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Glia and Psychiatry: A Narrative Review

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ABSTRACT

This work reviews the development of glial cells, gliotransmission, the glial role in brain aging, also the mechanisms of glial cell communication. Current concepts on the importance of glia are shown in pathologies such as schizophrenia, autism spectrum disorders, affective disorders, anxiety, acute/post-traumatic stress disorders, and Alzheimer's disease.

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Introduction

Glial tissue was described more than a century ago by Virchow and later by Ramón y Cajal. It was thought that they only worked to passively support neurons; however, neuroglia is composed of very heterogeneous cell types responsible for numerous homeostatic functions [1]. Glia represents more than half of the cells in the human nervous system, have multiple functions, and unlike previously hypothesized, are involved in novel processes such as nervous system development, neuronal plasticity enhancer, neuroinflammation, and neuropsychiatric diseases, among others [2].

In 1988, George Somjen advanced important insights into the role of glial cells in the brain; however, in the last two decades, the fundamental role of glial cells in mental illness has become evident. These glial cells play a transcendental role in the development, function of the brain, and the physiopathology of neuropsychiatric diseases. In the central nervous system (CNS), astrocytes, oligodendrocytes, and microglia emerge as the major glial cell types, each with significant importance in synaptic function, neuronal metabolism, and cell migration [3,4].

It is vital to recognize the relevance of glial cells and their close interaction with the other components of the nervous system; to better understand brain function and neuropsychiatric diseases. Appropriately addressing the role played by glial cells in these diseases may provide a more complete picture and allows the development of new therapeutic targets.

Glial Cell Development

During the Cambrian period, about 500-540 million years ago, glia is thought to have emerged, which would have played a crucial role in CNS protection in emerging vertebrates. It is postulated that early glia contributed to axonal myelin sheathing and improved the efficiency of the potential of action of neurotransmission. Therefore, glia is hypothesized that has a fundamental role in brain homeostasis and immune response in present-day organisms [5].

The marked disparity in neuronal density between humans and other primates, such as chimpanzees, is notable. This difference suggests that humans possess a greater volume of glial cells compared to neurons. This cellular arrangement shows that glial cells play a prominent role in the processing of information in the human brain. Over the past 2 million years, there have been significant changes in neurohormonal regulation in the human brain, driven by self-amplifying feedback processes. These modifications in neurohormonal regulation and glial cell interaction have contributed not only to the increased size and function of the modern human brain but also to an increased susceptibility to psychopathology [5].

An example of these changes is seen in Homo erectus (1-8 million years ago), which exhibited a marked increase in physical activity levels and total energy expenditure compared to australopithecine and great ape lineages. These selective processes enhanced aerobic mechanisms and modified the thermoregulatory response, which in turn led to increased production of growth factors, such as brain-derived neurotrophic factor (BDNF), through regulation of genes such as peroxisome proliferator-activated receptor, coactivator-activated receptor γ (PGC-1α), and myocyte enhancer

factor 2 (MEF2), which stimulate BDNF expression. Changes in thermoregulatory processes that were crucial for increased physical activity in archaic human lineages could have had evolutionary consequences on BDNF-dependent glia expression, with altered proinflammatory markers in the nervous system associated with neuropsychiatric disorders. These findings suggest that the interaction between BDNF and glia plays a key role in the evolution of the human brain and the emergence of neuropsychiatric disorders, opening new perspectives to address and treat these disorders from an evolutionary perspective [1,5].

These changes and differences in glia in humans have diverged and acquired unique properties during evolution. This supports a more complex and functionally diverse neuronal network in hominins. However, although this diversification and enhanced functionality of astrocytes may be beneficial, it may also have a negative effect, as their dysfunction may be linked to the occurrence of neuropsychiatric and neurodegenerative disorders in humans [6]. The origin and development of glial cells from regional progenitors play a role in the diversity of their functions. Radial glial cells act as stem cells in the developing CNS and generate both neurons and microglial cells, including astrocytes and oligodendrocytes. These cells undergo different phases of neurogenic and gliogenic competence [6].

Oligodendrocytes develop from oligodendrocyte progenitor cells (OPCs), which undergo a series of stages including proliferation, differentiation, maturation, and migration [4,5]. Molecules secreted by astrocytes, such as neuroregulin, BDNF, ciliary neurotrophic factor (CNTF), insulin-like growth factor 1 (IGF1), and osteopontin, play a key role in the regulation of oligodendrocyte myelination. However, it has also been observed that astrocytes can secrete factors such as BMP2/4 and hyaluronan, that inhibit this process, showing a dynamic activity [6-8].

On the other hand, studies in rodents have identified that microglia develop from primitive mesodermal myeloid myeloid precursor cells in the yolk sac, they migrate to the CNS before the formation of the blood-brain barrier (BBB). This process is also conserved in human embryonic development [5,9,10].

Astrocytes originate from neural progenitor cells or radial glial cells in the ventricular zone of the brain. During the first weeks after birth in rats, increased proliferation of astrocytes is observed in the hippocampus. These newly generated astrocytes migrate into the cortex through the processes of radial glial cells, where they proliferate and mature until they reach their final location [9].

Glial Neurotransmission

In most regions of the brain, neuronal synapses are accompanied by the presence of astrocytes, which is a third component that interacts with synaptic terminals, also called tripartite synapses. These astrocytes play a crucial role as regulators of synapses by modulating and coordinating the levels of neurotransmitters and neuroactive ions while preventing the propagation of erratic signals to adjacent synapses. Their proximity to the synaptic cleft is essential to support synaptic activity. In addition, perisynaptic astrocytes can sense neuronal activity through specific receptors, which triggers intracellular responses such as modulation of calcium levels, among others [6,11,12].

By feedback, astrocytes respond to calcium and neurotransmitters, which regulates the release of "gliotransmitters" such as purines, D-serine, lactate, thrombospondins, among others. These molecules modulate the activity of surrounding glial cells and local neurons, establishing a bidirectional communication between astrocytes and neuronal synapses. In addition, recent research has revealed that astrocytes also send direct signals to neuronal synapses by releasing cytokines with a significant impact on the development and maturation of synapses and brain circuits [6,8,11-13].
Lactate is involved in the production of BDNF, an essential factor for neuronal plasticity and learning [12,14].

In recent years, the concept of the "quaternary synapse" has also been consolidated, whose fourth actor is the extracellular matrix (ECM) and its components, such as glycoproteins and CSPGs (chondroitin sulfate proteoglycans), which play an essential role in brain development and plasticity [14,15].

Other molecules of the ECM include: HepaCAMs (hepatic and glial cell adhesion molecules), which are highly expressed in astrocytes near inhibitory synapses and regulate synapse density and function; neuroligins, present in both neurons and astrocytes are associated with neuropsychiatric disorders and play a role in regulating the balance between excitation and inhibition at synapses; and finally, neuronal cell adhesion molecules (NRCAMs) are involved in binding between astrocytes and neurons and influence the formation of inhibitory synapses [1,6,14,15].

Glia in Brain Development and Function

Glial cells are fundamental components of the CNS and play a key role in the brain's immune response. Microglia and astrocytes are responsible for regulating and maintaining the balance of neuroinflammation in the CNS, playing essential roles in the homeostasis and protection of neuronal tissues. In addition to their role in myelination, oligodendrocytes play a crucial function in regulating potassium balance, providing metabolic support [4,15].

Microglia are activated by pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), releasing cytokines and chemokines that fight neurotoxicity and neurodegeneration. During activation, microglia change morphology, microglia phagocytoses apoptotic neurons, eliminates weak synapses and promotes the survival of pyramidal neurons. It also regulates AMPA and NMDA receptor expression at thalamocortical synapses and participates in the production and migration of inhibitory cells in the cerebral cortex. Activated microglia produces cytokines and nitric oxide, polarizing towards M1 (proinflammatory) or M2 (anti-inflammatory) phenotypes. M1 polarization is induced by interferon-alpha (IFN-α) and tumor necrosis factor-alpha (TNF-α), whereas M2 polarization is triggered by interleukins IL-4, IL-13, and IL-25. However, these concepts are still under scientific discussion [5,9].

Microglia are involved in early neurodevelopment through the process called synaptic pruning, it plays a phagocytic role through the complement system by labeling and eliminating synapses, apoptotic cells, or other cellular structures, specifically C1q, C3, and C4 molecules. These molecules act as signaling molecules for microglia to eliminate labeled synapses during neurodevelopment and aging. Studies in mice have shown that inhibition of C1q or C3 interferes with normal microglia-mediated synapse elimination, which can result in aberrant synaptic elimination, as has been found in Alzheimer's disease [6,9,16].

Astrocytes are involved in the formation and integration of neuronal networks. They release various molecules, such as BDNF, hevin, thrombospondin, and TGF-β, which promote synaptogenesis and

strengthen synaptic connections by stabilizing AMPA receptors. They are involved in the formation and maturation of dendritic spines and neuronal survival. They regulate cerebral blood flow, form part of the BBB, respond to changes in neuronal activity, and mediate cerebral water and potassium homeostasis. They express transporters to uptake GABA and glutamate from the synaptic cleft. These neurotransmitters are broken intracellularly into glutamine, which is then supplied to neurons, as an energetic material [6,9,11].

Glia and Aging

Brain aging is a complex and multifactorial process that includes among others: a decrease in synaptic plasticity, intercellular communication, oxidative stress, neuroinflammation, altered neurotransmission, decreased neurotrophic factors, and altered water-ion balance. However, oxidative stress and neuroinflammation are the most important findings [17]. During normal aging, the number of neurons does not change significantly, but there is a decrease in the number of synapses. Glial dysfunction is one of the causes leading to brain aging and neurodegeneration [18-20].

Aging is possibly caused by changes in glial cells, leading to an inflammatory microenvironment and thus to neuronal and synaptic loss. However, at the cellular level, it has not been elucidated how glia changes and modifies their structure and function. In aging: a decrease in white matter, change in cholesterol synthesis, mitochondrial dysfunction, decrease in energy production, and antioxidant action have been described. An important finding is that microglia in aging show reduced branching, increased growth, and increased production of cytokines, chemokines, and trophic factors; but altered remyelination of the white matter of the brain remains the core finding [12,19,20].

Glia and Neuropsychiatric Diseases

Alterations in white matter associated with genetic aberrations in oligodendrocytes have been observed in some mental disorders, such as anxiety, obsessive-compulsive disorder (OCD), depression, bipolar disorder (BD), autism spectrum disorder (ASD), schizophrenia (SCZ), among others. These abnormalities are related to symptoms in motor coordination, breathing, language, sensory and cognitive perception. Abnormal neuroinflammatory responses of glial cells are important in synaptic pathology through dysregulated communication. These findings support the hypothesis that myelin defects and dysfunctional glial responses contribute to the affective and cognitive symptoms in mental disorders [3,5,9,15,21,22].

Oligodendrocytes express connexin genes such as the human (GJC2) and mouse (mCx47). In humans and animals, expression of GJC2 and mCx47, respectively, is essential for oligodendrocyte function and ensures proper myelination [6,11,15].

Gap junction channels (GJC) between oligodendrocytes and astrocytes have been studied, which have documented their relevance in glial cell homeostasis, as well as in the renewal and maintenance of myelin in the CNS. It has been postulated that communication through these interglial connections is crucial to ensure an adequate energy supply. Indeed, loss of this intercellular communication can result in energetic dysfunction, which triggers demyelination and axonal degeneration. Studies in rodents have provided additional evidence suggesting that pharmacological inhibition of GJCs and hemichannels can elicit behavioral symptoms characteristic of some mental illnesses. Microglial activation in combination with additional neuroinflammatory mechanisms affects neuronal integrity and synaptic plasticity through dysregulated cytokine production that alters protein release and synaptic pruning [5,9,22].

Glia and Schizophrenia

Postmortem studies in SCZ patients revealed alterations in oligodendrocytes, including changes in size and density, as well as myelin damage in brain areas such as the prefrontal cortex and striatum. This is suggested to be related to increased microglial density and activation [3,15,22,23]. These findings support oligodendroglial dysfunction and myelin disruption as important factors in SCZ, and point to a complex interplay between oligodendrocyte, myelin, and glial cell inflammatory responses in the pathophysiology of the disease [3,5,9,24,25].

SCZ is associated with an increased inflammatory state, in which microglia express increased amounts of proinflammatory cytokines such as IL-1β, IL-6, among others. Studies analyzing CSF samples from patients with SCZ demonstrated high albumin levels and increased release of the proinflammatory cytokines IL-6, IL-8, and TNFα leading to an impaired BBB and interfering with CNS insulation from harmful immune responses [5,9,24-29].

Abnormal elimination of synapses by microglia has been found in SCZ, possibly due to an altered expression of proteins of the complement system. This has led to the study of the use of anti-inflammatory drugs including minocycline, which possibly reverses this expression; minocycline could not only reduce the severity of negative symptoms in SCZ patients but also have neuroprotective effects and reverse the effects of inflammation in the hippocampus in rodent models [5,9,16,22,25,27,28,30].

There is evidence that astrocytes show changes in gene expression, morphology, and function in SCZ; among them, the expression of several genes, such as excitatory amino acid transporter 2 (EAAT2), d-amino acid oxidase (DAO), thrombospondin1 (THBS1) and calcium-binding protein S100B (S100β). In addition, key oligodendrocyte, and myelin-related genes, such as the oligodendrocyte lineage (Olig) genes, MOG, and the proteolipid protein (PLP) coding region have been found to decrease in SCZ [3,25-27]. Alterations in the expression of astrocytic proteins have also been reported in SCZ, such as GFAP and aldehyde dehydrogenase1 of the L1 family (ALDH1L1), which are common markers of astrocytes in the CNS [9].

Likewise, there is a reduction in the number of astrocytes in the nucleus accumbens, basal nuclei, cingulate cortex, and substantia nigra pars compacta; with the motivational implications that these findings contemplate. Increased numbers of astrocytes in the periventricular space have been also found in this disorder. Decreased oligodendrocytes in the anterior thalamic nucleus in patients with SCZ and alterations in oligodendrocytes in the prefrontal cortex, manifested by dystrophic and degenerative changes in the ultrafine structure of pericapillary oligodendrocytes could have implications for brain function and symptoms associated. However, these results are not consistent across studies, suggesting that the astrocyte response depends on the affected brain region [3,9,23].

Research has observed that primary astrocytes from DISC1 mutant mice show decreased glucose uptake and lactate production. This metabolic dysfunction is relevant as SCZ is associated with altered CSF glucose levels; leading to think astrocytes may influence brain metabolism and have consequences for neuronal dysfunction affecting energy supply and metabolic processes for proper brain

functioning [9,22,23,27,31].

In the two-hit hypothesis of SCZ, the first hit is the dysregulation of the glucose signaling pathway in the CNS. This dysregulation primes the brain for pathological response to the second hit, which occurs through the astrocytic glycogenolysis signaling pathway. This model established concepts in enzyme kinetics and glucose metabolism and suggests that both events are necessary to trigger SCZ symptomatology. These findings highlight the importance of investigating the metabolic mechanisms involved in this neuropsychiatric disease to develop more effective and novel therapeutic approaches [9,25,27,32].

Astrocytes play a key role in regulating glucose delivery to neurons via glucose transporters. However, in a dysregulated astrocyte-neuron compartment, glucose uptake dysfunction occurs, resulting in glucose leakage into the interstitial space [9,25,27,32].

This alteration in glucose gradients, between the interstitial fluid and blood vessels causes activation of surrounding microglial cells. The activated microglial cells respond by increasing the production of proinflammatory cytokines, such as interleukin-1β (IL-1β), IL-6, and BDNF that would let to the expression of psychotic symptomatology. Glucose deprivation may further sensitize microglial cells and increase the release of inflammatory mediators [9,24-26,29,31].

Changes in CSPG, the main component of the ECM, have also been described in this pathology, which could play a central role in the neuropathology of the disease. Studies have shown a significant increase in glial cells, mainly astrocytes, expressing CSPG in areas such as the lateral nucleus of the amygdala and lateral entorhinal cortex in patients with SCZ, without evidence of reactive astrogliosis. Also reduced CSPG contents have been observed in the perineuronal network (PNN) in these areas. This suggests that an alteration in the secretion or internalization of ECM components by astrocytes could be responsible for the observed changes and abnormalities in the PNN. In addition, a significant decrease in the number of PNN in the prefrontal cortex (layers III and V) has been observed in patients with SCZ. Abnormalities in CSPG and PNN expression have also been described in the olfactory epithelium of these patients, with a marked reduction in their expression around mature neurons [22].

Antipsychotics suppress microglial cell activity by inhibiting the secretion of inflammatory cytokines. Some specific interleukins, such as IL-10 and TGF-α, are considered markers of SCZ status and increase during the acute phases of the disease but normalize with the use of antipsychotic medication. On the other hand, IL-12, IL-2, interferon-α, and TNF-α are characterized as trait markers and remain elevated during the inter-critical phases, regardless of antipsychotic medication [5,24-26,29].

Cannabis has been associated with a worsening of schizophrenia symptoms and an increased risk of developing schizophrenia in vulnerable individuals. Glia express cannabinoid receptors. CB1 receptors in astrocytes are G-protein coupled which activates phospholipase C and increases intracellular calcium and then glutamate release occurs. CB1 receptors have the potential to modulate glutamatergic neurotransmission in schizophrenia. Administration of Δ9-THC leads to microglial activation and increases proinflammatory markers. A possible antipsychotic treatment with cannabidiol or CB1-CB2 antagonist could play a key role in the treatment of schizophrenia via glial cells [13,25,27,30].

Glia and Mood Disorders

In patients with major depressive disorder (MDD), white matter alterations have been found in the early stages and may worsen with each depressive episode. Patients with the first episode show alterations in fractional anisotropy on diffusion tensor neuroimaging in several white matter regions, including right middle frontal, left lateral occipito-temporal, and right parietal lobe angular and subgyral gyrus. In addition, reductions in fractional anisotropy were found in the corpus callosum, suggesting a decrease in interhemispheric communication and connectivity in the brain of depressed patients. Increased myelin-associated proteins have also been observed in serum, possibly due to the breakdown of myelin sheaths or that the BBB is similarly compromised in patients with MDD [4,15].

Post-mortem studies have revealed that in depressed patients who died by suicide, there is a reduction in the expression of astrocyte-specific connexin proteins (GJB6; mCx30 and GJA1; mCx43) and oligodendrocytes (GJB1; mCx32 and GJC2; mCx47) in cortical and subcortical brain regions. In addition, decreased mRNA of myelin-related proteins has been found in the orbitofrontal cortex of MDD patients. These findings suggest that MDD affects connexin expression in oligodendrocytes and astrocytes, also affecting brain myelin [15].

Several autopsy studies have reported a decrease in the number or density of GFAP-expressing reactive astrocytes in different brain regions of MDD patients. These regions include the locus ceruleus, orbitofrontal cortex, amygdala, and hippocampus. In addition, reduced levels of the GFAP protein and gene have been observed in other brain areas, such as the cerebellum, dorsolateral prefrontal cortex (DLPFC), prefrontal cortex, thalamus, and caudate nucleus in these patients [3,6,33].

Nerve injury-induced protein 2 (Ninj2), a membrane adhesion molecule, was initially identified in myelin-forming Schwann cells in the peripheral nervous system. Ninj2 has been shown to induce neurite outgrowth by facilitating cell interaction. In the central nervous system, Ninj2 is expressed mainly in cells belonging to the oligodendrocyte lineage. Loss of Ninj2 leads to an activation of TNFα-induced necroptosis by binding directly to TNFα receptor 1 (TNFR1) and increased production of C-C Motif chemokine ligand 2 (Ccl2), which could mediate signal transduction from oligodendrocytes to neurites. These findings highlight the importance of Ninj2 in communication between oligodendrocytes and neurons, and its disruption may contribute to depressive symptomatology [4].

In BD has been observed a specific decrease in four oligodendrocyte-associated proteins in the prefrontal cortex of patients. These proteins are 2′,3′-cyclic nucleotide 3′ phosphodiesterase (CNPase), MOG, myelin basic protein (MBP), and myelin proteolipid protein (MYPR). The decrease in the expression of these is more pronounced in patients with bipolar disorder compared to SCZ and MDD, although in the latter the decrease is also observed, although to a lesser extent [3].

The TRANK1 gene, which contains the tetratricopeptide repeat and ankyrin repeat 1, has been identified as a robust risk gene for BD. The TRANK1 protein is secreted by immune cells, and it is widely distributed in bodily tissues, including brain regions such as the hippocampus, and amygdala. Although the exact implications of the TRANK1 gene in BD are not fully clear, a recent analysis of the mRNA co-expression network has revealed that it interacts with genes like glycogen synthase kinase-3 (GSK-3α/β), which

are involved in modulating synaptic plasticity, neural growth, and circadian rhythm [21].

A recently recognized neuroinflammatory basis has emerged. Proinflammatory mediators have been found in the peripheral system, such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α), as well as neuroinflammatory markers in the CNS. These findings suggest that neuronal inflammation is relevant in BD and could be important for understanding its etiology and exploring new therapeutic strategies [21].

Glial Cells and Obsessive-Compulsive Disorder

Neuroimaging studies in patients with OCD have revealed alterations in white matter volume in different circuits, as well as changes in myelin integrity in regions such as the orbitofrontal and anterior cingulate cortex, insula, striatum, and thalamus. These findings have been associated with mutations in MOG. In terms of fractional anisotropy using diffusion tensor imaging, bidirectional changes in the cingulum bundle have been reported, with higher fractional anisotropy on the left side and reduced fractional anisotropy on the right side compared to control individuals [15].

Mutations in the oligodendrocyte transcription factor 2 gene have been associated with clinical features of patients with OCD, possibly related to the myelin alteration findings in this pathology [15].

Pharmacological treatment of OCD patients (sertraline, fluvoxamine, citalopram, paroxetine, clomipramine, risperidone, olanzapine, or haloperidol) induces changes in white matter myelination, evidenced by a generalized reduction in fractional anisotropy and increased diffusivity. Surprisingly, such changes were not observed in untreated OCD patients or healthy controls, suggesting that psychopharmacological medication modifies the structure of myelin sheaths in white matter tracts in these patients [15].

Glial Cells and Autism Spectrum Disorder

Microglia-mediated neuroinflammation has been observed in the pathophysiology of ASD. Studies have found increased microglial activation and higher microglial cell density in the dorsolateral prefrontal cortex of the human brain in patients with ASD. Additionally, post-mortem and animal model studies have revealed increased dendritic spine density along with altered synaptic pruning in layer V neurons of the temporal lobe, also with dysregulated levels of proinflammatory cytokines in the blood of patients with ASD, suggesting increased inflammation in this disorder. DNA methylation studies have also revealed dysregulation of the expression of various genes involved in microglial specification and synaptic pruning in ASD. Microglial activation and dysregulated microglial complement system, particularly in the C4 component, could impact synaptic pruning in ASD [5,9].

Like SCZ, astrocyte activation has been proposed to play a role in ASD. Analysis of post-mortem brain tissue from patients with ASD has revealed increased expression of GFAP in different brain regions, indicating astroglial activation. Furthermore, GFAP levels are elevated in the cerebrospinal fluid of patients with ASD [9].

It is suggested that activated astrocytes and microglia release inflammatory cytokines and chemokines, which can affect neuronal integrity, synapse formation, and function in patients with ASD [2,9].

Glial Cells, Stress, and Anxiety

White matter integrity has been shown impaired in acute stress. There is increasing evidence suggesting that oligodendrocytes in the gray matter of the brain contribute to behavioral symptoms in individuals exposed to trauma. It has been observed that myelin content in regions such as the hippocampus and amygdala of trauma-exposed individuals correlates with the overall severity of post-traumatic stress disorder (PTSD) symptoms. These findings have led to the idea that susceptibility to developing PTSD may be related to the extent of stress-induced alterations in white matter integrity, as well as the remyelination defects accompanying these alterations. Defects in myelination in patients with PTSD have been suggested to be associated with changes in the mRNA expression of myelination-related genes, such as myelin basic protein and oligodendrocyte-associated myelin basic protein, in the prefrontal cortex [15].

The role of glia in anxiety is less well-known, but there is a significant correlation between anxiety and depression. Prenatal stress is a risk factor for developing mental illness in the future. Reduction in GFAP, MBP, and the number of glial cells in the hippocampus has been observed in animals exposed to early stressful factors. It is well-known that epigenetic mechanisms play a role in early pathophysiological alterations associated with trauma. Neurogenesis and glial cell differentiation are also epigenetically mediated [34].

The proliferation, differentiation, and function of glia are highly vulnerable to changes in the activity of the hypothalamic-pituitary-adrenal (HPA) axis. This dysregulation causes hippocampal and prefrontal cortex changes that could lead to anxious symptoms [34,35].

Changes in extracellular glucocorticoid concentrations alter glial function leading to the development of altered circuits during synaptogenesis. However, chronic exposure to stress and glucocorticoids has deleterious effects on glial proliferation and, consequently on anxiety symptoms [34,35].

Brain myelination can be affected by various forms of acute and chronic stress. Healthy young individuals with high levels of anxiety show white matter alterations. Oligodendrocytes express glucocorticoid receptors throughout their lineage from precursor cells, and there is evidence that oligodendrocytes contribute to behavioral symptoms in trauma-exposed patients [15].

Astrocytes have a modulatory effect on neurotransmitters, especially in the regulation of basal glutamate tone, this could contribute to anxiety pathophysiology [36].

Glial cells are also responsible for the effect of antidepressant drugs. For example, connexin Cx43 is decreased in chronic stress, but with the administration of fluoxetine or duloxetine, its expression recovers in animal models [36].

Glial Cells and Alzheimer's Disease

Alzheimer's disease is the most common cause of dementia worldwide (Kunle). Cognitive impairments are part of the clinical symptomatology of some psychiatric conditions. The immune system has been implicated in the pathology of Alzheimer's disease, and it has been found that glial cells are involved in the immune processes of cognition in animal cells. It has been postulated that anti-inflammatory treatment could alleviate cognitive symptoms in many neuropsychiatric disorders [17,18,20,37,38].

The importance of astrocytes in the neuropathology of neurodegenerative diseases may be a distinguishing factor between the decline of homeostatic functions and the increase in toxic brain functions [20].

Glutamate is the primary excitatory neurotransmitter in mammalian brains and is involved in various neurological processes such as learning, memory, and neurodevelopment. However, glutamate-mediated toxicity has been implicated in neurodegenerative diseases such as Alzheimer's. It has been shown that astrocytes regulate glutamate levels, the availability of glutamine, the release of gliotransmitters as modulators of this neurotransmitter and others, and astrocytes contribute to glutamate neuronal activity by regulating the availability of NMDA receptors and thus the concentration of calcium [35,37].

Astrocytes play an important role in cerebral energy metabolism. Their close position to blood vessels and neurons allows them to have an essential role in this interface, taking up blood glucose and delivering it to the CNS to be used in various metabolic processes and neurodegeneration [12,17,39].

It has also been suggested that glial cells are activated by α-synuclein and, in the early stages of pathology, promote phagocytosis and clearance of protein aggregates that occur in Alzheimer's disease. This glial activation also leads to chronic inflammation, inhibiting phagocytosis and further increasing the accumulation of α-synuclein and β-amyloid [37,39].

Conclusion

Glial cells play an essential role in the development, functioning, and protection of the CNS. Their interaction with neurons and their involvement in neurohormonal regulation have been essential in the evolution and functioning of the human brain. Understanding these processes in detail and their implications in health and disease opens new perspectives in the research and treatment of neurological and neuropsychiatric disorders.

Glial cells play a noteworthy role in mental disorders such as SCZ, bipolar disorder, and depression, among others. Glial cells, including astrocytes, oligodendrocytes, and microglia, interact with neurons and contribute to normal brain function. However, when there is dysfunction or alterations in these cells, problems in neurotransmission, neuroinflammatory regulation, and brain metabolism can arise, triggering and worsening symptoms of mental disorders.

Understanding the importance of glia in these disorders is crucial for advancing research and developing more effective therapies. The identification of specific glia-related biomarkers can improve the diagnosis and prognosis of neuropsychiatric disorders.

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