



Astrocytes in Post-traumatic Stress Disorder

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Abstract Although posttraumatic stress disorder (PTSD) is on the rise, traumatic events and their consequences are often hidden or minimized by patients for reasons linked to PTSD itself. Traumatic experiences can be broadly classified into mental stress (MS) and traumatic brain injury (TBI), but the cellular mechanisms of MS- or TBI-induced PTSD remain unknown. Recent evidence has shown that the morphological remodeling of astrocytes accompanies and arguably contributes to fearful memories and stress-related disorders. In this review, we summarize the roles of astrocytes in the pathogenesis of MS-PTSD and TBI-PTSD. Astrocytes synthesize and secrete neurotrophic, pro- and anti-inflammatory factors and regulate the microenvironment of the nervous tissue through metabolic pathways, ionostatic control, and homeostatic clearance of neurotransmitters. Stress or trauma-associated impairment of these vital astrocytic functions contribute to the pathophysiological evolution of PTSD and may present therapeutic targets.

Keywords Astrocytes · Traumatic brain injury · Traumatic events · Neurotrophic factors · Serotonin

Introduction

Exposure to trauma, physical or mental, often acts as an etiological factor in various psychiatric disorders, including depression, anxiety, bipolar disorder, personality disorders, psychotic disorders, and post-traumatic stress disorder (PTSD) [1]. Diagnosis of PTSD as a nosological form is based on the presence of trauma exposure in the anamnesis with a minimum of one month of persistent symptoms and with at least one symptom representing one of the following four clusters: (i) intrusion, (ii) avoidance, (iii) negative mood and cognitive alterations, and (iv) arousal and reactivity [2]. The onset of the illness is triggered by traumatic life events including combat, injury, violence, or natural disasters. According to the different kinds of trauma, PTSD generally emerges consequent to mental stress and/or traumatic brain injury (TBI) with distinct pathophysiology. It is, however, difficult to distinguish between these etiologies; to avoid conflicting semantics, we classify PTSD into mental stress-induced (MS-PTSD) and to TBI-triggered (TBI-PTSD), although both types may (and often do) overlap.

PTSD is associated with substantial medical and economic burdens. Recently, it has been suggested that MS-PTSD should be prioritized as a public mental health focus [3]. As exposure to potentially traumatic events occurs frequently across the world, epidemiological research has drawn a clear link between exposure to traumatic stress and PTSD [4]. It is widely accepted that emotional stimulation involves acute and chronic stressors, both of which strongly impact the central nervous system (CNS), causing behavioral deficits [5–8] and dysregulating multiple physiological systems [9, 10]. Acute stress rapidly alters the activity of the CNS as well as the endocrine system [11]. Chronic stress leads to sustained changes in neural activity

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and gene expression that pathologically affect various molecular pathways [12–14]. Astrocytes play multiple roles in regulating neuronal activity and synaptic plasticity, with growing evidence implicating the contribution of astrocytes to acute and chronic stress in animal models, as well as in mood disorders in humans [15, 16].

Survivors of coronavirus disease-2019 (COVID-19) may be at high risk of PTSD [17]. Controlling the pandemic and taking care of patients with COVID-19 are major tasks worldwide. Epidemiological studies have demonstrated the substantial prevalence of mental health problems among survivors, victims' families, medical professionals, and the general public after epidemics of infectious disease such as the severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), Ebola, flu, HIV/AIDS epidemics [18]. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the pathogen of COVID-19, can damage brain endothelial cells by invading the host serine protease, the renin-angiotensin system, and mitochondria, and increase the susceptibility to PTSD [19]. Damaged endothelial cells contribute to the destruction of the blood-brain barrier (BBB), while increased BBB permeability allows a variety of stress-related molecules, such as angiotensin II, endothelin-1, and plasminogen activator-1, to enter the amygdala,

hippocampus and medial prefrontal cortex (PFC) and activate their receptors, causing downstream reactions [20–22]. The symptoms of PTSD may last long and result in distress and disability. Considering the already large and constantly increasing number of people being exposed to infection, emotional health services targeted at the prevention of PTSD among survivors need to be prioritized. Possible strategies may involve health education, psychosocial support, and counseling services for the general population as well as early therapeutic intervention including psychosocial support, psychotherapy, and pharmacological treatments for vulnerable and high-risk groups.

Astrocytes: Homeostatic and Protective Arm of the Central Nervous System

Astrocytes are homeostatic and defensive cells of the central nervous system (CNS); they are fundamental to the homeostasis of nervous tissue, performing extended and diversified supportive, metabolic, and protective roles (Fig. 1) [23]. Astrocytes contribute to the formation of the active milieu of nervous tissue [24] and provide, through multiple mechanisms, for the maintenance and regulation of synaptic transmission and plasticity [25, 26].

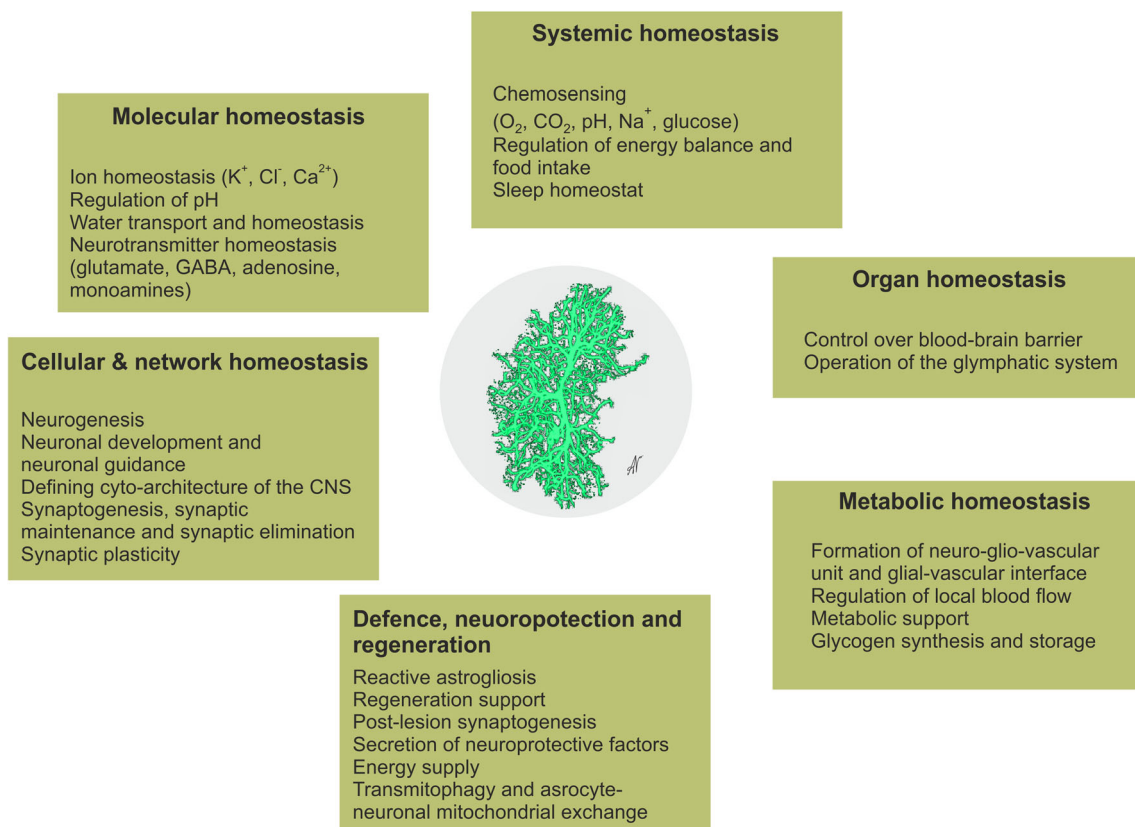


Fig. 1 Functions of astrocytes.

Astrocytes respond to neurochemical stimulation associated with neuronal activity with a transient increase in cytosolic ion concentrations, which are the basis for astrocytic excitability [27]. In particular, intracellular signals mediated by Ca^{2+} and Na^+ regulate homeostatic responses of astrocytes aimed at supporting neuronal function [28, 29]. Astrocytic contribution to the pathophysiology of all neurological diseases may be primary, when changes in astrocytes drive neuropathology; examples may include Alexander disease or psychiatric disorders associated with substantial astrocytic atrophy. Astrocytic changes may also be secondary to the pathological lesion; this class of astrocytopathies is mainly represented by reactive astrogliosis [30, 31]. Mounting recent evidence indicates that astrocytes are involved in the formation and pathological remodeling of fear memories and stress-related disorders [32, 33].

Astrocytes in TBI-PTSD

Mild TBI is a significant predictor of PTSD [34]. The amygdala, a genetically conserved limbic structure [35], is involved in processing emotional and stressful stimulation and is implicated in anxiety and PTSD [36, 37]. After diffuse TBI, neurons, localized in the region of the basolateral amygdala, exhibit increased dendritic intersections in the vicinity to the soma at 1, 7, and 28 days after injury, whereas glial fibrillary acidic protein (GFAP) immunoreactivity increases at 1 and 7 days, indicating the role of reactive astrogliosis in post-traumatic sequelae [38].

Astrocytes control CNS glutamate clearance and support the glutamate (GABA)-glutamine (Glu-Gln) shuttle [23]. Astrocytic glutamate transporters are fundamental for neuronal protection against glutamate excitotoxicity. Brain injury leads to the rapid increase in glutamate in the interstitium [39–41], reflecting massive neuronal release of glutamate following the lesion-induced loss of ionic homeostasis [42]. In recent years, imaging techniques such as magnetic resonance spectroscopy have found that under the pathological state of TBI, the changes of neural metabolites show a complex trend involving many factors, and the changes of various neural metabolites after TBI do not follow the same or similar paths [43]. In general, N-acetylaspartate (NAA) is reduced in the acute and subacute phases of injury and recovers over time. A continuous decrease of NAA reflects the progressive loss of ATP with these neurometabolic alterations modifying the gliotic response [44, 45]. Increases in glutamate and myoinositol, the latter applied as a magnetic resonance imaging (MRI) astrocyte marker because its concentration in astrocytes is several times higher than that in neurons,

occur in the chronic stage of injury [46–48]. Changes in choline, a membrane marker, elevation of which may indicate astrogliosis [49], are more variable and depend on the types and regions of TBI [46, 47, 50]. All these changes in metabolites may reflect altered neuronal viability, integrity, excitability, and astrogliosis [43]. Several magnetic resonance spectroscopy studies support the idea that the increase in myoinositol reflects glial hypertrophy and/or glial proliferation, while myoinositol elevation is also associated with an increase in GFAP expression and immunoreactivity [48, 51, 52]. Increased myoinositol content has found been to be associated with a TBI-related risk of suicide [48, 53]. An elevated myoinositol/ H_2O ratio has been reported in the anterior cingulate cortex impaired by TBI during its chronic stage, which again may be reflective of astrogliosis [48].

The Role of Astrocytes in TBI-induced Secondary Injury

TBI with severe focal tissue damage triggers neuroinflammation essential for the clearance of waste, formation of fibrotic scar, nervous tissue protection, and regeneration, with astrocytes playing key roles in all these processes [54]. Astrocytes can respond to and secrete many immunomodulatory molecules, including cytokines, chemokines, and inflammatory mediators; in addition stressed, injured, or dying astrocytes, similar to other neural cells, may produce and release danger-associated molecular patterns (DAMPs) and alarmins. Prototypical DAMPs, including high-mobility group Box 1, heat shock proteins, and S100 proteins, signal through pattern recognition receptors on phagocytic immune cells to promote the clearance of cytotoxic cellular debris and resolve inflammation [54]. Another archetypal DAMP is ATP, which is massively released from dying cells; ATP action is mediated, at least in part, by the activation of ionotropic P2X_7 receptors [55, 56]. Activation of P2X_7 receptors promotes cerebral edema and neurological injury following TBI in mice [57]. TBI activates Cx43 connexins in hippocampal astrocytes, which results in ATP release, stimulation of P2X_7 receptors, and down-regulation of expression of the glutamate transporter excitatory amino acid transporter EAAT2 [58]. Stimulation of astrocyte pattern recognition receptors by DAMPs activates nuclear factor- κB signaling and the production of proinflammatory cytokines such as tumor necrosis factor α (TNF- α) and α -chemokines as well as the inflammatory mediators cyclooxygenase-2 and matrix metalloproteinase 9 [59–61]. Pathogen-associated molecular patterns, known as PAMPs, such as lipopolysaccharide (LPS), bind to astrocytic pattern recognition receptors and elicit the

expression of immunomodulatory and proinflammatory molecules [62, 63].

In addition to pathogens directly entering the brain through penetrating wounds, the peripheral infection may occur due to peripheral immunosuppression after TBI [64], which may cause the extravasation of PAMPs into the CNS across the damaged BBB. PAMP signals to reactive astrocytes and innate immune cells potentiate inflammation by recruiting blood-borne monocytes, neutrophils, and lymphocytes into the injured brain [65]. Although this pathway is less important than that through the wound, it may occur in the case of secondary meningeal infection.

After TBI, the expression and cellular distribution of the astrocytic water channel aquaporin 4 (AQP4) are affected. These channels lose their polarization to end-feet and glia limitans with a consequent impact on tissue fluid homeostasis and edema formation [66]. Astrogliosis also affects the operation of the glymphatic clearance system [67, 68]. Recent evidence suggests a critical role of the glymphatic system in the clearance of various proteins, including GFAP and S100B, into the blood following TBI [69]. In our previous reports, a decreased presence of AQP4 in astrocytes was triggered in chronic mild stress-induced mice. In this stress-depression model, the function of the glymphatic system was also suppressed, which correlated with anxiety- and depressive-like behaviors [70]. Together, TBI-induced mental malfunction may be partly attributed to the impairment of the glymphatic system by altering the expression of astrocytic receptors and channels, such as AQP4.

TBI induces a significant increase in GFAP immunoreactivity in the basal amygdala 1 and 7 days after trauma [38]. In addition, after TBI, most cortical and subcortical regions show acute increases in glucose metabolism [71, 72] and long-lasting depression of global oxidative metabolism [73]. In contrast, the amygdala shows increased and persistent oxidative metabolic demand after experimental TBI as shown by fluid percussion injury (FPI) [73]. Preclinical models have even shown that FPI enhances fear learning and basolateral amygdala excitatory processing with evidence for reduced GABAergic inhibition [74, 75]. These studies suggest that neurons in the amygdala show different stress responses to TBI than other brain regions, suggesting that astrocytes, which are mainly responsible for neuronal metabolism, may also show specific metabolic patterns that respond to TBI, thus still needing deep studies.

Astrocytes in MS-PTSD

The density of GFAP-positive astrocytes in the hippocampus and frontal cortex decreases after exposure of animals to an inescapable footshock (1 mA at 60 Hz for 20 s) or

restraint stress (immobilized for 6 h/day for 21 days); these decreases correlate with mood and cognitive impairments (Fig. 2) [15, 76, 77]. Autopsy of suicides with depression shows a general decrease in the density of GFAP-positive astrocytes and vimentin-positive astrocytes in postmortem specimens from the dorsomedial prefrontal cortex, dorsal caudate nucleus, and medial thalamus, and a significant increase in the cluster of differentiation 31 (CD31)-positive vascularization in the white matter of the prefrontal cortex [78]. A detailed analysis of changes in the fine morphology of astrocytes and especially in leaflets contacting synapses is needed, as changes in these astrocytic structures are involved in the regulation of synaptic transmission [27]. Stress-enhanced fear learning (SEFL) is associated with an increase in hippocampal interleukin-1 β (IL-1 β), while inhibition of central IL-1 receptors after episodes of severe stress can prevent the development of SEFL. Astrocytes are a predominant source of stress-induced IL-1 β [79], and thus are directly involved in the described alterations.

Gene expression profiles of astrocytes are sensitive to stress disorders [80–82]. Dysregulation of astrocyte gap-junction channel protein expression in the prefrontal cortex of individuals with chronic stress may reflect epigenetic mechanisms [83]. The major astrocytic gap-junction channel-forming proteins connexin (Cx) 30 and 43 are down-regulated in chronic depression and suicidal individuals [80, 81]. These connexins are responsible for intercellular communication, including shuttling of energy substrates and metabolites within astrocytic syncytia [84, 85]. In addition, Cx30 and 43 have an impact on neuronal signaling and plasticity [86–88], while Cx30 is involved in the regulation of astrocytic morphology by limiting synapse invasion [86]. Thus astrocyte hypertrophy is associated with reduced gap-junction channel expression or function in stress disorders [80, 81, 89]. Chronic unpredictable stress, which is sufficient to drive behavioral abnormalities, is correlated with a down-regulation in Cx43 [90], while treatment with selective serotonin reuptake inhibitors (SSRIs) or the glucocorticoid receptor antagonist mifepristone ameliorate the effects of chronic stress on astrocytic Cx43 expression and reverse depressive-like behavior [90].

Sleep abnormalities are known to be associated with PTSD and depression [91–93]. Astrocytes control sleep homeostasis, contributing to the accumulation of adenosine acting on neuronal adenosine A1 receptors [94, 95]. The clinical antidepressive effects of deep brain stimulation depend on astrocyte function, specifically relating to adenosine release and the activation of neuronal A1 adenosine receptors [96]. The sleep-wake cycle is also affected by the astrocytic metabolic network regulated by connexin Cx43 gap junctions [97]. Transcription factor Sox-9 has been reported to be involved in the Wingless and

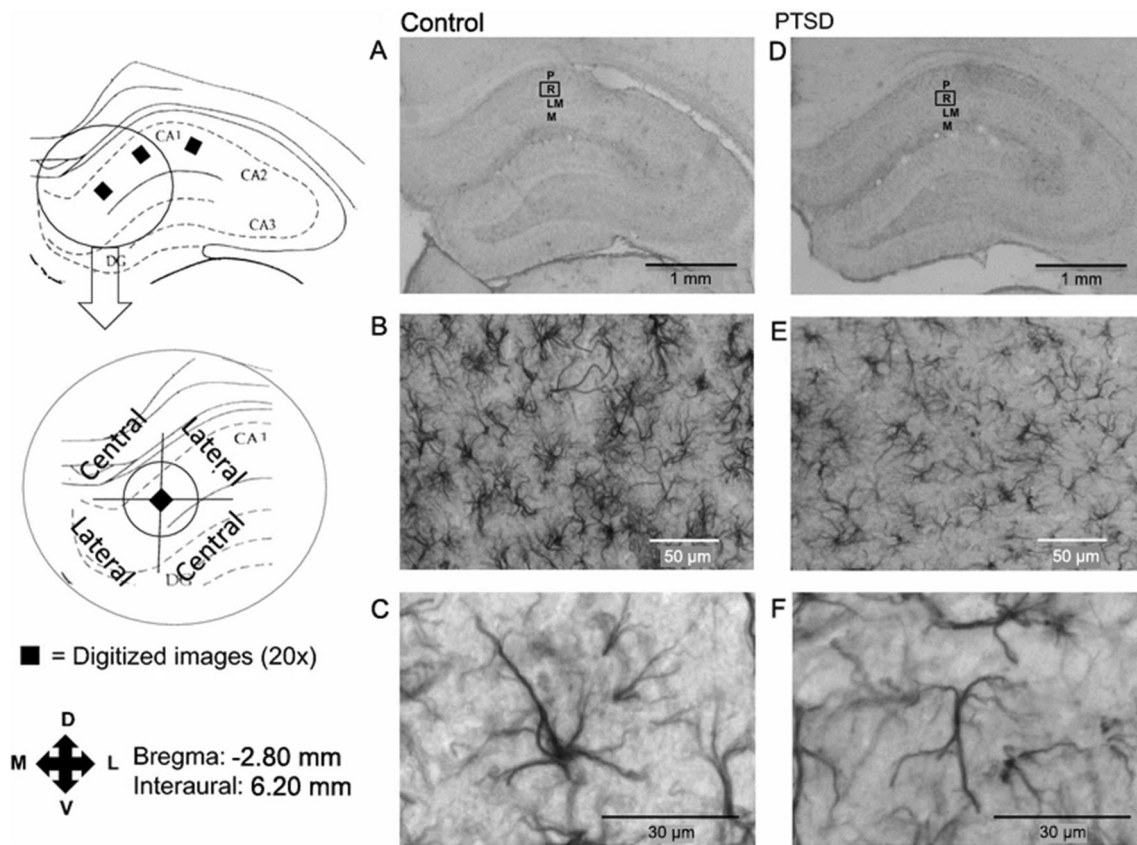


Fig. 2 Digitized images of the hippocampus after GFAP immunohistochemistry showing the CA1 region. **A–C** Control; **D–F** PTSD. **A, D** Digitized images at 1 \times ; **B, E** digitized images at 20 \times ; **C, F** digitized images at 40 \times . Square areas denote regions of interest at 20 \times . P, stratum pyramidale; R, stratum radiatum; LM, stratum

lacunosum moleculare; M, stratum moleculare. The central and lateral quadrants are defined in relation to the stratum pyramidale. Reproduced from Saur *et al.* 2016 [15] with permission from Springer-Nature.

Int-1 (Wnt)/ β -catenin signaling pathway, which regulates the protein expression of Cx43 [98]. Astrocytes specifically express Sox-9 [99], which is decreased in chronic depression and in suicidal individuals [80]. Sox-9 is also involved in the ATP-stimulated proliferation of cultured spinal cord astrocytes induced by extracellular matrix [100].

Chronic stress also affects the astroglia-specific Ca^{2+} -binding protein S100B [101]. This protein is released by astrocytes to control neuronal firing and rhythm generation [102]. The mRNA expression of S100 β in postmortem brain tissue of patients with major depressive disorder (MDD) is significantly decreased [101]. Conversely, the serum concentration of S100 β has been found to be increased during an episode of mood disorder [103]. Our previous studies demonstrated that chronic stress reduces the astrocytic kainate GluK2 receptor, 5-hydroxytryptamine 2B (5-HT_{2B}) receptor, and water channel AQP4, while the antidepressant fluoxetine rectifies those deficits [70, 104–107]. In addition, a recent study used positron emission tomography of the monoamine oxidase (MAO)-B probe [¹¹C] SL25.1188 in patients with PTSD to verify the levels of MAO-B in six

brain regions. It was found that the astrocytic enzyme MAO-B is down-regulated in PTSD, this decrease being greater in PTSD patients with MDD. This indicates that there is a possible loss of astrocytes or independent down-regulation of MAO-B in patients with PTSD, suggesting that PTSD with different phenotypes may be associated with different biological changes [108].

Astrocytes in the Pathophysiology of PTSD

Hippocampal atrophy is one of the most common morphological changes reported in patients with MS-PTSD [109–112]. Hippocampal atrophy, at least in part, may be caused by the loss of astrocytes reported in a PTSD animal model [15, 76]. A decrease in the astrocytic density may induce hippocampal functional impairments. Astrocytes are responsible for synthesizing and releasing many of the neurotrophic factors vital for neuronal health, such as brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor, fibroblast growth factor-2, and nerve

growth factor [113–115]. These neurotrophic factors regulate neuronal growth and are essential for neural plasticity. Reduced availability of neurotrophic agents may increase cellular vulnerability to stress or even contribute to cell death [116]. Reduction in the number and length of dendrites in the cornu ammonis 1 (CA1) region and dentate gyrus of the hippocampus has been reported in an animal model of PTSD [117]. In another animal model of restraint stress, reductions in synaptic spine density and dendritic length in CA1 neurons and atrophy of apical dendrites in CA3 neurons have also been identified [110, 118]. Chronic stress also reduces the length of astrocytic processes by 40%, volume by 56%, and the number of branches in the prefrontal cortex by 58% [119]. Astrocytic processes are critical for neuronal-glia interactions in the active milieu of nervous tissue [24]. In addition, PTSD changes the area of the astrocytic soma, and the single prolonged stress (SPS) model can cause astrocyte cell body atrophy and process thinning [115]. In rat models of heroin-induced fear learning with PTSD-like symptoms, IL-1 β secretion from astrocytes of the dorsal hippocampus is significantly increased, while heroin withdrawal induces a time-dependent, region-specific increase in astrocytic IL-1 β ; thus, subsequent fear learning is blocked by IL-1 receptor antagonism [120].

The noradrenergic (NE) stimulation of α 1-adrenoceptors (α 1-ARs) is implicated in MS-PTSD and other mental disorders that involve dysfunctions of the prefrontal cortex, a region that provides top-down control [121]. The effects of α 1-AR are specifically evident under stressful conditions of high NE release when they strengthen the effective functioning of the amygdala [122, 123] but weaken the cognitive abilities of the prefrontal cortex (PFC) [124]. In the monkey dorsolateral PFC (dlPFC), in which α 1-ARs are prominently expressed in dlPFC layer III astrocytes, increased α 1-AR stimulation contributes to the treatment of under-aroused subjects, whereas α 1-AR blockade is central to treating stress-related disorders such as PTSD [121]. The excitatory effects of α 1-AR arise from the presynaptic excitation of glutamate release, whereas postsynaptic actions suppress firing through Ca²⁺-protein kinase C opening K⁺ channels on spines. The latter may predominate under stressful conditions, leading to a loss of dlPFC regulation under uncontrollable stress. In the clinic, α 1-AR antagonists are widely used for disorders associated with stress and excessive NE signaling. Stress worsens or causes a variety of disorders associated with PFC dysfunction, including depression, bipolar disorder, schizophrenia, and PTSD. Animal studies also indicate that TBI may involve increased catecholamine release and α 1-AR stimulation in the PFC as a key etiological event [125, 126]. There is some evidence of increased α 1-ARs in the dorsal PFC of suicide patients [127] and extensive evidence that PTSD involves excessive NE signaling [128–130].

In addition, K⁺ inward-rectifying K_{ir}4.1 channels, exclusively expressed in astrocytes [131], are thought to be a potential therapeutic target for mental disorders [132, 133]. Astroglial K_{ir}4.1 channels in the lateral habenula drive neuronal bursts in depression (Cui *et al.* 2018), whereas specific inhibition of K_{ir}4.1 rapidly eliminates depression-like behaviors [132, 133]. In particular, K_{ir}4.1 plays critical roles in modulating astrocyte-neuron interactions [134]. In LPS- or SPS-treated mouse models, the expression of astrocytic K_{ir}4.1 is significantly increased in the hippocampus, while reducing hippocampal K_{ir}4.1 promotes fear extinction [135]. Treatment with ginsenoside Rg1 has protective effects by suppressing an increase in hippocampal K_{ir}4.1 induced by LPS or SPS; thus, the intracerebroventricular injection of TNF- α causes impairment of fear extinction by increasing Kir4.1 expression in the hippocampus [135].

Astrocytes and Neurological Complications of PTSD

The prevalence of depressive symptoms in individuals with PTSD suggests that pathophysiological mechanisms contributing to MDDs may be relevant to PTSD, especially for individuals with comorbid PTSD/MDD; however, potential mechanisms of this overlap are poorly understood [136]. A twin study found a significant genetic correlation between the pro-inflammatory cytokine marker IL-6 and depressive symptoms, indicating that the genetics of inflammation and mental health outcomes may be partially shared [137].

Sleep disturbances are the principal symptoms of PTSD [138, 139]. Approximately 70% of patients with PTSD have sleep problems [140]. Disrupted sleep, common to both depression and PTSD, has been linked to an altered hypothalamic-pituitary-adrenal axis (HPA) axis and IL-6 dynamics and to alterations in gene transcription, including that of circadian clock genes in the brain, including astrocytes, radial astrocyte stem cells responsible for adult neurogenesis, and neurons [95, 141–145]. While PTSD is associated with a decrease in hippocampal subfield volume, this is even more strongly associated with insomnia in the population studied [146, 147].

As reported by us previously, astrocytic NLR family pyrin domain containing 3 (NLRP3) inflammation is activated and associated with depressive-like behaviors in mice under sleep deprivation [148, 149]. Sleep deprivation promotes a gradual elevation in extracellular ATP, which activates astroglial P2X₇R purinoceptors. This, in turn, selectively down-regulates the expression of 5-HT_{2B} receptors in astrocytes (Fig. 3; [148]). In sleep-deprived mice, the antidepressant fluoxetine alleviates the activation of NLRP3 inflammation, the reduced release of IL-1 β /18,

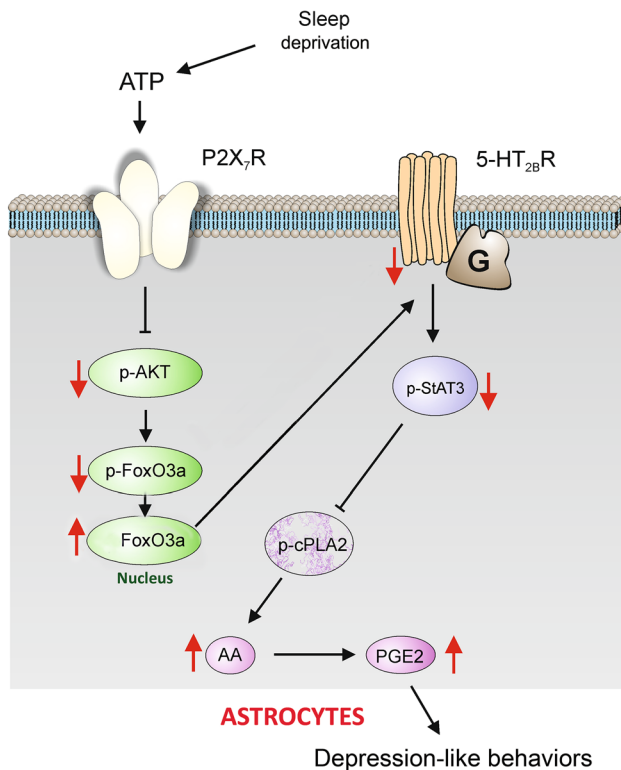


Fig. 3 The expression and function of 5-HT_{2B} receptors are selectively decreased by sleep deprivation (SD) through P2X₇ receptors in astrocytes. Prolonged SD stimulates P2X₇Rs by ATP, activated P2X₇Rs suppress the phosphorylation of AKT and forkhead box O3 (FoxO3a) in the cytoplasm, and the dephosphorylated FoxO3a accumulates in the nucleus of astrocytes. The increased FoxO3a down-regulates the expression of 5-HT_{2B}Rs, and the phosphorylation of signal transducer and activator of transcription 3 (STAT3) is also decreased, which relieves the inhibition of the phosphorylation of cPLA2. The activated cPLA2 promotes the release of arachidonic acid (AA) and prostaglandin E2 (PGE2), eventually causing depression-like behaviors. Red arrows indicate the increase of function; black arrows show stimulatory pathways, while black lines with the bar denote the inhibitory pathway. Reproduced from Xia *et al.* 2020 [148] with permission from Springer-Nature.

and depressive-like behaviors by stimulating 5-HT_{2B}R [148, 149]. Hence, astrocytes play key roles in the relationship between sleep disorders and depression and likely also PTSD.

Pharmacological Treatments of PTSD

Psychopharmacological treatment is commonly used to treat PTSD despite limited evidence of its effectiveness; only SSRIs sertraline and paroxetine are approved by the US Food and Drug Administration [150, 151]. The main therapeutic focus is on treating the consequences of PTSD, as the disease impacts an individual's ability to engage in daily activities, and on enabling those living with PTSD to

promote wellness, role competence, and satisfaction while improving their quality of life [152, 153].

Serotonergic modulation of mood, anxiety, and impulse control, and empirical demonstrations of abnormalities are strongly manifested in PTSD patients [154, 155]. SSRIs are used as therapeutics for PTSD. Relatively high doses of sertraline or paroxetine are sometimes prescribed to patients with PTSD as off-label treatments for non-responders [151]. SSRIs may help to treat PTSD by reducing amygdala hyperactivity: chronic daily administration of fluoxetine, paroxetine, and sertraline has been shown to be beneficial [37]. SSRIs act as emotional stabilizers, but the underlying pharmacological mechanisms are unclear. Generally, therapeutic strategies are aimed at neurons (monoamine hypothesis [156], hypercortisolism hypothesis [157], BDNF hypothesis [158], and myo-inositol hypothesis [159]). None of the antidepressants developed based on these theories can alleviate all the symptoms of mood disorders in all patients. More attention has therefore been paid to the role of astrocytes in the pathogenesis of depression and the pharmacological mechanism of antidepressants.

Five classic SSRIs, fluoxetine, fluvoxamine, sertraline, paroxetine, and citalopram, are widely used as antidepressants and anxiolytics in the clinic. Chronic treatment of cultured astrocytes with SSRIs increases the mRNA expression of Ca²⁺-dependent phospholipase A2 (cPLA2) [160, 161]. Chronic treatment of mice with fluoxetine increases the expression of cPLA2-specific mRNA solely in astrocytes, as has been demonstrated in experiments with fluorescence-activated sorting of neurons and astrocytes in transgenic animals [105]. When administered acutely, fluoxetine at 10 μmol/L triggers cellular Ca²⁺ signaling, transactivates the phosphorylation of epidermal growth factor receptor (EGFR), and phosphorylates downstream extracellular signal-regulated protein kinase 1/2 (ERK1/2). The latter enters cell nuclei and regulates the mRNA and protein expression of cFos and FosB, consequently changing the expression of several key proteins [162]. Chronic treatment with 10 μmol/L fluoxetine, which acts as an agonist of astrocytic 5-HT_{2B} receptors increases the protein expression of cPLA2, kainate receptor GluK2, subtype 2 of adenosine deaminases acting on RNAs, transient receptor potential canonical 1 channel, L-type Ca²⁺ channels Ca_v1.2, caveolin-1 and BDNF [104, 107, 149, 163–165]. Finally, at low concentrations (< 1 μmol/L), fluoxetine decreases the mRNA expression of c-Fos by the phosphoinositide 3-kinases/protein kinase B (PI3K/AKT) signaling pathway, whereas at higher concentrations (> 5 μmol/L), fluoxetine elevates c-Fos through the mitogen-activated protein kinase (MAPK)/ERK signaling pathway (Fig. 4; [166]).

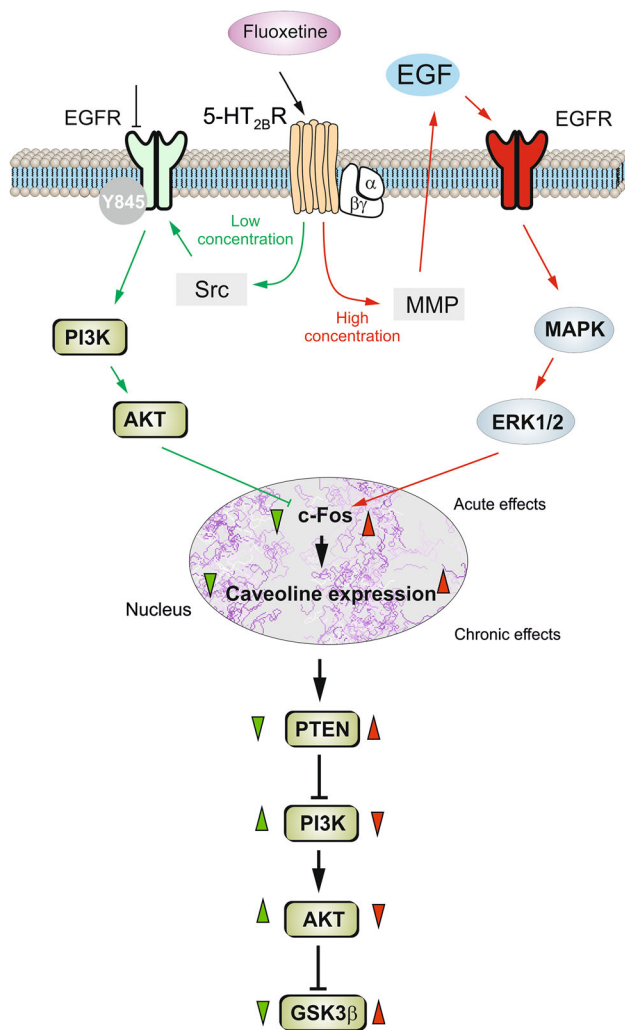


Fig. 4 Schematic of biphasic concentration-dependent regulation of caveolin-1 (*Cav-1*) gene expression and glycogen synthase kinase 3 β (GSK-3 β) activity by fluoxetine in astrocytes. Acute treatment with fluoxetine at low concentrations (green arrows) stimulates the Src protein tyrosine kinase which phosphorylates EGFRs and activates the PI3K/AKT signal pathway. The AKT phosphorylation by fluoxetine at low concentrations inhibits *cFos* gene expression, and subsequently decreases *Cav-1* gene expression (chronic effects) that in turn, decreases the membrane content of phosphatase and tensin homolog (PTEN), induces phosphorylation and stimulation of PI3K, and elevates GSK-3 β phosphorylation thus suppressing its activity. At higher concentrations, fluoxetine (red arrows) stimulates metalloproteinase and induces shedding of growth factor which stimulates the EGFR and activates the MAPK/ERK1/2 signal pathway. The ERK1/2 phosphorylation by fluoxetine at high concentrations stimulates *cFos* gene expression, and subsequently increases *Cav-1* gene expression (chronic effects), that acts on PTEN/PI3K/AKT/GSK-3 β in an inverse fashion. Green arrowheads show effects of low concentration, whereas red arrowheads show effects of high concentrations of fluoxetine. Reproduced from Li *et al.* 2017 [166] with permission from Springer-Nature.

Astrocytic dysfunction is potentially the main pathological basis for the co-morbidity of PTSD and sleep disturbances [106]. In particular, astrocytes support the

glymphatic system [167] responsible for the clearance of brain metabolic waste by paravascular pathways. Polarized expression of astrocytic AQP4 to the endfeet is critical for glymphatic operation [168]. In our previous report, chronic treatment with chronic mild stress or blockade of the glymphatic pathway *via* the AQP4 antagonist TGN-020 also increases the level of A β 42 in the frontal cortex and hippocampus [70]. Fluoxetine up-regulates the expression of AQP4 in astrocytes and promotes the clearance of A β 42 *via* accelerating the circulation of the glymphatic system, and the associated depressive-like behaviors are also improved [70]. Some special inducers, such as overloaded iron, worsen the dysfunction of the glymphatic system by triggered reactive astrogliosis in the cortex and hippocampus, as indicated by an increase in GFAP expression, and exacerbates the depressive-like and anxiety-like behaviors induced by chronic mild stress, associated with the more serious neuronal apoptosis [169].

Besides SSRIs, other agents have also been reported to have therapeutic effects on PTSD. Prazosin, an α_1 adrenoceptor antagonist, is effective for the reduction of nightmares and sleep-related hyperarousal in PTSD [170–173]. Cognitive deficits involving working memory and executive function in PTSD are associated with alterations in prefrontal dopamine function, so dopamine projections from the ventral tegmental area to the amygdala are directly involved in the processing of fear signals [174]. Roitman *et al.* (2014) [175] showed that treatment of 10 PTSD patients with δ -9 tetrahydrocannabinol, a naturally-occurring cannabinol receptor agonist found in the marijuana plant, results in a nonsignificant improvement in intrusive and recurring PTSD symptoms but significantly improves sleep disorders.

Conclusion and Future Directions for Research

We summarized the latest research advances in the etiology and therapeutics of PTSD as well as its peripheral complications. The pathophysiological and psychological mechanisms of PTSD are still unclear and as a result, treatments remain symptomatic. Astrocytes play important roles in the pathogenesis of PTSD. Astrocytes secrete numerous neuromodulatory, neurotrophic and inflammatory factors and sustain neuronal networks by providing metabolic support and removal of waste. Research on astrocytes in PTSD needs more rigor and effort. According to our previous studies, astrocytic 5-HT_{2B} receptors play key roles in mood disorders, including MDD and bipolar disorders, and sleep disorder-related emotional changes [106, 148, 149]. Meanwhile, five SSRIs can regulate the same targets, such as cPLA₂ in astrocytes [176]. Activation of cPLA₂ specifically releases arachidonic acid from the

sn-2 position of membrane-bound phospholipid [177]. It has repeatedly been reported that selective serotonin reuptake inhibitor (SSRI) treatment can normalize regional decreases in brain metabolism occurring during the major depression, decreases that are more pronounced with the lower the plasma concentrations of arachidonic acid [178]; similarly, emotional stabilizers (lithium salt, carbamazepine, and valproic acid salt) have the same sites (cPLA₂, inositol, GluK2, and others) in astrocytes [179]. Moreover, research on the effects of astrocytes on the pharmacological mechanisms of PTSD medicines is limited.

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Conflict of interests The authors declare no competing interests.

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