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Neuroprotective astroglial response to neural damage and its relevance to affective disorders

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Abstract

Astrocytes not only support neuronal function with essential roles in synaptic neurotransmission, action potential propagation, metabolic support, or neuroplastic and developmental adaptations. They also respond to damage or dysfunction in surrounding neurons and oligodendrocytes by releasing neurotrophic factors and other molecules that increase the survival of the supported cells or contribute to mechanisms of structural and molecular restoration. The neuroprotective responsiveness of astrocytes is based on their ability to sense signals of degeneration, metabolic jeopardy and structural damage, and on their aptitude to locally deliver specific molecules to remedy threats to the molecular and structural features of their cellular partners. To the extent that neuronal and other glial cell disturbances are known to occur in affective disorders, astrocyte responsiveness to those disturbances may help to better understand the roles astrocytes play in affective disorders. The astrocytic sensing apparatus supporting those responses involves receptors for neurotransmitters, purines, cell adhesion molecules and growth factors. Astrocytes also share with the immune system the capacity of responding to cytokines released upon neuronal damage. In addition, in responses to specific signals astrocytes release unique factors such as clusterin or humanin that have been shown to exert potent neuroprotective effects. Astrocytes integrate the signals above to further deliver structural lipids, removing toxic metabolites, stabilizing the osmotic environment, normalizing neurotransmitters, providing anti-oxidant protection, facilitating synaptogenesis and acting as barriers to contain varied deleterious signals, some of which have been described in brain regions relevant to affective disorders and related animal models. Since various of the injurious signals that activate astrocytes have been implicated in different aspects of the etiopathology of affective disorders, particularly in relation to the diagnosis of depression, potentiating the corresponding astrocyte neuroprotective responses may provide additional opportunities to improve or complement available pharmacological and behavioral therapies for affective disorders.

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Author contributions

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Conflicts of interest

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Keywords

Astrocytes; neuroprotection; glutamatergic; neurotrophins; synaptic; antioxidant; oligodendrocytes

Introduction

Astrocytes are now acknowledged not only for being general providers of metabolic and structural support to neurons and for their role in responses to gross CNS injury, but also due to their more specific, and no less critical, roles in locally regulating neurotransmitter actions around synapses, buffering cations during action potential propagation, stabilizing myelin maintenance and contributing to action potential regeneration in the WM[1]. Unregulated or persistent interruption of some of those homeostatic roles can surely lead to neural dysfunction and in specific cases to neuronal damage or death [2]. Accordingly, some of these essential properties of astrocytes have been shown to be substantially disrupted or deficient in various neuropsychiatric and neurological disorders, very likely providing a major contribution to their etiology and/or pathophysiology [3, 4]. In the same vein, a case has been made for targeting the restoration of pathologically changed astrocytes or mitigating the effects of their dysfunction as indirect neuroprotective approaches in the treatment of neuropsychiatric and neurological disorders, including affective disorders [5]. In the case of affective disorders, abundant evidence has accumulated showing that, mostly in major depressive disorder, the morphology of astrocytes and the expression of several proteins crucial to their function are reduced in various areas of the prefrontal cortex [3, 4, 6–12]. In human subjects diagnosed with depression specific alterations involve lower levels in the glutamate transporters expressed by astrocytes [4, 13], which are crucial for the regulation of neuronal excitability and synaptic transmission. In the homologous brain region of rodent models of chronic stress and other animal models with depressive-like behaviors there is also a decrease in those astrocytic transporters [14–16] or glutamate reuptake [17, 18]. In addition, animals chronically stressed and humans with major depression also show significantly lowered levels of astrocyte-expressed gap junction proteins connexin 43 (Cx43) and connexin 30 (Cx30), also in the prefrontal cortex [19–23], proteins that are crucial in the regulation of extracellular potassium as well as in the interaction of astrocytes with blood vessels and oligodendrocytes. The contributions of these alterations of astrocytes to the pathophysiology of depression and to behavioral changes in animal models of stress (as a major risk factor for depression) have been the subject of focused attention by many researchers [6], while some experimental approaches for the treatment of depression based on normalizing the decreased levels of the disturbed astrocytes components have been also proposed and explored in animal models of stress and clinical trials [24–30].

In addition to those critical roles played by dysregulation of astrocyte neurophysiology in affective disorders, knowledge is starting to rapidly accumulate showing that that astrocytes themselves can respond to dysfunction and/or damage undergone by neurons or oligodendrocytes to mount responses that protect these cell types from further damage, mitigate deleterious functional effects and ultimately contribute to the restoration of normal neural function [31]. These neurorestorative properties of astrocytes would exist together

with well-known responses of astrocytes that appear to result in variably temporary and localized impairment of neuronal or glial function and growth. The responsive abilities of astrocytes in the face of neural damage, although varied in nature, appear to lead to changes in astrocyte morphology and physiology that convert them into what, starting early in CNS damage studies, has been termed reactive astrocytes. Subtypes of reactive astrocytes as well as reactivity states have been distinguished that betray more or less permanent adaptions to specific environments or stages as they respond to damage or to significant alteration of the neuronal, metabolic or extracellular environment [32]. Astrocytes may also respond to surrounding anomalies in neuronal function/metabolism or to degenerative signals without turning into reactive astrocytes as classically described, but still participating in neuroprotective activity by limiting damage or enhancing restoration of function. Whether characteristically reactive or not, astrocytes would perform neuroprotective tasks by adapting their metabolism and morphology to the altered environment and by releasing metabolites and growth factors that would protect surrounding cells such as neurons, oligodendrocytes and microglia [33]. Thus, putative glia-based neuroprotective enhancements to treat affective and other psychiatric disorders may depend not only on facilitating recovery of astrocytes from their own dysfunctional pathology [34], but also on exploiting the ability of astrocytes to protect against decline or disruption of neuronal and oligodendrocyte morphology and physiology. The ability to profit from or enhancing these astrocytic capabilities to improve overall neural function in depression may provide additional avenues to treat or palliate psychiatric or neurological disorders. The present review, rather than discuss normal physiological and structural features of astrocytes that are compromised in affective disorders to disturb normal neuronal function, will discuss available knowledge on some important properties of astrocytes that activate after or positively contribute to the recovery from pathological disturbances occurring in neurons and oligodendrocytes in those disorders, and that could be leveraged in the treatment of major affective disorders such as major depression.

Neuroprotection and structural changes of astrocytes after neuronal and synaptic damage

The severity of damage to the nervous tissue varies with the type of injury, but when it is extensive or clearly localized as in trauma, infection, blood brain barrier disruption or direct exposure to toxins it often leads to the appearance of reactive astrocytes that proliferate and form a border limitans separating the bulk of the damaged tissue from the less affected surrounding regions [35, 36]. This subtype of reactive, proliferative astrocytes has been distinguished from non-proliferative reactive astrocytes, which will rather respond to less extensively of recognizably damaged pathological tissue and would not form a scar surrounding or within the damaged tissue. Some of these astrocytes have been described as undergoing hypertrophy without proliferations, mostly preserving the extent of tissue reached by the extent of their processes [37]. Since in neuropsychiatric disorders there is very little, if any, macroscopic or overt damage to neurons and myelin (although clearly some forms and localizations of neurological injury lead to psychiatric symptoms) it seems reasonable to think that astrocytes in psychiatric disorders may behave to some extent as that type of non-proliferating astrocytes that appears in some forms of brain trauma, and in

fact some studies in depression have observed that, together with some decreased population density of glial cells, there could be an hypertrophy in the cell bodies of astrocytes in the prefrontal cortex, although the actual significance of this finding is yet to be determined. This type of reactive astrocyte may be involved in responses to neuronal or oligodendrocyte-related dysfunction.

As hinted above, after severe neuronal damage a barrier or structure is formed by enlarged astrocyte processes with or without cell proliferation that was termed “glial scar” since early in CNS injury research, although it is not necessarily a scar in the same sense as scars formed after lesions or damage to tissues with a large connective tissue component, and in fact some researchers dispute that accumulation of reactive astrocytes and their processes should be rightly called a ‘glial scar’ as astrocytes are part of the normal structure of the brain parenchyma [32]. Regardless of the actual pathophysiology and terminology assigned to accretions of reactive astrocytes near damaged CNS tissue, the morphological changes undergone by astrocytes are in response to neuronal and glial damage in the surrounding tissue. An interpretation of the “scar” as a passive limitans zone has led to proposing that the neuroprotective properties of astrocyte-based accretions depend mainly on their ability to physically isolate the damaged tissue from healthier tissue around it, so contributing to avoid spread of the damage [35–37]. Although, on the other hand, the “scar” has been considered under a negative light because, particularly in the CNS of some vertebrates, the scar appears to impair to some extent axon and neurite growth and thus would contribute to reduced plasticity and a perpetuation of local damage [36]. This concept of passive and/or negative functions of reactive astrocytes has progressively changed to ascribe them an important positive neuroprotective role [31, 32, 37, 38] in responses to neuronal damage as researchers have found, for instance, that removal of intermediate filaments GFAP and vimentin, which are at the foundation of the enlargement and motility of astrocyte processes, results in a spread of the region of neuronal damage with only minor effects in facilitating neuroplasticity [39], although some studies show that in particular sites or environments, such as the hippocampus, absence of the cytoskeletal proteins may rather stimulate synaptogenesis [40, 41]. In fact, restrictive actions that contain and isolate damage, and the release/expression of factors that favor neuronal survival, neurite growth and synaptogenesis may be just two sides of the same coin that protects the function and structure of standing neurons from damaged tissue, and promotes their plasticity to effectively recover function [41].

Mitigation of neuronal damage by astrocytes after neuronal or synaptic disturbance may be triggered by astrocyte purinergic $P2Y_1$ receptor downregulation in response to signals provided from surrounding microglia. Agonist binding to those receptors activates Gq proteins leading inositol-triphosphate receptor-dependent stimulation and increases in astrocyte intracellular calcium that eventually may lead to increase neuronal damage [42], while reduced P2Y1 receptors would lead to neuroprotective activity of astrocytes [43]. However, in other conditions, IP3 receptor-dependent calcium increases in astrocytes may lead to increased astrocyte-derived production of cell adhesion molecule N-cadherin which would favor neuronal and synaptic neuroprotection [44], of importance since N-cadherin alterations have been implicates in major psychiatric disorders and the effects of stress [45]. Additionally, activation of GPCR receptors of astrocytes associated with

Gs-type subunits may also result from surrounding disrupted circuits, and lead to increased intracellular cAMP as, for instance, activation of dopamine receptors of astrocytes have been demonstrated to increase their production of GDNF and fibroblast growth factor 2 (FGF2), increases that would elicit neuroprotective responses [46].

Astrocytes have been found to release a variety of small molecules that act on neurotransmitter receptors of neurons and other glial cells. These molecules, some of them the same as neuronal transmitters, have been then called “gliotransmitters”. For instance, evidence is available that upon injury or distress the release of some gliotransmitters such as taurine mainly produced by astrocytes are increased in the CNS [47], increase that may be of importance since various studies have shown that upregulation of taurine in the CNS results in neuroprotection through a variety of mechanisms [48–50], while increases in blood taurine are found in subjects with major depression [51] and taurine itself has been found to show antidepressant-like effects in animal models [52–54].

Furthermore, when damage to the tissue is mild or does not cause a typical glial scar, experimentally impairing astrocytes actually leads to increased neuronal death and higher tissue damage [55]. These neuroprotective responses may depend at least partly on the activity of transcription factors such as STAT3 in astrocytes, as its deletion increases damage and demyelination after CNS injury [56]. A major pathway for astrocytes to detect neuronal injury may depend on the regulation of ciliary neurotrophic factor (CNTF) production by astrocytes. In non-injured brain astrocytes are the main producers of CNTF, although at very low levels [57]. After injury they significantly increase CNTF expression [58, 59]. There is evidence that interaction of neuronal surface molecules such as Thy-1 with integrins in the astrocyte cell membrane keeps the astrocytic expression of CNTF in check, but that in the presence of damaged or dying neurons reduced binding to integrins results in an upregulation of astrocyte-produced CNTF to favor CNTF’s neurotrophic and neuroprotective actions on surrounding neurons [58] and oligodendrocytes.

Responses of astrocytes to neural damage may also include the regulation of excess potassium in the synaptic environment since astrocytes have been found to increase potassium transporter following ischemia in vitro [60]. Increased glucose supply by astrocytes may also be a mechanism for neuronal protection at least in neurological disorders [60]. Both K+ control and glucose supply management may be implicated in depression mechanisms, and astrocytes could participate in regulating them to protect neuronal activity to prevent or mitigate the effects of depression mechanisms or their triggering factors. However, further studies are clearly needed to assess if aspects of extracellular ion regulation and metabolic mechanisms are actually relevant to neuroprotective mechanisms of astrocytes in psychiatric disorders [5, 41].

Neuroimmune activation and the neuroprotective role of astrocytes

When neurons or other glial cells that surround astrocytes are damaged or dysfunctional, abnormal changes in neurotransmitters, ions, metabolites or specific proteins may act as signals for astrocytes to engage their neuroprotective capabilities. In addition, some cells such as microglia, which rapidly activate upon brain trauma, emit signals capable

of downregulating astrocyte purinergic P2Y1 receptors and transform astrocytes into a neuroprotective phenotype that undergoes astrogliosis and protects neurons immediately outside of the damaged area from further damage while encircling and isolating damaged neurons [43]. Astrocytes can also exert neuroprotection by producing molecules such as TGF-ß or orosomucoid which result in attenuated microglial activation [61, 62]. Despite the neuroprotective responses of astrocytes in response to microglia-derived information, it must be stressed that (as in other instances of astrocyte responses during damage) in some circumstances the interaction with microglial cells or cytokines such as TNF-α and IL1-β released by them, rather triggers pathways that locally impair or reduce neuronal function [63], the specific direction of the astrocyte's responses depending on the magnitude, nature and location of the damage [64, 65].

Responses of astrocytes to microglia and cytokine signaling upon cell neuronal damage are of great relevance to understanding the roles of astrocytes in regulating neuronal function and structure in affective and stress-related disorders since depressive symptoms are known to be greatly influenced by alterations in both pro-and anti-inflammatory cytokines, and elevations or decreases of those cytokines are described in those disorders and their corresponding animal models [66, 67]. For example interleukin-6 is heavily released by astrocytes in response to neuronal or oligodendrocyte degeneration and may play a role in limiting release of proinflammatory cytokines by astrocytes themselves and by microglial cells [68] and thus prevent further neuronal damage. However, in depression the available evidence suggests that increased plasma and brain IL6 is due at least partly to astrocytes and may contribute to the activation of amygdalar neurons, which is correlated with enhanced depressive symptoms [68]. Thus, due to the complexity and versatility of astrocytes in immune activation/, leveraging the responses of astrocytes for neuroprotective ends will require specific knowledge of the triggers and intracellular pathway engaged in particular instances of damage.

In addition to a role of astrocytes in detecting and controlling cytokine and microglial disturbances in depression, astrocytes can also lead to neuroprotective responses to neuroinflammation due to their role in the metabolism of neuroinflammation-induced quinolinic (QA) and kynurenic acid (KYNA_ and their intermediaries, which in turn would participate in the alterations of glutamatergic signaling in the brain of subjects with affective disorders [26, 69]. QA and KYNA result from the metabolism of tryptophan (central to affective disorders by being the precursor for serotonin in raphe nuclei cells). Astrocytes hold a complex relationship to the metabolism of those endogenous compounds but the available evidence supports that the production of KYNA by astrocytes is neuroprotective because KYNA is an inhibitor of NMDA receptors [70], which would be overstimulated by excess extracellular glutamate in depression [71, 72]. Since some cytokines acting on microglia and lymphocytic cells stimulate the production of quinolinic acid (agonist of NMDA receptors), astrocytes would play another important role by limiting the actions on microglia and protecting neuronal circuits from excess NMDA activation that would happen because of augmented extracellular glutamate signaling in affective disorders.

Role of astrocytes in synaptic plasticity and reinnervation of neurons deprived of their synaptic inputs

Astrocytes play also important roles in facilitating positive reactivation of postsynaptic neurons in extreme cases of synaptic loss and plasticity. This aspect is exemplified by their role in facilitating synapse formation to repurposing brain areas fully deprived of their normal afferents as it happens in neurons of the visual cortex deprived of their synaptic input after monocular eye enucleation in rodents. In these conditions, the synaptic space vacated by the absent visual inputs is repopulated by neighboring synaptic terminals representing adjacent parts of the visual field or by terminals that are routed from axons of completely different sensory modality that eventually take over the vacated synapses [73, 74]. Remarkably, local astrocytes are not only necessary to the establishment of new contacts as shown by inducing their disappearance, but their experimental activation through Gi-type G protein coupled receptors located on their membranes enhances the process of synaptic plasticity [75]. To the extent that synaptic loss or misfunction is observed in the frontal cortex of subjects with depression or in animal models of stress-induced depression-like behaviors [25, 76–79], as well as in other psychopathologies [80–82] it is then possible that targeting specific astrocyte cellular pathways leading to synaptic plasticity contributes to neuroprotection through synapse normalization and restoration of synaptic function.

Role of astrocytes in neuroprotective regulation of the molecular environment of degenerating neurons

As stated above, some functions and activities of astrocytes are required in supporting neuronal activity in normal conditions, and thus their deficit is deleterious to neurons. However, those functions take on a positive neuroprotective role in the presence of direct damage to neurons as in the case of stroke or more generally hypoxia. For instance, damage to neurites or neuronal death leads to increasing glutamate levels in the extracellular space, which further increases neuronal damage and death. Furthermore, in these conditions, neural tissue injury results in release of factors such as fibroblast growth factor (FGF) and nerve growth factor (NGF), which promote the conversion of glutamate taken up by astrocytes into glutamine, effectively reinforcing the ability of astrocytes to remove extracellular glutamate and redirecting glutamine to neurons to eventually replenishing glutamate in synaptic vesicles [83]. Other neurotrophic factors such as epidermal growth factor (EGF), basic FGF, insulin-like growth factor 1 (IGF1) and CNTF, which are released during neuronal injury, also signal astrocytes to increase the levels or membrane localization of glutamate transporters [84, 85], positively protecting neurons from further harmful stimulation. After cerebral ischemia, this neuroprotective ability of astrocytes can be removed upon knockdown of their expression of glutamate transporter GLT1 with antisense technology [86].

These neuroprotective functions based on glutamate regulation are of relevance to the mechanisms and treatment of affective disorders because studies of functional neuroimaging and genetic polymorphisms have shown that levels of some glutamate transporters are reduced in depression and other psychiatric disorders [14, 87–90], and though in normal

circumstances the available glutamate transport capabilities of astrocytes may be sufficient in the face of increased demand for glutamate removal, their transporting capabilities in depression may be insufficient to protect neuronal function from excess glutamate and thus contribute to an aggravation of depression symptoms or its prognosis. Accordingly, molecules that enhance glutamate reuptake such as riluzole have been shown to mitigate some forms of depression [24, 91, 92].

Another example of a specific neuroprotective role of astrocytes is the production of the antioxidant tripeptide glutathione. Astrocytes contain very high concentration of glutathione as compared to other CNS cells. In stroke or other froms of damage that dramatically increase reactive oxygen species (and thus the risk for fast toxicity to neurons), glutathione released by astrocytes greatly limits neuronal damage due to its potent antioxidant properties [41] as demonstrated in models of hypoxia ischemia or in astrocytes from rodents lacking an enzyme necessary for the formation glutathione [93]. Likewise, several lines of evidence have demonstrated that oxidative mechanisms are increased in the brain of subjects with depression and other psychiatric diagnosis [94–96] making it possible that astrocyte-related antioxidant mechanisms such as glutathione activity limit the extent of the damage that could be reached without those mechanisms. In fact, some long term antidepressant treatments have been found to enhance or increase the levels of antioxidant chemical species in animal models and in successfully medicated patients [97–99], while antioxidant treatments themselves have been proposed to exert desirable antidepressant effects [100, 101].

The hypothesis that monoaminergic deficits are central to depression or other psychopathologies has been significantly modified over the years to recognize that changes in other neurotransmitter systems and the circuits that use them are also an important, if not essential, component of dysfunctional mechanisms in depression [102, 103]. In addition, it has become increasingly documented that some physiological mechanisms, such as those mediated by the stress response, normally trigger the involvement of various neurotrophic factors and other molecules that support neuronal growth and survival, but that, in some patients, the ability to recruit those neurotrophic mechanisms may be substantially diminished, contributing to an eventual diagnosis of depression [103]. In such circumstances, stimulation of the astrocyte capability to produce and deliver neurotrophic factors may prevent further deterioration, effectively providing a neuroprotective mechanism. Some antidepressant treatments originally deemed to simply act through actions on serotonin or norepinephrine transporters have been lately found to promote increases in neurotrophic factors, glutamate transport and even favor antioxidant mechanisms in animal models, suggesting that independent potentiation of neurotrophic mechanisms supported by astrocytes may be a major source of more specific treatments for depression and other psychopathologies with shared mechanisms [104].

In various pathological conditions that jeopardize the function or structure of neurons and their synapses, a role has been described for sex steroids in ensuring the protection of neurons from further damage [105]. In these conditions too, the growth-limiting properties of reactive astrocytes appear to be modulated by sex steroids [106]. However, in neuroinflammatory pathology and other types of neuronal damage, some responsive

astrocytes undergo induction of aromatase expression and consequently stimulation of estradiol production and release, allowing for the mitigation of cell death and the enhancement of neurogenesis brought about by those steroids [107–110]. This protective ability of astrocytes may substitute for the role of neurons in normal, non-injurious physiological conditions, when neurons are the main cells in the CNS expressing aromatase to provide physiological levels of estradiol intrinsic to the CNS [111, 112]. There are also sex differences in astrocyte, microglia and oligodendrocytes and myelin between males and females [106] that may contribute to explain sex-dependent differences in behavioral and metabolic responses may be leveraged for new avenues of treatment.

Accordingly, progesterone increases during brain damage tend to limit the expression of astrocyte features that impair neuron growth such as increased water transport through aquaporins, inflammatory cytokine release, increase in free radicals or excitatory cell death [113], while estradiol overexpression by astrocytes would rather have the opposing effects of enhancing the production by astrocytes of factors that favor neuronal survival and neurite growth [106]. For instance, estradiol is capable not only of reducing astroglial reactivity but also of inducing astrocytes to release neuroglobin and other neurotrophic factors, some of them with neuroprotective and anti-inflammatory properties [114–121]. Actions of estradiol produced by astrocytes in response to synaptic loss or dysfunction may also result in an increase in synapse formation or maturation as has been shown in neuronal cultures supplemented with astrocyte conditioning medium or estradiol itself, while in those conditions tamoxifen, an estrogen receptor modulator, prevents synapse formation induced by astrocyte medium [122].

Astrocytes are well-known for their ability to release metabolites, neurotransmitters and their derivatives as well as some cofactors through a vesicular release mechanism that involves fusion to the cell membrane [123, 124]. In addition, more recent research also shows that astrocytes are capable of forming and dispensing extracellular vesicles or exosomes to their immediate environment [125, 126]. These vesicles are of interest to the theme of these article because evidence is accumulating that the contents of these expelled vesicles may exert powerful neuroprotective action on the neurons exposed to them. For example, Xu et al (2019) [127] have described that microRNA miR-92b-3p contained in exosomes generated by preconditioned astrocytes protects neurons from oxygen/glucose deprivation. It is also possible that another microRNA contained in astrocyte-derived exosomes, miR-34c, plays a role in increasing the survival of neurons after ischemia/reperfusion as shown *in vitro* and *in vivo* rodent models [128]. Small extracellular vesicles derived from astrocytes also may play more specific roles in synaptic plasticity by facilitating synapse formation by using their fibulin-2 cargo, which leads to activation of TGF-beta signaling and enhancement of synapse formation at cortical spines [129]. This recent knowledge on extracellular vesicles complements previous findings that several cell-membrane linked cell-adhesion molecules of astrocytes, and their associated extracellular matrix proteins, are necessary for the formation and maturation of functional synapses [130]. Given recent findings that the cargo of extracellular vesicles in subjects with depression may play specific roles in the disease process and contain markers of neuropathological changes [131], greater attention may have to be given to the ability of astrocytes of producing vesicles with contents that regulate the function or structure of neurons and other glial cells.

Astrocytes in the protection of oligodendrocytes and myelin

Astrocytes not only mount responses that protect the structure and function of neurons and synapses, but are also involved in or are capable of ensuring the maintenance of oligodendrocytes and their myelin [132–134] through a variety of released factors in normal and pathological conditions, as well as of supporting oligodendrocyte precursor (NG2 cells) in the face of several types of damage [135, 136]. Accordingly, despite the neurite growth inhibitory properties of fully declared “glial scars” in severe injury, reactive astrocytes in milder forms of injury, whether scarring or non-scarring, actually can promote remyelination and *de novo* formation of oligodendrocytes [137–139]. This protective function can include enhancing the survival of NG2 cells against oxidative stress, starvation, or oxygen-glucose deprivation through mechanisms mediated by the MEK/ERK and PI3K/Akt intracellular pathways [140], while other studies *in vitro* have shown that erythropoietin (EPO) released by astrocytes can protect NG2 cells subjected to hypoxia, by acting on EPO receptors expressed by NG2 cells [141]. The ability of detecting damage to oligodendrocytes or their myelin and react to promote myelination and survival may be of importance in advancing new treatments for depression, because studies in prefrontal regions of the human brain have shown that, even in the absence of patent demyelination, the expression of some oligodendrocyte-related proteins and/or their corresponding mRNAs as well as microRNAs such as miR21 (abundant in oligodendrocytes) are significantly changed in depression and in animal models of chronic stress [142]. Nevertheless, any enthusiasm derived from our knowledge about NG2 protection by astrocyte activation in experimental models may have to be moderated by a possible involvement of subcortical WM astrocytes in limiting NG2 cell proliferation and myelination after subcortical WM stroke by releasing Inhibin A, which blocks the stimulating actions of Matrilin-2 on NG2 cell proliferation and may delay motor recovery [143].

Another pathway that may be of relevance to the promotion of axon growth and myelination is the binding of TGF-alpha to EGFR in astrocytes, which leads to increased invasiveness of these cells while increasing penetration and axon outgrowth in the lesion [137–139]. Another factor which is also upregulated in dysfunctional or injured states CNTF, has been shown to promote myelination in vitro [144].

Other astrocytic factors with depression-relevant neuroprotective properties

In addition to neurotrophic factors, neurotransmitter related metabolites, anti-oxidant compounds and steroids, proteins or factors that don’t easily fall within those categories have been more recently shown to be significantly upregulated after neuronal and synaptic losses in specific degenerative processes. For instance, the astrocyte-produced humanin, a peptide encoded in the mitochondrial genome, has been suggested to play a protective role for synapses in the hippocampus, and also to be involved in preventing further synaptic dysfunction and cognitive deficits that at times are associated with menopause [145]. Interestingly, it seems that the expression of an isoform of humanin, humanin-like 8, is increased in the prefrontal cortex in major depression [146] and that humanin genes

are differentially methylated in subjects with obsessive compulsive disorder [147], further suggesting a role of these astrocyte-generated humanins in promoting neuronal integrity despite cellular stress in psychiatric disorders, because humanin has been found to exert neuroprotective and antiapoptotic actions in various other conditions [148–151].

Clusterin, an antiapoptotic protein, also known as apoJ, though expressed in both astrocytes and neurons, increases greatly in astrocytes after different types of injury and in neurological disorders [152–154], likely limiting ongoing neuronal damage. Relevant to the present discussion is that clusterin expression in astrocytes has been shown to be neuroprotective in *in vivo* rodent models of ischemia and Alzheimer-like pathology [155, 156], although some *in vitro* experiments have provided conflicting results [157, 158]. Since the bulk of the evidence rather suggests that clusterin potentiates neuroprotection [159], it is possible that its increased expression in astrocytes may contribute to limit neuronal damage, and that this role may limit the consequences of stress in subjects with major depression and other psychiatric disorders. For instance, significant elevations of extracellular clusterin have been detected in the dorsolateral prefrontal cortex of subjects with schizophrenia, being interpreted as a neuroprotective response to continuing neuronal dysfunction and damage in that disorder [160], while in animal models of stress-related behaviors caused by social defeat there appears to be an increase in levels of serum clusterin [161]. In subjects diagnosed with depression in remission, clusterin is also elevated in plasma [162]. Elevated concentrations of corticosteroids, which occur in some forms of depression and are a feature of stress (in itself a major risk factor for depression) can result in significant increases of clusterin expression by astrocytes [163]. These alterations of clusterin in the brain may remain rather local and not necessarily correlate with clusterin changes in the peripheral circulation [164–167], pointing to specific and localized neuroprotective actions on brain circuits.

Conclusion

Depression and other affective disorders involve a plethora of pathological alterations at cellular and molecular levels in several brain regions dedicated to emotional and cognitive processing. The ubiquity of astrocytes, their activation following neural damage and dysfunction, and the variety of sensing mechanisms, metabolites, hormones, neurotransmitter transporters, growth factors, and specific proteins upregulated in astrocytes after damage suggest a complexity of pathways that would be involved in positively protecting injured or threatened neurons and oligodendrocytes. This putative ability of astrocytes to provide neuroprotection coexists with other actions that may aggravate damage in particular circumstances and brain areas. Thus, leveraging the neuroprotective activity of astrocytes to develop or complement new therapeutic approaches for affective disorders will require specific targeting of brain regions and astrocytic pathways that maximize neuroprotective responses while minimizing actions that block neural plasticity.

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Abbreviations

Akt	Ak strain transforming factor
cAMP	Cyclic adenosine monophosphate
CNS	central nervous system
CNTF	ciliary neurotrophic factor
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
ERK	extracellular signal-regulated kinase
FGF	fibroblast growth factor
FGF2	Fibroblast growth factor 2
GDNF	Glia-derived neurotrophic factor
GFAP	glial fibrillary acidic protein
GLT1	glutamate transporter 1
GPCR	Guanine nucleotide-binding protein-coupled receptor
Gq	Phospholipase C-activating guanine nucleotide-binding protein
Gs	Stimulatory guanine nucleotide-binding protein
IL1-β	interleukin-1 β
IL6	interleukin-6
IGF1	insulin-like growth factor 1
KYNA	Kynurenic acid
MEK	mitogen-activated protein kinase (MAPK) kinase
NG2	nerve/glial antigen 2
PI3K	phosphoinositide 3-kinase
QA	Quinolinic acid
STAT3	signal transducer and activator of transcription 3
TGF	transforming growth factor
TNF-α	tumor necrosis factor α
WM	white matter

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