Mini Review

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Glial pathology in neuropsychiatric disorders: a brief review

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Abstract:

Neurons have been considered the major functional entities of the nervous system that are responsible for most of the functions even though glial cells largely outnumber them. However, recent reports have proved that glial cells do not function just like glue in the nervous system but also substantially affect neuronal function and activities, and are significantly involved in the underlying pathobiology of various psychiatric disorders. Dysfunctional astrocytes and degeneration of glial cells are postulated to be critical factors contributing to the aggravation of depressive-like symptoms in humans, which was proved using animal models. Alteration in glial cell function predominantly targets three main brain regions – the prefrontal cortex, limbic areas including the hippocampus, and the amygdala, which have been extensively studied by various researchers across the globe. These studies have postulated that failure in adopting to the changing neurophysiology due to stress will lead to regressive plasticity in the hippocampus and prefrontal cortex, but to progressive plasticity in the amygdala. In this present review, an effort has been made to understand the different alterations in chronic stress models in correlation with clinical conditions, providing evidence on the defective maintenance of glial function and its potential role in the precipitation of neuropsychiatric disorders.

Keywords: amygdala, depression, glial cells, hippocampus, prefrontal cortex, stress

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Introduction

In the 19th century, an anatomist named Rudolf Virchow was the first to identify non-neuronal elements, and he called those as “glial cells.” These specialized, quiet, and supportive “glue” cells were thought to be adhered to neurons and are unable to participate in information processing. However, present-day research has reformed this perception by providing solid evidence in support of the glia being a very important and dynamic partner to neuronal cells. This supportive cell helps neurons in driving brain metabolism and synaptic neurotransmission, as well as helps the communication between neurons in an active form [1]. There are four types of glial cells: astrocytes, oligodendrocytes, microglia that are present in the central nervous system, and Schwann cells that are present in the peripheral nervous system. Along with the aforementioned supporting cells, a few population of cells are also found in the brain called polydendrocytes (NG2 cells), which function in re-myelination and have the capability to proliferate and differentiate after demyelination during insult due to excitotoxicity [2]. Astrocytes are known to play a key role in inflammatory and neurodegenerative processes. They are transformed into reactive astrocytes to release various inflammatory cytokines like interleukins (ILs) and tumour necrosis factor (TNF), along with activation of microglia and oligodendrocytes. These reactive astrocytes are mainly expressed under pathological conditions, and their main function is the regulation of neuroinflammation and revamping of tissue [3]. During this condition, glutamate, an excitatory neurotransmitter, is released, which is balanced by the inhibitory action of γ -aminobutyric acid (GABA). Astrocytes play a very important role in the maintenance of the glutamate/GABA balance in the central nervous system. Malfunctioning of GABA neurotransmitters is involved in the defective uptake, metabolism, and recycling of glutamate, which causes abnormal glutamate/GABA balance and leads to excessive accumulation of glutamate in the synapse. The glutamate/GABA balance is maintained by the glial cells, and any kind of instability in their ratio leads to imbalance. Alongside astrocytes, the microglia is responsible for triggering innate immunity by participating in events through synaptic maintenance during injury or neuroinflammation [4]. Activation of microglia

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near the site of inflammation releases a large amount of glutamate, leading to microglial-induced neurotoxicity, regulating poor N-methyl-D-aspartate (NMDA) receptor signaling [5], as shown in Figure 1. This condition drives the microglia to release pro-inflammatory cytokines such as IL-1 β , IL-6, interferon- γ , and TNF, causing damage to the microenvironment. Following this, many caspase-dependent cascades are activated, leading to neurodegeneration by microgliosis. Studies in magnetic resonance spectroscopy have shown glial loss due to reduced GABA release, leading to precipitation of depressive episodes. In parallel to this, evidence suggests that the spillage of glutamate will be cleared by glial excitatory amino acid transporters present in glial cells, and these are found to be altered in the depressive phenotype [6]. Hence, impaired synaptic glutamate balance may lead to glutamate-induced overactivation of extrasynaptic glutamate receptors, causing excitotoxicity and cell death, which are hallmark causative factors of several neurodegenerative disorders.

Figure 1: Normal synaptic transmission (A) and glutamate-induced excitotoxicity (B). In normal condition, glutamate activates metabotropic glutamate receptors (mGluR), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), and NMDA and signaling. Altogether, they increase calcium, which, in turn, favours the activation of several biochemical cascades (CaMK, ERK, and CREB) responsible for the formation of trophic factors for LTP. Excess glutamate is taken away from the synaptic cleft by the excitatory amino acid transporter (EAAT) present on glial cells. This will be converted to glutamine (Gln) and back to glutamate (Glu) by astrocytes. During pathological conditions, calcium ions increase due to overactivation of receptors triggered by unnecessary glutamate release by microglial cells, neurons, and damaged reactive astrocytes in the post-synaptic cleft. The recycling mechanism of unnecessary Glu fails due to the degeneration of astrocytes along EAATs. Ultimately, this causes various metabolic pathways that result in the death of the microenvironment due to glutamate excitotoxicity.

Chronic stress and glial pathology

Stressful events lead to a dysfunctional hypothalamo-pituitary-adrenal (HPA) axis. In response to chronic stress, the HPA axis is activated by triggering the release of glucocorticoids (GCs) from adrenal glands. Increased GC is a predisposing factor for the physiological basis of dysfunction, including hypertension, ulceration, suppression of the immune system, and reproductive impairment. The neurocircuitry response of stress includes the activation of the paraventricular nucleus of the hypothalamus, which triggers the release of the corticotrophin-releasing factor (CRF). The CRF influences the anterior pituitary to release adrenocorticotrophic hormone into the bloodstream, stimulating the adrenal cortex to synthesize and release GCs. Prolonged stress mainly causes the hyperactivation of the HPA axis, resulting in increased release of GC, which co-releases glutamate, producing excitotoxicity [7]. HPA axis dysfunction leads to hippocampal and cortical atrophy, which will further disinhibit the HPA axis. This condition instigates degeneration of astrocytes due to excessive accumulation of glutamate in the synaptic cleft, leading to disruption, damage, degeneration, and death of surrounding neurons. This insult relates to glial cell ablation, and manifest in the progression of depression and related symptoms in stressed animals. The development of depressive-like symptoms may be due to glutamatergic overexcitation led by neuromodulatory dysfunction, indicated by the differential expression of glial fibrillary acidic protein (GFAP) in different brain areas.

Glial alterations were not only reported in depressed patients, but were also seen in several animal models of depression [8]. A growing body of evidence coincides with the neuropathology, signifying the role of glial function and dysfunctions related to psychiatric disorders, such as major depression and anxiety-related diseases. During chronic stress conditions, the microglia undergoes remodelling, which helps its cells engulf the toxins released as the end product of degenerative changes. In particular, three regions are more vulnerable to degenerative changes due to the impact of chronic stress: the hippocampus – important for the formation and consolidation of new memories; the amygdala – associated with fear and anxiety; and the prefrontal cortex

(PFC) – important in decision making, working memory, and extinction of learnt memories. The hippocampus and PFC, which provide negative feedback regulation of the stress response, are particularly vulnerable to degenerative changes [9]. In contrast, the amygdala, which is critically involved in mediating a positive feedback regulation on the stress response, increases anxiety-like behaviour [10], and this might influence stress-related effects by precipitating into depressive behaviour and modulating hippocampal function [10].

Chronic stress-induced glial alteration in the frontal cortex, hippocampus, and amygdala leading to depression

Frontal cortex

Hypersecretion of the stress hormones adrenalin and cortisol results in an imbalance of physiological and behavioral responses. During the acute stress response, this may be beneficial, as it may promote improvement in memory and help in staying viable for future exposure. Yet, repeated stress for a longer duration triggers increase in enhancement stress mediators, initiating neuronal atrophy and impairment in memory in the hippocampus and PFC. Hence, stressful events result in excessive release and accumulation of GCs, which are seen predominantly in the above-mentioned regions of the brain. Due to failure in negative feedback regulation of the HPA axis during stress, there is an excessive accumulation of glutamate, leading to excitotoxicity, atrophy, and death of hippocampal and fronto-cortical neurons. Banasr and co-workers [11] have extensively reported the glial pathobiology with respect to depression. GFAP, a marker of astrocytes in the CNS, was found reduced in some of the cortical and limbic/fronto-limbic areas of depressed subjects as well as in animal models used in studies on stress and depression. The GFAP levels were low in the hippocampus, amygdala, and cerebellum of patients with stress and stress-associated disorders such as major depression, bipolar disorder, and schizophrenia. Hence, it is validated that astrocytes play a crucial role in modulating synaptic function during the stress and in many alterations particularly with GABAergic, serotonergic, noradrenergic, and glutamatergic pathways of neuromodulatory systems. Abnormal glutamatergic pathways have also been shown to contribute to excitotoxicity and impaired uptake of glutamate and reduced glutamate metabolism due to chronic stress [12].

The strongest glial pathology was seen in the PFC of patients with mood disorders [13] with astrocytic abnormalities leading to neuronal pathology. Evidence from morphological studies of the PFC indicates the reduced neuronal size and glial cell density in depressed patients. The decrease in the GFAP level was also documented in the frontal cortex of younger depressive patients, which includes the dorsolateral PFC, orbitofrontal cortex, anterior cingulate cortex [14], and hippocampus [15]. However, it is unclear whether this glial loss plays a direct role in the expression of depressive symptoms. Banasr and co-workers [12] have reported that chronic unpredictable stress (CUS) leads to reduced glial cell numbers along with depressive-like behavior. CUS animals administered with L-alpha-aminoadipic acid, gliotoxin, showed reduced glial cell count and symptoms of depressive disorders. Moreover, CUS relatively increases caspase-3 expression in pyramidal neurons and disrupts glial metabolism, thereby reducing the expression of GFAP in the PFC [11]. Furthermore, histological studies on post-mortem brain samples showed reductions in other glial subtypes like oligodendrocytes in the anterior cingulate cortex, oligodendroglial satellite cells and dorsolateral PFC in schizophrenia [16]. These changes lead to volumetric reductions along with demyelination of neurons, resulting in dysfunctions in the frontal lobes. Defective information processing in the PFC due to glial alterations is accompanied by cognitive and emotional disturbances, which are some of the most common features seen in major depressive disorder (MDD) patients, resulting in impaired decision making and loss of interest or attention with suicidal tendencies [17].

Hippocampus

The hippocampus plays an instrumental role and is the most crucial among the brain structures, as it is implicated in learning and memory. The memory storage and retrieval processes involved in episodic, declarative, and spatial learning are the main functions of the hippocampal subregions. Spatial navigation and emotion-related functions are unsurprising because of the structural complexity of distinct subregions of the hippocampus. All these are achieved due to its highly sensitive brain possessing component with a remarkable degree of plasticity regulated by the neuroendocrine response [18]. However, chronic stress is known to alter the density and size of neuronal and glial cells in the fronto-limbic brain regions, leading to neurodevelopmental abnormalities and progressive changes. However, budding evidence specifies that glial pathology could be a factor that

contributes to the pathophysiology and possibly the etiology of stress-induced depression. Animals subjected to CUS show decreased GFAP expression with depressive-like behavior [19]. The reduction of the glial population [11] forms a very vital factor that may contribute to the reduction of volumes [20] due to elevation in GCs by lowering the GFAP levels [20, 21]. Western blotting and immunohistological studies have shown that the decrease in the expression of GFAP and GFAP-expressing glial cells possibly due to excitotoxicity in the different areas of the hippocampus [22]. Chronic stress causes profound atrophy of the astrocytic processor length, branching, and volume, with the decrease in astrocyte numbers by GFAP labelling [23]. Cytological and imaging studies of patients with schizophrenia manifested abnormalities in the white matter to myelin ratio, and its integrity has been well studied using myelin-associated markers indicating a decrease in oligodendrocytes [24]. Neuroinflammation indicated by microglia is responsible for releasing cytokines and free radicals that damage the white matter, precipitating psychological symptoms [25]. Reduction in hippocampal neurogenesis aggravates depressive-like symptoms, which are associated with cognitive abnormalities like learning and memory impairment, difficulties in decision making, and loss of interest or attention, which is co-morbid with suicidal tendencies. Chronic stress induces secretion of GCs, which are known to cause a significant redistribution of apical dendrites and alters spine density [26]. In addition, chronic stress causes significant reduction of GC receptors (GRs), which take part in metabolism and the regulation of stress and neurotrophic factors like brain-derived neurotrophic factor (BDNF) and its receptor required for plasticity [21]. Apart from BDNF, other neurotrophic factors such as nerve growth factor, glial cell-derived growth factor, vascular endothelial growth factor (VEGF), neurotrophin-3 (NT), and NT-4/5 are responsible for maintaining a favourable microenvironment for the nourishment of neurons and for balancing the glial ratio [27]. Based on post-mortem and neuroimaging surveys done in MDD patients, many studies draw a linear similarity in chronic stress models with a reduction in hippocampal neurogenesis and decreased trophic support, contributing abnormal neurotransmission by glial cells.

The glial population plays a major role during angiogenesis and neurogenesis by enabling protection to migrate neuronal precursors, which will be interrupted by chronic stress, leading to the death of newly formed neurons. These glial cells tremendously support and nurture neuronal precursors, which are essential for neuronal survival, growth and differentiation of progenitors, and enhancement of synaptic plasticity with good synaptic efficiency [28]. Glial cells also release neurotrophic factors, and withdrawal will change the normal glia to reactive astrocytes and lead to a predisposition to cell death or damage. Hence, the formation of new glial cells via gliogenesis is equally important to neurogenesis through the precursor NG2.

Hence, the glia plays a prominent role as a potential therapeutic target for different antidepressants, as chronic administration of medications and electroconvulsive seizure increases the neurotrophic support produced by the glia [29]. It is also significant that the chronic stress-induced decrease in neuronal density may also be affected by the death of older granule neurons, which shifts the fluid balance, resulting in shrinkage of the hippocampus.

Amygdala

The neural circuitry of chronic stress and depressive conditions shows overactivation of the HPA axis, which is reflected through elevated plasma cortisol levels and adrenal gland hypertrophy. The HPA axis is negatively regulated by the hippocampus, and the PFC is critical for certain forms of learning and memory. Contrarily, the HPA axis is positively regulated by the amygdala [30], which is involved in signature symptoms of stress, i.e. regulating fear and anxiety phenotypes. Patients with HPA axis and limbic system dysfunction also exhibit hippocampal and cortical atrophy as a causative factor for depression [31]. In the amygdala, extensive progressive dendritic remodelling [10], [32] was seen, and this was due to the positive modulation of the HPA axis during stressful events (Figure 2). The impact of stress on amygdalar function has also been studied in detail at several levels of its organisation. At the cellular level, stress causes persistent dendritic growth with the formation of new dendritic spines in the basolateral nucleus of the amygdala [33]. Studies have shown the development of anxiety-like behaviour after chronic stress exposure [34]. This was signified with retraction of the spines in the medial nucleus of the amygdala facilitated by molecular changes like overexpression of serine protease tissue-plasminogen activator in the amygdala, and BDNF [21]. Furthermore, transgenic overexpression of the neurotrophin BDNF has also revealed an initiator effect on anxiety-like behaviour due to increased spinogenesis in the basolateral amygdala. Therefore, stress affects the amygdala in a contrasting fashion compared to the hippocampus, and the structural plasticity of the amygdala may be a key substrate that may help in investigating affective pathologies related to stress-induced depression. It has been shown that amygdalar gliosis and aberrant NG2 cell expression are associated with psychiatric disorders like temporal lobe epilepsy and schizophrenia [35]. Post-mortem studies suggest that schizophrenic patients exhibit decreased oligodendrocyte density in the amygdala compared with age-matched controls [36].

Figure 2: Impact of chronic stress-induced changes at three major areas of the brain related to cognitive functions. Failure of the hippocampal and frontal regions in controlling stress effects leads to hypotrophy, whereas amygdalar hyperactivation induces hypertrophy.

Acute and chronic stress resulting in neuronal remodelling of synapses and dendritic branching in the basolateral amygdala (BLA) and medial amygdala are accompanied by an increase in anxiety. Exposure of rodents to chronic stress has shown abundance in GR immunoreactivity in amygdalar cells both in neurons and astrocytes. This is in parallel with post-mortem samples of depressed patients showing significantly higher GR protein level in the amygdala compared to control subjects. The GR protein levels in the human amygdala are the signposts of increase in cortisol by chronic stress, and this may be responsible for the aetiology of stress, anxiety, and associated depression. Most chronic stress models have shown alterations in the volumes of the amygdala, but there is only one cue-based study on fear conditioning demonstrating increased volumes of the bed nucleus of stria terminalis (BNST), but not the amygdala. Although the BNST is directly involved in the regulation of the HPA axis, it did not alter the amygdalar architecture but showed hyper-anxiety without influencing fear conditioning or locomotion and exploratory activity. Hence, this confirms that chronic stress influences the BNST structure and function to modulate emotional behaviour due to maladaptive response [37]. Astrocytic number reduction affects neuroplasticity due to maladaptive synapse maintenance and inappropriate secretion of neurotrophin. This may predominantly affect different brain areas in a region-specific manner and is thought to be involved in the neuropathology of many psychiatric illnesses. The relevance of the glia population is a topic of discussion nowadays in many preclinical studies. For example, chronic stress and corticosterone administration have shown a significant reduction in cell proliferation in the medial PFC. It was found through microarray and quantitative PCR (qPCR) that the level of several oligodendrocyte markers in the PFC was lowered in patients with bipolar disorder [38]. Extreme loss of myelination induced by cuprizone, a demyelinating drug, exacerbates anxiety and associated behavioural response in preclinical experiments; hence, it is linked with human psychotic circumstances [39]. A study from Tynan and co-workers [23] has shown stress-induced profound atrophy of astrocyte process length, branching, and volume without changing the number of astrocytes marked with GFAP-positive stain in immunohistological studies. This suggests that stress may lead to astrocyte-mediated disturbances, due to remodelling of the astrocyte network, without disrupting the quantity. The alteration in GFAP expression was also documented in other studies, like in Alzheimer's disease [40]. In addition, overexpression of neurotrophic growth factors like BDNF and VEGF was seen followed by chronic stress in the amygdalar area. This was correlated with upregulation of GFAP, which, in turn, led to increased basolateral amygdala volumes, which also contributed to anxiety-like phenotype in stressed animals. These animals also exhibited defective hippocampal-dependent learning and memory in a partially baited radial arm maze task, with reduced GFAP and GRs in the hippocampus and PFC [21].

Conclusion

Glutamate release is one of the main culprits of numerous psychiatric illnesses like depression and anxiety due to excitotoxicity. Excitatory neurotransmitter glutamate released by glial cells plays a significant role in the pathophysiology of stress and associated abnormalities. Most important, the glia subtypes like oligodendrocytes, astrocytes, and microglia are modifiers that play critical roles in the release and uptake of glutamate in the synaptic cleft, and any abnormalities in them can cause damage to surrounding areas. Hence, the glial cell structure and morphology indicates the degeneration of astrocytes in an animal model of stress and depression. However, the existing reports are insufficient to explain the structural, biochemical, and behavioural responses caused by glial alterations or neuronal dysregulation. They are interlinked, and it is very difficult to distinguish anatomically how nervous system alterations are led by supportive cells. Overall data from var-

ious studies show a linear correlation indicating the role of the glia in aggravating the symptoms of several psychiatric illnesses.

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