The special relationship: glia–neuron interactions in the neuroendocrine hypothalamus

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Abstract | Natural fluctuations in physiological conditions require adaptive responses involving rapid and reversible structural and functional changes in the hypothalamic neuroendocrine circuits that control homeostasis. Here, we discuss the data that implicate hypothalamic glia in the control of hypothalamic neuroendocrine circuits, specifically neuron–glia interactions in the regulation of neurosecretion as well as neuronal excitability. Mechanistically, the morphological plasticity displayed by distal processes of astrocytes, pituicytes and tanycytes modifies the geometry and diffusion properties of the extracellular space. These changes alter the relationship between glial cells of the hypothalamus and adjacent neuronal elements, especially at specialized intersections such as synapses and neurohaemal junctions. The structural alterations in turn lead to functional plasticity that alters the release and spread of neurotransmitters, neuromodulators and gliotransmitters, as well as the activity of discrete glial signalling pathways that mediate feedback by peripheral signals to the hypothalamus. An understanding of the contributions of these and other non-neuronal cell types to hypothalamic neuroendocrine function is thus critical both to understand physiological processes such as puberty, the maintenance of bodily homeostasis and ageing and to develop novel therapeutic strategies for dysfunctions of these processes, such as infertility and metabolic disorders.

Glial cells are not a single homogeneous population but a group of highly specific cell types with distinct functions that go far beyond merely providing structural or trophic support to neurons (BOX 1). The most studied glial cells are astrocytes — star-shaped cells that outnumber neurons in the brain. Astrocytes consist of several subgroups, each with distinct morphologies, gene expression profiles and functions[1]. The distinct subgroups of astrocytes exhibit distinct properties linked to the specificity of the neural networks in which they are integrated[2,3]. Several other glial cell types exist, including some that have similar developmental origins but take on specialized roles depending on their location or function[4] (BOX 1). For example, tanycytes of the hypothalamus share the same radial glial lineage as astrocytes, but unlike astrocytes, tanycytes retain their radial-glia-like morphology throughout life.

The field of neuroendocrinology, in particular work focusing on the hypothalamus, has driven research on the role of neuron–glia interactions in the mammalian brain[4–11]. This is in part due to the nature of the hypothalamus itself — a brain region that, despite its unimpressive size, regulates several vital functions. Moreover, the hypothalamus plays a double role — that of a conventional integrator and generator of information and, more uniquely, that of a secretory organ endowed with specific structural and functional adaptations. This combination of roles and their concentration within a small anatomical area permit the visualization of several processes that might be absent or missed elsewhere in the brain. In this Review, we discuss the physiology of glial cells in the hypothalamus. We pay particular attention to the interactions between neuroendocrine neurons, astrocytes and tanycytes that have improved our understanding of the mechanisms underlying neuron–glia communication.

Magnocellular neuroendocrine system

The magnocellular neuroendocrine system is part of the hypothalamo–neurohypophyseal system and comprises two distinct populations of magnocellular neurons — the oxytocin-secreting neurons and the vasopressin-secreting neurons (FIG. 1). Oxytocin-secreting neurons and vasopressin-secreting neurons are located both in the supraoptic nucleus and paraventricular nucleus of the hypothalamus. Each oxytocin or vasopressin neuron

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Key points

- The hypothalamus is the single most important integrator of vegetative and endocrine regulation in the body
- Neuroendocrine secretory neurons establish a permanent dialogue with hypothalamic glial cells to maintain body homeostasis
- Hypothalamic astrocytes control the extracellular levels of neurotransmitters and neuromodulators in the neuroendocrine networks regulating body homeostasis
- Hypothalamic tanycytes control both neuroendocrine secretions and the access of key peripheral homeostatic signals into the brain
- The recognition of the clinical relevance of glia–neuron interactions in the hypothalamus might pave the way for the development of new treatment strategies in the central loss of body homeostasis in human syndromes

sends a unique axon towards the neurohypophysis, where it ramifies and releases its neurohormone directly into the systemic circulation[12]. Oxytocin is released in a pulsatile manner during parturition and milk ejection from the mammary glands. Vasopressin, the antidiuretic hormone, is released gradually following a decrease in blood osmolality and acts on the kidneys to promote water reabsorption[13,14]. Oxytocin also acts on the kidney to stimulate natriuresis and maintain plasma osmolality, thereby complementing the actions of vasopressin[15]. The release of oxytocin and vasopressin is highly nonlinear, graded and dependent on the increasing frequency of bursts of action potentials propagated along neurosecretory axons[13,14,16]. A distinctive feature of oxytocin-secreting neurons is the overall synchronization of their bursting activity during parturition and the milk-ejection reflex[13].

Morphological plasticity

The supraoptic nucleus contains numerous glial cells, the majority of which are radial astrocytes, in addition to magnocellular neurons. The cell bodies of these radial astrocytes are located in the ventral portion of the supraoptic nucleus and send long processes enwrapping magnocellular neurons and their synapses[17,18]. Seminal studies conducted in the 1970s and 1980s highlighted the importance of glia in the magnocellular neuroendocrine system[19–21]. These pioneering studies uncovered the striking neuronal–glial reorganization that occurs during high physiological demand such as dehydration[19,21], parturition and lactation[20]. Under dehydration, before parturition and during the entire period of lactation, astrocytes in the supraoptic nucleus and neurohypophyseal pituicytes retract their processes from between adjacent magnocellular neurons and neuroendocrine terminals, respectively[22].

Researchers initially thought that the neuronal–glial reorganization in the supraoptic nucleus was the mechanism responsible for the pulsatile secretion of oxytocin by facilitating neuron-to-neuron contact and electrical interactions[23]; however, further studies by the same groups have brought this idea into question[13,14,24]. One hypothesis, which is based on *in vitro* data, suggests that the dendritic release of oxytocin increases the sensitivity of oxytocin-secreting neurons to incoming external inputs that stimulate milk ejection[14,16]. The most supported hypothesis, however, involves the autocrine regulation of the activity of magnocellular neurons through the somatodendritic exocytosis of oxytocin[25,26]. Magnocellular neurons express oxytocin receptors[27], and their cell bodies and dendrites are packed with dense-core vesicles containing oxytocin[25]. Furthermore, the extracellular concentration of oxytocin within the supraoptic nucleus increases before each milk-ejection burst[28]. The unilateral injection of oxytocin into this nucleus facilitates milk-ejection bursts during lactation and the synchronization of the bursting activity of magnocellular neurons in the contralateral nucleus[29] through the modulation of excitatory and inhibitory synaptic inputs[30–32]. These data suggest that the somatodendritic release of oxytocin contributes to the synchronization of magnocellular neurons via an autocrine positive-feedback mechanism.

Researchers have taken advantage of the structural plasticity of the magnocellular neuroendocrine system to study neuron–glia interactions and the contribution of astrocytes to neuronal and synaptic functions[22]. One study has demonstrated that the withdrawal of astrocytic processes from between adjacent magnocellular neurons observed during physiological changes influences the tortuosity of the extracellular space[33]. Tortuosity, which depends on the volume, geometry and molecular composition of the environment, represents an index for the restriction of diffusion of a substance within a tissue compared with an obstacle-free medium[9]. Changes in the tortuosity of the extracellular space in the magnocellular neurosecretory system can affect the transmission of neurotransmitters and neuromodulators (glutamate, GABA or endocannabinoids) that diffuse out of the synaptic cleft to reach distant synapses and the bioavailability of several gliotransmitters (ATP, D-serine and taurine). Therefore, we hypothesize that glial remodelling ultimately influences the excitability of magnocellular neurons and consequently the secretion of oxytocin and vasopressin. We discuss studies supporting this hypothesis in the following section.

Astrocytic modulation of diffusion

Glutamate. One of the major functions of astrocytes is to take up extracellular glutamate, a process that occurs via glutamate transporter 1 (also known as excitatory amino acid transporter 2) and the glutamate–aspartate transporter (also known as excitatory amino acid transporter 1), both of which are highly enriched in astrocytic processes[34]. In the supraoptic nucleus of dehydrated rats and lactating rats, the withdrawal of astrocytic processes from the synapse causes an accumulation of extracellular glutamate. This build-up of glutamate has a range of effects on synaptic and neuronal activity. For instance, the glutamate that overflows the synaptic cleft (a process termed spillover) can inhibit glutamate release by activating presynaptic metabotropic glutamate receptors[35,36]. In addition, spillover of synaptic glutamate can increase the excitation of magnocellular neurons *in vitro*[37,38] and *in vivo*[39] by diffusing away from the synapse and causing tonic activation of extrasynaptic NMDA (*N*-methyl-D-aspartate) receptors located outside the synaptic cleft on the postsynaptic cell (FIG. 2).

Neurohypophysis
Neural lobe (or posterior lobe) of the pituitary, where the unmyelinated axons of the magnocellular secretory neurons of the supraoptic and paraventricular hypothalamic nuclei project and release oxytocin and vasopressin directly into the general circulation for delivery to target tissues. In this protrusion of the brain, the neuroendocrine terminals of those secretory neurons interact closely with pituicytes that modulate their direct access to the pericapillary space.

Tonic activation
Persistent membrane receptor activation resulting from the random and sustained release of transmitters in the extracellular space. Tonic activation is opposed to phasic activation, a transient membrane receptor activation resulting from a more spatially and temporally discrete release of transmitters in the synaptic cleft.

Box 1 | **Glial cells**

Glial cells can be separated into six major groups: astrocytes (the most abundant glial cell type in the adult brain[227]), microglia, oligodendrocytes, NG2 glia, tanycytes, radial glial cells and pituicytes.

Astrocytes
Besides supporting neuronal function by supplying energy metabolites and maintaining water and ion homeostasis, astrocytes (part **a**) are endowed with calcium excitability and actively participate to the tripartite synapse by sensing neurotransmitters and releasing neuroactive substances[55]. They also contribute to neurovascular coupling and the maintenance of the blood–brain barrier[228]. The morphology and functions of astrocytes are highly heterogeneous and depend on their location in the central nervous system[2,3]. For instance, in the rodent brain, protoplasmic astrocytes in the grey matter have a radial morphology and contact synapses and capillaries, while fibrous astrocytes in the white matter have an elongated morphology and contact oligodendrocytes and myelinated axons.

Microglia
In a simplified view, microglia (part **b**) are the immunocompetent and phagocytic cells of the CNS[216]. In contrast to other glial cells, they do not originate from the ectodermal tissue but from the yolk sac progenitors that only settle into the brain during development. Besides surveying the healthy tissue, microglia contribute to synaptic pruning during development[229] and to synaptic modulation in normal and pathological conditions[230].

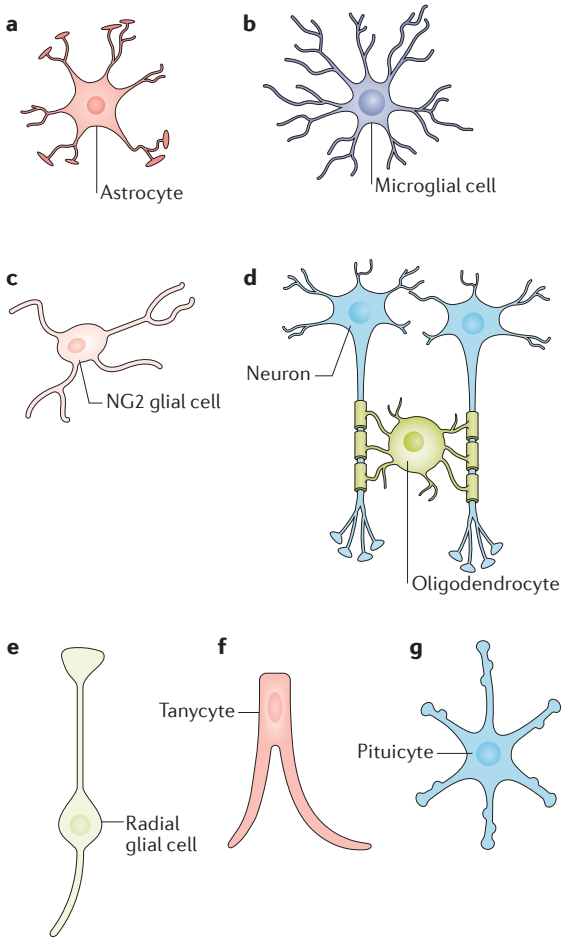
NG2 glia
Also known as oligodendrocyte progenitor cells, NG2 glia (part **c**) are the precursors of mature oligodendrocytes within the oligodendrocyte lineage and keep producing mature myelinating oligodendrocytes throughout life[231,232]. Intriguingly, NG2 glia are also the only highly proliferative cells in the brain parenchyma[232], giving them characteristics analogous to stem cells. They also have the ability to form functional synapses with neurons[233], although the function of these synapses remains unclear. They are precursors of mature oligodendrocytes within the oligodendrocyte lineage.

Oligodendrocytes
Oligodendrocytes are myelin-producing cells that insulate axons to facilitate electrical impulse conduction (part **d**). Like astrocytes, oligodendrocytes are metabolically coupled to neurons through the supply of energy metabolites such as lactate[234,235].

Radial glial cells
These cells possess a periventricular cell body and an elongated process that extends from a ventricular attachment to an endfoot anchored to the opposing pial surface. Radial glial cells (part **e**) act as neural stem cells and/or progenitor cells, and they guide newly formed neurons to their final destination[236,237]. After birth, radial glial cells persist in some areas of the CNS as specialized glial cells, such as Müller glia of the retina and Bergmann glia of the cerebellum[238].

Tanycytes
These are specialized ependymoglial cells that have the same radial glial lineage as astrocytes, but unlike astrocytes, they conserve their radial-glia-like morphology throughout life (part **f**)[238,239]. Anatomically, tanycyte cell bodies line the floor and lateral walls of the third ventricle and send long, slender processes towards the hypothalamic parenchyma and the fenestrated capillaries of the external zone of the median eminence. In contrast to more dorsally located ependymal cells, tanycytes do not possess beating cilia[212,240]. Growing evidence suggests that tanycytes have a variety of physiological functions, from barrier properties to participation in neuroendocrine, neurogenic and metabolic processes[95,108,241,242].

Pituicytes
These astrocytic-like cells are the dominant non-neuronal elements of the posterior lobe of the pituitary (part **g**). Pituicytes enclose neurosecretory fibre terminals via their processes[239]. Glia–neuron remodelling occurs in the posterior lobe of the pituitary (also called the neurohypophysis) to regulate the direct access of magnocellular neurosecretory axons to the pericapillary space and control the potential paracrine and autocrine actions of secreted peptides[22,243].



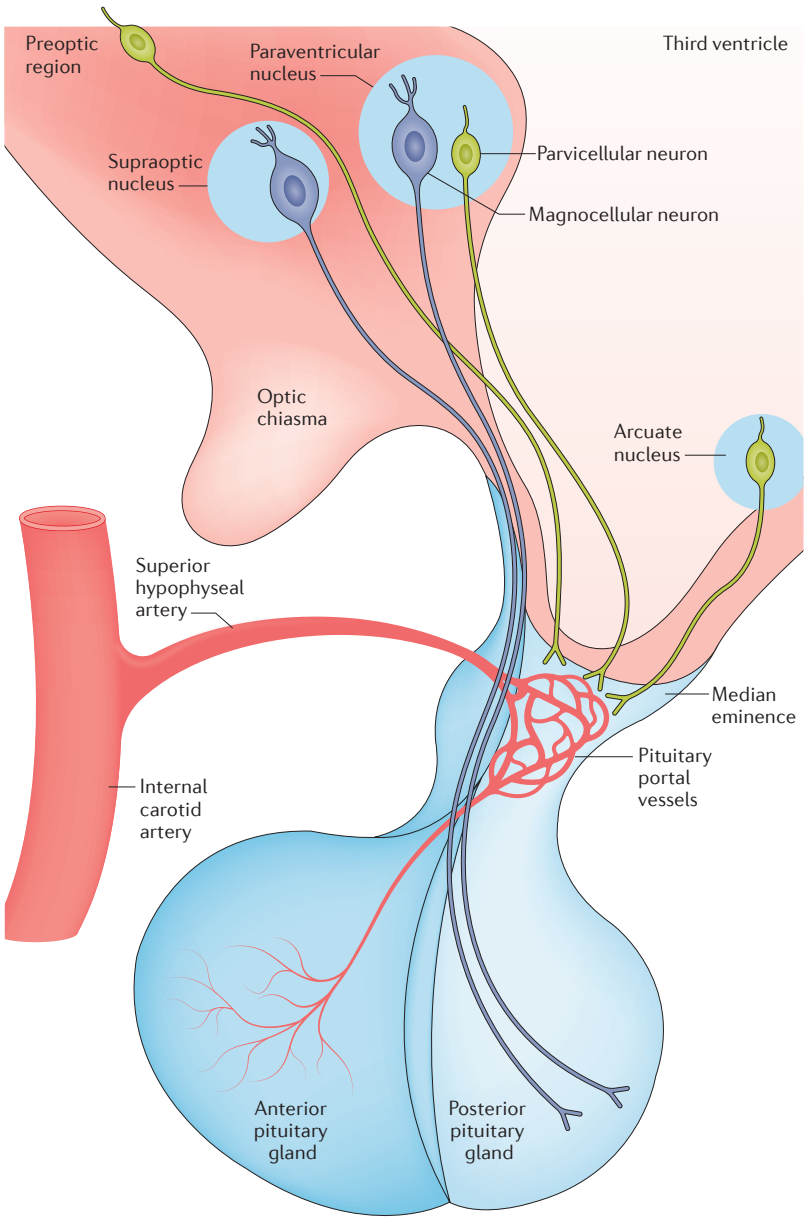


Figure 1 | **The adult neuroendocrine axes.** Neuroendocrine systems are the final common pathway for the central control of neurohormone secretion. As such, they are subject to a complex array of excitatory and inhibitory trans-synaptic inputs that modulate their activity. Magnocellular neurons (blue) of the hypothalamo–neurohypophyseal system release oxytocin and vasopressin directly into the general circulation. Parvicellular neurons (green) of the hypothalamo–antehypophyseal system project to the median eminence of the hypothalamus, where they make contact with the pericapillary space bordering the pituitary portal blood vessels. Following their release into the pituitary portal system, neurohormones travel to the pituitary to stimulate the synthesis and secretion of pituitary hormones. Blood-borne pituitary hormones act on target glands — including the gonads, the thyroid gland and the adrenal gland — to regulate their function. TSH-releasing hormone is secreted from the cell bodies of parvicellular neurons in the paraventricular nucleus[107,108], while parvicellular neurons in the preoptic region secrete gonadotropin-releasing hormone (GnRH; abundant GnRH cell bodies can also be found in the tuberal region of the hypothalamus in primates)[134,135]. Cell bodies of parvicellular neurons expressing dopamine, growth hormone-releasing hormone and somatostatin are also located in the tuberal region of the hypothalamus, including the arcuate nucleus of the hypothalamus[92].

Work performed on the supraoptic nucleus of rats suggests that glial coverage can also influence synaptic crosstalk between glutamatergic and GABA (γ-amino-butyric acid)-ergic (GABAergic) synapses converging on the same targets[33,40]. The spillover of synaptic glutamate caused by the withdrawal of synaptic glial coverage in lactating rats inhibits the release of GABA as glutamate targets distant presynaptic metabotropic glutamate receptors[33] and kainate receptors[40] located on neighbouring GABAergic terminals (FIG. 2). This phenomenon, called heterosynaptic depression, might amplify the transmission of excitatory information elicited during high hormonal demand (such as during milk ejection during suckling[41]) by inhibiting adjacent GABAergic synapses. In turn, the inhibition of GABAergic synapses can induce the local excitation of the postsynaptic magnocellular neuron.

These studies suggest that the influence of glial coverage on intersynaptic crosstalk between glutamatergic and GABAergic synapses involves a presynaptic mechanism, but data from 2013 provide evidence for postsynaptic modulation[38]. In that work, the authors demonstrated direct crosstalk between postsynaptic NMDA and GABA type A ($GABA_A$) receptors. Of note, the degree of efficacy of $GABA_A$ receptors is modulated by glial coverage. To be precise, glutamate escaping the synapse during the withdrawal of glial coverage in the supraoptic nucleus of dehydrated rats targets extrasynaptic NMDA receptors located on magnocellular neurons. The reduction in glial coverage at extrasynaptic NMDA receptors evokes the potentiation of postsynaptic $GABA_A$ receptors through a calcium-dependent process that involves a kinase-dependent phosphorylation mechanism (FIG. 2). When coordinated with an increase in presynaptic GABA release and extracellular ambient GABA (see paragraph below)[42], this NMDA–$GABA_A$ inter-receptor crosstalk could represent a considerable source of inhibition to compensate for NMDA receptor-mediated over-excitation[38]. This idea is supported by evidence showing that the aforementioned coupling between the NMDA receptor and $GABA_A$ receptor is impaired in rats with congestive heart failure — a disease characterized by the over-secretion of vasopressin, which alters body fluid balance and causes cardiac dysfunctions[38]. Altogether, these studies suggest that astrocytes surrounding synapses in the supraoptic nucleus have a pivotal role in modulating two different modes of intersynaptic crosstalk, which together are essential for maintaining the balance between excitatory and inhibitory transmission.

In addition to their role in modulating synaptic efficacy in the supraoptic nucleus, astrocytic processes can indirectly regulate the membrane properties and excitability of magnocellular neurons[43]. During dehydration, the glutamate that overflows the synaptic cleft can target extrasynaptic NMDA receptors to inhibit a transient voltage-gated A-type potassium channel in a manner dependent on calcium and protein kinase C (FIG. 2). The result of this inhibition is an increase in magnocellular neuron membrane excitability and firing activity[43]. As A-type potassium channels can modulate dendritic calcium entry and excitability, their inhibition initiated

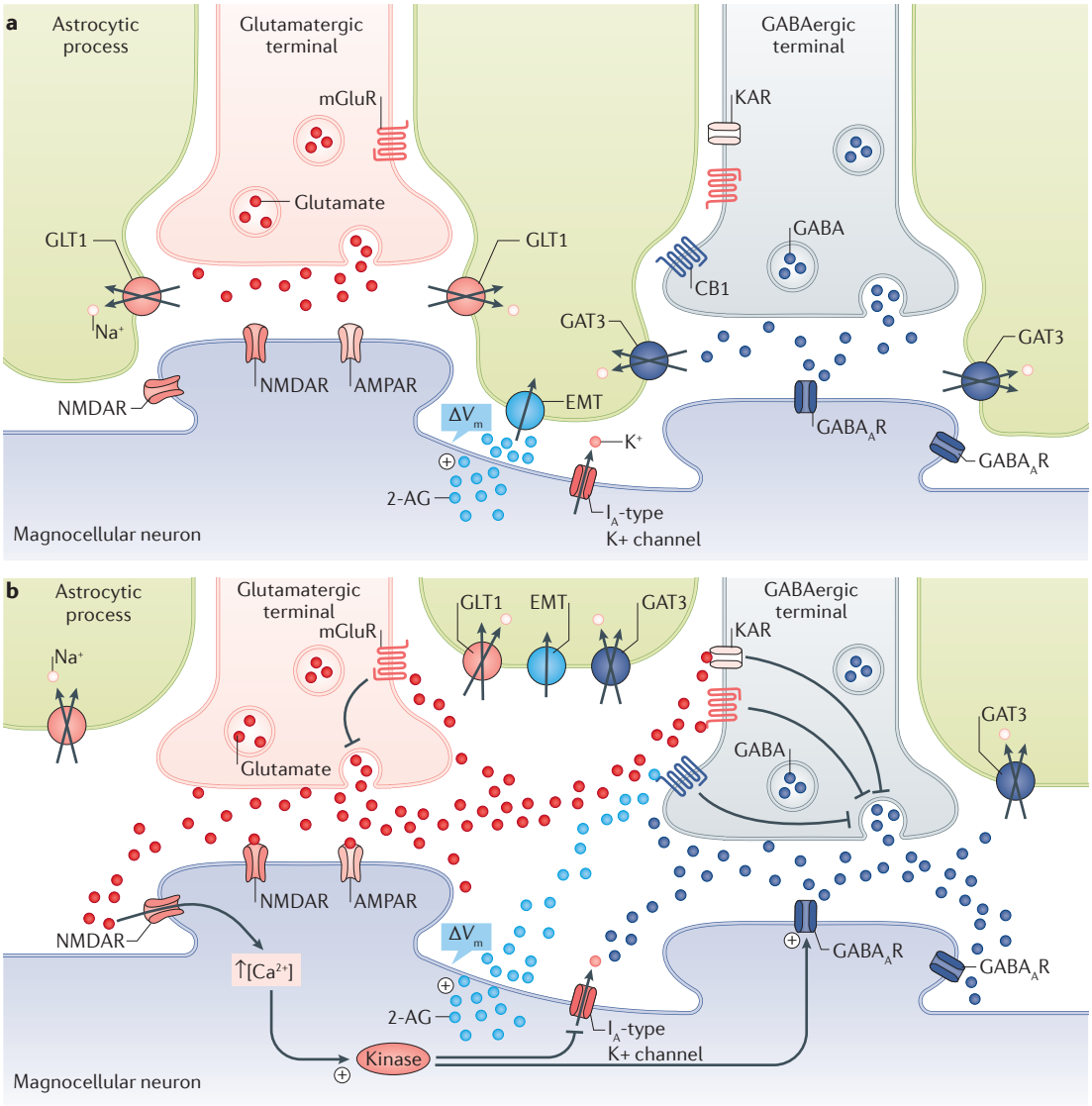


Figure 2 | **The effects of the structural plasticity of astrocytes in the magnocellular neurosecretory system on the extracellular concentration and diffusion of transmitters. a** | Astrocytic processes envelop synapses and take up transmitters through the activity of transporters such as glutamate transporter 1 (GLT1), endocannabinoid membrane transporter (EMT) and GABA transporter 3 (GAT3), decreasing their concentration and diffusion through the extracellular space. At the glutamatergic terminal, glutamate that is released into the synaptic cleft targets the postsynaptic NMDA receptor (NMDAR) and the AMPA receptor (AMPAR). Excess glutamate is quickly removed from the synaptic cleft by the GLT1 located on astrocytic processes, thereby limiting the diffusion of the neurotransmitter through the extracellular space[35]. During membrane depolarization (ΔV_m), induced by a voltage step applied during whole-cell patch clamp recording, magnocellular neurons can produce and release the endocannabinoid 2-arachidonoylglycerol (2-AG)[50], which is an inhibitory retrograde messenger. EMT on astrocytic processes transports 2-AG from the synaptic cleft into the astrocytic process, which prevents 2-AG from diffusing away from the synapse and from binding to presynaptic cannabinoid receptor 1 (CB1) located on GABAergic terminals. At the GABAergic synapse, GABA released into the synaptic cleft targets the postsynaptic $GABA_A$ receptor ($GABA_AR$). GAT3 on astrocytic processes takes up GABA into astrocytic processes, therefore preventing excess GABA from diffusing away from its release site[42,44,45]. **b** | During physiological challenges, such lactation or dehydration, the withdrawal of astrocytic processes results in increases in the extracellular concentrations of 2-AG, GABA and glutamate and facilitates their diffusion through the extracellular space. Excess glutamate around the synapse can activate presynaptic metabotropic glutamate receptors (mGluRs) to inhibit glutamate release[35,36]. Glutamate can also diffuse away from the synapse to target presynaptic kainate receptors (KAR)[40] and metabotropic glutamate receptors[33] located on GABAergic terminals and inhibit GABA release. Glutamate can also act postsynaptically on extrasynaptic NMDARs. Calcium (Ca^{2+}) entry through extrasynaptic NMDARs increases the intracellular concentration of calcium in the magnocellular neuron, which stimulates kinase activity and results in the inhibition of the I_A-type K^+ channel[43] and the potentiation of $GABA_AR$ activation[38]. During the withdrawal of astrocytic processes, 2-AG released by the magnocellular neuron during membrane depolarization can diffuse towards the presynaptic CB1 located on GABAergic terminals to inhibit GABA release[50]. Similarly to glutamate, excess GABA around the synapse caused by the withdrawal of astrocytic processes can act postsynaptically on the extrasynaptic $GABA_ARs$[42,45].

by NMDA receptor activation could help potentiate dendritic peptide release — a process that is important for maintaining neuronal network behaviour during physiological challenges[43].

GABA. Astrocytes in the supraoptic nucleus and paraventricular nucleus can also modulate extracellular concentrations of the inhibitory neurotransmitter GABA through the activity of GABA transporters[42,44] (FIG. 2) and vesicular GABA transporters[45]. For example, a study that investigated the pharmacological blockade of GABA transporter 3 in astrocytes reported the presence of a tonic inhibitory GABAergic current in magnocellular neurons[42]. This tonic inhibitory current, specifically mediated by extrasynaptic $GABA_A$ receptors, led to a persistent membrane hyperpolarization that reduced the excitability of magnocellular neurons[42]. In addition, a hypo-osmotic challenge in living acute hypothalamic slices can transiently inhibit the firing of vasopressin-secreting neurons in the supraoptic nucleus through an increase in the expression of astrocytic vesicular GABA transporters, which enhances GABA release[45]. These data further support the astrocytic control of ambient GABA levels in the magnocellular secretory system. Interestingly, some researchers have suggested that β-alanine, an astrocytic osmolyte that acts as an endogenous inhibitor of GABA transporter 3, is also released during hypo-osmotic stress[45,46]. Therefore, the timely coordination of these two astrocytic mechanisms (increase in astrocytic GABA release and reduction in GABA uptake) could result in a transient increase in extracellular levels of GABA, potentiating the GABAergic inhibition of vasopressin-secreting neurons during the early stages of hypo-osmotic stress[45].

Endocannabinoids. In addition to their involvement in the regulation of extracellular glutamate and GABA levels, astrocytes can regulate ambient levels of neuromodulators, including endocannabinoids. In the brain, endocannabinoids suppress glutamatergic and GABAergic transmission[47]. Anandamide and 2-arachidonoylglycerol, which are the major endocannabinoids in the central nervous system, are synthesized in the postsynaptic element following an increase in cell excitation[47]. These endocannabinoids mainly act as retrograde messengers through presynaptic type 1 cannabinoid receptors to inhibit neurotransmitter release[47–49].

A 2013 study in rats showed that astrocytes in the supraoptic nucleus can control inhibitory GABAergic transmission by taking up extracellular endocannabinoids via endocannabinoid membrane transporters[50]. The authors reported that the endocannabinoid-mediated suppression of GABAergic transmission, which was triggered by the depolarization of magnocellular neurons in the supraoptic nucleus, only occurred during chronic dehydration, when astrocytic processes were withdrawn from synapses[50]. This activity-dependent inhibitory effect on GABA release was mediated by the actions of 2-arachidonoylglycerol on the type 1 cannabinoid receptor[50] (FIG. 2). The inhibitory effects on GABAergic transmission were abolished in dehydrated rats when extracellular diffusion was impeded by the introduction of dextran — a large, neutral, membrane-impermeant molecule — into the extracellular space, further implicating the astrocytic environment in this phenomenon[50]. Importantly, the inhibitory effect of endocannabinoids on GABA release can be experimentally induced in hydrated rats by blocking the metabolism and functions of astrocytes with the glial toxin fluorocitrate. These data indicate that the glial reuptake of endocannabinoids might be involved in this process[50].

In line with the latter supposition, the pharmacological blockade of endocannabinoid reuptake in normally hydrated rats also reduces GABA transmission[50]. Of note, a similar endocannabinoid-mediated suppression of synaptic transmission also targets glutamatergic synapses in the supraoptic nucleus[32,51,52]. Although this mechanism occurs during normal conditions and does not depend on glial plasticity, it could serve, together with the endocannabinoid-mediated suppression of GABA release, to dampen the surge of excitation that occurs in magnocellular neurons in the supraoptic nucleus during chronic dehydration[53].

Overall, these studies suggest that the morphological plasticity of astrocytes in the magnocellular neurosecretory system can influence the actions of neurotransmitters (glutamate and GABA) and neuromodulators (endocannabinoids) during physiological and pathological conditions (FIG. 2). These studies also reveal the major role of astrocytes in controlling the heterosynaptic crosstalk between glutamatergic and GABAergic transmission in the magnocellular system, a process that is essential for adjusting neuronal activity to hormonal demand.

Release of gliotransmitters

d-Serine. The retraction of astrocytic processes in the supraoptic nucleus of lactating rats results in a reduction in the levels of extracellular D-serine[54], an amino acid identified as one of the main gliotransmitters released by astrocytes[55]. Given that D-serine acts as an endogenous co-agonist of the NMDA receptors[56,57] (FIG. 3), the direct consequence of a decrease in the availability of D-serine at the synapse is reduced synaptic NMDA receptor function. The reduction in synaptic NMDA receptor function is accompanied by an alteration in all forms of synaptic plasticity mediated by NMDA receptors, such as long-term potentiation and long-term depression[54].

These compelling data indicate that neuron–glia communication mediated by D-serine in the supraoptic nucleus actively participates in the processing of information by modulating excitatory neurotransmission in rats. Continuous suckling causes an upregulation in excitatory neurotransmission resulting in the sensory information (a pup suckling on the teat) being relayed to oxytocin neurons[13,14], which initiates the burst firing of oxytocin-secreting neurons[13,14]. Burst firing is critical for triggering the pulsatile release of oxytocin and milk ejection[58]. Combined with an increase in ambient glutamate resulting from reduced glial coverage, the control of extracellular D-serine by astrocytes could contribute to the modulation of excitatory neurotransmission during the milk-ejection reflex[8].

Glial coverage
Degree of ensheathment (physical apposition) of a synapse or a soma by peripheral astrocytic processes.

GABA transporters
Transporters that are involved in the synaptic reuptake of GABA.

Vesicular GABA transporters
Transporters that are involved in the vesicular packaging of GABA.

Heterosynaptic crosstalk
Dialogue between two synapses of different natures, in which the activity of one influences the other.

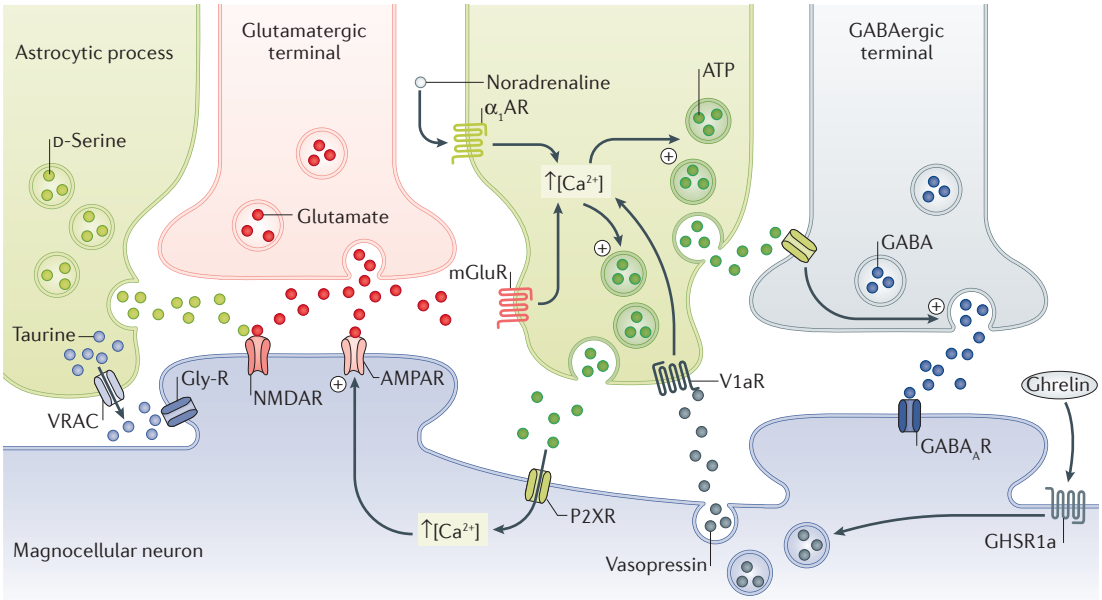


Figure 3 | **Gliotransmission in the magnocellular neurosecretory system.** Astrocytic processes enwrapping synapses in the magnocellular neurosecretory system release several gliotransmitters, such as D-serine, taurine and ATP. D-Serine released by astrocytes targets the postsynaptic NMDA receptor (NMDAR) and acts as a co-agonist to promote NMDAR function[54]. During hypo-osmotic conditions, astrocytes release taurine through the volume-regulated anion channel (VRAC), which targets the extrasynaptic glycine receptor (GlyR) and inhibits the activity of magnocellular neurons[59]. The activation of the astrocytic metabotropic glutamate receptor (mGluR) by glutamate released by the presynaptic glutamatergic terminal[67], or the astrocytic α_1-adrenergic receptor (α_1AR) by noradrenaline released by noradrenergic inputs[68] during an osmotic challenge, increases intracellular calcium (Ca^{2+}) concentrations. This increase in Ca^{2+} triggers the release of ATP, which activates the postsynaptic P2X purinoceptor (P2XR) located on magnocellular neurons[68]. Ca^{2+} influx through the P2XR into the magnocellular neuron promotes the insertion of the AMPA receptor (AMPAR) at the cell surface and potentiates synaptic efficacy[68]. Of note, during physiological challenges, such as lactation or dehydration, the withdrawal of glial coverage from the synapse results in decreases in the levels of D-serine[54], taurine[59] and ATP[68] in and around the synapse, thereby decreasing the activity of NMDARs[54], GlyRs[59] and AMPARs[68], respectively (see main text for details). ATP is also released by astrocytes following the activation of the vasopressin 1a receptor (V1aR) by vasopressin and acts on presynaptic P2XR located on GABAergic terminals to stimulate GABA release[69]. In this case, vasopressin is postsynaptically released from dendrites of magnocellular neurons following the activation of the growth hormone secretagogue receptor 1a (GHSR1a) by the peripheral orexigenic hormone, ghrelin[69].

Taurine. In addition to D-serine, taurine, another free amino acid, has been identified as a gliotransmitter in the magnocellular neurosecretory system[59]. Taurine, which is highly expressed by neurons and astrocytes[60], acts as an agonist of glycine receptors[61] and thereby exerts inhibitory actions in the central nervous system[61]. Taurine is released via volume-regulated anion channels following the swelling of glial cells under hypo-osmotic conditions[62] and inhibits the firing of magnocellular neurons in the supraoptic nucleus through the activation of extrasynaptic glycine receptors[63,64]. Therefore, taurine might be involved in the regulation of body fluid homeostasis[65].

An elegant study performed in rats identified astrocytes as a potential source of taurine[59] (FIG. 3). The authors reported a tonic, glycine receptor-mediated inhibition of the firing of vasopressin-secreting neurons in the supraoptic nucleus[59]. Furthermore, this receptor-mediated inhibition was suppressed when taurine was depleted and following the administration of fluorocitrate, which blocks astrocytic metabolism[59], suggesting the existence of functional taurinergic gliotransmission in the supraoptic nucleus. In addition, the authors showed that volume-regulated anion channels are completely absent from neurons in the supraoptic nucleus but present in astrocytes[59], indicating that these glial cells are the sole source of taurine in this region. The latter hypothesis is further supported by the fact that the tonic inhibition mediated by glycine receptors is severely attenuated under dehydration[59]. By triggering the withdrawal of the glial coverage of magnocellular neurons, dehydration decreases the extracellular concentrations of astrocytic taurine. Altogether, these data indicate that rat astrocytes act as direct osmosensors and relay this information to vasopressin-secreting neurons via the release of taurine, thus contributing to the regulation of body fluid homeostasis.

ATP. ATP, which is the most ubiquitous gliotransmitter[66], is another important modulator of the excitability of magnocellular neurons[67,68]. In the context of osmoregulation, astrocytic ATP can relay information from brain regions containing osmosensitive neurons that send noradrenergic and glutamatergic projections to

the supraoptic nucleus and paraventricular nucleus[67,68]. For example, the stimulation of α_1-adrenergic receptors[68] and metabotropic glutamate receptors 1 and 5 (REF. 67) in astrocytes of the paraventricular nucleus increases intracellular calcium and triggers the release of ATP. The ATP released from astrocytes in turn acts on calcium-permeable P2X purinoceptor channels located on magnocellular neurons of the paraventricular nucleus (FIG. 3). The activation of P2X7 receptor channels enables calcium influx, which promotes the insertion of postsynaptic glutamatergic AMPA receptors into the cell membrane and increases synaptic strength and membrane excitability[68]. Most importantly, in dehydrated rats, the noradrenergic input-dependent increase in synaptic strength is compromised during the retraction of the astrocytic processes from magnocellular synapses, which probably causes a decrease in the availability of extracellular ATP[68]. These data advance the notion that this astrocyte-dependent mechanism contributes to osmoregulation.

A 2014 study reported that ATP gliotransmission is an intermediary mechanism that relays the action of peripheral ghrelin onto neurons that integrate both energy homeostasis with fluid homeostasis[69]. Ghrelin, which is the orexigenic hormone, is produced by the digestive tract before a meal[70,71] and during fasting[72]. Of note, by stimulating the secretion of vasopressin[73], ghrelin can affect drinking behaviour and blood osmolality[74], in addition to feeding behaviour[75]. The authors of the study reported a complex neuronal–glial mechanism that is recruited by ghrelin to activate vasopressin-secreting neurons in the paraventricular nucleus and regulate body fluid homeostasis[69] (FIG. 3). Specifically, ghrelin acts on the active form of the growth hormone secretagogue receptor 1a, which is present on vasopressin-secreting neurons in the paraventricular nucleus, to induce the release of vasopressin from their dendrites[69]. This vasopressin then acts as a retrograde messenger to stimulate presynaptic GABAergic neurons[69]. Interestingly, once released, vasopressin stimulates an increase in intracellular calcium levels in astrocytes by activating the Gq protein-coupled vasopressin V1a receptor, which triggers the release of ATP[69]. In turn, astroglial ATP acts directly on P2X purinoceptor channels located on presynaptic GABAergic neurons to stimulate the release of GABA, which then feeds back on vasopressin-secreting neurons in the paraventricular nucleus[69].

Given that prior studies have shown that GABA could be excitatory in vasopressin-secreting neurons of the adult rat paraventricular nucleus[76], the main consequence of this glial ATP-induced synaptic GABA release is an increase in the firing rate of vasopressin-secreting neurons[69]. Support for the physiological importance of this mechanism comes from the fact that the effect of ghrelin on GABAergic synaptic inputs is potentiated during fasting[69], a physiological state during which ghrelin secretion is increased[72]. Presynaptic GABA release, triggered by ghrelin during food deprivation, could facilitate the release of vasopressin and the retention of water in order to maintain critical hydration and minimize the loss of essential electrolytes.

Although the mechanism by which peripheral ghrelin is conveyed to the paraventricular nucleus is unclear[77], the aforementioned data identify ghrelin as an endocrine metabolic signal capable of recruiting, in a nutritional-state-dependent manner, a neuronal–glial circuit. In this context, the role of the neuronal–glial circuit is to specifically activate excitatory GABA inputs to vasopressin-secreting neurons in the paraventricular nucleus in order to coordinate homeostasis of both energy and body fluid. An important point to note, however, is that the putative excitatory effect of GABA on vasopressin-secreting neurons in the paraventricular nucleus described above[76] stands in contradiction to earlier works[78,79]. Furthermore, these earlier data were re-examined in 2015 using a variety of approaches[80]. The authors of the earlier studies and the study that re-evaluated the data reported that GABA has an inhibitory effect on the firing of vasopressin-secreting neurons in the paraventricular nucleus. These data call into question the notion that GABA could have an excitatory effect on vasopressin neurons, with important implications for our understanding of the network basis for the regulation of magnocellular neurosecretory cells.

Once released, ATP can also be rapidly converted into adenosine by a combination of extracellular enzymes[81]. Adenosine exerts a variety of effects on neuronal and synaptic activity via four subtypes of G-protein-coupled adenosine receptors (A_1, A_{2A}, A_{2B} and A_3)[82]. Magnocellular neurons express A_1 and A_{2A} receptors[83–85], and endogenous adenosine can therefore modulate their activity. For instance, the antagonism of A_1 receptors increases the firing rate of phasic vasopressin-secreting neurons[86,87] and modulates the intrinsic properties of oxytocin neurons towards a shortening of bursts and the termination of milk-ejection bursts[86,87]. Endogenous adenosine also acts presynaptically on A_1 receptors to inhibit excitatory and inhibitory synaptic inputs to magnocellular neurons[88]. In addition to its inhibitory effects mediated by A_1 receptors, endogenous adenosine exerts excitatory effects on magnocellular neurons by causing a depolarization-induced increase in firing rate via the activation of postsynaptic A_{2A} receptors[83,84]. Taken together, these results demonstrate the importance of endogenous adenosine in modulating the activity of magnocellular neurons; however, whether astrocyte-derived ATP represents one of the main sources of adenosine in the magnocellular neurosecretory system as in other brain regions[81,89] remains unclear.

The aforementioned studies indicate that, in response to physiological challenges, astrocytes modulate neuronal network activity in the magnocellular secretory system by releasing neuroactive substances and influencing their effects through morphological plasticity (FIGS. 2,3). Therefore, astrocytes from the supraoptic nucleus and paraventricular nucleus actively participate in the regulation of hormonal secretion during suckling, dehydration and fasting. An important note, however, is that glia in other brain regions also release some of the neuroactive substances released by astrocytes in the magnocellular secretory system[55]. The aforementioned astrocytic plasticity mechanisms recruited under physiological challenges, however, remain specific to the supraoptic nucleus

and paraventricular nucleus. Morphological plasticity is also observed in brain areas such as the hippocampus, but its functional role is still unknown[90,91].

Parvicellular neuroendocrine system

In addition to magnocellular neurons, the hypothalamus contains a second set of neurosecretory neurons, the parvicellular neuroendocrine neurons. These neurons synthesize and release several neuropeptides and neurotransmitters into the pituitary portal circulation that regulate the activity of the anterior pituitary gland[92,93] (FIG. 1). The parvicellular neuroendocrine neurons are scattered around the third ventricle, from the preoptic area towards the tuberal region of the hypothalamus. In this section, we focus on two specific populations of parvicellular neurons that are known to be influenced by glial cells — neurons releasing TSH-releasing hormone (TRH) and neurons releasing gonadotropin-releasing hormone (GnRH).

TRH neuroendocrine system

Hypothalamic glia and energy metabolism. Energy homeostasis is the control of numerous neuroendocrine functions that integrate metabolic feedback and adapt the response of the organism to physiological demands[94]. Studies conducted in the past 5 years have revealed the role of neuron–glia interactions in the regulation of energy homeostasis[94–97]. For instance, we now know that hypothalamic astrocytes can sense metabolic signals. Hypothalamic astrocytes can sense insulin and leptin and co-regulate behavioural responses and metabolic processes via the control of brain glucose uptake and glial ensheathment of the anorexigenic proopiomelanocortin neurons in the arcuate nucleus of the hypothalamus, respectively[98–100]. Intriguingly, studies from 2017 suggest that diet-induced structural changes in the distal processes of hypothalamic astrocytes involve the IKKβ–NF-κB signalling pathway[101,102], which is also linked to hypothalamic inflammation[94]. Astrocytes also supply energy metabolites, such as glucose and lactate, through gap-junction-mediated astrocytic networks to sustain the activity of specific neuronal populations in the hypothalamus, including the wake-promoting orexin neurons in the lateral hypothalamic area[103].

Tanycytes also have a role in energy homeostasis. They undergo nutritional-status-dependent molecular changes that alter their barrier properties, which are critical for the contact between circulating energy metabolites and neurons in the arcuate nucleus of the hypothalamus in the adaptive metabolic response to fasting[104]. In parallel, tanycytes are the gatekeepers for the hypothalamic entry of circulating metabolic hormones such as leptin[105] and ghrelin[106]. In addition, tanycytes are central to the feedback effects of thyroid hormone on TRH-expressing hypophysiotropic neurons (see below).

Interactions between glia and TRH neurons: a nodal role in energy homeostasis. TRH-secreting parvicellular neuroendocrine neurons, in the medial and caudal portions of the paraventricular nucleus synthesize and release TRH[107,108] (FIG. 1). TRH-secreting neuroendocrine neurons project to the external zone of the median eminence, a neurohaemal organ located at the ventral surface of the tuberal region, where they release TRH into the hypothalamo–pituitary portal system. TRH reaches the anterior pituitary and acts on thyrotropic cells to stimulate the synthesis and secretion of TSH. In turn, TSH stimulates the thyroid gland to synthesize and secrete T_4. Of note, T_4 is converted to the active T_3 by type 1 iodothyronine deiodinase (DIO1) and type 2 DIO (DIO2). An additional deiodination by type 3 DIO (DIO3) is necessary to produce the inactive T_2. The functions of T_4 thus rely on the activity of DIO1, DIO2 and DIO3 (REF. 109). Through its peripheral and central actions, T_3 regulates a large range of functions such as tissue growth and differentiation, lipid metabolism and energy homeostasis[108,110]. In addition, T_3 controls the levels of TRH through a classic negative feedback loop by acting directly on TRH-secreting neurons[108].

Several lines of evidence suggest that tanycytes are involved in the regulation of the hypothalamic–pituitary–thyroid (HPT) axis, primarily by regulating the release of TRH[108]. An interesting point to note is that as with GnRH axons, tanycytic endfeet intertwine with the axon terminals of TRH-secreting neurons within the external zone of the median eminence (described in further detail below)[111]. Tanycytes express pyroglutamyl peptidase II (also known as TRH-degrading ectoenzyme), which controls TRH degradation[112], suggesting that tanycytes can directly regulate the bioavailability of TRH before its entry into the pituitary portal circulation[108].

A 2017 paper demonstrated that tanycytes regulate the HPT axis *in vivo* by showing that the activation of TRH receptor 1 elevates intracellular calcium levels in tanycytes of the median eminence through a Gαq/11-coupled pathway. The authors reported that the activation of TRH receptor promoted the outgrowth of the tanycytic processes engulfing TRH neuroendocrine terminals and an upregulation of pyroglutamyl peptidase II[113]. The result of tanycytic process outgrowth and pyroglutamyl peptidase II upregulation might be the blockade of TRH release into the portal blood vessels. Indeed, the selective blunting of Gαq/11 signalling in tanycytes increases circulating TSH levels when TRH neurons are activated[113].

Tanycytes of the median eminence can also contribute to the feedback regulation of the HPT axis[108]. In fact, these tanycytes are the major DIO2-expressing cells in the brain[114–116]. Interestingly, results from a 2013 study suggest the critical DIO2-mediated conversion of T_4 to T_3 takes place within tanycytes of the tuberal region of the hypothalamus, not astrocytes[117]. In addition, tanycytes express several transporters for the uptake of T_4 and T_3, including the organic anion-transporting polypeptide OATP1C1 (REFS 118,119) and monocarboxylate transporter 8 (REF. 120). Therefore, tanycytes in the median eminence can take up T_4 from the circulation or from the cerebrospinal fluid and convert it to the active T_3 (REF. 108) — an important process for negative feedback on TRH synthesis[121–123]. Once released from the tanycytic endfeet, T_3 can be taken up by neighbouring TRH nerve terminals and transported to their cell bodies[124] to inhibit TRH transcription[108].

T_3 derived from tanycytes could also contribute to energy homeostasis by acting directly on the arcuate nucleus of the hypothalamus[108,110], which contains the orexigenic neurons that secrete neuropeptide Y (NPY) and agouti-related protein (AgRP) and the anorexigenic proopiomelanocortin-secreting neurons[125] — the two main populations of neurons in the regulation of energy expenditure and food consumption. In line with this hypothesis, studies have shown that energy demand caused by food deprivation upregulates DIO2 expression in tanycytes of the median eminence, leading to a global increase in concentration of T_3 in the hypothalamus[126]. The upregulation of DIO2 and subsequent increase in concentrations of T_3 is critical for the orexigenic response of NPY/AgRP neurons to fasting[126]. Consistent with these studies, the central administration of T_3 increases food intake in rats[127].

The control of hypothalamic T_3 bioavailability by tanycytes in the context of energy homeostasis is further supported by the fact that tanycytes exhibit photoperiodic changes in DIO2 and DIO3 gene expression[128]. For instance, DIO2 is upregulated while DIO3 is downregulated in tanycytes from seasonal birds and rodents, such as the quail and Djungarian hamster, during the long photoperiod. This photoperiodic shift in the expression of DIO2 and DIO3 results in an increase in the bioavailability of T_3 in the hypothalamus[129]. An increase in T_3 bioavailability promotes appetite and energy storage in the form of fat, which allows seasonal animals to adapt to the short photoperiod when food becomes rare[128]. In addition, photoperiodic changes in T_3 bioavailability alter the reproductive activity of seasonal birds and rodents so that offspring are born at the most advantageous time of year for their survival[130]. An intriguing article from 2017 even shows that tanycytes in the Siberian hamster could have a fundamental role during fetal development in the programming of the reproductive and metabolic life of the progeny by relaying photoperiodic information conveyed by maternal melatonin to the fetus[131].

Tanycytes could therefore constitute a crucial crossroads for interactions between neural circuits controlling the survival of the individual (by regulating energy metabolism) and those controlling the survival of the species (by regulating reproduction).

GnRH system: puberty and fertility

Sexual maturation, puberty and adult fertility all rely on the activity of a small population of neurons that secrete GnRH[132]. A deficit in the production, secretion or action of GnRH causes incomplete or absent puberty and infertility, a condition named congenital hypogonadotropic hypogonadism in humans[133]. In rodents, the cell bodies of GnRH-secreting neurons are diffusely distributed in the forebrain and are enriched in the preoptic region; in humans and other primates, they are also present in the tuberal region of the hypothalamus[134,135]. GnRH-secreting neurons send axon terminals to the external zone of the median eminence. Here, GnRH is released directly into the pituitary portal blood circulation, where it is transported to act on the anterior pituitary to control the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH)[136,137]. In turn, LH and FSH target the gonads to stimulate gametogenesis and the production of sex steroid and peptidic hormones, which signal back to the hypothalamic–pituitary–gonadal (HPG) axis. Within the brain, sex steroids influence GnRH secretion via neuroendocrine feedback loops.

In addition to trans-synaptic inputs, a body of evidence spanning >20 years suggests that glial cells regulate GnRH secretion. In the next section, we discuss the studies that have identified astrocytes and tanycytes as regulators of the molecular and cellular mechanisms involved in the control of GnRH neuronal activity and secretion.

Astrocyte–GnRH neuron communication

Morphological plasticity and astrocyte-to-neuron signalling pathways. As with astrocytes in the supraoptic nucleus and paraventricular nucleus in rats, astrocytes in the tuberal region of the hypothalamus undergo morphological rearrangements following physiological stimuli in non-human primates. A 1991 study showed that the steroid milieu could affect the glial coverage of GnRH-secreting neurons along with the number of synaptic inputs onto their cell bodies[138]. In this study, ovariectomy in the rhesus monkey increased the glial coverage of GnRH-secreting neurons while decreasing the number of synaptic contacts with their somata. This phenomenon was reversed by oestrogen replacement[138].

Data from a neuroanatomical study conducted in 2007 show that tight morphological interactions between astrocytes and GnRH neuronal cell bodies also occur in the human hypothalamus[139]. Advanced metabolic imaging techniques have provided further insight into neuron–glia interactions within the GnRH neural network. For example, neuron–glia interactions might be subject to sex-steroid-related plastic changes in women throughout the artificial menstrual cycle[140]. Activation of the HPG axis during the pill-free interval of oral contraceptive use is associated with transient microstructural and metabolic changes in the female hypothalamus, as assessed by water diffusion and proton magnetic resonance spectra measurements[140]. In the tuberal region of the rodent brain, the arcuate nucleus of the hypothalamus, which is closely involved in the control of GnRH secretion in rodents[132], also undergoes striking changes in glial structure throughout the oestrous cycle[141]; however, whether or not these morphological rearrangements in the arcuate nucleus of the hypothalamus are of functional importance for the activity of the HPG axis remains to be explored.

Pioneering studies conducted >40 years ago identified prostaglandin E_2 as a powerful regulator of reproductive function[6,11]. The central injection of prostaglandin E_2 directly into the preoptic area of rats, where GnRH neuron cell bodies are located, strikingly increases plasma levels of LH[142]. Data on the effects of blocking the endogenous synthesis of prostaglandin E_2 further support its physiological role in reproductive function. In one study, investigators blocked prostaglandin E_2 synthesis using cyclooxygenase inhibitors, which they delivered into

Photoperiodic changes
Annual changes (homeostatic process) that occur in seasonal species based on day length in order to adapt to seasonal cycles.

the preoptic and tuberal hypothalamic regions of adult rats. The authors reported that following cyclooxygenase inhibitor administration, the pulsatile release of LH was perturbed, as were the oestrogen-induced surge in LH[143] and ovulation[144].

In addition, prostaglandin E_2 is one of the key factors regulating the onset of puberty[145]. For instance, the progressive increase in oestradiol production by the developing ovaries, which triggers the first preovulatory surge of GnRH and LH at puberty onset, is correlated with a progressive increase in prostaglandin E_2 synthesis[146]. In agreement with these data, a deficiency in prostaglandin E_2 synthesis in the hypothalamus of female rats during early life strikingly delays the onset of reproductive capacity by up to 1 week (puberty in rats occurs at approximately 38 days of age)[147]. Astrocytes are also involved in this prostaglandin E_2-mediated activation of the reproductive axis during postnatal development. A 2003 study showed that the selective genetic impairment of one of the signalling pathways leading to prostaglandin E_2 synthesis in astrocytes causes delayed puberty in mice[148].

A growing body of evidence identifies astrocytes as the major hypothalamic source of prostaglandin E_2, which can directly act on GnRH-secreting neurons through prostaglandin E_2 membrane receptors during postnatal sexual maturation[6]. Circulating oestrogens seem to tightly regulate prostaglandin E_2 synthesis in astrocytes. In addition, synthesis requires the activation of astrocytic autocrine or paracrine growth factor-dependent glial signalling pathways in astrocytes. These data suggest the activation of the erythroblastosis family of receptor tyrosine-protein kinases (ERBB1 (also known as EGFR), ERBB2, ERBB3 and ERBB4) is also required[6]. Although ERBB1, ERBB2 and ERBB4 and some of their ligands (transforming growth factor α and neuregulins) are absent in GnRH-secreting neurons, they are highly expressed in hypothalamic astrocytes of rodents and humans[149,150]. Importantly, the progressive increase in gonadal steroids at puberty onset causes an increase in the expression of ERBBs and their ligands, a phenomenon that is restricted to the hypothalamus[145]. Data showing that the selective genetic disruption of the signalling pathways of ERBB1, ERBB4 or both delays the onset of reproductive capacity in mice further supported the importance of ERBBs in puberty onset[148,151]. In addition, the ligand-mediated activation of ERBBs in hypothalamic astrocytes elicits GnRH secretion from GnRH-releasing neuronal cell lines or median eminence explants by triggering the astrocytic release of prostaglandin E_2 (REFS 148,151).

The aforementioned processes for communication from astrocytes to GnRH-secreting neurons involving glial ERBB4 activity and prostaglandin E_2 release are important for the onset of mini-puberty, which occurs during the second week of postnatal life in mice[148]. Mini-puberty is the first gonad-independent centrally driven activation of the HPG axis after birth both in humans[152] and rodents[145]. Indeed, the selective expression of a dominant-negative form of ERBB4 in astrocytes blunts the infantile FSH surge[148]. As this surge in FSH stimulates the growth of the first pool of ovarian follicles destined to ovulate at puberty[145], the blunting of it results in impaired postnatal sexual maturation in female mice[148]. During this critical period in infantile development, a dramatic change in the production of hypothalamic GnRH also occurs. This change in GnRH is operated by a switch in microRNA expression within GnRH-secreting neurons themselves and that is key to the GnRH-fuelled run-up to puberty initiation[153,154]. Interestingly, one of the microRNAs that are upregulated in GnRH-secreting neurons at mini-puberty is miR-7a[155], which has been shown to modulate the prostaglandin signalling pathway[156]. Knocking out the gene encoding miR-7a, however, results in hypogonadotropic hypogonadism in mice[156]. Altogether, these findings raise the intriguing possibility that prostaglandin signalling, which is potentially set in motion by a dialogue between astrocytes and GnRH-secreting neurons, and miRNAs might be involved in the pathophysiology of certain cases of idiopathic hypogonadotropic hypogonadism in humans[157].

Interestingly, the activation of ERBBs, which also naturally occurs in the hypothalamus around the time of puberty[145], can induce morphological rearrangements in hypothalamic astrocytes *in vitro*[149]. These data raise the possibility that ERBB signalling might influence the glial coverage of GnRH-secreting neurons *in vivo*[4]. Such a phenomenon could affect neurotransmitter spillover around GnRH cell bodies and dendrites, and consequently influence the trans-synaptic control of GnRH-secreting neurons. Two studies have demonstrated that neurotransmitter spillover around synapses can also cause a local release of prostaglandin E_2 by astrocytes[158,159]. In line with these studies, glutamate, which increases GnRH secretion[160] and accelerates the onset of puberty[161,162], co-activates metabotropic glutamatergic and AMPA glutamatergic receptors in hypothalamic astrocytes. The activation of these receptors initiates a signalling cascade that allows the recruitment of ERBBs and their ligands at the cell surface[150] and leads to the synthesis and release of prostaglandin E_2 by astrocytes[150], which can then signal back to GnRH-secreting neurons (FIG. 4).

Intriguingly, studies have shown that crosstalk involving astrocytic prostaglandin E_2 could also occur between the oxytocin-expressing magnocellular neuroendocrine system and GnRH-secreting neurons during sexual maturation. Oxytocin seems to act on hypothalamic astrocytes, which express the oxytocin receptor and respond to oxytocin by releasing prostaglandin E_2 in the immature female hypothalamus, thus accelerating pulsatile GnRH release in the rat[163]. Of note, the median eminence is another site where prostaglandin E_2 action regulates GnRH secretion[4,5]. For instance, *in vivo* studies in rats have shown that the injection of prostaglandin E_2 into the tuberal region, where GnRH axon terminals are located, increases plasma levels of LH[142]. The injection of cyclooxygenase inhibitors to block prostaglandin E_2 synthesis into the same region, by contrast, perturbs ovulation[144,164]. Furthermore, data from *in vitro* studies suggest that prostaglandin E_2 stimulates GnRH release from rat median eminence explants containing GnRH-secreting neuroendocrine terminals but not GnRH cell bodies. The mechanism of action involves prostaglandin E_2 membrane receptors and intracellular calcium mobilization[165,166].

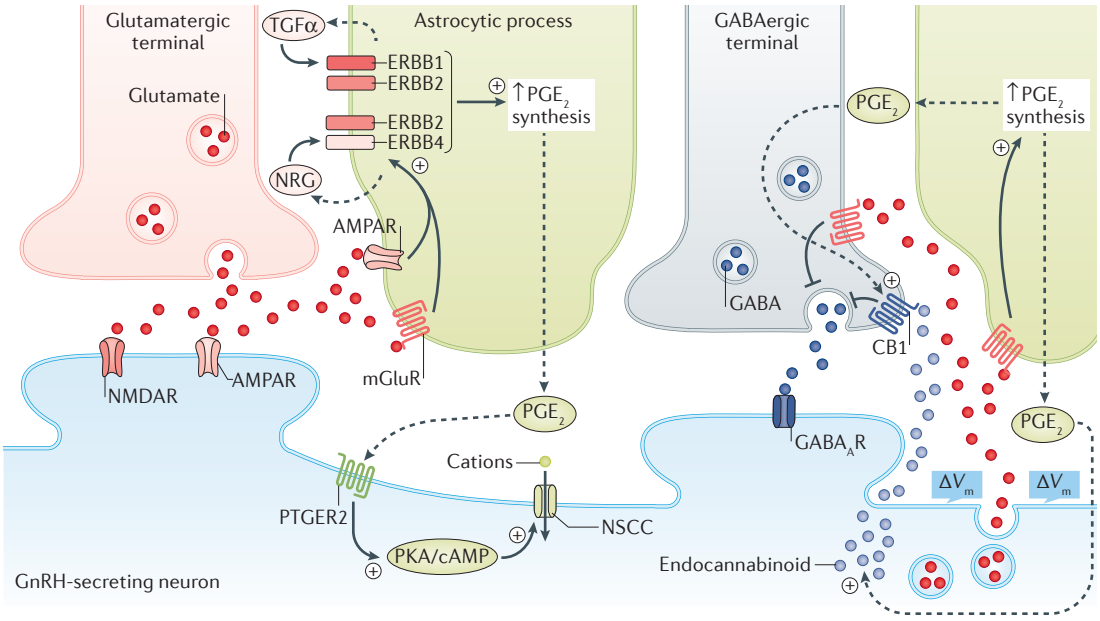


Figure 4 | **Prostaglandin E_2 as a gliotransmitter in the gonadotropin-releasing hormone (GnRH) system.** In the GnRH system, two different mechanisms, each with different effects on GnRH neuronal activity, control the release of prostaglandin E_2 (PGE_2). In the first mechanism (left hand side of the figure), the synaptic release of glutamate from the glutamatergic terminal triggers the release of PGE_2 by astrocytes via the activation of astrocytic AMPA receptors (AMPARs) and astrocytic metabotropic glutamate receptors (mGluRs)[150]. The activation of these receptors promotes the recruitment of growth factors, TGFα and neuregulin (NRG), along with their respective receptors, ERBB1 and ERBB4, to the cell membrane of astrocytes[150]. TGFα and NRG activate ERBB1/ERBB2 and ERBB4/ERBB2 heterodimers, respectively, thereby stimulating the synthesis and release of PGE_2 (REF. 150). In turn, PGE_2 acts on PGE_2 receptor (PTGER2) located on GnRH-secreting neurons, which leads to the activation of a non-selective cation channel (NSCC) through a cAMP/protein kinase A (PKA)-dependent pathway[170]. Cation influx through the NSCC induces membrane depolarization and increases firing of GnRH-secreting neurons[170]. In the second mechanism (right hand side of the figure), glutamate released from depolarized (ΔV_m) GnRH-secreting neurons triggers the release of PGE_2 from astrocytes[159]. Membrane depolarization of GnRH-secreting neurons (ΔV_m) also induces the release of endocannabinoids[159]. Glutamate and endocannabinoids activate presynaptic mGluRs and cannabinoid receptor 1 (CB1), respectively, to inhibit the release of GABA, which acts on the postsynaptic $GABA_A$ receptor ($GABA_AR$)[159]. Given that GABA is an excitatory neurotransmitter in the GnRH system, this provides a negative feedback loop in which depolarized GnRH-secreting neurons reduce their own activity by inhibiting the activity of excitatory GABAergic inputs. PGE_2 released by astrocytes following activation of mGluR can then act postsynaptically and presynaptically to increase endocannabinoid synthesis and CB1 trafficking, respectively, potentiating this local inhibitory feedback circuit[159].

Since 2011, several studies in mice and rats have reported the involvement of glial signalling molecules in the regulation of the GnRH neuroendocrine system and, in particular, the onset of female puberty[11]. Among these molecules, synaptic cell adhesion molecule (SynCAM, also known as CADM1), which is found in astrocytes and GnRH-secreting neurons, has been shown to drive the adhesiveness of astrocytes to the cell bodies of GnRH-secreting neurons[167]. In the hypothalamus, the adhesive properties of SynCAM depend on the activity of astrocytic ERBB4 (REFS 167,168). The ligand-mediated activation of ERBB4 in astrocytes triggers a physical interaction between ERBB4 and SynCAM via their intracellular domains, which in turn promotes the adhesiveness of SynCAM (REFS 167,168). In addition, SynCAM is required for the ligand-mediated activation of astrocytic ERBB4, which in turn induce the synthesis of prostaglandin E_2 and the release of GnRH from neuroendocrine terminals[168]. Data showing that the expression of SynCAM increases at puberty in female non-human primates further support the physiological importance of the adhesion and paracrine communication between astrocytes and GnRH-secreting neurons[169]. In addition, the selective disruption of the function of the intracellular domain of SynCAM delays puberty and alters both the ovarian cycle and fertility in female mice[168].

Altogether, these studies suggest that glial remodelling, crosstalk between astrocytes and excitatory neurotransmission, and adhesion and paracrine communication between astrocytes and GnRH-secreting neurons act to coordinate neuroendocrine development. The data indicate that these processes ultimately result in the timely onset of puberty and facilitate reproductive function in adults.

Gliotransmission. The role of prostaglandin E_2 in the control of GnRH secretion was described >30 years ago, but its effect on GnRH neuronal activity was not reported until 2011 (REF. 170). In this study, our group conducted patch clamp recordings in acute slices of the preoptic area of the

hypothalamus from adult GnRH–GFP transgenic mice. We demonstrated that prostaglandin E_2 depolarizes and excites >70% of GnRH-secreting neurons in male mice as well as in female mice, independent of the oestrous cycle[170]. This excitatory effect is caused by the opening of a non-selective cation channel in GnRH-secreting neurons[170]. In addition, we showed that the effect of prostaglandin E_2 is mimicked by the prostaglandin E_2 receptor 2 (PTGER2; also known as EP2) agonist butaprost[170]. These data are consistent with other studies demonstrating that adult GnRH-secreting neurons express PTGER2 (REFS 166,171).

The prostaglandin E_2-associated depolarization and excitation of GnRH-secreting neurons is mediated by the cAMP–PKA signalling pathway[170]. This pathway is coupled to PTGER2 (REF. 172) and is involved in the stimulatory effect of prostaglandin E_2 on GnRH secretion[165]. Blocking the synthesis of endogenous prostaglandin E_2 in acute slices of the preoptic area by using the cyclooxygenase inhibitor indomethacin leads to a dramatic suppression of spontaneous action potential firing in GnRH-secreting neurons[170]. Most importantly, the inhibition of astrocytic metabolism with the glial toxin fluoroacetate or the genetic blockade of astrocytic ERBB4, which decreases prostaglandin E_2 production and GnRH secretion[148,151], mimics the inhibitory effect of indomethacin on GnRH neuronal activity[170]. These data indicate that astrocytes are the main source of prostaglandin E_2 in the preoptic area. Conversely, the exogenous delivery of prostaglandin E_2 to acute slices of the preoptic area rescues the loss of activity of GnRH-secreting neurons[170]. This finding suggests that endogenous prostaglandin E_2 production by astrocytes is necessary and sufficient to sustain GnRH neuronal activity (FIG. 4).

In addition to acting directly on the cell bodies of GnRH-secreting neurons, prostaglandins of glial origin can also target the presynaptic inputs to modulate neuronal excitability[159]. Indeed, prostaglandins produced by astrocytes contribute to the local inhibitory feedback circuit between GnRH-secreting neurons and excitatory GABAergic afferents[173] by influencing the activity of both presynaptic metabotropic glutamate receptors and presynaptic type 1 cannabinoid receptors[159]. In addition, its sensitivity to the oestrogenic milieu means that this circuit might be one of the targets of oestradiol feedback effects[159]. Altogether, these studies identify prostaglandin E_2 as a major gliotransmitter in the GnRH neuroendocrine system, capable of modulating GnRH neuronal excitability by acting at both presynaptic and postsynaptic sites (FIG. 4).

Tanycytes and GnRH-secreting neurons

Morphological plasticity and underlying cellular and molecular pathways. As described above, GnRH-secreting neurons send nerve terminals towards the external zone of the median eminence, where they release GnRH directly into the fenestrated pituitary portal blood vessels. Of note, GnRH nerve terminals within the median eminence are in very close apposition to the endfeet of tanycytes[174,175]. Based on this anatomical relationship between GnRH-secreting neurons and tanycytes, some have suggested that these glia can functionally interact with the terminals of GnRH-secreting axons to influence GnRH release[174,176].

The cell bodies of tanycytes constitute the floor and the walls of the third ventricle. The tanycytes that comprise the floor send long and slender processes towards the external zone of the median eminence. Here, they border the perivascular space of the fenestrated portal capillaries and enclose GnRH neuroendocrine terminals en passant[174,175]. In contrast, tanycytes lining the walls of the third ventricle extend processes arching into the hypothalamic parenchyma and contact both neurons and microvessels with features of the blood–brain barrier[177]. Tanycytes in the median eminence undergo oestrogen-dependent morphological plasticity — a property that is essential for successful reproductive function[4,5,178]. For instance, we have shown that in female rats, the tanycytic endfeet that enwrap GnRH-secreting axon terminals retract on the day of pro-oestrus — the stage of the oestrous cycle when circulating levels of oestrogens are at their highest — just before ovulation. The retraction of tanycytic endfeet provides GnRH nerve terminals with direct access to the pericapillary space and therefore facilitates the release of GnRH into the pituitary portal circulation, which is required for the preovulatory surge in LH[179,180].

Data show that prostaglandin E_2 is also a key molecular factor underlying the changes in tanycyte structure in pro-oestrus. For instance, prostaglandin E_2 treatment promotes the retraction of tanycytic processes in primary cultures of tanycytes or median eminence explants. In living hypothalamic explants containing the median eminence, the retraction of tanycytic processes correlates with the physical progression of GnRH-secreting axon terminals towards the pericapillary space of fenestrated portal blood vessels[164]. A number of mechanisms underlie the tanycytic and astrocytic synthesis of prostaglandin E_2 in the median eminence. The first[11] involves the aforementioned activation of the neuregulin–ERBB4 signalling pathway in astrocytes[148] and TGFα–ERBB1 signalling in astrocytes and tanycytes[148,181]. The second mechanism involves an endothelial cell–tanycyte communication process, whereby nitric oxide (NO) produced by fenestrated endothelial cells of the median eminence tightly modulates cyclooxygenase activity in tanycytes[164,182]. Importantly, tanycytic ERBB signalling requires several hours to promote morphological changes in tanycytes following activation[181]. Endothelial NO, however, seems to be able to promote structural changes in tanycytes within a very short period of time (<30 min) in *in vitro* co-culture models[164,182] and in median eminence explants[182]. Intriguingly, oestradiol, which accentuates the endothelial NO-mediated morphological plasticity of tanycytes[164], acts locally in the median eminence to stimulate GnRH release[183] (FIG. 5). The acute oestradiol-promoted GnRH release in the median eminence requires NO production in rodents[183], and evidence suggests that it occurs in primates *in vivo*[184,185].

The physiological importance of these neuron–glia–endothelial cell interactions is further supported by the fact that oestradiol upregulates the expression and/or activity of TGFα in astrocytes[186], cyclooxygenase in tanycytes and endothelial NO synthase in endothelial cells[164,187,188]. In addition, the *in vivo* pharmacological inhibition of either NO synthase or cyclooxygenase in

En passant
Of synapses, contacts established with axons or cell bodies along the trajectory of neural cell processes targeting deeper tissue structures.

Semaphorins
Members of a family of secreted guidance molecules known to control the embryonic migration of neurons secreting gonadotropin-releasing hormone.

the median eminence alters the ovarian cycle in young adult female rats[164,182]. Equally intriguing is that T_3, which is photoperiodically regulated (see above), seems to control tanycytic endfeet ensheathment of GnRH-secreting nerve terminals in the median eminence[189] in some seasonal species, such as the Japanese quail. The proposed mechanism regulating this process is thought to involve tanycytic TGFα–ERBB signalling[190].

Two seminal *in vivo* studies demonstrated the importance of the tripartite communication between tanycytes, GnRH-secreting neurons and fenestrated endothelial cells in the median eminence for the neuroendocrine control of reproduction using advanced genetic tools[191,192]. These studies showed that semaphorins regulate GnRH and LH release in adulthood by altering how accessible pituitary portal blood vessels are to GnRH-secreting neuronal terminals[191,192] (FIG. 5). One semaphorin, SEMA3A, which is encoded by *Sema3a* and has a key role in the development of the GnRH system during embryogenesis[193,194], is also expressed in the termination field of GnRH-secreting neurons in the adult brain of rats and mice[191]; however, the secretion of SEMA3A is tightly regulated by oestrogens and is restricted to the fenestrated endothelial cells of the median eminence. From the median eminence, SEMA3A diffuses into the parenchyma to promote (through the neuropilin 1 receptor) the outgrowth of GnRH-secreting axons towards the pericapillary space on the day of pro-oestrus, when, as mentioned earlier, the preovulatory surge of GnRH and LH occurs[191] (FIG. 5). The functional consequence of SEMA3A secretion on GnRH axonal plasticity has been demonstrated by the selective invalidation of endothelial SEMA3A in the median eminence of adult *Sema3a*$^{loxP/loxP}$ mice by the intravenous injection of the recombinant TAT–Cre protein, which blunts the amplitude of the preovulatory LH surge[191].

Another semaphorin, SEMA7A, exerts its effects by binding to two well-characterized receptors, PlexinC1 and β1-integrin[195,196]. As with SEMA3A, SEMA7A acts as a guidance factor for migratory GnRH-secreting neurons during embryogenesis[197,198]; however, SEMA7A expression in the termination field of GnRH-secreting neurons in the adult brain is restricted to tanycytes of the median eminence[192]. The expression of SEMA7A in tanycytes varies throughout the oestrous cycle in response to ovarian steroids. More precisely, tanycytic SEMA7A expression is low when circulating oestrogens levels are high (during pro-oestrus) and reaches its peak when circulating progesterone levels are elevated but oestrogens levels are at their lowest (in dioestrus)[192]. Interestingly, tanycytes isolated *in vivo* using fluorescence-activated cell sorting and tanycytes in primary cultures *in vitro* express high levels of progesterone receptors[192]. Progesterone-stimulated SEMA7A expression in tanycytes requires

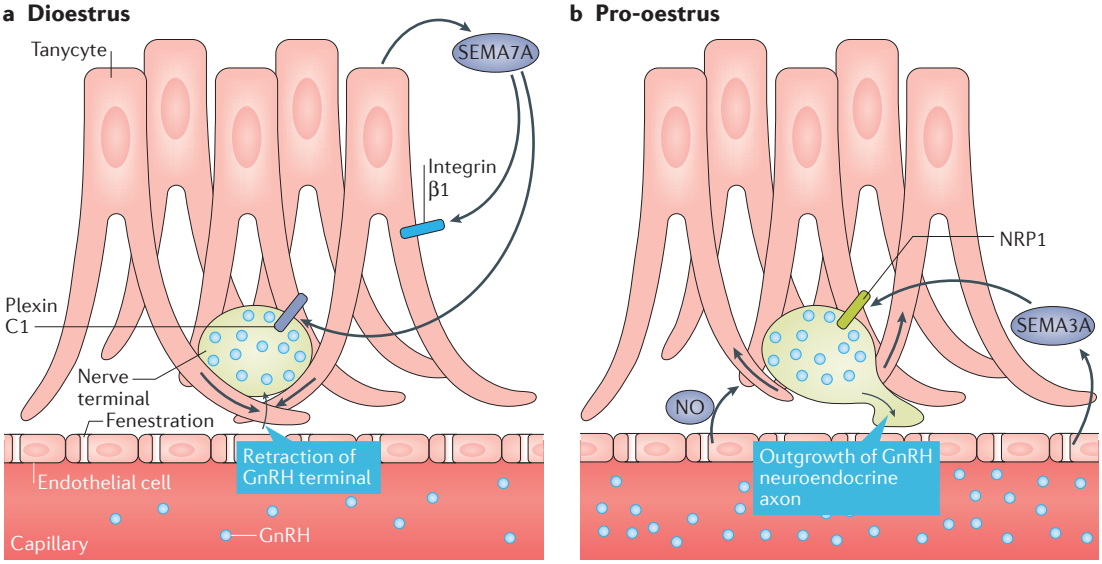


Figure 5 | **Coordinated glial–endothelial–neuronal interactions that regulate the neurosecretion of gonadotropin-releasing hormone (GnRH).** In the external zone of the median eminence GnRH terminals access to pericapillary space is regulated in two separate ways. **a** | In dioestrus, high levels of progesterone in a context of low circulating levels of oestrogens promotes the secretion of SEMA7A by tanycytes in the median eminence[192]. SEMA7A activates integrin β1, which is expressed by tanycytes, via a paracrine and/or autocrine action. Integrin β1 activation promotes the growth of tanycytic endfeet (thick black arrows), which engulf GnRH neuroendocrine terminals and form a diffusion barrier impeding GnRH release into the pericapillary space and fenestrated capillaries[192]. In parallel, tanycytic SEMA7A acts on the receptor PlexinC1, which is expressed by GnRH neuroendocrine terminals, to induce the retraction of GnRH terminals from the pericapillary space (thin black arrow)[192]. **b** | In pro-oestrus, high circulating levels of oestrogens promote the release of nitric oxide (NO) and SEMA3A from the fenestrated endothelial cells of the median eminence. The release of NO promotes the retraction of tanycytic endfeet from the parenchymatous basal lamina (thick black arrows)[164,182], whereas SEMA3A acts on neuropilin 1 (NRP1) to promote the outgrowth of GnRH neuroendocrine axons guided by a scaffold of tanycytic processes towards the pericapillary space (thin black arrow) thus facilitating the release of GnRH into the pericapillary space and fenestrated capillaries[191].

the paracrine release of TGFβ1[192] — a tanycytic growth factor[181,199] that is expressed differentially throughout the oestrous cycle. In addition, as with *Sema7A*, TGFβ1 expression is at its highest during dioestrus[192]. Treatment with SEMA7A induces *ex vivo* morphological rearrangements typical of dioestrus in median eminence explants collected from rats on the day of pro-oestrus. This structural remodelling, which occurs within 30 minutes of SEMA7A application, results in the concomitant retraction of GnRH-secreting terminals from the pericapillary space and sprouting of tanycytic endfeet (FIG. 5). The process ends with tanycytic endfeet engulfing the GnRH-secreting nerve terminals[192]. A notable decrease in GnRH release from pro-oestrous median eminence explants accompanies treatment with SEMA7A. These data support the idea that the sprouting of tanycytic endfeet impedes the free diffusion of the GnRH into portal blood vessels[192].

Experiments conducted in immortalized GnRH cell lines suggest that Sema7A promotes the retraction of GnRH neuroendocrine terminals through the PlexinC1-mediated inactivation of RAP1 (also known as TERF2IP) and cofilin. In addition, work on primary cultures of tanycytes has shown that tanycytic endfoot expansion promoted by SEMA7A might involve β1-integrin and its intracellular downstream molecules FAK, ERK1/2 and AKT[192]. In agreement with these *in vitro* data, PlexinC1-null mice display a more robust innervation of the median eminence than their wild-type littermates, in addition to ovarian defects and subfertility[192]. In contrast, the selective invalidation of *Itgb1* (the gene encoding β1-integrin) in adult tanycytes via the intracerebroventricular infusion of TAT–Cre in *Itgb1*$^{loxP/loxP}$ mice results in the retraction of tanycytic endfeet from the pericapillary space of the external zone of the median eminence. The retraction occurs with a corresponding increase in the space occupied by GnRH-secreting nerve terminals, some of which directly contact the parenchymatous basal lamina[192] — an event that is otherwise rarely seen[179]. The increased access of GnRH nerve terminals to the pericapillary space is associated with a persistent increase in circulating levels of LH and the arrest of the oestrous cycle in the oestrous phase[192]. Overall, these results indicate that tanycytic SEMA7A is involved in the plasticity of the median eminence across the ovarian cycle by controlling periodic morphological remodelling involving both GnRH nerve terminals and the endfeet of tanycytes. In addition, these data demonstrate that such neuronal–glial crosstalk is required for the acquisition and maintenance of fertility.

Ageing and disease. The aforementioned studies provide insight into the molecular mechanisms responsible for the progression of the oestrous cycle in rodents. The data suggest that this phenomenon relies, at least in part, on a balance of antagonistic effects of distinct signalling pathways in the median eminence involving glial and endothelial factors that are influenced periodically by circulating sex steroids. Whether or not the expression of these glial and endothelial factors alters with age, therefore contributing to GnRH-related systemic ageing[200,201], remains to be investigated. Data show that the morphology of tanycytes seems to be altered with age[202]. The authors of this study reported that with age tanycytes lost their processes and specific markers, such as DARPP32 (also known as PPP1R1B)[202]. In addition, the expression of cytoskeletal intermediate-filament proteins (including GFAP), which are typically observed in astrocytes, increased with age[202]. Age-related structural changes between GnRH-secreting nerve terminals and tanycytic endfeet have been observed following transmission electron microscope studies in rats. In these studies, the investigators showed a notable reduction in the interaction between the two cell types with age[203,204].

In humans, although morphological interactions between GnRH-secreting terminals and tanycytes are observed in the median eminence of aged individuals[139], a study from 2017 indicates that the organization of vimentin-immunoreactive processes might be disrupted in elderly women compared with young women. Of note, however, the authors reported that the total number of tanycytic cell bodies did not seem to change with age[205]. Irrespective of their morphological interaction with GnRH axons, ultrastructural studies conducted in non-human primates show that glial cell processes are markedly enlarged in the median eminence of aged females compared with young females[206]. Altogether, these studies raise the possibility that a structural alteration in the contacts between GnRH-secreting neurons and non-neuronal cells of the median eminence might contribute to the senescence of the reproductive axis.

Data showing that gonadal steroids promote structural changes in the hypothalamus of young women during the menstrual cycle[140], together with those showing that mutations in *SEMA7A* are present in patients with congenital normosmic hypogonadotropic hypogonadism[207], led to the recognition that SEMA7A–β1-integrin signalling in tanycytes might be required for the extension of tanycytic endfeet and for normal reproductive cycles in humans. This might have important clinical implications and hold therapeutic potential for infertility of hypothalamic origin. The disruption of the oestrous cycles, with a predominance of the oestrous phase and elevated circulating levels of LH in mice in which β1-integrin is selectively deleted in tanycytes[192] seems to recapitulate, at least in part, the neuroendocrine reproductive phenotype observed in two models of polycystic ovary syndrome. In the first model, prenatal androgen exposure leads to the induction of pathologically elevated levels of LH, increased LH pulse frequency and a lengthening of the oestrous cycle with an increased duration of oestrus[208,209]. In the second, treatment with anti-Müllerian hormone, an ovarian hormone of the TGFβ1 superfamily whose circulating levels are highly elevated in patients with polycystic ovary syndrome, leads to an increase in GnRH release from acute living median eminence explants and an increase in LH pulse frequency *in vivo*[210]. Because tanycytes express high levels of the receptor for anti-Müllerian hormone[210], and this receptor can heterodimerize with the tanycytic TGFβR1 to transduce its signal[211], a tempting speculation is that the effects of anti-Müllerian hormone on

Parenchymatous basal lamina
Basement membrane delimitating the surface of the brain tissue. In the median eminence, the parenchymatous basal lamina delineates the pericapillary space the secretory neuroendocrine terminals about to release their neurohormone into the hypothalamic–pituitary portal blood system.

Vimentin-immunoreactive processes
Cellular extensions rich in vimentin, an intermediate filament protein that is selectively expressed in classical ependymal cells with beating cilia and tanycytes *in vivo*. Vimentin immunoreactivity heavily decorates the long and slender extensions sent by tanycytes towards the nervous parenchyma and hence is a good marker of tanycytic processes.

GnRH and LH release are mediated by the action of anti-Müllerian hormone on tanycytes, potentially interfering with the SEMA7A signalling pathway and changing the morphology of tanycytes[192].

Taken together, an alteration in the morphological plasticity of tanycytes during the oestrous cycle might play an important and unexpected role in the aetiology of some forms of hypothalamic infertility. In addition, the recognition of the clinical relevance of this structural plasticity might pave the way for the development of new treatment strategies in the central loss of reproductive competence in human syndromes and/or new contraceptive strategies.

Conclusions

Hypothalamic glial cells, particularly astrocytes and tanycytes, regulate a variety of molecular mechanisms involved in the secretion of neurohormones and systemic homeostasis. The underlying mechanisms come in various forms; morphological remodelling that alters neurotransmitter dynamics at the synapse or controls the access of neurosecretory terminals to their target areas; the release of gliotransmitters capable of altering neuronal activity, excitability or feedback; metabolic pathways that directly activate or inactivate the neurohormones they regulate; and controlling the entry of peripheral signals into the brain. Furthermore, depending on the hypothalamic region, function and pathophysiological context involved, cells that we perceive as being the same cell type might actually have very different roles in neural circuit regulation[2,3,212,213].

Despite the many advances in our understanding of glia–neuron interactions in the neuroendocrine hypothalamus over the past decade, many questions remain unanswered. We know that hypothalamic glial cells are involved in the secretion of the four major neurohormones discussed in this Review — oxytocin, vasopressin, TRH and GnRH. In addition, data show that the hypothalamus is involved in the secretion of several other neurohormones, including growth hormone-releasing hormone; dopamine; somatostatin; corticotropin-releasing factor; and gonadotropin inhibitory hormone[137,214,215]. At present, however, no data exist regarding whether similar mechanisms of structural remodelling or gliotransmission are involved in the release of the aforementioned neurohormones.

In addition, and perhaps more intriguingly, the roles of other types of glial cells of the hypothalamus, such as microglia and oligodendrocytes, in these release mechanisms are unclear. For example, mounting evidence indicates that in addition to astrocytes and tanycytes, microglia might also be involved in hypothalamic function. We primarily consider microglia as being associated with inflammatory states, but they also play vital roles in axonal or dendritic growth and synaptic pruning and function[216,217]. This dual nature is also evident in the hypothalamus — obesity in humans and rodents is associated with hypothalamic inflammation, including microglial activation[94,218] — but microglia in the arcuate nucleus of the hypothalamus also help potentiate leptin-induced signal transduction in the hypothalamus[219,220]. Similarly, microglia are involved in both systemic ageing and reproductive function. For example, hypothalamic microglia-mediated inflammation results in reduced GnRH production by the hypothalamus and therefore an increase in systemic ageing[200]. Microglia also seem to be essential for normal reproductive function. In males, microglia are involved in the regulation of the oestradiol–prostaglandin E_2-induced masculinization of the brain[221], and in females, microglia are required for the correct oestrogen feedback responses during puberty and the oestrous cycle[222]. Finally, evidence from the posterior pituitary shows that microglia endocytose magnocellular neuronal terminals in response to osmotic stress and therefore potentially regulate neuroendocrine secretion[223]. These data raise the possibility of similar interactions with the various neurosecretory neuronal populations of the hypothalamus. In addition, NG2 glial cells (also known as oligodendrocyte precursors) play a role in the maintenance of neuronal processes in the median eminence[224]; however, whether these cells can also regulate neuroendocrine axon dynamics remains unclear.

Future investigations into the biology of not only hypothalamic tanycytes and astrocytes but also these other glial populations, microglia and oligodendrocytes, will undoubtedly improve our understanding of the regulation of neuroendocrine systems, and more generally, of neuron–glia interactions in the central nervous system. In addition, males and females have distinct propensities to develop distinct forms of infertility and homeostatic disorders[133,225,226], in part under the influence of gonadal hormones, which are themselves controlled by the hypothalamic GnRH network. Therefore, by documenting putative sex differences in how the glia–neuron communication processes regulate bodily homeostasis, we might be able to eventually develop effective strategies for the prevention of infertility and homeostatic disorders.

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