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Minireview: Role of Glia in Neuroendocrine Function

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Long relegated to the backwaters of neuroendocrinology, it is becoming increasingly apparent that glial cells of the central and peripheral nervous system are key participants because they are capable of both sending and receiving hormonal signals. Hormones are also a critical component of neuronal/glial cross talk, leading to neuromodulatory and neurotrophic actions under physiological and pathological conditions. In the peripheral nervous system, hormonal actions on Schwann cells and hormonal metabolites produced by these glial cells promote myelin formation and the remyelination and regeneration of injured nerves. In the central nervous system, glial cells participate in the hormonal regulation of synaptic function, synaptic plasticity, myelin formation, cognition, sleep, and the response of nervous tissue to injury. In addition, central glial cells participate in the regulation of hormonal secretion by hypothalamic neurons. Therefore, glial cells are a key element to understanding hormonal actions in the nervous system and the regulation of neuroendocrine events. (*Endocrinology* 145: 1082–1086, 2004)

THE NAME OF glia derives from the German word for glue because Rudolf Virchow, in his original description of these cells in 1846, considered that they were the "glue" of the brain that gives structural support to neurons. Now, our view of glial cells is very different (1). We know that these cells are functional components of the neural tissue that express receptors for neurotransmitters and show excitability based on intracellular Ca^{2+} variations. Glial cells integrate signals emanating from neurons and other glial cells, including hormonal inputs. They also regulate extracellular concentrations of ions, metabolites, and neurotransmitters to coordinate the differentiation, metabolism, and excitability of neurons and modulate synaptic transmission (1). There is limited evidence that glial cells contain vesicles and release transmitters in much the same way as neurons (2). The preferential localization of glia around synapses further enhances their ability to modulate excitability in the brain and has led to the coining of the term "tripartite synapse" (3, 4).

Hormones regulate the development and function of the nervous system to influence physiology and behavior. Fifty years of research have focused on the effects of hormones on neurons or neuronal systems to modulate physiology and behavior, with scarcely a mention of glial cells of any variety. This is not a condemnation of the science of neuroendocrinology because the same was more or less true for all of neuroscience. We now know that hormonal actions in the brain are exerted equally on neurons and glial cells, and that the ability of glia to both respond to and produce hormones has profound functional implications in virtually every neuroendocrine system. Glial cells express many of the same hormone receptors as found on neurons, such as receptors for melatonin, thyroid and steroid hormones, vasopressin, oxytocin, leptin, corticotropin-releasing factor, glucagon, insulin, and IGF-I. The closer we look, the more it becomes apparent that glial cells play a critical role as mediators of these hormonal messages to the nervous system. Glial cells regulate the activity of neurosecretory neurons, participate in the control of hormonal release, and can even serve as the source of hormone themselves. Here we review some of the recent advances in the study of the role of glial cells in mediating hormonal actions in the nervous system and in the regulation of hormonal secretion. In our view, the additional role of hormones in modulating the tripartite synapse lends a level of complex control that maximizes the ability of the organism to respond to dynamic changes in the internal as well as external environment.

Who Is Who among Glial Cells?

Glial cells are classified in two main groups: microglia and macroglia. Microglia are macrophage-like cells that regulate the inflammatory response of the neural tissue to injury or infection. Macroglia are subdivided in four specialized cell types: ependymal cells, Schwann cells, oligodendroglia, and astroglia. Ependymal cells line the cerebral ventricular cavities and the central canal of the spinal cord and are in direct contact with the cerebrospinal fluid. Schwann cells and oligodendroglia are responsible for the formation of myelin, an essential component facilitating action potential propagation. Schwann cells form the myelin in the peripheral axons and oligodendroglia in central axons. In addition, both cell types regulate axonal excitability. Astroglia refers to a heterogeneous population that includes astrocytes, marginal glia, radial glia in the developing brain, Bergmann cells in the cerebellar cortex, Müller cells in the retina, pituicytes in the neurohypophysis, and tanycytes in the hypothalamus. All of these cells are grouped as astroglia because they have in common the expression of glial fibrillary acidic protein

Abbreviations: GABA, γ-Aminobutyric acid; GFAP, glial fibrillary acidic protein; PGE_2, prostaglandin E_2.

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(GFAP). However, this is probably an artificial classification that groups together cells with different functions. Astroglia processes maintain contact with blood vessels, neurons, and other glial cell types. Astrocytic processes rarely extend beyond a 50-μm radius, allowing them to exert largely local control. However, propagation of Ca^{2+} waves through networks of astrocytes, via the release of signaling molecules such as ATP, may affect the activity of distant neurons integrated in different neuronal circuits (1, 3, 4).

Glia Cells Mediate Hormonal Signaling

Integration of hormonal signaling by glial cells occurs in at least two fundamental ways: 1) the hormone acts directly on the glia, which in turn signals to the neuron to modulate its function (5, 6). Signaling to the neuron may involve secretion of a growth factor, neurohormone, or transmitter-like substance (a variation of this involves the glia signaling to the neuron by physically interacting with it, meaning that the membranes become immediately juxtaposed or disassociated); and 2) the hormone acts first on the neuron, which then releases a substance to signal to the glia, which presumably then signals back to that or to other neurons (5, 6).

Untangling precisely what type of cross talk between neurons and glial cells is occurring is extremely challenging, and the distinctions we have made are largely operationally defined. It is plausible that in some cases where steroids appear to be acting directly on astrocytes, further examination may reveal a previously undiscovered preliminary step involving neurons. Nonetheless, examples for each can be found. For instance, the profound influences of thyroid hormone (T_3) on brain development are in part due to its direct actions on astroglia and oligodendroglia (6, 7). T_3 signaling is necessary to promote the complete differentiation of oligodendrocyte precursor cells and, therefore, the formation of central myelin (7, 8). T_3 also regulates Schwann cell function and differentiation, thereby affecting peripheral myelin (9). Progesterone and progesterone derivatives such as dihydroprogesterone and tetrahydroprogesterone, also promote central and peripheral myelination acting on oligodendrocytes (10) and Schwann cells (11), respectively.

There is limited evidence that gonadal hormones also act directly on glial cells to regulate the building and remodeling of synaptic contacts (5). For instance, estradiol reorganizes astrocytic laminin into extracellular fibrillar arrays that facilitate neurite extension (12), although the precise mechanisms of the estrogen effect on laminin have not been established. The hormone also increases expression of TrkA receptors in astrocytes. As a consequence, the hormone may regulate axonal growth and synaptic plasticity because nerve growth factor, the ligand for TrkA, stimulates astrocytes to function as substrates for axon growth (13). In addition, gonadal hormones interact with growth factors secreted by glial cells to promote axonal growth of developing neurons in the central nervous system, and this likely involves the hormone acting directly on the neuron but requiring the involvement of the glial cell (14). Finally, direct hormonal actions on microglia and reactive astroglia may affect the endogenous inflammatory response of the nervous system and the outcome of neurodegenerative processes (6, 15–18).

Examples that involve steroids acting first on neurons to initiate a circular conversation between neurons and astrocytes that ultimately returns to neurons are found in the developing brain. Gonadal steroid-mediated sex differences in astrocyte morphology have been correlated with changes in dendritic spine synapse density in the neonatal brain (19, 20). In the case of the developing arcuate nucleus, it is clear that the primary effect of the steroid is at the neuron, to promote release of γ-aminobutyric acid (GABA), which then promotes the extension and branching of astrocytic processes (21). A second example is found in the nearby preoptic area where astrocytes can induce dendritic spine synapse formation by local release of glutamate. Of critical importance is that the glutamate release from the astrocytes is signaled by prostaglandin E_2 (PGE_2), which is synthesized in neurons. The control of PGE_2 synthesis is via estradiol acting on the rate-limiting enzyme cyclooxygenase 2 (22). Thus, an endocrine signal initiated in the neuron is transmitted to the astrocyte, which then feeds back on the neurons to regulate synapse formation.

Glial Cells Synthesize Active Hormonal Metabolites

Glial cells metabolize hormones as well as synthesize active metabolites that affect neuronal function. Combined metabolism and synthesis is the case for thyroid hormones, where astrocytes and tanycytes play a key role in the conversion of T_4 to the active metabolite T_3 (6). Glial cells can also convert steroids into neuroactive steroids. In particular, glial cells metabolize native steroid hormones into their 5α- and 3α-hydroxy-5α reduced derivatives via the enzymatic complex formed by the 5α-reductase and the 3α-hydroxysteroid dehydrogenase. Thus, testosterone is converted into dihydrotestosterone and then into 5α-androstane-3α and 17β-diol, progesterone is converted into dihydroprogesterone and subsequently into tetrahydroprogesterone, corticosterone into dihydrocorticosterone, and deoxycorticosterone into dihydrodeoxycorticosterone and then into tetrahydrodeoxycorticosterone (23, 24). The presence of the enzyme steroid 21-hydroxylase, which is required for the conversion of progesterone to its downstream metabolites, was recently confirmed in cultured astrocytes (25).

The steroids produced by glial cells may serve a paracrine role regulating synaptic function as these steroids are known to modulate anxiety, cognition, sleep, ingestion, aggression, and reinforcement (23, 24). Some of them are positive modulators of *N*-methyl-D-aspartate receptors and enhance cognitive performance. Other steroids produced by glial cells, such as tetrahydroprogesterone and tetrahydrodeoxycorticosterone, are highly selective and extremely potent modulators of the $GABA_A$ receptor and elicit marked anxiolytic and stress reducing effects, as well as increase feeding and promote sleep (23, 24). The metabolism of steroid hormones by glial cells is important under pathophysiological conditions. For instance, progesterone and progesterone derivatives produced by Schwann cells promote axonal regeneration and remyelination after peripheral nerve lesions, whereas steroid metabolites produced by central glial cells are protective against neurodegenerative stimuli (23, 26).

Glial Cells Modulate Hormonal Secretion by Hypothalamic Neurons

In addition to being a target for hormonal action, glial cells act as modulators of hypothalamic neurosecretory neurons. The best example has been provided by the laboratory of Sergio Ojeda, showing that neuron-glia signaling mediated by growth factors of the epidermal growth factor family and the expression of their associated erbB tyrosine kinase receptors in hypothalamic astrocytes are a requisite for the timely initiation of mammalian puberty in female animals (27, 28). Astrocytes control GnRH neurons by different mechanisms. These glial cells mediate estrogen-induced synaptic plasticity in GnRH cells and in hypothalamic areas that project to GnRH neurons (5, 6, 12). In addition, astrocytes and tanycytes, in response to hormonal steroids, release factors that control the activity of GnRH neurons, such as PGE_2, the TGFα, β1 (TGFβ1), β2 (TGFβ2), the basic fibroblast growth factor, and the IGF-I (12, 29, 30). Astrocytes also regulate the local intraneuronal formation of steroids able to intervene as negative or positive signals in the feedback control of GnRH neurons (31). Changes during the estrous cycle in the extension of tanycyte cell processes in the external zone of the median eminence, modulate the access of GnRH nerve terminals to the portal vasculature (32, 33). In addition tanycytes release factors, such as IGF-I that are involved in the estrogen-induced synaptic remodeling of hypothalamic neurons involved in the control of GnRH cells (33) (Fig. 1).

Involvement of glial cells in the regulation of hypothalamic hormone release has also been demonstrated for the magnocellular neurosecretory neurons of the supraoptic and paraventricular nuclei (34, 35). Under conditions of intense neurohypophysial hormone secretion, such as lactation, parturition, and chronic dehydration, astrocytic processes in these nuclei retract and the glial coverage of neuronal membranes decreases. This change in glial coverage is accompanied by a remodeling of synaptic contacts and probably has additional important consequences for neuronal excitability because it modifies extracellular ionic homeostasis and glutamate neurotransmission (34, 35). Similar changes in the extension of glial processes associated with hormone release have been observed in pituicytes, the glial cells of the neurohypophysis. Under conditions of low hormonal demand, pituicyte processes surround neurosecretory axon terminals at the neurovascular contact zone. In contrast, when hormonal demand is enhanced, pituicytes withdraw their processes, apparently playing a permissive role for hormonal

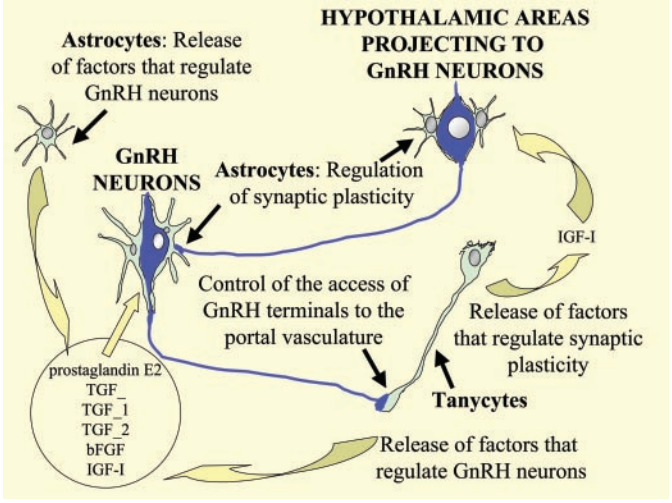

FIG. 1. Summary of the sites of action and the mechanisms involved in the regulation of GnRH secretion by astroglia. 1) Astrocytes secrete PGE_2 and growth factors [TGFs, basic fibroblast growth factor (bFGF), IGF-I] that act on GnRH neurons (6, 28–30, 33). 2) Astrocytes regulate synaptic connectivity on GnRH neurons and in hypothalamic areas projecting to GnRH neurons, such as the hypothalamic arcuate nucleus (5, 33) Tanycytes control the access of GnRH terminals to portal vasculature in the median eminence and release factors that affect GnRH neurons or modulate synaptic plasticity of hypothalamic neurons involved in the control of GnRH cells (6, 28–30, 33).

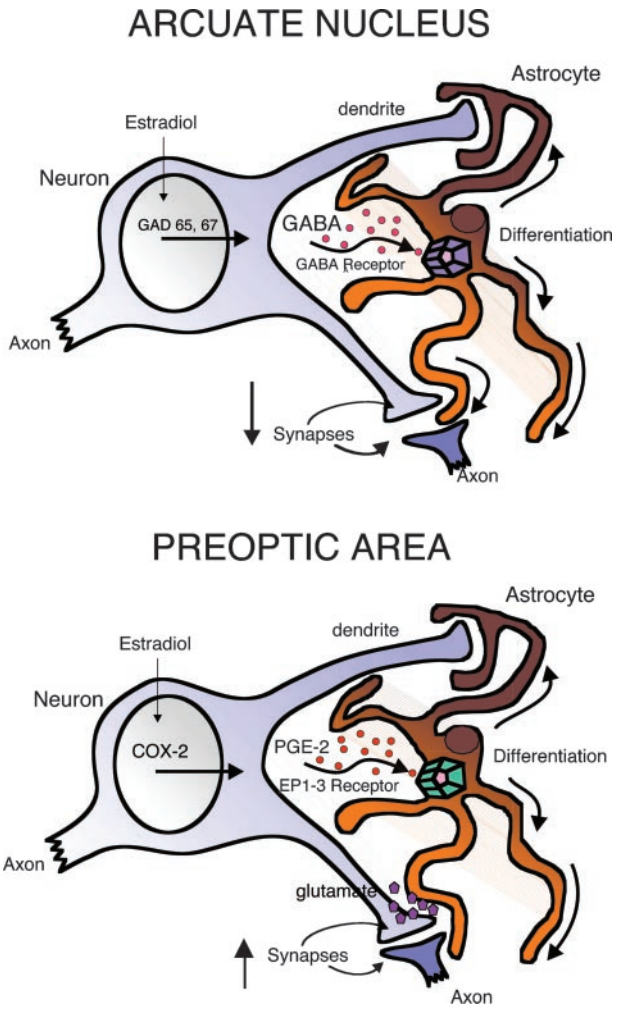

FIG. 2. Neuronal/glial cross talk is region specific. In the developing arcuate nucleus, estradiol-mediated increases in neuronal GABA synthesis and release leads to increased stellation of neighboring astrocytes. The increased complexity of astrocytes is inversely correlated with the density of dendritic spine synapses on arcuate neurons, but a mechanistic relationship between these two architectures has not yet been established (19–21). In the developing preoptic area, estradiol-mediated increases in PGE_2 synthesis and release results in increased stellation of astrocytes and a corresponding increase in the density of dendritic spines on neighboring neurons. The increase in dendritic spines induced by PGE_2 is dependent on activation of AMPA receptors by glutamate, which is presumably released from the astrocytes (22). COX-2, Cyclooxygenase 2; EP1–3, PGE_2 1–3 receptors.

release (34, 35). Furthermore, astrocytes and pituicytes may release taurine in response to hypo-osmotic stimulation. Taurine, in turn, activates glycine receptors in neurosecretory neurons and inhibits vasopressin release (36). The interaction of pituicytes with vasopressinergic axons represents a good example of the interaction between glia and neurons to regulate a defined physiological function.

Glial/Neuronal Cross Talk Is Regionally and Developmentally Specific

Neuroendocrine function is tightly regulated by discrete groups of neurons, and the astrocytes that interact with those populations can be expected to have a distinct phenotype as well. Regional variation in development has offered a unique window into site specificity by the simple nature of the fact that different areas of the brain develop at different rates. This is in part reflected by the astrocytes themselves. As mentioned, previously, expression of GFAP is a distinguishing characteristic for a large and varied group of astroglia. GFAP is also a hallmark of astroglia maturation and as such its expression pattern varies from region to region. Interestingly, both the preoptic area and arcuate nucleus, two brain regions importantly involved in neuroendocrine regulation and highly sexually differentiated, have robustly GFAP-expressing astrocytes as early as the day of birth. Hormonal modulation of synaptic development in both these brain regions involves cross talk between astrocytes and neurons (Fig. 2). In contrast, the mediobasal hypothalamus has immature astrocytes at birth and synaptogenesis is static between males and females at this developmental stage. Thus, differences in the maturation of astrocytes in particular brain regions may preclude or allow hormonal modulation of developmental processes (37).

We have mentioned the variety of receptor types expressed by astrocytes, and just as with neurons, it would be expected that these would vary regionally and developmentally as well. An additional critical mediator of hormonal modulation in astrocyte-neuron cross talk is the presence or absence of nuclear receptors. Hormonal nuclear receptors in glia show developmental regulation and have regionally specific distributions (6, 37–47). The relative contribution to neuroendocrine function of regionally specific glia phenotype and developmental regulation of hormone receptors in glia will no doubt be the continued focus of future studies and lead inevitably to questions of how such variance is established and maintained.

In summary, although there is still much to be learned on the role of glial cells in neuroendocrine regulation and hormonal signaling, we know that glial cells are able to respond to hormonal and neuronal signals and then to propagate the activation to other glial cells and to neurons for long distances. This provides glial cells with the capacity to amplify and expand hormonal effects to distant uncoupled neuronal circuits. It also provides glial cells with the capacity to coordinate over time, for phasic hormonal release, the activity of distant neurons involved in neuroendocrine regulation. Furthermore, glial cells may produce local active hormonal metabolites when and where they are needed under physiological and pathological conditions. Developmentally, glial cells may contribute to the establishment and permanent maintenance of sexually dimorphic synaptic patterning that mediates adult differences in sexual behavior and neuroendocrine function. Therefore, glial cells represent a very relevant cellular element to be taken in consideration to understand the mechanisms of neuroendocrine regulation.

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