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Responses of glial cells to stress and glucocorticoids

F. Jauregui-Huerta¹, Y. Ruvalcaba-Delgadillo², R. Gonzalez-Castañeda¹, J. Garcia-Estrada^{1,3}, O. Gonzalez-Perez¹, and S. Luquin¹

¹ Microscopía de Alta Resolución. Departamento de Neurociencias. Universidad de Guadalajara

² Instituto de Neurociencias. Centro Universitario de Ciencias Biológicas y Agropecuarias. Universidad de Guadalajara

³ Laboratorio de Neuroendocrinología Celular y Molecular. Centro de Investigación Biomédica de Occidente. IMSS

Abstract

A growing body of evidence suggests that glial cells are involved in practically all aspects of neural function. Glial cells regulate the homeostasis of the brain, influence the development of the nervous system, modulate synaptic activity, and carry out the immune response inside the brain. In addition, they play an important role in the restoration of the nervous system after damage, and they also participate in various neurodegenerative disorders. In a similar way, the importance of stress and glucocorticoids (GCs) on brain function is being increasingly recognized. Within the brain, stress hormones target both neurons and glial cells. Through their actions on these cells, glucocorticoids exert organizational functions on various processes of the developing brain and contribute to neuronal plasticity in the adult brain. Moreover, stress and glucocorticoids have become especially attractive in the study of a number of neurodegenerative disorders. However, studies on the mechanisms behind glucocorticoid-induced regulation of brain function have been classically focused on their effects on neurons. In this review, we start by describing the main functions of glial cells and then proceed to present data highlighting the effects of stress and GCs on brain function. We conclude the review by presenting recent evidence linking stress and glucocorticoids to glial cell function.

Keywords

Glial cells; glucocorticoids; stress; inflammation; reactive gliosis; neurodegenerative disorders

Introduction

Glial cells: basic knowledge

In the Central Nervous System (CNS), there are two major cell types: neurons and glial cells. Traditional views on brain organization consider neurons to be the functional unit of the brain with glial cells playing only a supportive role; however, it has become clear that glial cells are as important as neurons for the normal function of the brain. Glial cells have gradually been recognized to be central players in practically all aspects of neural function. There is now an explosion of information indicating that glial cells, besides their historically assigned role in the support of neurons, also contribute actively to a myriad of non-classical

Corresponding Authors Address: Ma. Sonia Luquin de Anda, Address: Monte Blanco 300, Colonia Independencia Ote., Guadalajara, Jalisco. México., C.p. 44340, Telephone/Fax: +52-33-10-58-52-97, sonialu@prodigy.net.mx. Joaquín García Estrada, Address: Monte Blanco 300, Colonia Independencia Ote., Guadalajara, Jalisco. México., C.p. 44340, Telephone/Fax: +52-33-10-58-52-97, jgarciaestrada@gmail.com.

functions including brain development, brain homeostasis, cognition, neural regeneration, synaptic transmission, immune response, and endocrine system control (for reviews see [1,2]).

There are two main groups of glial cells in the CNS: macro- and microglia. These groups can be functionally and phenotypically subdivided into various types of cells (see figure 1).

Microglia encompass a set of very active and versatile cells, traditionally considered the immune cells of the CNS [3]. These macrophage-like cells originate from macrophages that invade the brain during early development, and are ubiquitous in the CNS. In the normal, uninjured brain, they are referred to as “resting microglial”. Although the functions of the microglia under normal physiological conditions have been practically neglected, it has been recently proposed that “resting” microglia serve as very active sensors of the biochemical or bioelectric microenvironment [4]. To this end, microglial cells are equipped with receptors for neurotransmitters, neuropeptides, hormones, immune signals, and other molecules that allow the microglia to efficiently scan their territory [5]. Microglial cells are, in addition, the earliest detectors of brain injury. In response to damage, microglia become “activated”, altering their morphology, surface phenotype, proliferative, and gene expression pattern. Activated microglia prevent further brain damage and contribute to the restoration of normal homeostasis in the nervous system [4]. Thus, microglial cells play crucial roles in the normal healthy brain as well as in the injured or pathologic brain.

Macroglia, on the other hand, include ependymal cells, Schwann cells, oligodendroglia, and astroglia. Ependymocytes line the cavities of the CNS and form the walls of the ventricles in the brain and the central canal in the spinal cord. Oligodendroglia and Schwann cells are known for their role in myelinating axons in the central and peripheral nervous system, respectively. Astroglia, the dominant and functionally more dynamic glial cell type, refers to morphologically complex cells expressing a common cytoskeleton protein named glial fibrillary acidic protein (GFAP). Astroglia include astrocytes, radial glia, Bergmann cells, Muller cells, pituicytes, and tanycytes. In consideration of the importance of their roles for brain function, astrocytes and oligodendrocytes will be described in further detail next.

Astrocytes are the most abundant cells in the brain, and they are involved in a diversity of functions in the CNS. These functions include: regulation of synaptogenesis, support of neurogenesis and gliogenesis, guidance in neuronal migration, regulation of cerebral microcirculation, provision of energy substrates for neurons, regulation of extracellular ion concentrations and extracellular pH, modulation of neurotransmitter signaling and recycling, regulation of the brain water homeostasis, modulation of synaptic transmission, integration and regulation of synaptic networks, and modulation of neuroendocrine functions (for reviews see [1,6,7]). Thus, astrocytes are not only the most numerous cells in brain, but probably the most versatile as well.

Oligodendroglia consist of cells that are morphologically similar to astrocytes, yet smaller in size and with fewer, less branched processes. They may be called perineuronal or interfascicular oligodendrocytes depending on their location. Mature oligodendrocytes are known for their role in myelinating axons in the CNS. The myelin sheath is a fatty insulating layer that facilitates conduction of the action potential. In addition, recent studies have suggested that oligodendroglial cells can also function as modulators of neuronal function. Furthermore, it is now known that these cells synthesize and provide trophic signals to nearby neurons, suggesting a role in the regulation of proliferation, survival and differentiation of neurons (for review see [8]).

Stress, glucocorticoids, and the central nervous system

Stress refers to “any threatening situation that induces behavioral or physiological re-adjustments aimed to preserve homeostasis” [9]. Stressors are recognized by specific brain regions that in turn initiate a myriad of changes known as “the stress response”. Stress responses, are composed of alterations in behavior, autonomic function and the secretion of multiple hormones. The hypothalamic-pituitary-adrenal (HPA) axis plays a pivotal role in the coordination of these actions [10]. When a stressor is perceived, the hypothalamus releases corticotrophin-releasing hormone (CRH) which acts on the anterior pituitary to promote the secretion of adrenocorticotrophic hormone (ACTH). This hormone then stimulates the adrenal cortex to release glucocorticoids (GCs) into the bloodstream [11]. In addition, GCs feedback onto pituitary and hypothalamic sites to inhibit the secretion of CRH and ACTH [12]. Through the HPA axis and other systems, the brain regulates the physiological and behavioral responses to stress, with, the brain itself being a target of the mediators of those responses (Fig. 2 summarizes some of the well-known neuroendocrine circuits that participate in the stress response).

GCs in turn, have a varied array of effects upon the brain. These hormones affect all brain cells, including glia [13]. Actions of GCs on brain cells are restricted by the distribution of corticosteroid receptors. There are currently two known corticosteroid receptors in brain: the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR).

MRs have a high affinity for corticosteroids, so they are active even during periods when circulating GCs levels are low. MRs are highly expressed in the hippocampus and the septum, and moderately expressed in subnuclei of the amygdala, the hypothalamic paraventricular nucleus (PVN) and the locus coeruleus (all of them involved in the cognitive, emotional and neuroendocrine processing of stress) [11]. Globally, MR prevents disturbance of homeostasis by regulating the basal HPA tone [10].

GRs are highly expressed in numerous brain regions. These receptors mediate the negative feedback at the hypothalamic and pituitary level of the HPA axis and in other limbic structures [11]. GRs have tenfold lower affinity for corticosteroids than MRs and thus, are highly active only during periods of abundant GC secretion (circadian peak or following stress). Globally, GR activation controls energy metabolism, facilitates recovery of cellular homeostasis, restrains stress-induced responses, promotes information storage and behavioral adaptation [10,13–15].

In the absence of a ligand, these two receptors reside predominantly in the cytoplasm. Upon hormone binding, they are translocated into the nucleus where they act as regulators of gene transcription. Within the nucleus, these ligand-activated receptors interact with other transcription factors or bind to specific DNA response elements resulting in the up- or downregulation of the expression of numerous genes. Through this mechanism, GCs influence the activity of approximately 10% of our genes including those concerned with inflammation and immunity, cell growth, differentiation and apoptosis, endocrine function and metabolism, signal transduction and membrane transport, neurotransmission, and bone turnover [13] (Fig. 3 illustrates the classic intracellular actions of GCs).

The effects of stress and GCs on brain function are being increasingly recognized. Steroid hormones released during stressful conditions substantially influence processes like brain development, reproduction, sexual differentiation, cognition, memory, behavior, synaptic plasticity, neurogenesis, brain homeostasis, and the central immune response (for reviews see [16–19]). Physiologically, GCs facilitate the ability to cope with, adapt to, and recover from stress. However, abnormalities in the HPA and other brain structures have been described in a number of psychiatric and neurological conditions. For example, stress and

high GC levels can suppress neurogenesis [20], compromise cell survival [21,22], induce dendritic atrophy [23], increase loss of excitatory synapses [24], generate imbalances in some neurotransmitter systems [25], change the GR/MR system ratio [16], reduce the production or effectiveness of neurotrophic factors and cell adhesion molecules [26], and so on. With regard to pathological circumstances, there is evidence linking stress and GCs to depression, anxiety disorders, schizophrenia, sleep disturbances, drug abuse, memory loss, and dementia among others (for review see [27]). In addition, some structural changes in areas of the brain that are involved in the regulation of the HPA system as well as anxiety, memory, and decision-making, have been described linked to these conditions. For example, the hippocampus undergoes atrophy in a number of psychiatric disorders, and it responds to chronic or intense stress with dendritic atrophy and a reduction in the number of neurons [28]; the amygdala becomes hyperactive in posttraumatic stress disorder and depressive illness [29]; and the frontal cortex of patients with major depression has been found to exhibit loss of neuronal elements associated with changes in HPA activity [30]. Additionally, glucocorticoids are especially relevant in the therapeutic context. Exogenous GCs are used in the management of a wide spectrum of diseases. Prenatally, their primary use is in the promotion of lung maturation. Postnatally, GCs are used for a variety of diseases, such as autoimmune disorders, hypoglycemia, CNS trauma, meningitis, and myoclonic seizures [13].

Neurobiological mechanisms linking stress and glucocorticoids to glial cell functions

In view of the data covered in the previous sections of this review, it would seem logical to assume that glial cells and glucocorticoids influence a number of common neurobiological processes. On the one hand, glial cells are crucial to understanding hormonal actions in the brain and almost every neuroendocrine event. More precisely, they mediate hormonal signaling in brain, metabolize and synthesize active hormonal metabolites that affect neuronal function, and act as modulators of neurosecretory neurons [2,31]. On the other hand, stress and GC hormones are key modulators of neuronal energy metabolism, central immune response, brain development, synaptic plasticity (for review see [32–34]). Similar to glial cells, stress hormones are often vinculated to pathological conditions of the CNS. In recent years, the existence of both GRs and MRs in glial cells has been clearly demonstrated (see Table 1 for a sample of genes reported to be regulated by stress and GCs in glial cells), yet potential role of glia in stress and the actions of GCs have remained virtually unexplored. In the next section, we present data from a number of studies supporting the central role of particular glial elements in the response of the brain to stress and GCs.

Effects on astrocytes

Among glial cells, astrocytes are the most frequently occurring cells. They are also the most widely studied glial cell, in the context of glial response to steroid hormones and stress-related pathologies.

Recent animal and human postmortem studies strongly suggest that deficits in astrocyte density and function in the limbic regions of the brain contribute to the pathology of stress and glucocorticoid overproduction. Indeed, one of the most consistent findings in animal models of chronic stress is a selective reduction in volume of both, the hippocampus and prefrontal cortex [34]. Yet, the mechanisms behind the GC-induced volume reductions have been classically focused on their effects on neurons. It was shown, for example, that corticosterone treatment and psychosocial stress downregulate neuronal proliferation in the dentate gyrus of adult hippocampus [20]. However, in postmortem studies of patients with a history of high-dose steroid treatment, no reduction in the number of neurons was observed

[30]. This suggests that the volume reduction cannot be completely explained by a stress-induced reduction of neurogenesis. Interestingly, those studies did report a noticeable decrease in the density and number of glial cells [30]. Parallel to these findings, recent animal experiments showed that chronic stress results in depleted gliogenesis in limbic structures such as the hippocampal formation and prefrontal cortex [35]. Moreover, *in vitro* studies showed that dexamethasone –a synthetic glucocorticoid- selectively blocks spontaneous astrogliogenesis from neural precursor cells [36]. Based on these findings, it can be proposed that the stress-induced reduction in astroglia is likely to contribute to the region-specific volume changes commonly observed in stress-related pathologies [35].

It is well known that astrocytes are implicated in neurodegenerative diseases and inflammatory processes [37]. When the brain is injured, they become activated and change their profile of gene expression. Reactive astrocytes are characterized by high levels of glial fibrillary acidic protein (GFAP). GFAP is the main intermediate filament protein in mature astrocytes, and it is highly relevant to the pathogenesis of various CNS pathologies [38]. Accounting for stress and glucocorticoids, this intermediate filament protein has received the most attention. Studies of astrocyte cultures found an increase in GFAP gene expression after short (6 or 24h) and long (3 weeks) exposure to corticosterone. Interestingly, GFAP mRNA levels decreased when astrocytes were co-cultured with neurons [39]. Initial *in vivo* studies reported a decrease in GFAP mRNA content in the rat hippocampus and cortex after chronic corticosterone treatment [40,41]. However, immunohistochemical studies suggest that chronic corticosterone actually increases GFAP immunoreactivity in a dose and subregion-dependently manner [21,42]. Furthermore, in more recent years, animal models of stress have shown that there is a 30% increase in GFAP-immunoreactive astrocytes within the hippocampus after six days of stressful activity [43]. However, reduced density of GFAP-immunoreactive astrocytes has been found in various limbic regions of adult rats exposed to an early-life chronic stress model [44]. These seemingly contradictory results suggest that the regulation of GFAP is very complex. GFAP can be part of a neural protective mechanism at one point, and then it may subsequently produce neural damage depending on dose, brain region and lifetime period.

Astrocytes express virtually all of same receptor types and ion channels found in neurons [8,45]. They have an important function in glutamatergic synaptic transmission. Astrocytes are responsible of eliminating and recycling glutamate from synapses, they uptake glutamate through glial transporters, and then they convert it to glutamine through the activity of the enzyme glutamine synthetase (GS), which is later uptaken by neurons [46]. A current hypothesis holds that excessive glutamatergic activity, especially extra-synaptic glutamate, may be deleterious for neurons and could contribute to the atrophy of apical dendrites seen in hippocampal pyramidal neurons from stressed rats [28]. In this regard, studies on regulation of GS expression established that glial GS is highly regulated by glucocorticoids [46]. Similarly, upregulation of the glial glutamate transporter (GLT-1) in the hippocampus has been reported after chronic stress [47,48]. Thus, corticosteroids might play an important role in the regulation of the recycling of glutamate by induction of GS, and by GLT-1 expression in specific subpopulations of astrocytes in a time-dependent manner [24]. In addition to this, it is now known that GCs inhibit glucose uptake throughout the brain. As a result, astrocytes and neurons have less energy available for the costly task of high-affinity glutamate reuptake, increasing the vulnerability of the brain to other insults. Support for this theory comes from a study conducted in an animal model of chronic cerebral hypoperfusion. This study concluded that chronic mild stress exacerbates the consequences of chronic cerebral hypoperfusion [49]

Astrocytes have also close relationships with blood vessels. Since astrocytes interact with endothelial cells of the blood-brain barrier, then they may play an important role in

maintenance of the barrier properties [50]. Thus, a complex interaction between GCs, astrocytes and other cells of the neurovascular unit has been demonstrated resulting in a modulation of the barrier 'tightness' [51].

Astrocytes can modulate neuronal synaptic plasticity as well. One molecule that might be involved in glia-to-neuron signaling is the calcium-binding protein S100 β . S100 β is found primarily in the cytoplasm of astrocytes, although it is eventually secreted to the extracellular space. A variety of intra- and extracellular functions have been suggested for S100 β , including cell growth, energy metabolism, calcium homeostasis and synaptic plasticity [52,53]. It is not surprising then, that GCs or intense stress can influence the expression or function of S100 β . In this regard, it has been reported that maternal administration of betamethasone (a synthetic glucocorticoid) reduces S100 β concentration in the hippocampal formation and serum in the neonate rat [54]. Stress exposure, on the other hand, increases S100 β concentration in cerebrospinal fluid after either acute predator stress [55] or after chronic restraint stress [56]. Thus, as proposed for other regulative actions of GCs on astrocytes, it looks like S100 β response to stress and GCs follows a biphasic response. Such biphasic response has indeed been observed in astrocyte cultures exposed to dexamethasone [57].

Finally, a new hypothesis proposes that astrocytes may coordinate their function through a newly discovered signaling mechanism, described as Ca²⁺ excitability. This kind of signaling is based on oscillations and the propagation of Ca²⁺ waves via gap junctions. Surprisingly, glucocorticoids were identified as potent modulators of astrocytic calcium signaling via cytosolic receptors[58], suggesting that GCs could also modulate this newly found form of glial cell function.

Effects on microglia and the inflammatory response

Microglial cells are the innate immune cells of the brain. Like astrocytes, they have a role in the regulation of the extracellular milieu and they participate in neuronal regeneration [4]. Like other immune cells, they respond quickly to injury and produce a wide variety of pro-inflammatory molecules, neurotrophic factors, and neurotransmitters [59]. Microglial cells can be activated by several factors including systemic infection, physical trauma, oxygen and energy depletion, and some neurodegenerative disorders [60].

Psychological stress and glucocorticoids have long been shown to suppress immune responses [61]. Thus, GCs could be expected to exert immunosuppressive actions on brain resident microglia. Consistent with this immunosuppressive hypothesis, *in vitro* studies have shown that treatment of microglia with GCs decreases the ability of these cells to proliferate [62], to produce proinflammatory cytokines [63,64], and to produce toxic radicals [65]. These anti-inflammatory actions were confirmed in a spinal cord injury model treated with methylprednisolone [66]. However, recent *in vivo* studies suggested that stress and GCs can enhance immune function within the brain [67]. Restraint stress combined with water immersion, for example, induces massive microglial activation in the rodent brain [68]. In addition, brief tail-shock [68], immobilization [69], and social isolation stress [70] increase the expression of interleukin-1 β (IL-1 β) in the rat brain [71]. Moreover, four sessions of restraint stress were capable of increasing the proliferation of microglia, apparently due to corticosterone-induced, NMDA receptor activation [72]. This proinflammatory evidence has led to the suggestion that stress-induced microglial activation may be involved in the progression of neurodegenerative disorders [73].

Therefore, the aforementioned data suggest that GCs and stress should exert biphasic effects on inflammation in brain. As suggested recently by Sorrels and Sapolsky, GCs and stress are not uniformly anti-inflammatory. In the injured nervous system, only high stress levels of

GCs are pro-inflammatory, while basal or low stress levels have traditional anti-inflammatory effects. Furthermore, the pro-inflammatory effects can depend upon the brain region, kind of GC (synthetic vs. endogenous), and timing of GC exposure [61].

Effects on oligodendrocytes

Oligodendrocytes are small and contain few ramifications. They are found in both, the gray and white matter of the brain. Perineuronal oligodendrocytes are found in the gray matter in close proximity to the neuronal soma, and interfascicular oligodendrocytes are found in the white matter ensheathing unmyelinated fibers. In addition, a new type of non-myelinating glia has been found in brain. These cells express the NG2 proteoglycan and are called *oligodendrocyte precursor cells* because they give rise to oligodendrocytes during brain development [74]. The most important function of oligodendrocytes is the myelination and maintenance of myelin sheaths in the axons of the brain. Myelination is important for rapid axonal conductance and information flow between distant brain areas [75]. Interestingly, glucocorticoids play an important role in myelination and remyelination. In recent years, it has been reported that prolonged glucocorticoid treatment in rodents strongly suppresses the proliferation of oligodendrocyte progenitors (NG2 cells) throughout the white and gray matter of the brain [76], and the injured spinal cord [66]. In addition, early developmental studies suggest that GCs modulate oligodendrocyte differentiation and myelogenesis during development by regulating expression of key oligodendroglial proteins such as glycerol phosphate dehydrogenase (GPDH), myelin basic protein (MBP), and proteolipid protein (PLP) [77]. Moreover, a more recent study conducted during varying fetal stages, found decreased MBP immunoreactivity and oligodendrocyte numbers in response to treatment with betamethasone, with the severity of the effect depending on the gestational age. This suggests a maturation-dependent susceptibility to betamethasone in myelination of the fetal white matter tracts [78].

Glucocorticoids, on the other hand, can exert protective actions on myelinating cells. It was recently found that methylprednisolone (a synthetic GC) selectively inhibits oligodendrocyte but not neuronal cell death [79]. Consistent with this result, dexamethasone treatment was found to accelerate the time of initiation and enhance the rate of myelin formation in cell cultures [80]. Therefore, glucocorticoid effects on oligodendrocytes seem to be dual, ranging from protective to deleterious actions depending on doses, maturational stages or neural regions.

Conclusion

The amount of evidence that has been accumulated over recent years regarding the responses of glial cells to stress and glucocorticoids is likely to change our view on the role of these cells in the neurobiology of the stress response. In this context, further research is still needed into the role of glial cells in the pathogenesis of the so-called stress-related disorders. Whereas studies focusing on the effects on neurons have increasingly reported advances and gained adepts, some questions remain unanswered and should be addressed under complimentary paradigms that take into account glial cells. These cells, making up “the other half of the brain” represent an enormous opportunity to gain deeper understanding into the functioning of the brain in healthy and pathological conditions and might be the key to resolving many of the remaining problems in neurobiology. Accumulated evidence indicates an unknown role of glia in the central response to stress and glucocorticoids. These studies have provided a wealth of data delineating the crucial role of glia, but much remains to be done to fully understand how the stress-glia-glucocorticoid interactions produce pathological or neuroprotective effects. We believe that factors like gliogenesis, reactive gliosis, mielogenesis, glia-to-neuron signaling, inflammatory response or the neurovascular unit (between other glial-related processes), may play an important role in posttraumatic

stress disorder, depression, addiction, schizophrenia, amnesia, and other stress- or glucocorticoid-related pathologies.

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Fig. 1. Glial cells in the adult brain

Astrocytes make contacts with neurons and blood vessels and appear to be strongly associated with synapses. Astrocytes modulate synaptic activity and provide neurons with nutrients. Microglial cells constantly screen CNS tissue and change their appearance as the microenvironment changes. Resting microglia show a characteristic ramified morphology. Activated microglia exhibit a transformed, amoeboid-like phenotype. Oligodendrocytes provide support to axons and produce the myelin sheath, which insulates axons.

Fig 2. HPA axis function

Neuroendocrinological diagram that shows how a perceived threat or stressor activates the Hypothalamic-Pituitary-Adrenal Axis. When the brain perceives stress, the hypothalamus releases corticotropin-releasing factor (CRF), which triggers the release of adrenocorticotrophic (ACTH) from the pituitary gland. ACTH travels through the bloodstream and stimulates the adrenal glands to release glucocorticoids (GCs).

Fig. 3. Intracellular actions of glucocorticoids

The actions of GCs are mainly mediated by the intracellular receptors MR and GR. In the absence of ligands, these receptors predominantly reside in the cytoplasm. Upon hormone binding, they are translocated into the nucleus where they act as regulators of gene transcription. Within the nucleus, these ligand-activated receptors interact with other transcription factors or bind to specific DNA response elements resulting in the up- or down regulation of the expression of numerous genes.

Table 1

Examples of stress-regulated genes in glial cells.

GENE NAME	EXPRESSING CELL	FUNCTION	STIMULI	REFERENCE
Glial Fibrillary Acidic Protein (GFAP)	Astrocytes	Cytoskeleton protein	GCs	[41]
Nerve growth factor (NGF)	Astrocyte cultures	Neurotrophic Factor	GCs	[57]
Interleukin-1 receptor (IL-1R)	Glioblastoma cell line	Immune system receptor	GCs	[81]
Basic fibroblast growth factor (bFGF)	Astrocyte cultures	Neurotrophic Factor	GCs	[57]
Lipocortin-1	Astrocyte cultures	Annexin superfamily	GCs	[82]
Myelin basic protein (MBP)	Oligodendrocytes	Myelinating structural protein	GCs	[77]
Proteolipid protein (PLP)	Oligodendrocytes	Myelinating structural protein	GCs	[77]
Glycerol phosphate dehydrogenase (GPDH)	Oligodendrocytes	Biosynthesis of phosphatides (membrane components)	GCs	[77]
S100β	Astrocytes	astroglial-specific neurotrophic factor	Stress	[83]
Vimentin	Astrocytes	Cytoskeleton protein	GCs	[84]
Transforming growth factor β (TGF-β1)	Microglia	Neurotrophic Factor	GCs	[85]
N-myc downstream- regulated Gene (Ndrβ2)	Astrocytes	Cell differentiation factor	GCs	[85]
Glutamine synthetase (GS)	Astrocytes	Recycling of the neurotransmitter glutamate	GCs	[46]
Glial glutamate transporter (GLT-1)	Astrocytes	Recycling of the neurotransmitter glutamate	Stress	[48]
Na-G ion channel	Astrocytes and Schwann cell cultures	Fast voltage-gated Na(+) channel	GCs	[86]