their respective role in brain function. In this review, we explore the current literature on the action of OT on astrocytes, and we propose new models that could explain several observed phenomena.

## 2. Oxytocin effects on astrocytes

### 2.1. The oxytocin receptor is expressed in astrocytes

In the brain, OT is mainly synthesized in three distinct hypothalamic nuclear formations: the paraventricular nucleus, supraoptic nucleus and scattered accessory nuclei. A feature of OTR neurons is the somato-dendritic release, which prompted researchers to explore the role of OT in the hypothalamus. In the mid-80 s, it was shown that following high secretion/infusion of OT in this structure, active changes in the morphology of astrocytes occur in vivo (Salm et al., 1985; Theodosis

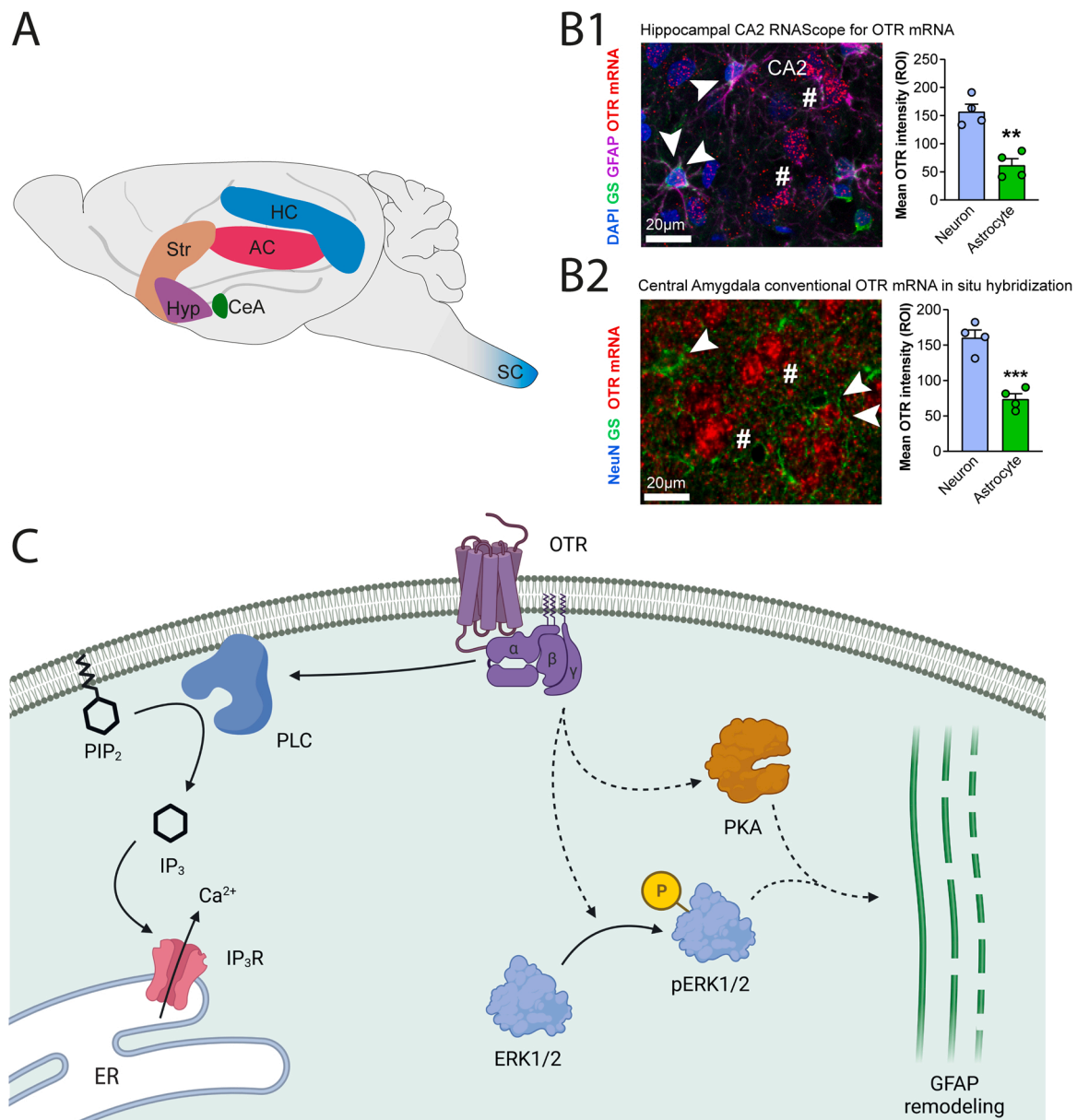
et al., 1986a; Theodosis et al., 1986b). Thus, Di Scala-Guenot and Strosser performed binding studies to investigate whether cultured astrocytes from the hypothalamus express the OTR. Using autoradiography of radioactive ligands, they found that the OTR is distributed all over the soma and processes of cells morphologically similar to those expressing the glial fibrillary acidic protein (GFAP), suggesting their astrocytic identity (Di Scala-Guenot and Strosser, 1992). In addition, using the same methods, OTR have been found in GFAP-expressing cells in primary cultures of spinal astrocytes (Evrard et al., 1997). With the help of in situ hybridization or immunolabeling, recent studies detected OTR expression in rodent astrocytes in the supraoptic nucleus of the hypothalamus (Wang and Hatton, 2006), the auditory cortex (Mitre et al., 2016), the central amygdala (Wahis et al., 2021), the ventral striatum (Amato et al., 2022), the hippocampus (Althammer et al., 2022b) and even in the frontal cortex of humans (McKay et al., 2019) (Fig. 1A). Moreover, OTR can be co-immunoprecipitated with GFAP in supraoptic nucleus (SON) lysates, indicating that the receptor is bound to the astrocytic cytoskeleton (Wang et al., 2017). While each of these results suffer from inherent technical limitation, inviting to prudence when interpreting the presented data, OTR seems widely expressed in astrocytes of several brain structures.

In all cases, this evidence does not provide proof of the receptor functionality. It must be noted here that albeit OTR expression in neurons is observed in a myriad of species and brain regions (Gould and Zingg, 2003; Mitre et al., 2016; Newmaster et al., 2020; Young and Song, 2020), these studies did not investigate actual OTR expression levels in neurons on a quantitative, single cell basis. To the best of our knowledge, no studies have been published yet that directly assessed and compared neuronal and astrocytic OTR expression levels. However, a reanalysis of published in situ hybridization data for OTR mRNA suggest that astrocytic OTR levels could be 2–3-fold lower in the amygdala (Althammer et al., 2022a; Wahis et al., 2021) and dorsal CA2 region (Althammer et al., 2022b) (Fig. 1B). This constitutes an experimental challenge for scientists willing to study the cell-type specific OTR. Thus, a combination of single cell RNA sequencing or cell-type specific western blots together with precise pharmacological experiments would be needed to unequivocally demonstrate the presence and function of astrocytic OTR. In addition, a new generation novel genetic models could help to provide a deeper insight into cell-type specific OTR expression and function.

### 2.2. Astrocytic oxytocin receptors are functional

The first indication of a direct action of OT on glial cells dates back to the mid-90 s, when Di Scala-Guenot and colleagues performed calcium imaging on cultured hypothalamic astrocytes. They observed that OT or [Thr<sup>4</sup>Gly<sup>7</sup>]-oxytocin (TGOT, a selective OTR agonist) application triggers monophasic calcium responses in the majority of recorded astrocytes, but also calcium oscillation in ~15 % of them (Di Scala-Guenot et al., 1994). Such observation done in pure astrocytic culture suggests that astrocyte directly react to oxytocin. However, cultured astrocytes are known to be really different from those found in situ, both in term of morphology, protein expression and calcium signaling (Foo et al., 2011; Shigetomi et al., 2010a, 2010b).

More recently, it has been showed that optogenetic photostimulation and subsequent release of OT from axonal terminals within the central amygdala triggers calcium transients in local astrocytes *ex vivo* (Wahis et al., 2021). This strongly suggests that endogenous OT release is sufficient to induce astrocyte calcium signaling. Yet, this effect could result indirectly from the activation of OTR on neighboring neuron terminals/fibers. Using a Cre/Lox approach, we knock out the OTR in GFAP expressing cells and observed a decrease of OTR-induced calcium responses in astrocytes. Despite the potential issue regarding a putative Cre leakage from GFAP positive cells (Hu et al., 2020b; Stifter and Greter, 2020) this experiment corroborates the hypothesis that OT-mediated astrocyte activity might be dependent on astrocytic OTR



**Fig. 1.** Astrocytic oxytocin receptor distribution in the brain. **A.** Known localization of astrocytic oxytocin receptor (OTR) in the rodent brain. Described in situ: Striatum (Str), Hypothalamus (Hyp), Central Amygdala (CeA), Auditory Cortex (AC). Described in culture: Spinal Cord (SC). **B1.** Combined RNAScope for OTR mRNA and immunohistochemical staining against glutamine synthetase and GFAP in dorsal CA2 of a wistar rat. Single white arrowhead highlights OTR-negative astrocyte, double arrowhead highlights OTR-positive astrocyte and hashtags highlight OTR-positive, GS-negative neurons. Bar graph shows that respective OTR mRNA transcript levels in astrocytes are significantly lower than neuronal OTR mRNA levels ( $n = 4$  rats per group, 70–120 cells analyzed per animal,  $**p < 0.01$ ). Recreated from Wahis et al., 2021. **B2.** Combined approach of conventional in situ hybridization for OTR mRNA and immunohistochemical staining against glutamine synthetase in the central amygdala of a wistar rat. Single white arrowhead highlights OTR-negative astrocyte, double arrowhead highlights OTR-positive astrocyte and hashtags highlight OTR-positive, GS-negative neurons. Bar graph shows that respective OTR mRNA transcript levels in astrocytes are significantly lower than neuronal OTR mRNA levels ( $n = 4$  rats per group, 70–120 cells analyzed per animal,  $***p < 0.001$ ). Recreated from Althammer et al. (2022b). **C.** Intracellular pathways triggered by the activation of astrocytic OTR. Left: activation of the  $G_{\alpha_q}$  protein triggers the activation of the PLC-IP<sub>3</sub> pathway that results in a calcium release from the endoplasmic reticulum (ER). Right: dissociation of the  $\beta\gamma$  complex is suggested to mediate the sequential activation of ERK1/2 and PKA that ultimately results in a reorganization of the GFAP cytoskeleton.

(Wahis et al., 2021). However, even if this GFAP OTR KO model highlights the involvement of OTR in astrocyte activity, it does not rule out a potential participation of a neurotransmitter co-released together with OT from OTRergic axon terminals.

Based on these observations, it seems plausible that functional OTR could be expressed in astrocytes in several regions of the central nervous system. To fully understand the precise effect of OT on astrocytes, it is important to have a close look at the intracellular pathway triggered by binding of OT to astrocytic OTR.

### 2.3. Oxytocin receptor-dependent signaling in astrocytes

The oxytocin receptor (OTR) is a member of the class A G-protein coupled receptors (GPCR) family, composed of seven transmembrane domains. In mammals, the OTR is encoded by a single gene, however, its intracellular coupling is complex. The intracellular loops and the intracellular C-terminal domain link heterotrimeric G protein complexes. Each of them is composed of three subunits:  $G_{\alpha}$ ,  $G_{\beta}$ ,  $G_{\gamma}$ . Upon binding of their ligands, conformational changes of the receptor lead to

the replacement of the guanine diphosphate bound to the  $G_\alpha$  by a guanine triphosphate.  $G_\alpha$  then dissociate from the  $G_{\beta\gamma}$  complex and act on various enzymes that produce second messengers. Interestingly, the OTR is functionally coupled to  $G_q$  and/or  $G_{i/o}$  proteins and its activation can produce a calcium surge from intracellular calcium stores (Busnelli and Chini, 2018; Gimpl and Fahrenholz, 2001; Jurek and Neumann, 2018; Phaneuf et al., 1993). Apart from its effect on calcium signaling, the activation of OTR can activate various intracellular pathways second messengers, including cAMP, phospholipase C (PLC) and protein kinase C (PKC) (Chatterjee et al., 2016) (Fig. 1C).

In astrocytes, OT-induced intracellular pathways are currently unclear, with yet few studies raising different hypothesis. Indeed, application of OT or an OTR agonist on astrocyte cell cultures seems to trigger calcium transients via a mechanism that is independent of extracellular calcium influx but depends on endoplasmic reticulum stores (Di Scala-Guenot et al., 1994). These seminal data suggest are in accordance with the recruitment of the classical PLC-dependent  $G_q$  pathway in cultured hypothalamic astrocytes.

In addition, OT application on SON slices increased the quantity of phosphorylated extracellular signal-regulated kinase 1/2 (ERK 1/2), strengthening the hypothesis that OTR activation in astrocytes affects the MAPK pathway in astrocytes (Wang and Hatton, 2007). Wang and colleagues further showed that OT decreases the expression of GFAP in SON astrocytes (Wang et al., 2017). This effect seems to be mediated by the  $G_{\beta\gamma}$  subunits of the G protein coupled to the OTR, which triggers the sequential activation of ERK1/2 and protein kinase A (PKA) (Wang et al., 2017). It is noteworthy that activation of ERK1/2 and PKA seems to have antagonistic effects on GFAP stability and that the consecutive action of ERK and PKA is needed: PKA initially provokes the breakdown of GFAP filament and then ERK1/2 stabilizes newly synthesized filaments (Wang et al., 2017). Recently, a study in astrocyte-like cells from astrocytoma showed that knockdown of OTR prevented OT-induced phosphorylation of ERK and interfered with the proliferation and antioxidant effects of OTR activation (Alanazi et al., 2020), thereby strengthening the idea of an OTR-mediated regulation of the MAPK pathway (Fig. 1C).

As previously mentioned, OTR can also couple  $G_{i/o}$  proteins (Busnelli and Chini, 2018; Busnelli et al., 2012; Hoare et al., 1999; Phaneuf et al., 1993; Strakova et al., 1998) but to our knowledge, no evidence has shown that stimulation of astrocytic OTR can trigger the activity of  $G_{i/o}$  proteins in astrocytes. It is also possible that the OTR couples different G-protein in the same cell type as shown in neuron-like cells (Gravati et al., 2010). This coupling might also depend on OTR localization in different microdomains of the plasma membrane (Rimoldi et al., 2003).

### 3. Oxytocin-induced modulation of astrocyte morphology and functions

Knowing that functional OTR are expressed in astrocytes, one can investigate the effect of OTR activation in those cells. Several studies indicate that binding of OT to astrocytic OTR triggers astrocyte calcium transients (Kuo et al., 2009; Wahis et al., 2021; Zatkova et al., 2018). However, the downstream targets and ultimate consequences of astrocytic OTR signaling remain somewhat elusive. In this chapter we summarize the consequences of OTR activation on astrocyte morphology and neuronal network activity.

#### 3.1. Morphological consequences of astrocytic oxytocin receptor activation

Hypothalamic OT neurons release the peptide locally, a phenomenon known as somato-dendritic release (Ludwig and Leng, 2006). This form of peptide release is thought to facilitate a local feedback mechanism, as well as to prime the neuroendocrine cells during challenging physiological situations such as parturition, lactation or other homeostatic challenges (Brown et al., 2013, 2020).

Already in the mid 80's it was reported that these conditions induce a strong OT release and lead to an important decrease in GFAP staining density within SON (Salm et al., 1985; Wang and Hatton, 2009). Furthermore, OT infusion in the SON resulted in an increase of neuronal somata contacts (Langle et al., 2003; Theodosios et al., 1986a, 1986b). This strongly suggests that OT can modify astrocyte morphology. This hypothesis was further confirmed in hypothalamic SON slices. Indeed, under normal conditions, there is almost no neuronal juxtaposition, as astrocytic processes separate them, but OT application triggers the retraction of astrocytic processes, leaving OTergic neurons in close contact. This modification of the astrocytic cytoarchitecture appears to be calcium-dependent (Langle et al., 2003). While authors did not provide an explanation for this interesting observation, it can be speculated that activation of astrocytic OTR alters the astrocytic cytoskeleton by interfering with microtubule/actin dynamics. Indeed, it has been shown that calcium transients in astrocytes can regulate actin-remodeling proteins, such as cofilin. This has been demonstrated in the hippocampus where long term potentiation triggers withdrawal of peridendritic astrocyte processes from potentiated synapses (Henneberger et al., 2020). Interestingly, such OT-mediated reorganization of the actin cytoskeleton has been observed in SON neurons, and probably in nearby astrocytes following OT application (Wang and Hatton, 2007) (Fig. 2).

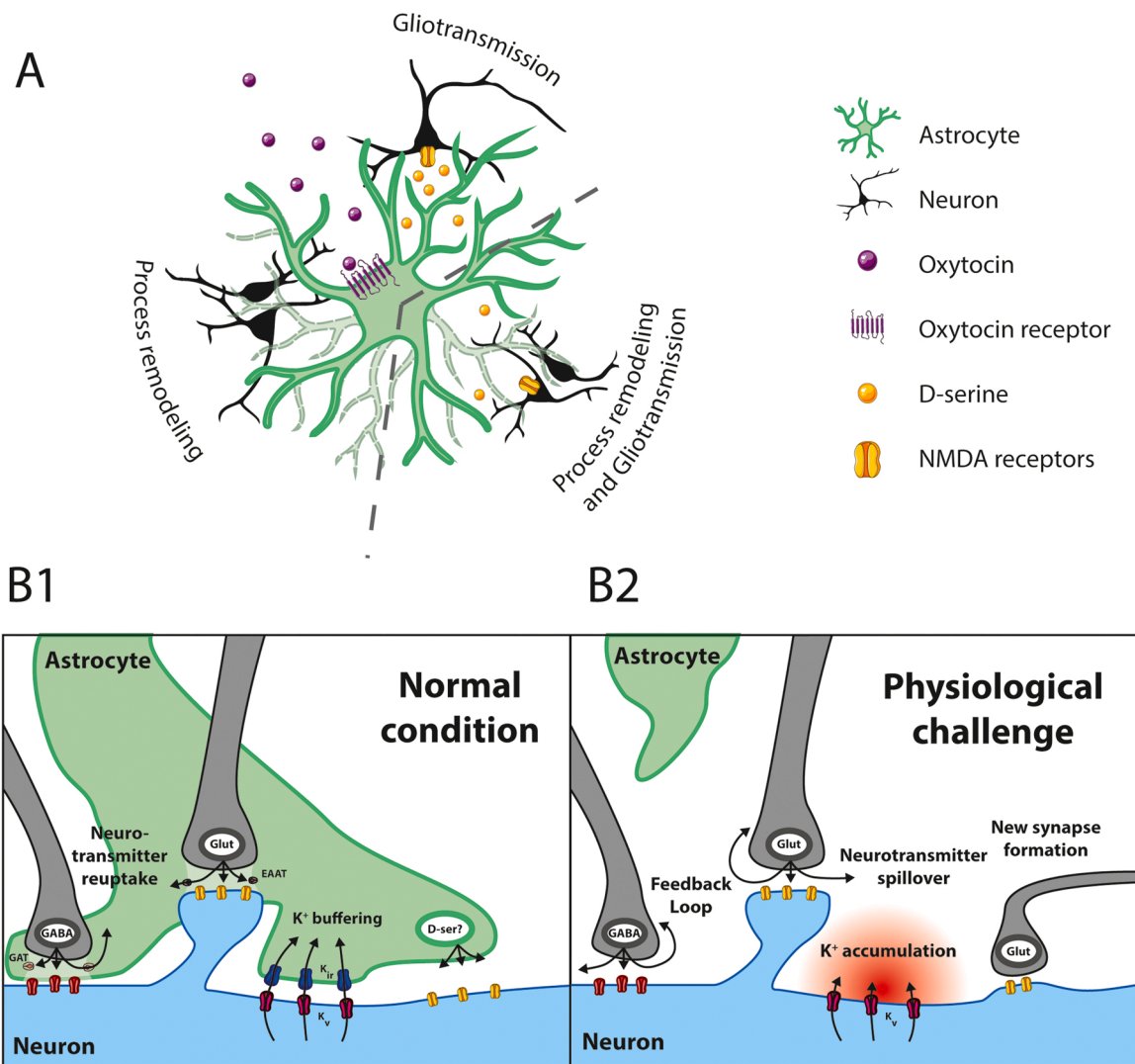
These morphological changes of hypothalamic astrocytes could potentially have many drastic and long-lasting consequences on the overall network activity. First, astrocytes maintain homeostasis for ions like potassium, which is known to be strongly implicated in neuronal excitability (Verkhatsky and Nedergaard, 2018). Thus, a reduction in astrocytic coverage could lead to important changes of the membrane potential of neighboring neurons. Second, astrocytes are important mediators of neurotransmitter clearance from the synaptic cleft. For example, GLT-1 and GAT transporters are present on the astrocytic processes and facilitate clearing of extracellular glutamate and GABA, respectively. Thus, a reduction in the clearance rate inevitably results in an increased extracellular concentration of neurotransmitters, which ultimately results in an amplification of post-synaptic currents. Moreover, the neurotransmitters can spill over the synaptic cleft and activate presynaptic (e.g. mGluRs) or extrasynaptic (e.g. NMDA) receptors to promote a feedback regulatory effect or to modulate the efficiency/potency of neighboring synapses (Oliet et al., 2008). Third, the retraction of astrocytic processes may declutter the extracellular space, allowing the formation of new synapses, as suggested for the hypothalamus (Hatton et al., 1984) (For a more general review on the effects of astrocytes morphological modification, see Lawal et al., 2022).

In addition, astrocytes are known to release neuroactive molecules described as gliotransmitters. By retracting astrocytic processes, it is plausible that less gliotransmitters reach their receptors expressed by the surrounding neurons, leading to a change in the transmission of information.

#### 3.2. Astrocytic oxytocin receptor functions in gliotransmission

The concept of communication from astrocytes to neurons by the release of gliotransmitters was first introduced in the 90's (Grandes et al., 1991) but the first demonstration of a direct communication between astrocytes and neurons was done by Parpura and colleagues, when they observed that glutamate released from astrocytes caused an increase in calcium activity of nearby neurons (Parpura et al., 1994). Later, adenosine triphosphate (ATP) was also shown to act on neuronal P2X receptors after being released by astrocytes (Zhang et al., 2003). It is important to note, however, that the mechanism underlying gliotransmission is still somewhat controversial (Fiacco and McCarthy, 2018; Sloan and Barres, 2014), albeit the majority of researchers in the field seem to acknowledge its existence (Araque et al., 2014; Savtchouk and Volterra, 2018).

In the SON, Panatier and colleagues showed that astrocytes express the serine racemase, an enzyme that converts L-serine to D-serine and



**Fig. 2.** Effects of OTR activation on astrocytes. **A. Top:** OTR activation modulate astroneuronal communication. This gliotransmission has been seen in the hypothalamus where OT stimulation decreases the amount of available D-serine, and in the central amygdala where the opposite action has been observed. **Bottom left:** astrocytic OTR activation triggers the remodeling of astrocytic processes, as seen by their retraction in the hypothalamus and their length increased in cultured astrocytes. **Bottom right:** suggested hypothesis in which both mechanisms could occur at the same time. For instance, a retraction astrocytic processes could explain the decrease in D-serine availability observed in the hypothalamus. **B.** Proposed astrocyte-neuron interactions under normal conditions (astrocyte process extension, B1) and during physiological challenge (astrocyte process retraction, B2) based on our own experimental data.

that this D-serine is the endogenous ligand of the glycine site on NMDAR in the SON (Panatier et al., 2006). Furthermore, they demonstrated that NMDA currents are strongly impaired in D-amino acid oxidase (DAAO)-treated SON slices, an enzyme that breaks down extracellular D-serine. This impairment is rescued by the acute application of exogenous D-serine. These results suggest that astrocytes synthesize and release D-serine to induce an NMDA-dependent signal. Panatier and colleagues also performed *ex vivo* recordings of NMDA currents in SON neurons from virgin or lactating rats. They showed that in lactating rats, the AMPA/NMDA ratio was similar compared to virgin animal slices treated with DAAO and could also be rescued when applying D-serine. Given that NMDAR activation appeared to be essential for the establishment of long-term potentiation (LTP), they investigated the involvement of this receptor using several LTP protocols in neurons of the SON of virgin or lactating animals. In virgin animals, they observed a normal establishment of LTP compared to lactating rats in which no LTP occurred unless they supplied the slice with D-serine. Hence, it seems that D-serine supply from astrocytes is essential for neuronal plasticity in the SON (Panatier et al., 2006). However, it is noteworthy that the astrocytic

origin of D-serine is still under debate (Coyle et al., 2020; Ivanov and Mothet, 2019; Papouin et al., 2017).

More recently, we studied the implication of astrocytes in the lateral part of the central amygdala (CeL) in the regulation of neuronal activity in response to OT. In this structure, a population of CeL astrocytes seems to express the OTR and its activation triggers an increase in their calcium activity (Wahis et al., 2021). Furthermore, these changes in calcium activity seem to be linked to an increase in the electrical activity of neighboring CeL neurons. This increase is dependent on NMDAR and sensitive to the D-serine degrading enzyme DAAO, suggesting that astrocytes modulate the activity of CeL neurons by releasing D-serine (Fig. 2). At a behavioral level, this neuronal network modulation seems to reduce negative emotional values such as anxiety. This demonstrates that CeA astrocytes are actively involved in the OT-induced modulation of a neuronal network (Wahis et al., 2021).

Another circuit where astrocytes have been involved in the regulation of neuronal circuits can be found in the medial basal hypothalamus (Parent et al., 2008). In this structure, authors found no OTR *in vivo* on GnRH neurons, but on neighboring cells thought to be astrocytes, as

suggested by OTR expression in astrocytes in vitro (Parent et al., 2008). Interestingly, intraperitoneal injection of OT reduced the GnRH interpulse interval known to be involved in sexual maturation. Suggesting that only astrocytes express the OTR in this structure, one can wonder how OT modulates GnRH release in the blood (ie. GnRH neuron activity). Given that OT induce the Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) release (Strakova et al., 1998), they hypothesized that it might mediate the communication between astrocytes and GnRH neurons. Indeed, they found that PGE<sub>2</sub> mimicked the OT effect by decreasing the GnRH interpulse interval. This study suggests that OT acts directly on astrocytes of the medial basal hypothalamus to trigger PGE<sub>2</sub> release, which then acts on GnRH neurons to modulate the pulsatile neuronal secretion of GnRH and, ultimately, the sexual maturation.

Based on these observations, OT-activated astrocytes could communicate with neighboring neurons by releasing several gliotransmitters, such as D-serine or PGE<sub>2</sub>.

#### 4. Oxytocin and astrocytes: a glimpse into future research directions

Within the last years, OTergic signaling in astrocytes emerged as an important mechanism involved in the regulation of astrocyte morphology, calcium signaling and even affects physiological regulation and emotional processing. However, several key questions about OTR-expressing astrocytes and their interaction with nearby neural cells remain.

##### 4.1. Can an astrocytic relay explain the pleiotropic effects of oxytocin?

One of the biggest enigmas in OTergic research is that one neuropeptide seems to facilitate a seemingly endless list of behaviors (Froemke and Young, 2021; Jurek and Neumann, 2018; Mitre et al., 2018). To exert these functions, OTergic fibers and OTR are found in various brain regions such as the cortices, amygdala, hippocampus, hypothalamic nuclei, septum and thalamus (Knobloch et al., 2012; Mitre et al., 2016; Zhang et al., 2020). However, astrocytic OTR have been identified in only a few of them (see section *The oxytocin receptor is expressed in astrocytes*). In addition, their functions are even less studied, with evidences of functional OTR existing only in the hypothalamic astrocyte cultures (Di Scuala Guenot et al., 1994) and in the amygdala (Wahis et al., 2021) (see section *Astrocytic oxytocin receptors are functional*).

Intriguingly, OT occasionally seems to elicit opposing behaviors depending on the involved brain regions or social context (De Dreu et al., 2011; Jurek and Meyer, 2020; Ma et al., 2015; Neumann and Slattery, 2016). Thus, it is important to note that astrocytes are known to be more than simple relays to neurotransmitters, even reversing the excitation/inhibition polarity of an input. This mechanism, called “incongruent”, has been demonstrated in several models such as the CA3-CA1 synapse where a GABA input is transformed into glutamate release (Caudal et al., 2020). However, if and how astrocytes are involved in the contradictory effects of OT on neural circuits and behavior, is currently unclear.

Furthermore, neuropeptidergic cells co-express and co-release various neurotransmitters (Nusbaum et al., 2001; Svensson et al., 2018; van den Pol, 2012). In hypothalamic OT neurons, several studies showed co-release of both glutamate and OT (Althammer et al., 2021; Eliava et al., 2016; Grinevich and Ludwig, 2021; Hasan et al., 2019; Hrabovszky and Liposits, 2008; van den Pol, 2012). There are several potential cross-talks between the glutamatergic and the oxytocinergic system, which could explain some of the pleiotropic context-, experience- and brain region-dependent effects of OT release (Froemke and Young, 2021; Grinevich and Stoop, 2018; Jurek and Neumann, 2018; Lee et al., 2009; Mitre et al., 2018). For instance, varying degrees of OT and glutamate could be released from the same axonal terminal, and potentially act on different postsynaptic elements, thus providing

fine-tuning of neural circuits. Moreover, OT-induced calcium transients can be blocked with an mGluR1a antagonist and promoted by an agonist (Kuo et al., 2009). This suggests that mGluR1a can form functional heteromers with OTR, thus adding a new level of complexity to the OTR intracellular pathways. However, no physical interaction has been demonstrated to date.

Since OT has been shown by suggested modulate the activity of TRPV1 channel (Nersesyan et al., 2017), and given that astrocytes also express these channels in various species and brain regions (reviewed in (Kong et al., 2017) it is also possible that some OT actions on astrocytes may be mediated through these channels. Aside, there is currently no evidence that OT can directly activate TRPV1 channels in astrocytes (Gonzalez-herandez and Charlet, 2018). Finally, it has recently been shown that OTR can physically heteromerize with the A2A adenosine receptor in the striatum. The functional effect of this association has been tested in striatal gliosomes and it was observed that OT prevents evoked glutamate release only if the A2A is not activated (Amato et al., 2022). In future studies, it will be interesting to evaluate the effect of the concomitant activation of these receptors in a basal condition. Moreover, it has been shown that OTR can heteromerize with D2R in the striatum (Romero-Fernandez 2013). Given the intricate cooperation of the oxytocin and the dopamine systems in social behaviors such as partner preference (Young and Wang, 2004), it can be interesting to assess the presence of such heteromers in astrocytes.

Therefore, the study of astrocytes involvement in OT-induced modulation of brain functions, in all its complexity, might be the key to unravel how OT exert its pleiotropic functions through modulation of numerous brain regions. However, this should be completed by considering the whole brain environment, from physiology to pathology.

##### 4.2. Do astrocytes-mediated oxytocinergic functions vary in a brain region or pathophysiological state manner?

To date, the functions of putatively OT-activated astrocytic have only been studied in exceptional physiological conditions such as lactation and parturition in the SON (Pantatier et al., 2006), sexual maturation in the medial basal hypothalamus (Parent et al., 2008) and chronic pain in the CeA (Wahis et al., 2021). However, the default role of OT-activated astrocytic subpopulation also remains unclear. This can be explained by a confounding factor inherent of biological studies. Indeed, it is easier to study mechanisms that involve strong changes in physiological processes rather than small, everyday challenges that slightly modify the activity of neuronal circuits. There might be physiological processes during which OTergic activation of OT-sensitive astrocytes is not critical and where activation of OTR-expressing neurons is sufficient.

One can also imagine that OT can trigger different effects according to the targeted region. For instance, it has been shown in the hypothalamus that OT triggers retraction of astrocytic processes during high-demanding OT situations, which is linked to a reduction in D-serine release by the astrocytes (Pantatier et al., 2006). Conversely, OTR activation in the CeL seems to trigger the release of D-serine by the astrocytes (Wahis et al., 2021), suggesting morphological effect different than the retraction observed in the SON. This hypothesis is supported by in vitro assessment of OT action on glial morphology that reveal an unforeseen OT-mediated increase in astrocytes-like U-87 MG cells processes length (Zatkova et al., 2018). Thus, OT effects on astrocyte morphology and functions could be region-dependent.

Therefore, it will not be surprising to discover that OT effects on astrocyte morphology is region- and function-specific, paving the way to a better understanding of the plural OT functions in pathophysiological conditions.

#### 4.3. What are the relative contributions of astrocytes and neurons to OT functions?

Given that OTR has been shown to be expressed in both astrocytes and neurons, it is coherent to interrogate their respective contribution to OT functions. At first sight, one may suggest that OT acts on neuronal OTR to trigger a rapid, short lasting neuromodulation. On the other side, OT action on astrocytes may result in slower and longer mechanisms such as the metabolic regulation, release of lactate or gene regulation.

However, CeA ablation of astrocytic OTR impaired the OT-induced neuromodulation of the local microcircuit (Wahis et al., 2021). This absence of OT-evoked neuromodulation despite the presence of neuronal OTR raises two hypotheses: i) OT only needs to act on astrocytes to exert its neuromodulatory effect, ii) OT needs to activate simultaneously astrocytic and neuronal OTR. In the first scenario, OT initially acts on astrocytes to trigger the release of gliotransmitters which, in turn, increases neuronal excitability. However, this seems less probable since a higher portion of CeA neurons express OTR compared to astrocytes. The alternative scenario involves the concomitant activation of both cell types: OT could act on OTR-expressing neurons to increase membrane potential, thus priming CeA neurons and enabling an astrocyte-driven long-lasting, sustained activation of the neural network. In fact, besides its intracellular calcium releasing action by the  $G_q$ -PLC-IP<sub>3</sub>R pathway, OT was shown to inhibit Na<sup>+</sup>-activated K<sup>+</sup> leak channels in the myometrium (Ferreira et al., 2019) and spinal cord (Breton et al., 2009). These mechanisms can keep neurons closer to their firing threshold potential, thus making them more likely to respond to incoming stimuli. At the same time, OT can bind to astrocytic OTR to triggers calcium transients and ultimately, the release of gliotransmitters such as D-serine. Knowing the role of OT signaling in synaptic plasticity (Rajamani et al., 2018) and LTP formation (Lin et al., 2012), it seems plausible that coordinated dual activation of both NMDA and OTR could result in a potentiated neural response.

In addition, OT can act directly on OTR-expressing neurons and indirectly on other neurons. For instance, CeA neurons can be broadly divided into SOM-expressing and PKC $\delta$ -expressing neurons (Haubensak et al., 2010; Hunt et al., 2017), which are thought to have antagonistic functions, at least in fear, anxiety (Janak and Tye, 2015) and pain expression (Wilson and Murphy, 2009). Haubensak and colleagues have shown that OTR expressing cells are more likely to be PKC $\delta$ , congruently with the fear-OFF function of those cells (Haubensak et al., 2010). In this context, one can imagine that OT directly activates PKC $\delta$ -positive neurons and indirectly inhibits PKC $\delta$  negative neurons, thus favoring a disinhibition of PKC $\delta$ -expressing neurons.

To decide between those hypotheses, it will be interesting to specifically ablate neuronal, but not astrocytic, OTR and to evaluate the effect of OT on those cells.

#### 4.4. Are intracellular pathways recruited downstream of the OTR different between astrocytes and neurons?

As mentioned before, the OTR has the surprising feature to couple both the  $G_{i/o}$  and the  $G_q$  pathways (Busnelli and Chini, 2018). This point is of crucial importance given that activation of  $G_q$  and  $G_{i/o}$  proteins have opposite functions on neuronal excitability, with the former favoring neuronal spiking and the latter preventing it. To our knowledge, all published studies investigating the effect of OT on neuronal firing found an activity increase, suggesting no  $G_{i/o}$  coupling in neurons (Alberi et al., 1997; Barrett et al., 2021; Crane et al., 2020; Eliava et al., 2016; Hu et al., 2020a; Knobloch et al., 2012; Ryan et al., 2017; Wang and Hatton, 2004, 2007). However, since the recruitment of both pathways in astrocytes was shown, independently of OTR, to trigger calcium transients (Durkee et al., 2019; Mehina et al., 2017), differentiating the pathway recruited cannot be done based on their calcium activity. To overcome this issue, biased agonists have been developed to trigger preferentially the recruitment of  $G_{i/o}$  proteins (e.g. Atosiban) or

$G_q$  proteins (e.g. Carbetocin) (Busnelli et al., 2012). It will be interesting for the next studies to investigate the recruitment of one pathway or the other in astrocytes and neurons.

## 5. Conclusions

Research in the last two decades has shown that astrocytes are much more than passive cells needed for neuronal support. It has become evident that astrocytes play a major role in metabolism, homeostasis, sensory information processing and cognitive functions. Many neuromodulators that influence these functions also modulate astrocytic calcium activity, suggesting that astrocytes may be involved in the regulation of neuronal circuit activity. Among these neuromodulators, OT has been shown to trigger calcium transients in astrocytes, highlighting a way of integrating OTergic information in the central nervous system. The difference in the temporal dynamic between astrocytes and neurons allows for an intricate interplay between the two cell types and could drastically influence the function of neuromodulators.

The finding that OT induces morphological changes in hypothalamic astrocytes and thus directly affects neuronal transmission gives rise to a series of interesting hypotheses. OT could potentially gate a precise and temporally restricted enhancement of neurotransmission in local microcircuits during important physiological situations. Retraction of astrocytic processes does not only make room for more extracellular signaling, but also impedes astrocytic clearing of transmitters via specific transporters. Thus, OTergic priming of astrocytes could potentially have long-lasting effects on neural network activity. This would be in line with the idea that astrocytes can integrate, process and transmit information as part of an astro-neuronal network. Future studies are needed to precisely assess the role of neuronal OTR in these astrocyte-neuron networks. It seems plausible that activation of astrocytes by OT precedes OTR-mediated activation of neurons and that OTergic signaling in neurons enables sustained activity of the astrocyte-neuronal networks. Finally, it remains unknown how OTergic signaling in astrocytes affects various behavioral paradigms and diseases, in which a compromised OT has been identified as an underlying cause such as autism spectrum disorder (Anagnostou et al., 2014; Domes et al., 2013; Ford and Young, 2021; Gordon et al., 2013; Guastella et al., 2010), Prader-Willi syndrome (Swaab, 1997; Swaab et al., 1995; Tauber et al., 2017, 2011) or PTSD (Anagnostou et al., 2014; Domes et al., 2013; Ford and Young, 2021; Frijling, 2017; Frijling et al., 2014; Gordon et al., 2013; Guastella et al., 2010; Meyer-Lindenberg et al., 2011; Olf et al., 2010; Swaab, 1997; Swaab et al., 1995; Tauber et al., 2017).

## Acknowledgement

This work was supported by the Centre National de la Recherche Scientifique contract UPR3212, the Université de Strasbourg contract UPR3212, and the Agence Nationale de la Recherche (ANR) Jeune Chercheuse Jeune Chercheur (JCJC) grant n° 19-CE16-0011-0 (to AC), the Graduate School of Pain EURIDOL, ANR-17-EURE-0022 (to AC and ECC), and the Foundation of Prader-Willi Research post-doctoral fellowship (to CPS and FA).

## Author contributions

All authors discussed and elaborated the ideas, wrote the first draft and corrected it until the final version was obtained. All authors contributed to the article and approved the submitted version.

## References

- Alanazi, M.M., Havranek, T., Bakos, J., Cubeddu, L.X., Castejon, A.M., 2020. Cell proliferation and anti-oxidant effects of oxytocin and oxytocin receptors: role of extracellular signal-regulating kinase in astrocyte-like cells. *Endocr. Regul.* 54, 172–182.



- Alberi, S., Dreifuss, J.J., Raggenbass, M., 1997. The oxytocin-induced inward current in vagal neurons of the rat is mediated by G protein activation but not by an increase in the intracellular calcium concentration. *Eur. J. Neurosci.* 9, 2605–2612.
- Althammer, F., Eliava, M., Grinevich, V., 2021. Central and peripheral release of oxytocin: relevance of neuroendocrine and neurotransmitter actions for physiology and behavior. *Handb. Clin. Neurol.* 180, 25–44.
- Althammer, F., Krause, E.G., de Kloet, A.D., Smith, J., Grinevich, V., Charlet, A., Stern, J. E., 2022a. Identification and three-dimensional reconstruction of oxytocin receptor expressing astrocytes in the rat and mouse brain. *STAR Protoc.* 3, 101160.
- Althammer, F., Roy, R.K., Lefevre, A., Najjar, R.S., Schoenig, K., Bartsch, D., Eliava, M., Feresin, R., Hammock, E.A.D., Murphy, A.Z., Charlet, A., Grinevich, V., Stern, J.E., 2022b. Altered PVN-to-CA2 hippocampal oxytocin pathway and reduced number of oxytocin-receptor expressing astrocytes in heart failure rats. *J. Neuroendocr.*
- Amato, S., Averna, M., Guidolin, D., Pedrazzi, M., Pelassa, S., Capraro, M., Passalacqua, M., Bozzo, M., Gatta, E., Anderlini, D., Maura, G., Agnati, L.F., Cervetto, C., Marcoli, M., 2022. Heterodimer of A2A and oxytocin receptors regulating glutamate release in adult striatal astrocytes. *Int. J. Mol. Sci.* 23.
- Anagnostou, E., Soorya, L., Brian, J., Dupuis, A., Mankad, D., Smile, S., Jacob, S., 2014. Intranasal oxytocin in the treatment of autism spectrum disorders: a review of literature and early safety and efficacy data in youth. *Brain Res.* 1580, 188–198.
- Araque, A., Carmignoto, G., Haydon, P.G., Oliet, S.H., Robitaille, R., Volterra, A., 2014. Gliotransmitters travel in time and space. *Neuron* 81, 728–739.
- Augusto-Oliveira, M., Arrifano, G.P., Takeda, P.Y., Lopes-Araujo, A., Santos-Sacramento, L., Anthony, D.C., Verkhratsky, A., Crespo-Lopez, M.E., 2020. Astroglia-specific contributions to the regulation of synapses, cognition and behaviour. *Neurosci. Biobehav. Rev.* 118, 331–357.
- Bakos, J., Srancikova, A., Havranek, T., Bacova, Z., 2018. Molecular mechanisms of oxytocin signaling at the synaptic connection. *Neural Plast.* 2018, 4864107.
- Barrett, L.R., Nunez, J., Zhang, X., 2021. Oxytocin activation of paraventricular thalamic neurons promotes feeding motivation to attenuate stress-induced hypophagia. *Neuropsychopharmacology* 46, 1045–1056.
- Bazargani, N., Attwell, D., 2016. Astrocyte calcium signaling: the third wave. *Nat. Neurosci.* 19, 182–189.
- Breton, J.D., Poisbeau, P., Darbon, P., 2009. Antinociceptive action of oxytocin involves inhibition of potassium channel currents in lamina II neurons of the rat spinal cord. *Mol. Pain* 5, 63.
- Brown, C.H., Bains, J.S., Ludwig, M., Stern, J.E., 2013. Physiological regulation of magnocellular neurosecretory cell activity: integration of intrinsic, local and afferent mechanisms. *J. Neuroendocr.* 25, 678–710.
- Brown, C.H., Ludwig, M., Tasker, J.G., Stern, J.E., 2020. Somato-dendritic vasopressin and oxytocin secretion in endocrine and autonomic regulation. *J. Neuroendocr.* 32, e12856.
- Buijs, R.M., 1983. Vasopressin and oxytocin—their role in neurotransmission. *Pharm. Ther.* 22, 127–141.
- Busnelli, M., Chini, B., 2018. Molecular basis of oxytocin receptor signalling in the brain: what we know and what we need to know. *Curr. Top. Behav. Neurosci.* 35, 3–29.
- Busnelli, M., Sauliere, A., Manning, M., Bouvier, M., Gales, C., Chini, B., 2012. Functional selective oxytocin-derived agonists discriminate between individual G protein family subtypes. *J. Biol. Chem.* 287, 3617–3629.
- Caudal, L.C., Gobbo, D., Scheller, A., Kirchhoff, F., 2020. The paradox of astroglial Ca<sup>2+</sup> signals at the interface of excitation and inhibition. *Front Cell Neurosci.* 14, 609947.
- Chatterjee, O., Patil, K., Sahu, A., Gopalakrishnan, L., Mol, P., Advani, J., Mukherjee, S., Christopher, R., Prasad, T.S., 2016. An overview of the oxytocin-oxytocin receptor signaling network. *J. Cell Commun. Signal* 10, 355–360.
- Coyle, J.T., Balu, D., Wolosker, H., 2020. D-Serine, the shape-shifting NMDA receptor Co-agonist. *Neurochem Res* 45, 1344–1353.
- Crane, J.W., Holmes, N.M., Fam, J., Westbrook, R.F., Delaney, A.J., 2020. Oxytocin increases inhibitory synaptic transmission and blocks development of long-term potentiation in the lateral amygdala. *J. Neurophysiol.* 123, 587–599.
- Dale, H.H., 1906. On some physiological actions of ergot. *J. Physiol.* 34, 163–206.
- De Dreu, C.K., Greer, L.L., Van Kleef, G.A., Shalvi, S., Handgraaf, M.J., 2011. Oxytocin promotes human ethnocentrism. *Proc. Natl. Acad. Sci. USA* 108, 1262–1266.
- van den Pol, A.N., 2012. Neuropeptide transmission in brain circuits. *Neuron* 76, 98–115.
- Di Scala-Guenot, D., Strosser, M.T., 1992. Oxytocin receptors on cultured astroglial cells. Kinetic and pharmacological characterization of oxytocin-binding sites on intact hypothalamic and hippocampal cells from foetal rat brain. *Biochem J.* 284 (Pt 2), 491–497.
- Di Scala-Guenot, D., Mougnot, D., Strosser, M.T., 1994. Increase of intracellular calcium induced by oxytocin in hypothalamic cultured astrocytes. *Glia* 11 (3), 269–276. <https://doi.org/10.1002/glia.440110308>, 7960031.
- Domes, G., Heinrichs, M., Kumbier, E., Grossmann, A., Hauenstein, K., Herpertz, S.C., 2013. Effects of intranasal oxytocin on the neural basis of face processing in autism spectrum disorder. *Biol. Psychiatry* 74, 164–171.
- Durkee, C.A., Covelo, A., Lines, J., Kofuji, P., Aguilar, J., Araque, A., 2019. Gi/o protein-coupled receptors inhibit neurons but activate astrocytes and stimulate gliotransmission. *Glia* 67, 1076–1093.
- Eliava, M., Melchior, M., Knobloch-Bollmann, H.S., Wahis, J., da Silva Gouveia, M., Tang, Y., Ciobanu, A.C., Triana del Rio, R., Roth, L.C., Althammer, F., Chavant, V., Goumon, Y., Gruber, T., Petit-Demouliere, N., Busnelli, M., Chini, B., Tan, L.L., Mitre, M., Froemke, R.C., Chao, M.V., Giese, G., Sprengel, R., Kuner, R., Poisbeau, P., Seeburg, P.H., Stoop, R., Charlet, A., Grinevich, V., 2016. A new population of parvocellular oxytocin neurons controlling magnocellular neuron activity and inflammatory pain processing. *Neuron* 89, 1291–1304.
- Evrard, M.E., Strosser, M.T., Di Scala-Guenot, D., 1997. Pharmacological characterization of oxytocin-binding sites in rat spinal cord membranes: comparison with embryonic cultured spinal cord neurones and astrocytes. *J. Neuroendocr.* 9, 553–560.
- Ferreira, J.J., Butler, A., Stewart, R., Gonzalez-Cota, A.L., Lybaert, P., Amazu, C., Reini, E.L., Wakle-Prabakaran, M., Salkoff, L., England, S.K., Santi, C.M., 2019. Oxytocin can regulate myometrial smooth muscle excitability by inhibiting the Na<sup>+</sup>-activated K<sup>+</sup> channel, Slo2.1. *J. Physiol.* 597, 137–149.
- Fiacco, T.A., McCarthy, K.D., 2018. Multiple lines of evidence indicate that gliotransmission does not occur under physiological conditions. *J. Neurosci.* 38, 3–13.
- Foo, L.C., Allen, N.J., Bushong, E.A., Ventura, P.B., Chung, W.S., Zhou, L., Cahoy, J.D., Daneman, R., Zong, H., Ellisman, M.H., Barres, B.A., 2011. Development of a method for the purification and culture of rodent astrocytes. *Neuron* 71, 799–811.
- Ford, C.L., Young, L.J., 2021. Refining oxytocin therapy for autism: context is key. *Nat. Rev. Neurosci.*
- Frijling, J.L., 2017. Preventing PTSD with oxytocin: effects of oxytocin administration on fear neurocircuitry and PTSD symptom development in recently trauma-exposed individuals. *Eur. J. Psychotraumatol* 8, 1302652.
- Frijling, J.L., van Zuiden, M., Koch, S.B., Nawijn, L., Goslings, J.C., Luitse, J.S., Biesheuvel, T.H., Honig, A., Bakker, F.C., Denys, D., Veltman, D.J., Olf, M., 2014. Efficacy of oxytocin administration early after psychotrauma in preventing the development of PTSD: study protocol of a randomized controlled trial. *BMC Psychiatry* 14, 92.
- Froemke, R.C., Young, L.J., 2021. Oxytocin, neural plasticity, and social behavior. *Annu Rev. Neurosci.* 44, 359–381.
- Fuxe, K., Borroto-Escuela, D.O., Romero-Fernandez, W., Ciruela, F., Manger, P., Leo, G., Diaz-Cabiale, Z., Agnati, L.F., 2012. On the role of volume transmission and receptor-receptor interactions in social behaviour: focus on central catecholamine and oxytocin neurons. *Brain Res* 1476, 119–131.
- Gautvik, K.M., de Lecea, L., Gautvik, V.T., Danielson, P.E., Tranque, P., Dopazo, A., Bloom, F.E., Sutcliffe, J.G., 1996. Overview of the most prevalent hypothalamus-specific mRNAs, as identified by directional tag PCR subtraction. *Proc. Natl. Acad. Sci. USA* 93, 8733–8738.
- Gimpl, G., Fahrenholz, F., 2001. The oxytocin receptor system: structure, function, and regulation. *Physiol. Rev.* 81, 629–683.
- Gonzalez-Hernandez, A., Charlet, A., 2018. Oxytocin, GABA, and TRPV1, the Analgesic Triad? *Front Mol Neurosci* 11 (398), 00398. <https://doi.org/10.3389/fnmol.2018.00398>.
- Gordon, I., Vander Wyk, B.C., Bennett, R.H., Cordeaux, C., Lucas, M.V., Eilbott, J.A., Zagoory-Sharon, O., Leckman, J.F., Feldman, R., Pelphrey, K.A., 2013. Oxytocin enhances brain function in children with autism. *Proc. Natl. Acad. Sci. USA* 110, 20953–20958.
- Gould, B.R., Zingg, H.H., 2003. Mapping oxytocin receptor gene expression in the mouse brain and mammary gland using an oxytocin receptor-LacZ reporter mouse. *Neuroscience* 122, 155–167.
- Grandes, P., Kq, K.Q.D., Morino, P., Cuenod, M., Streit, P., 1991. Homocysteate, an excitatory transmitter candidate localized in glia. *Eur. J. Neurosci.* 3, 1370–1373.
- Gravati, M., Busnelli, M., Bulgheroni, E., Reversi, A., Spaiardi, P., Parenti, M., Toselli, M., Chini, B., 2010. Dual modulation of inward rectifier potassium currents in olfactory neuronal cells by promiscuous G protein coupling of the oxytocin receptor. *J. Neurochem* 114, 1424–1435.
- Grinevich, V., Stoop, R., 2018. Interplay between oxytocin and sensory systems in the orchestration of socio-emotional behaviors. *Neuron* 99, 887–904.
- Grinevich, V., Neumann, I.D., 2020. Brain oxytocin: how puzzle stones from animal studies translate into psychiatry. *Mol. Psychiatry*.
- Grinevich, V., Ludwig, M., 2021. The multiple faces of the oxytocin and vasopressin systems in the brain. *J. Neuroendocr.* 33, e13004.
- Grinevich, V., Knobloch-Bollmann, H.S., Eliava, M., Busnelli, M., Chini, B., 2016. Assembling the puzzle: pathways of oxytocin signaling in the brain. *Biol. Psychiatry* 79, 155–164.
- Guastella, A.J., Einfeld, S.L., Gray, K.M., Rinehart, N.J., Tonge, B.J., Lambert, T.J., Hickie, I.B., 2010. Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. *Biol. Psychiatry* 67, 692–694.
- Gwee, P.C., Tay, B.H., Brenner, S., Venkatesh, B., 2009. Characterization of the neurohypophysial hormone gene loci in elephant shark and the Japanese lamprey: origin of the vertebrate neurohypophysial hormone genes. *BMC Evol. Biol.* 9, 47.
- Hasan, M.T., Althammer, F., Silva da Gouveia, M., Goyon, S., Eliava, M., Lefevre, A., Kerspern, D., Schimmer, J., Raftogianni, A., Wahis, J., Knobloch-Bollmann, H.S., Tang, Y., Liu, X., Jain, A., Chavant, V., Goumon, Y., Weislogel, J.M., Hurlmann, R., Herpertz, S.C., Pitzer, C., Darbon, P., Dogbevia, G.K., Bertocchi, I., Larkum, M.E., Sprengel, R., Bading, H., Charlet, A., Grinevich, V., 2019. A fear memory engram and its plasticity in the hypothalamic oxytocin system. *Neuron* 103 (133–146), e138.
- Hatton, G.I., Perlmutter, L.S., Salm, A.K., Tweedle, C.D., 1984. Dynamic neuronal-glia interactions in hypothalamus and pituitary: implications for control of hormone synthesis and release. *Peptides* 5 (Suppl 1), 121–138.
- Haubensak, W., Kunwar, P.S., Cai, H., Ciochi, S., Wall, N.R., Ponnusamy, R., Biag, J., Dong, H.W., Deisseroth, K., Callaway, E.M., Fanselow, M.S., Luthi, A., Anderson, D. J., 2010. Genetic dissection of an amygdala microcircuit that gates conditioned fear. *Nature* 468, 270–276.
- Havranek, T., Lestanova, Z., Mravec, B., Strbak, V., Bakos, J., Bacova, Z., 2017. Oxytocin modulates expression of neuron and glial markers in the rat hippocampus. *Folia Biol. (Praha)* 63, 91–97.
- Henneberger, C., Bard, L., Panatier, A., Reynolds, J.P., Kopach, O., Medvedev, N.I., Minge, D., Herde, M.K., Anders, S., Kraev, I., Heller, J.P., Rama, S., Zheng, K., Jensen, T.P., Sanchez-Romero, I., Jackson, C.J., Janovjak, H., Ottersen, O.P.,

- Nagelhus, E.A., Oliet, S.H.R., Stewart, M.G., Nagerl, U.V., Rusakov, D.A., 2020. LTP induction boosts glutamate spillover by driving withdrawal of perisynaptic astroglia. *Neuron* 108 (919–936), e911.
- Hoare, S., Copland, J.A., Strakova, Z., Ives, K., Jeng, Y.J., Hellmich, M.R., Soloff, M.S., 1999. The proximal portion of the COOH terminus of the oxytocin receptor is required for coupling to  $g(q)$ , but not  $g(i)$ . Independent mechanisms for elevating intracellular calcium concentrations from intracellular stores. *J. Biol. Chem.* 274, 28682–28689.
- Hrabovszky, E., Liposits, Z., 2008. Novel aspects of glutamatergic signalling in the neuroendocrine system. *J. Neuroendocr.* 20, 743–751.
- Hu, B., Boyle, C.A., Lei, S., 2020a. Oxytocin receptors excite lateral nucleus of central amygdala by phospholipase C $\beta$ - and protein kinase C-dependent depression of inwardly rectifying K(+) channels. *J. Physiol.* 598, 3501–3520.
- Hu, N.Y., Chen, Y.T., Wang, Q., Jie, W., Liu, Y.S., You, Q.L., Li, Z.L., Li, X.W., Reibel, S., Pfrieger, F.W., Yang, J.M., Gao, T.M., 2020b. Expression patterns of inducible cre recombinase driven by differential astrocyte-specific promoters in transgenic mouse lines. *Neurosci. Bull.* 36, 530–544.
- Hunt, S., Sun, Y., Kucukdereli, H., Klein, R., Sah, P., 2017. Intrinsic circuits in the lateral central amygdala. *eNeuro* 4.
- Inoue, T., Yamakage, H., Tanaka, M., Kusakabe, T., Shimatsu, A., Satoh-Asahara, N., 2019. Oxytocin Suppresses inflammatory responses induced by lipopolysaccharide through inhibition of the eIF-2-ATF4 pathway in mouse microglia. *Cells* 8.
- Insel, T.R., Young, L.J., 2001. The neurobiology of attachment. *Nat. Rev. Neurosci.* 2, 129–136.
- Ivanov, A.D., Mothet, J.P., 2019. The plastic d-serine signaling pathway: sliding from neurons to glia and vice-versa. *Neurosci. Lett.* 689, 21–25.
- Janak, P.H., Tye, K.M., 2015. From circuits to behaviour in the amygdala. *Nature* 517, 284–292.
- Jurek, B., Neumann, I.D., 2018. The oxytocin receptor: from intracellular signaling to behavior. *Physiol. Rev.* 98, 1805–1908.
- Jurek, B., Meyer, M., 2020. Anxiolytic and anxiogenic? how the transcription factor MEF2 might explain the manifold behavioral effects of oxytocin. *Front Endocrinol. (Lausanne)* 11, 186.
- Knobloch, H.S., Charlet, A., Hoffmann, L.C., Eliava, M., Khrulev, S., Cetin, A.H., Osten, P., Schwarz, M.K., Seeburg, P.H., Stoop, R., Grinevich, V., 2012. Evoked axonal oxytocin release in the central amygdala attenuates fear response. *Neuron* 73, 553–566.
- Kong, W.L., Peng, Y.Y., Peng, B.W., 2017. Modulation of neuroinflammation: Role and therapeutic potential of TRPV1 in the neuro-immune axis. *Brain Behav. Immun.* 64, 354–366.
- Kuo, J., Hariri, O.R., Micevych, P., 2009. An interaction of oxytocin receptors with metabotropic glutamate receptors in hypothalamic astrocytes. *J. Neuroendocr.* 21, 1001–1006.
- Landgraf, R., Neumann, I.D., 2004. Vasopressin and oxytocin release within the brain: a dynamic concept of multiple and variable modes of neuropeptide communication. *Front Neuroendocr.* 25, 150–176.
- Langle, S.L., Poulain, D.A., Theodosis, D.T., 2003. Induction of rapid, activity-dependent neuronal-glia remodelling in the adult rat hypothalamus in vitro. *Eur. J. Neurosci.* 18, 206–214.
- Lawal, O., Ulloa Severino, F.P., Eroglu, C., 2022. The role of astrocyte structural plasticity in regulating neural circuit function and behavior. *Glia* 70 (8), 1467–1483. <https://doi.org/10.1002/glia.24191>.
- Lee, H.J., Macbeth, A.H., Pagani, J.H., Young 3rd, W.S., 2009. Oxytocin: the great facilitator of life. *Prog. Neurobiol.* 88, 127–151.
- Leng, G., Ludwig, M., 2008. Neurotransmitters and peptides: whispered secrets and public announcements. *J. Physiol.* 586, 5625–5632.
- Lin, Y.T., Huang, C.C., Hsu, K.S., 2012. Oxytocin promotes long-term potentiation by enhancing epidermal growth factor receptor-mediated local translation of protein kinase Mzeta. *J. Neurosci.* 32, 15476–15488.
- Ludwig, M., Leng, G., 2006. Dendritic peptide release and peptide-dependent behaviours. *Nat. Rev. Neurosci.* 7, 126–136.
- Ludwig, M., Stern, J., 2015. Multiple signalling modalities mediated by dendritic exocytosis of oxytocin and vasopressin. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 370.
- Ma, Y., Liu, Y., Rand, D.G., Heatherington, T.F., Han, S., 2015. Opposing oxytocin effects on intergroup cooperative behavior in intuitive and reflective minds. *Neuropsychopharmacology* 40, 2379–2387.
- Maicas-Royo, J., Leng, G., MacGregor, D.J., 2018. A predictive, quantitative model of spiking activity and stimulus-secretion coupling in oxytocin neurons. *Endocrinology*.
- Mairesse, J., Zinni, M., Pansiot, J., Hassan-Abdi, R., Demene, C., Colella, M., Charriaud-Marlangue, C., Rideau Batista Novais, A., Tanter, M., Maccari, S., Gressens, P., Vaiman, D., Soussi-Yanicostas, N., Baud, O., 2019. Oxytocin receptor agonist reduces perinatal brain damage by targeting microglia. *Glia* 67, 345–359.
- McKay, E.C., Beck, J.S., Khoo, S.K., Dykema, K.J., Cottingham, S.L., Winn, M.E., Paulson, H.L., Lieberman, A.P., Counts, S.E., 2019. Peri-infarct upregulation of the oxytocin receptor in vascular dementia. *J. Neuropathol. Exp. Neurol.* 78, 436–452.
- Mehina, E.M.F., Murphy-Royal, C., Gordon, G.R., 2017. Steady-State Free Ca(2+) in astrocytes is decreased by experience and impacts arteriole tone. *J. Neurosci.* 37, 8150–8165.
- Meyer-Lindenberg, A., Domes, G., Kirsch, P., Heinrichs, M., 2011. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nat. Rev. Neurosci.* 12, 524–538.
- Mitre, M., Minder, J., Morina, E.X., Chao, M.V., Froemke, R.C., 2018. Oxytocin modulation of neural circuits. *Curr. Top. Behav. Neurosci.* 35, 31–53.
- Mitre, M., Marlin, B.J., Schiavo, J.K., Morina, E., Norden, S.E., Hackett, T.A., Aoki, C.J., Chao, M.V., Froemke, R.C., 2016. A distributed network for social cognition enriched for oxytocin receptors. *J. Neurosci.* 36, 2517–2535.
- Nersesyan, Y., Demirkhanyan, L., Cabezas-Bratesco, D., Oakes, V., Kusuda, R., Dawson, T., Sun, X., Cao, C., Cohen, A.M., Chelluboina, B., Veeravalli, K.K., Zimmermann, K., Domene, C., Brauchi, S., Zakharian, E., 2017. Oxytocin modulates nociception as an agonist of pain-sensing TRPV1. *Cell Rep.* 21, 1681–1691.
- Neumann, I.D., Slattery, D.A., 2016. Oxytocin in general anxiety and social fear: a translational approach. *Biol. Psychiatry* 79, 213–221.
- Newmaster, K.T., Nolan, Z.T., Chon, U., Vanselow, D.J., Weit, A.R., Tabbaa, M., Hidema, S., Nishimori, K., Hammock, E.A.D., Kim, Y., 2020. Quantitative cellular-resolution map of the oxytocin receptor in postnatally developing mouse brains. *Nat. Commun.* 11, 1885.
- Nusbaum, M.P., Blitz, D.M., Swensen, A.M., Wood, D., Marder, E., 2001. The roles of co-transmission in neural network modulation. *Trends Neurosci.* 24, 146–154.
- Olf, M., Langeland, W., Witteveen, A., Denys, D., 2010. A psychobiological rationale for oxytocin in the treatment of posttraumatic stress disorder. *CNS Spectr.* 15, 522–530.
- Oliet, S.H., Panatier, A., Piet, R., Mothet, J.P., Poulain, D.A., Theodosis, D.T., 2008. Neuron-glia interactions in the rat supraoptic nucleus. *Prog. Brain Res* 170, 109–117.
- Owen, S.F., Tuncdemir, S.N., Bader, P.L., Tirkko, N.N., Fishell, G., Tsien, R.W., 2013. Oxytocin enhances hippocampal spike transmission by modulating fast-spiking interneurons. *Nature* 500, 458–462.
- Palanisamy, A., Kannappan, R., Xu, Z., Martino, A., Friese, M.B., Boyd, J.D., Crosby, G., Culley, D.J., 2018. Oxytocin alters cell fate selection of rat neural progenitor cells in vitro. *PLoS One* 13, e0191160.
- Panaro, M.A., Benamer, T., Porro, C., 2020. Hypothalamic neuropeptide brain protection: focus on oxytocin. *J. Clin. Med* 9.
- Panatier, A., Gentles, S.J., Bourque, C.W., Oliet, S.H., 2006. Activity-dependent synaptic plasticity in the supraoptic nucleus of the rat hypothalamus. *J. Physiol.* 573, 711–721.
- Papouin, T., Henneberger, C., Rusakov, D.A., Oliet, S.H.R., 2017. Astroglial versus neuronal D-serine: fact checking. *Trends Neurosci.* 40, 517–520.
- Parent, A.S., Rasier, G., Matagne, V., Lomniczi, A., Lebrethon, M.C., Gerard, A., Ojeda, S.R., Bourguignon, J.P., 2008. Oxytocin facilitates female sexual maturation through a glia-to-neuron signaling pathway. *Endocrinology* 149, 1358–1365.
- Parpura, V., Basarsky, T.A., Liu, F., Jęftinija, K., Jęftinija, S., Haydon, P.G., 1994. Glutamate-mediated astrocyte-neuron signalling. *Nature* 369, 744–747.
- Phaneuf, S., Europe-Finner, G.N., Varney, M., MacKenzie, I.Z., Watson, S.P., Lopez Bernal, A., 1993. Oxytocin-stimulated phosphoinositide hydrolysis in human myometrial cells: involvement of pertussis toxin-sensitive and -insensitive G-proteins. *J. Endocrinol.* 136, 497–509.
- Rajamani, K.T., Wagner, S., Grinevich, V., Harony-Nicolas, H., 2018. Oxytocin as a modulator of synaptic plasticity: implications for neurodevelopmental disorders. *Front Synaptic Neurosci.* 10, 17.
- Rimoldi, V., Reversi, A., Taverna, E., Rosa, P., Francolini, M., Cassoni, P., Parenti, M., Chini, B., 2003. Oxytocin receptor elicits different EGFR/MAPK activation patterns depending on its localization in caveolin-1 enriched domains. *Oncogene* 22, 6054–6060.
- Romero-Fernandez, W., Borroto-Escuela, D.O., Agnati, L.F., Fuxe, K., 2013. Evidence for the existence of dopamine D2-oxytocin receptor heteromers in the ventral and dorsal striatum with facilitatory receptor-receptor interactions. *Mol Psychiatry* 18 (8), 849–850. <https://doi.org/10.1038/mp.2012.103>.
- Rosso, L., Peteri-Brunback, B., Vouret-Craviari, V., Deroanne, C., Van Obberghen-Schilling, E., Mienville, J.M., 2002. Vasopressin and oxytocin reverse adenosine-induced pituitary cell death via calcium-dependent activation of Cdc42. *Eur. J. Neurosci.* 16, 2324–2332.
- Ryan, P.J., Ross, S.I., Campos, C.A., Derkach, V.A., Palmiter, R.D., 2017. Oxytocin-receptor-expressing neurons in the parabrachial nucleus regulate fluid intake. *Nat. Neurosci.* 20, 1722–1733.
- Salm, A.K., Smithson, K.G., Hatton, G.I., 1985. Lactation-associated redistribution of the glial fibrillary acidic protein within the supraoptic nucleus. *Immunocytochemical Study Cell Tissue Res.* 242, 9–15.
- Savtchouk, I., Volterra, A., 2018. Gliotransmission: beyond black-and-white. *J. Neurosci.* 38, 14–25.
- Shigetomi, E., Kracun, S., Khakh, B.S., 2010a. Monitoring astrocyte calcium microdomains with improved membrane targeted GCaMP reporters. *Neuron Glia Biol.* 6, 183–191.
- Shigetomi, E., Kracun, S., Sofroniew, M.V., Khakh, B.S., 2010b. A genetically targeted optical sensor to monitor calcium signals in astrocyte processes. *Nat. Neurosci.* 13, 759–766.
- Sloan, S.A., Barres, B.A., 2014. Looks can be deceiving: reconsidering the evidence for gliotransmission. *Neuron* 84, 1112–1115.
- Stifter, S.A., Greter, M., 2020. STOP floxing around: specificity and leakiness of inducible Cre/loxP systems. *Eur. J. Immunol.* 50, 338–341.
- Stoop, R., 2012. Neuromodulation by oxytocin and vasopressin. *Neuron* 76, 142–159.
- Strakova, Z., Copland, J.A., Lolait, S.J., Soloff, M.S., 1998. ERK2 mediates oxytocin-stimulated PGE2 synthesis. *Am. J. Physiol.* 274, E634–E641.
- Svensson, E., Apergis-Schoute, J., Burnstock, G., Nusbaum, M.P., Parker, D., Schiöth, H.B., 2018. General principles of neuronal co-transmission: insights from multiple model systems. *Front Neural Circuits* 12, 117.
- Swaab, D.F., 1997. Prader-Willi syndrome and the hypothalamus. *Acta Paediatr. Suppl.* 423, 50–54.
- Swaab, D.F., Purba, J.S., Hofman, M.A., 1995. Alterations in the hypothalamic paraventricular nucleus and its oxytocin neurons (putative satiety cells) in Prader-Willi syndrome: a study of five cases. *J. Clin. Endocrinol. Metab.* 80, 573–579.
- Tasker, J.G., Oliet, S.H., Bains, J.S., Brown, C.H., Stern, J.E., 2012. Glial regulation of neuronal function: from synapse to systems physiology. *J. Neuroendocr.* 24, 566–576.

- Tauber, M., Mantoulan, C., Copet, P., Jauregui, J., Demeer, G., Diene, G., Roge, B., Laurier, V., Ehlinger, V., Arnaud, C., Molinas, C., Thuilleaux, D., 2011. Oxytocin may be useful to increase trust in others and decrease disruptive behaviours in patients with Prader-Willi syndrome: a randomised placebo-controlled trial in 24 patients. *Orphanet J. Rare Dis.* 6, 47.
- Tauber, M., Boulanouar, K., Diene, G., Cabal-Berthoumieu, S., Ehlinger, V., Fichaux-Bourin, P., Molinas, C., Faye, S., Valette, M., Pourrinet, J., Cessans, C., Viaux-Sauvelon, S., Bascoul, C., Guedeny, A., Delhanty, P., Geenen, V., Martens, H., Muscatelli, F., Cohen, D., Consoli, A., Payoux, P., Arnaud, C., Salles, J.P., 2017. The use of oxytocin to improve feeding and social skills in infants with prader-willi syndrome. *Pediatrics* 139.
- Theodosis, D.T., Chapman, D.B., Montagnese, C., Poulain, D.A., Morris, J.F., 1986a. Structural plasticity in the hypothalamic supraoptic nucleus at lactation affects oxytocin-, but not vasopressin-secreting neurones. *Neuroscience* 17, 661–678.
- Theodosis, D.T., Montagnese, C., Rodriguez, F., Vincent, J.D., Poulain, D.A., 1986b. Oxytocin induces morphological plasticity in the adult hypothalamo-neurohypophysial system. *Nature* 322, 738–740.
- Theofanopoulou, C., Gedman, G., Cahill, J.A., Boeckx, C., Jarvis, E.D., 2021. Universal nomenclature for oxytocin-vasotocin ligand and receptor families. *Nature* 592, 747–755.
- Tirko, N.N., Eyring, K.W., Carcea, I., Mitre, M., Chao, M.V., Froemke, R.C., Tsien, R.W., 2018. Oxytocin transforms firing mode of CA2 hippocampal. *Neurons Neuron* 100 (593–608), e593.
- Tobin, V., Leng, G., Ludwig, M., 2012. The involvement of actin, calcium channels and exocytosis proteins in somato-dendritic oxytocin and vasopressin release. *Front Physiol.* 3, 261.
- Verkhatsky, A., Nedergaard, M., 2018. Physiology of astroglia. *Physiol. Rev.* 98, 239–389.
- von Bartheld, C.S., Bahney, J., Herculano-Houzel, S., 2016. The search for true numbers of neurons and glial cells in the human brain: A review of 150 years of cell counting. *J. Comp. Neurol.* 524, 3865–3895.
- Wahis, J., Baudon, A., Althammer, F., Kerspern, D., Goyon, S., Hagiwara, D., Lefevre, A., Barteczko, L., Boury-Jamot, B., Bellanger, B., Abatis, M., Da Silva Gouveia, M., Benusiglio, D., Eliava, M., Rozov, A., Weinsanto, I., Knobloch-Bollmann, H.S., Kirchner, M.K., Roy, R.K., Wang, H., Pertin, M., Inquimbert, P., Pitzer, C., Siemens, J., Goumon, Y., Boutrel, B., Lamy, C.M., Decosterd, I., Chatton, J.Y., Rouach, N., Young, W.S., Stern, J.E., Poisbeau, P., Stoop, R., Darbon, P., Grinevich, V., Charlet, A., 2021. Astrocytes mediate the effect of oxytocin in the central amygdala on neuronal activity and affective states in rodents. *Nat. Neurosci.*
- Wang, P., Qin, D., Wang, Y.F., 2017. Oxytocin rapidly changes astrocytic GFAP plasticity by differentially modulating the expressions of pERK 1/2 and protein kinase A. *Front Mol. Neurosci.* 10, 262.
- Wang, Y.F., Hatton, G.I., 2004. Milk ejection burst-like electrical activity evoked in supraoptic oxytocin neurons in slices from lactating rats. *J. Neurophysiol.* 91, 2312–2321.
- Wang, Y.F., Hatton, G.I., 2006. Mechanisms underlying oxytocin-induced excitation of supraoptic neurons: prostaglandin mediation of actin polymerization. *J. Neurophysiol.* 95, 3933–3947.
- Wang, Y.F., Hatton, G.I., 2007. Interaction of extracellular signal-regulated protein kinase 1/2 with actin cytoskeleton in supraoptic oxytocin neurons and astrocytes: role in burst firing. *J. Neurosci.* 27, 13822–13834.
- Wang, Y.F., Hatton, G.I., 2009. Astrocytic plasticity and patterned oxytocin neuronal activity: dynamic interactions. *J. Neurosci.* 29, 1743–1754.
- Wilson, Y.M., Murphy, M., 2009. A discrete population of neurons in the lateral amygdala is specifically activated by contextual fear conditioning. *Learn Mem.* 16, 357–361.
- Young, L.J., Wang, Z., 2004. The neurobiology of pair bonding. *Nat. Neurosci.* 7, 1048–1054.
- Young, W.S., Song, J., 2020. Characterization of oxytocin receptor expression within various neuronal populations of the mouse dorsal hippocampus. *Front Mol. Neurosci.* 13, 40.
- Zatkova, M., Bacova, Z., Puerta, F., Lestanova, Z., Alanazi, M., Kiss, A., Reichova, A., Castejon, A.M., Ostatnikova, D., Bakos, J., 2018. Projection length stimulated by oxytocin is modulated by the inhibition of calcium signaling in U-87MG cells. *J. Neural Transm. (Vienna)* 125, 1847–1856.
- Zhang, B., Qiu, L., Xiao, W., Ni, H., Chen, L., Wang, F., Mai, W., Wu, J., Bao, A., Hu, H., Gong, H., Duan, S., Li, A., Gao, Z., 2020. Reconstruction of the hypothalamo-neurohypophysial system and functional dissection of magnocellular oxytocin neurons in the brain. *Neuron*.
- Zhang, J.M., Wang, H.K., Ye, C.Q., Ge, W., Chen, Y., Jiang, Z.L., Wu, C.P., Poo, M.M., Duan, S., 2003. ATP released by astrocytes mediates glutamatergic activity-dependent heterosynaptic suppression. *Neuron* 40, 971–982.