Chapter

Impact of Hypoxia on Astrocyte Induced Pathogenesis

Farwa Munir, Nida Islam, Muhammad Hassan Nasir, Zainab Anis, Shahar Bano, Shahzaib Naeem, Atif Amin Baig and Zaineb Sohail

Abstract

Astrocytes are the most abundant cells of the central nervous system. These cells are of diverse types based on their function and structure. Astrocyte activation is linked mainly with microbial infections, but long-term activation can lead to neurological impairment. Astrocytes play a significant role in neuro-inflammation by activating pro-inflammatory pathways. Activation of interleukins and cytokines causes neuroinflammation resulting in many neurodegenerative disorders such as stroke, growth of tumours, and Alzheimer's. Inflammation of the brain hinders neural circulation and compromises blood flow by affecting the blood–brain barrier. So the oxygen concentration is lowered, causing brain hypoxia. Hypoxia leads to the activation of nuclear factor kappa B (*NFkB*) and hypoxia-inducible factors (*HIF*), which aggravates the inflammatory state of the brain. Hypoxia evoked changes in the blood–brain barrier, further complicating astrocyte-induced pathogenesis.

Keywords: astrocyte, hypoxia, inflammation, neuroinflammation, brain

1. Introduction of astrocytes

In the nervous system, astrocytes are isotypes of neuroglia, also identified as astrocytic cells. They are Star-shaped; their countless progressions enclose synopses prepared by nerve cells. A particular astrocytic cell can simultaneously act together with the human being by two billion synapses. These specialized glial cells are more numerous than neurons by above fivefold. They closely tile the central nervous system (CNS) and apply for multiple important diverse roles in the energetic CNS. Astrocytes react to all methods of CNS offences through a procedure stated as reactive astrogliosis, which has developed a pathological mark of CNS fundamental abrasions. Two main subtypes of astrocytes are classified based on their structural and anatomical position. Those names are protoplasmic astrocytes and fibrous astrocytes. Protoplasmic astrocytes seem to spread equally in the interior of cortical grey matter, while the fibrous astrocytes are structured with white matter regions [1]. Astrocytes of the brain and spinal cord are very different in morphology and function. Brain cells

(astrocytes) are accountable for the homeostasis of ions and neurotransmitters in the synaptic cleft, native metabolic sustenance, and relief of sensitive oxygen species. Pathology of many nervous disorders containing neuropsychiatric and neurodegenerative syndromes is well-defined by loss of homeostatic role. Astrocytes play a significant role in the homeostasis of the central nervous system (CNS). Brain cells or astrocytes are extremely diverse cells that regulate the network, emergence and function, and homeostasis. Since it's involved in protective astrogliosis, it's become an essential component of neuropathology. Most neuropathology astroglial cells are impacted by degenerative alterations that inhibit their functional and neuroprotective capacities, allowing the pathology to proceed [2]. Astrocytes play an important role in data handling, and communicative mechanism proficiencies of brain circuits are unknown. Around all research studying the correlation among astrocyte cells' structure and function concentrates on its influences on nervous system activity and flexibility under functional and syndrome conditions. At synapses, a collective subject important to these outcomes is that astrocytes analyse, respond to, and control glutamate release and post-synaptic activity.

Removal and postponement of PAPs in reaction to glutamate improve post-synaptic responses, inhibit trans-synaptic activation, and prevent additional glutamate proclamation. Still, astrocyte operational flexibility exchange is not recognized upon declaration of other GABA, dopamine, somatostatin, serotonin, acetylcholine, etc. (neurotransmitters) [3]. The appearance of glial fibrillary acid protein (GFAP) has become a typical indicator for immunohistochemically astrocytic cells [4]. Research on transgenic mice showed that the appearance of GFAP isn't necessary for the usual form and role of the furthermost astrocytic cell in the energetic, nervous system of transgenic mice. Still, it's essential to develop reactive astrogliosis and glial scar development. Over and above, concerning the procedure of GFAP as an astrocyte indication, it's compulsory to pay attention that GFAP expression isn't limited to protoplasmic and fibrous astrocytes. In the interior of the nervous system, GFAP is too expressed by numerous cells that can be reflected as part of prolonged astroglial cells. On the outer side of the nervous system, GFAP is articulated extensively in countless nerves via a range of cell forms **Figures 1–4** [5].

2. Anatomical association

Astrocytes tile the whole CNS in a touching, non-covering, organized, and efficient way. Comparative individual astrocyte areas show up liable to exist in white matter. However, this has not yet been as broadly written about. Astrocytes are giant, intricate, and different from astrocytes in rodents. Astrocytes show controlled proliferation in intracellular calcium absorption [Ca++], which signifies a method of astrocyte excitability. An enormous suggestion is now obtainable that these delimited proliferations in astrocyte [Ca++] remain of purposeful importance in astrocyte and astrocyte-neuron intercellular communication. The advice is that calcium signalling permits astrocytes to show a direct role in synaptic transmission. It's worth noting that astrocytes do communicate with one another via gap junctions generated by connexins. Gap junctional partnering of astrocytes into multicellular systems may contribute to normal function and CNS disorders. The suggestion is that calcium signalling permits astrocytes to show a natural interest in synaptic transmission.

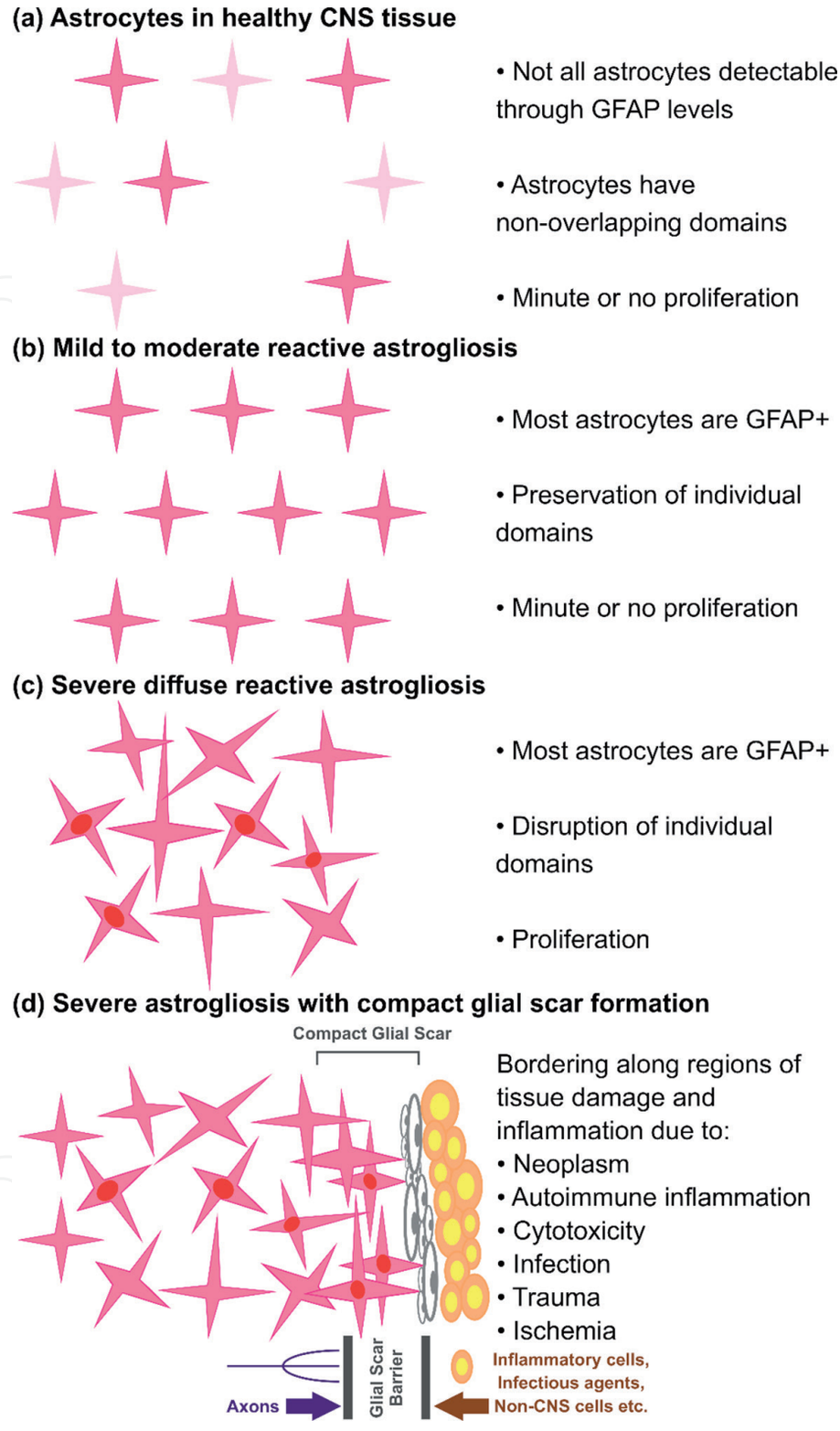

Figure 1.
Astrogliosis and GFAP articulation in astrocytes.

3. Astrocyte-induced pathogenesis

ASTROCYTIC cells are central homeostatic and protective cells of the nerves, and every kind of astrocyte plays an integral part in neuropathological changes. Hence, the decline in nerve cells or astrocytes causes a disease-permissive landscape and

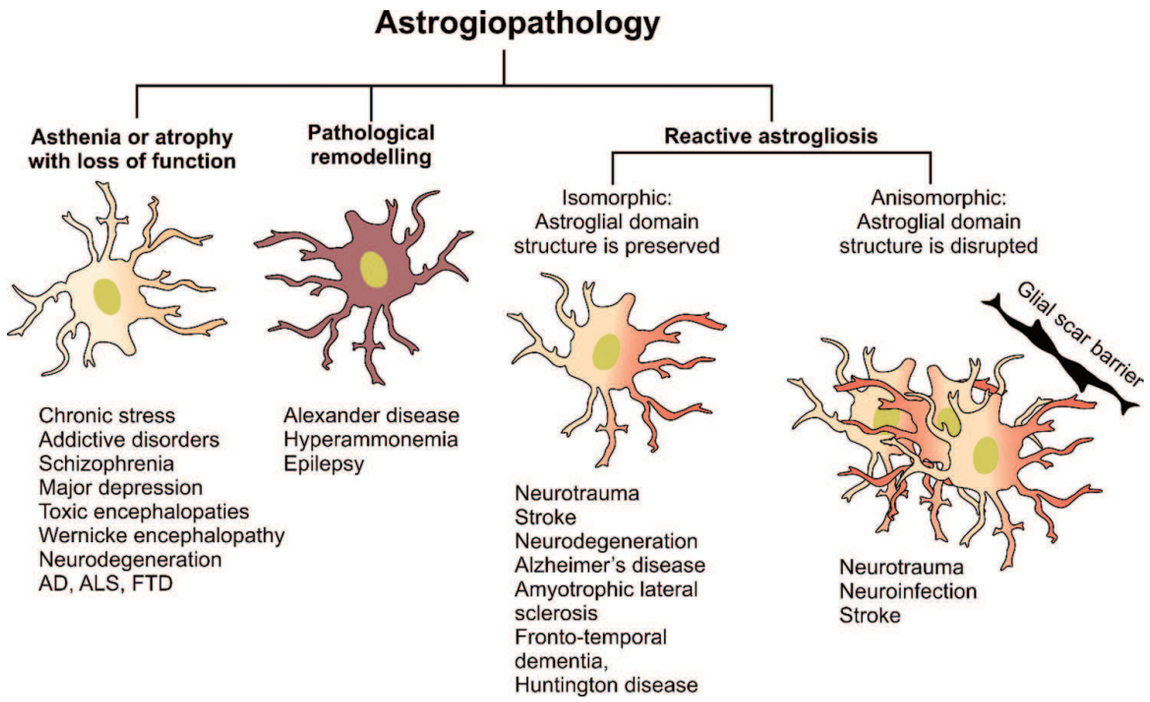

Figure 2.
Astroglial asthenia/atrophy and astrogliosis in neuropathology.

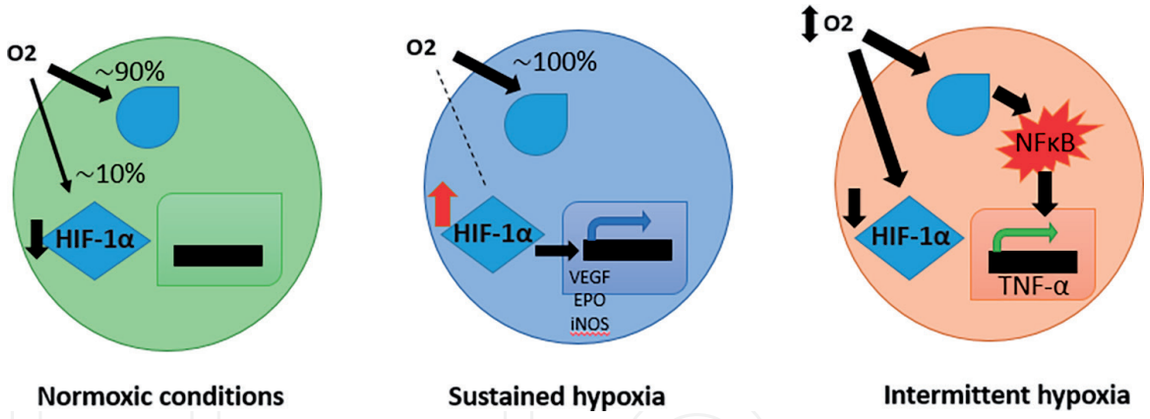

Figure 3.
Hypoxia and HIF-1α stabilization in brain.

triggers nerve cell malfunction, nerve cell death, and nerve cell deficiency. Glia cells are essential for sustaining nerve function, and nerves survive bodily procedures and pathology [6]. Most essential findings concerning astrocyte's functional significance depend on the dead animal model research. It's given a durable but incomplete base for a complete astrocyte role in physiopathology [7]. They are categorized into three kinds that are reactive astrogliosis, Astro-degeneration with astroglial atrophy, and pathological remodelling and loss of function of astrocytes. Altogether these pathological feedbacks proceed together. It's categorized on the base of neuroanatomical and severity. According to neuroanatomical, astrocytes are further distributed into isomorphic and isomorphic astrogliosis [8]. The isomorphic astrogliosis conserves astroglial defensive areas that are changeable.

In contrast, anisomorphic astrogliosis continues through the destruction of the defensive regions, cell relocation and territorial overlap, development of astroglial palisades, and eventually scar formation. While in severity, astrogliosis is categorized

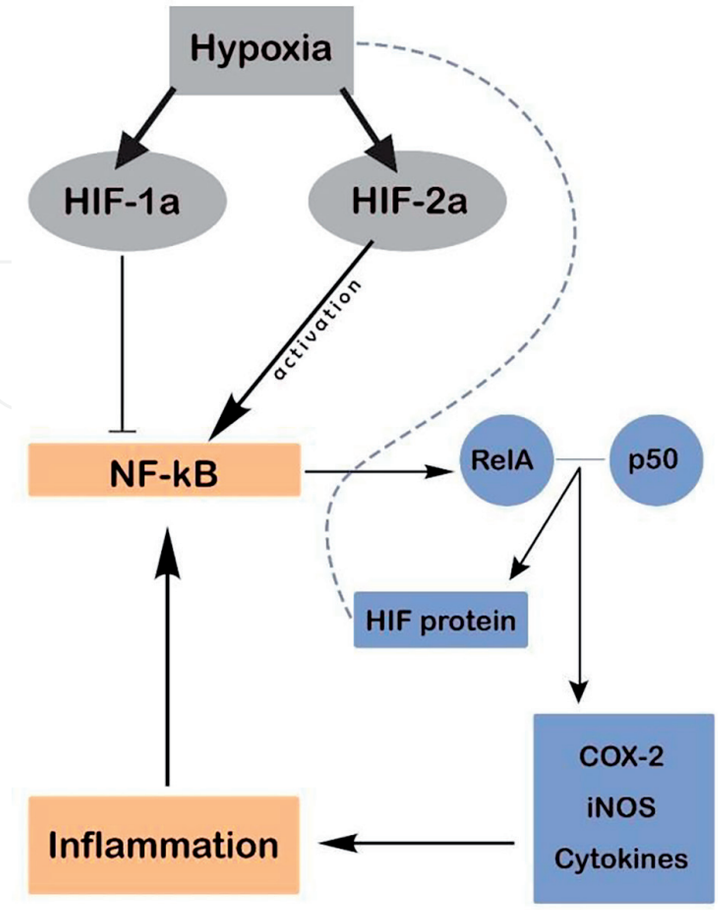

Figure 4.
Role of hypoxia in activation of inflammatory pathway.

into slight to adequate astrogliosis, severe diffuse astrogliosis and severe astrogliosis by dense scar development [9]. Astroglial atrophy is mainly noticeable in major psychiatric illnesses. For example, schizophrenia, a primary depressing condition, Wernicke–Korsakoff encephalopathy, and addictive disorders decrease the storing concentration of astrocytic cells. The conclusion is furthermost particularly accompanied by glutamate-glutamine shuttle and glutamate homeostasis; both are impaired in these conditions [10]. It promotes several leukodystrophies, especially Alexander disease, megalocephalic leukoencephalopathy with subcortical lumps or disappearing white matter disease, in which the astrocyte-pathy pledges destruction of the white matter [11]. It also describes mesial temporal lobe epilepsy, in which astrocytes obtain abnormal cell structure, decreases gap junction coupling, and decrease Kir4.1 channel expression; these alterations weaken K+ homeostasis, contributing to seizure start [12].

4. Pathology of astroglia in neurological diseases

Reactive astrogliosis and glial scar realization are noticeable structures of CNS trauma and are progressively involved by playing significant parts in the decisive prolonged medical result. Glial formation of scar and severe reactive astrogliosis at the location of the neurons trauma are glowing familiar to inhibit axonal regeneration and are extensively observed as harmful to medical results. Contagions of the CNS

triggered by microbes, parasites, fungi, and viruses are categorized into inflammation of meninges, active tissues of the brain, or (pus-filled pocket of infected material in your brain) cerebral abscess. Not all germs can attack the nervous system. Somewhat, merely confirmed neurotropic parasites, fungi, bacteria, and viruses can enter obsessed by the cerebral and vertebral column. Utmost of the microbe are efficiently stopped by the cerebral obstacles [13].

The SAE (Sepsis-associated encephalopathy) explicitly uses a scientific disorder linked through the common cerebral disorders that progresses in sepsis to the lack of core contagion of the neural tissue. In the cerebral parenchyma, sepsis is frequently linked with the production of inflammations and tiny inflammation directly related to the SAE. Particularly in the initial phases, the disease associated with structural infection remains frequently linked through 'sickness behaviour' [14].

Dense metals are a source of extreme cephalic disorder with intellectual deficiencies, mainly targeting neuroglia. Heavy metals that are manganese, lead, aluminium or mercury primarily gather into an astrocytic cell by diverse plasma lemma transporters. Overall, it's also a down-regulating astroglial expression of glutamate transporters, reducing glutamate permission and activating excitotoxicity [15]. Aluminium toxic encephalopathy is demonstrated via mental losses, communication variations, seizures, and flapping wrist shake (asterixis) [16]. It disturbs the cerebrum due to liver encephalopathy, which is described by mental and developmental damage signs including misperception, amnesia, bad temper, and alterations in perception, such as fatigue and sleepiness. Cerebral swelling, unconsciousness, and death also occur in the severity of Hyperammonemia. In stroke, a blood vessel ruptures that restricts blood supply to the brain or parts of the brain due to a systemic decrease of vascular occlusion in blood supply, all-cause disruptions in blood flow. This is known as brain ischemia. As a result, cerebral ischemia could be either focal or global, the latter of which can lead to a stroke. In stroke, astrocytes serve as both neurotoxic and neuroprotective agents, complicating and diverse astrgliopathology [17]. In cases of Congenital Glutamine Deficiency with Glutamine, Synthetase Mutations newborns expire in a while after delivery. The prominent pathophysiological contrivance is related to the weakened capacity of astrocytes to yield glutamine, which disturbs excitatory and inhibitory conduction; furthermore, lacking glutamine synthetase cannot accurately decontaminate ammonium. Pyruvate carboxylase is principally articulated in neuroglia. Pyruvate carboxylase deficit is an autosomal recessive disease linked to a diminished metabolic rate. The warning sign comprises delay of cerebral growth, persistent seizures, and increased plasma acidity.

Aceruloplasminemia is a congenital condition of iron metabolism due to the deficiency of ceruloplasmin action. Most important abrasions describe this disorder as neuroglia, which disturbs their structure and consequences in the presence of frothy spheroid forms at the vascular end feet. Aceruloplasminemia is also linked with brain demise and the exterior of iron deposition [18].

Alexander disease is an exceptional, long-lasting, and ordinarily neurodegenerative severe condition. Its consequences on or after a dominant gain-of-function mutation of the gene encoding GFAP. It is sub-categorized into Type I and types II [19]. Autism Spectrum Disorders (ASD) are a few medically introverted conditions connected to cerebral inadequacies. Astrocytes are accountable for neuroprotection and detoxifying harmful bodies like receptive oxygen species. The principle procedure of ASDs is undoubtedly associated with brain network mutation and abnormal neurotransmission during the undeveloped turn of events [20]. In Down

syndrome, the thickness of astrocytes is fundamentally diminished in the cortex with diminished capacity to uphold synaptogenesis and neuronal development appropriately. Astroglial asthenia, loss of homeostatic capacities, atrophy, and perhaps pathogenic remodelling are all related to schizophrenia, although reactive alterations are not. Epilepsy, mood disorders, and addictive disorders are linked with astrogliopathology [12].

5. Astrocyte up-regulation

Astrocyte is the essential part of the blood–brain barrier (BBB) that can be damaged by traumatic brain injury (TRI) or ischemia. Astrocytes provide the morphological and physiological link between neural networks and cerebral circulation. Astrocytes have the power to adjust blood flow to the brain to keep the brain parenchyma's PCO2 and PO2 steady [21]. The formation of ATP in the brainstem through local astrocytes aids respiration and counters hypoxia-induced respiratory network depression. Hypoxia-induced alterations in brain inflammation, neuroprotection, and blood–brain barrier permeability against ischemic injury appear to be mediated by astrocytes. Astrocytes play a critical function in neuronal function in everyday situations and pathological conditions when the supply of oxygen to the brain is disrupted [22].

The telomerase reverse transcriptase (TERT) gene is linked to cell injury and stress resistance. After hypoxia-ischemia, protein and TERT mRNA were increased in neurons after a few days but moved to astrocytes [23]. TERT overexpression decreased astrocyte multiplication by upregulating the cell-cycle regulatory protein p15. While neurons were cultured with precondition medium from astrocytes with TERT inhibition contrasted to neurotrophin-3 expression, TERT overexpression in astrocytes decreased, resulting in higher death [24]. In TERT-overexpressing brains with hypoxia-ischemia, neuronal damage and Ki67-positive astrocytes were also suppressed [25].

Matrix metalloproteinase (MMP)-9 is an endo-peptidase that plays a crucial role in Blood–Brain Barrier proteolysis post-trauma and leads to cell death with persistent convulsions [26]. Activation of mitogen-activated protein kinases (MAPKs) in astrocytes can be caused by thrombin, oxidative stress, tissue plasminogen activator, or tumour necrosis factor- α and includes stimulation of MMP-9. In astrocytes, albumin causes a rise in MMP-9 synthesis, which requires ROS formation and motivation of the MAPK pathway [27]. These results add albumin to signalling molecules that activate MMP-9 in astrocytes alongside thrombin. These findings connect albumin to MMP-9-mediated cellular mechanisms such as intracerebral haemorrhage, neuronal damage, dendritic remodelling, and epileptogenesis [28].

Stroke and Traumatic Brain Injury (TBI) are frequently linked with hypoxia, which causes glial initiation. Glial cells, particularly astrocytes, play an essential part in stress prevention and the homeostasis of the CNS by offering structural and metabolic stability [29]. Hypoxia can cause astrocyte homeostasis to be disrupted, resulting in cell enlargement. Wnt pathway suppression was the most substantially disrupted signalling pathway in the mechanism of hypothermia-induced responses in human astrocytes after oxidative stress activation and hypoxia [30]. Global suppression of Wnt signalling can be troublesome because of its essential role in controlling critical mechanisms associated with the functional regulation of immune and stem cells and its effect on post-mitotic neuronal and glial cells [31].

6. Brain hypoxia

Molecular oxygen (O2) is required for most organisms on the planet because it supports intracellular biogenesis and is utilized by several metabolic activities. As a result, low oxygen level (hypoxia) is a crucial stress factor that usually disrupts aerobic species' lives and is a common feature of pathologic conditions such as cardiovascular abnormalities, inflammation, wounds, bacterial infection, and cancer [32]. Since it is required throughout breathing, oxygen is essential in life. In oxidative phosphorylation, O2 acts as the ultimate electron acceptor, raising the possibility of reactive oxygen species formation (ROS). ROS interact with biological macromolecules, changing their metabolic or physical characteristics and causing cell death or malfunction [33].

To sustain a wide range of cellular functions to secure life, organism cells require sufficient oxygen. The oxygen concentration in the body and localized tissues fall (hypoxia) whenever the need for oxygen increases, resulting in a physiological crisis that compromises physiological processes and survivability. Organisms have formed an effective and quick oxygen sensing system called (hypoxia-inducible factors (*HIF*s) because of the importance of oxygen in metabolism, survival, and respiration [34].

Arterial and central chemoreceptors detect changes in the oxygen content in the external environment. The brainstem's medulla, beneath the respiratory centres, contains central chemoreceptors. The carotid and aortic bodies include arterial chemoreceptors [35]. The stimulation of arterial chemoreceptors promotes neurotransmission and alters the function of neprilysin (NEP), a neutral endopeptidase that changes the biological response to hypoxia by hydrolytic component P [36]. Neuroendocrine cells in neuroepithelial bodies also govern oxygen sensing by imposing chemosensitivity, critical for oxygen sensing in the early stages of life. These exciting chemoreceptors enhance sympathetic nervous activity (SNA) and the systemic and arterial pulmonary blood flow to receive enough oxygen. Therefore, in organism cells, the expression of many adapted genes is activated to improve the oxygen supply and enable anaerobic ATP production. Hypoxia-inducible factors regulate these hypoxic responses (*HIFs*) [37].

There is a difference between sustained and intermittent hypoxia. Mitochondrial respiration utilizes more than 90% oxygen in humans during every day physiological situations [38]. The remaining (10%) oxygen is used to degrade *HIF-1*. The mitochondria use practically all oxygen or eliminate free cytosolic oxygen during the response to sustained hypoxia, enabling *HIF-1* to stabilize quickly. *HIF-1* activation causes enhanced transcription of several genes, including EPO, inducible nitric oxide synthase (iNOS), and *VEGF* [39]. These variables contribute to the recovery after early hypoxic shocks by boosting oxygenation and tissue perfusion as part of the adapted strategy to hypoxia. A free oxygen deficit is not adequately generated in intermittent hypoxia to enable *HIF-1* stabilization. Due to oxidative stress, intermittent hypoxia can cause a delayed elevation in *HIF*-1, leading to the stimulation of *NFkB*-driven inflammation [40].

7. Role of HIF 1a in causing hypoxia in the brain

A transcription factor that binds to specific nuclear cofactors and transactivates several genes, causing a range of adaptive responses in response to low oxygen levels

in the body, is called Hypoxia Inducible Factor *HIF* [41]. *HIF-1* alpha and beta subunits form an active heterodimer under hypoxic settings, driving the transcription of approximately 60 genes involved in cell survival, adaptability, anaerobic metabolism, cytokine generation, vascularization, immunological response, and tissue homeostasis [42]. The two isoforms of *HIFα*, *HIF1α,* regulate erythropoietin (EPO), whereas *HIF2α* regulates the heme-regulating gene (hemopoietin genes). Increased *HIF* signalling in the body can contribute to inflammation and tumour progression. *HIF2α* activation has been observed because it plays a fundamental role in inflammation. HIF-1α has neuroprotective properties, but it can potentially be neurotoxic. *HIF-1* is involved in forming the early brain and the proliferation of neural precursor cells. *HIF-1* is recognized as critical in hypoxic–ischemic brain damage under pathological conditions [43]. During hypoxia, *HIF-1* participates in the apoptotic process to increase the stability of the tumour suppressor protein p53, which has neurotoxic consequences.

The brain is the most vulnerable organ to hypoxia, resulting in coma, convulsions, cognitive impairment, other neurological impairments, and brain death if left untreated [44]. Cardiac arrest, asphyxia, or systemic metabolic abnormalities affecting the blood's oxygen content, systemic hypoxia, severe anaemia, and systemic hypotension can lead to hypoxic brain damage [45]. Hypoxia-induced autophagy is linked to the HIF-1 signalling pathway. According to studies, hypoxic preconditioning protection is lost in HIF-1α knockout mice exposed to neonatal hypoxia/ischemia [46]. HIF1α hydroxylation is prevented by blockage of prolyl- and asparaginyl-hydroxylases in hypoxic environments. Prolyl-hydroxylase inhibitors reduce HIF1α breakdown, resulting in fast *HIF1α* protein build-up [47]. Phosphorylation of the *HIF1α* protein causes it to dimerize with *HIF1α*. The *HIF1α*/*HIF1β* dimer interacts with p300/CBP, causing hypoxia response elements in *HIF* target genes to be activated [48].

PI3K (Phosphatidylinositol 3-kinase) and Akt (protein kinase B) signalling pathway is related to hypoxia-ischemia injury as it increases the phosphorylation of downstream molecules such as apoptosis-related family members, transcription factors, mammalian target of rapamycin (mTOR), and glycogen synthase kinase-3. Phosphatase and tensin homologue (PTEN) is a lipid phosphatase that inhibits the PI3K/Akt pathway by hydrolysing PIP-3 to PIP-2 and preventing downstream p-Akt. PI3K and its downstream effector. Akt is a member of a well-studied family of signal transduction enzymes that regulate cellular activation, inflammation, and apoptosis [49].

8. Role of hypoxia in activating inflammatory pathways such as interleukins, cytokines, *NFk-B1*

Chemokines and cytokines are low-molecular-weight proteins produced mostly by lymphocytes and macrophages. As neurotransmitters and hormones, they mediate intracellular and extracellular interactions in an autocrine, endocrine, and paracrine manner. They regulate various biological activities, including local and systemic anti- and pro-inflammation, chemotaxis, metabolism, cellular proliferation, and tissue repair, by adhering to certain cell surface receptors [50].

HIF-1α attenuates periapical inflammation and tissue destruction, resulting in downregulation of nuclear factor-kappa B (*NF-κB*) and gene expressions. These two substances also prevented macrophages from activating *NF-κB* and producing

pro-inflammatory cytokines. Furthermore, stimulation of HIF-1 reduced lipopolysaccharide-stimulated macrophage differentiation into M1 cells, resulting in a higher ratio of M2 macrophages to M1 cells [51]. In another study, *HIF-2a* activation by pro-inflammatory cytokines increases iNOS expression and activity via the *NF-κB* pathway, resulting in nitric oxide (NO) production, which causes liver damage when generated in excess [52].

cAMP-mediated signalling pathways might be changed in the presence of HIF1A, causing inflammatory-like processes to worsen. Only in the presence of Ni-induced hypoxia-inducible factor 1 (*HIF1α*) does prostaglandin (*PGE2*) synergistically accelerate Ni-induced Interleukin (IL-8) production [53]. Elevated IL-13 expression can cause eosinophilia and pathologies such as excessive mucus production. IL-13 can activate genes in the hypoxia signalling pathway, producing CD73 (immunoinhibitory protein) on the cell surface [54].

9. Effect of hypoxia on astrocyte functioning

Astrocytes have a crucial role in maintaining the normal oxygen levels in the brain. If the PO2 goes less than 17MMHg, astrocytes robust the Calcium ions into the brain; they act as the source of ATP in the hypoxic state of the brain. Astrocytes also have the potential to sense an increase in PCO2 levels too [21]. This chemosensation helps the cells to provide the astroglial networks with ATPS that help spread Ca + 2 activation and excitation. It also increases breathing to maintain homeostasis. It suggests that ATP released helps to keep living in the face of the hypoxia-evoked depression of the respiratory network [55].

In the previous century, it has also become clear that astrocytes can protect neurons under hypoxia conditions. The potential process is similar to "hypoxic preconditioning," in which a temporary interval of moderate hypoxia protects neurons from subsequent ischemia episodes that are generally fatal [56]. Mild hypoxia synthesizes several protective astrocytic factors that help neurons survive. Hypoxia increases the production of specific proteins, such as connexin 43, which may promote ATP/adenosine transit towards the interstitial space [57]. Astrocytes release erythropoietin in reaction to hypoxia, which has a significant neuroprotective impact. The erythropoietin expression in astrocytes is increased once hypoxia-inducible factors are activated. HIF-1α and HIF-2α are two transcription factors. [58]. In an adult brain, astrocytes can alter and monitor synaptic functionality. It was believed that synaptic plasticity is solely based on neurons, but in recent research, it has been found that the glial network and astrocytes alter synaptic transmissions [59]. The activation of metabotropic receptors modulates synaptic alterations by astrocytes. It helps release glutamate, gliotransmitter ATP, and D-serine, which act on neurons [60]. As per Astrocyte-induced pathogenesis, astrocytes can cause adenosine accumulation that affects glial cells and cause sleep deprivation and cognitive impairment [61]. Experimental investigations have found that the astrocytes sense synaptic activity with the help of astrocytic calcium. Astrocytes elevate their Ca + levels to sense neural activity with the help of the Gq-coupled protein pathway [62].

10. Conclusion

Astrocytes play a significant role in the homeostasis of the central nervous system. Astrocytic cells are central homeostatic and protective cells of the nerves. The decline

in nerve cells or astrocytes causes a disease-permissive landscape and triggers nerve cell malfunction, nerve cell death, and nerve cell deficiency. Astroglial atrophy is mainly noticeable in major psychiatric illnesses. Severe reactive astrogliosis and glial scar formation at the location of the neurons trauma are glowing familiar to inhibit axonal regeneration. More research into the processes of Astrocytes protection, particularly the substances they produce, will give crucial insights into how to protect the Blood–Brain Barrier throughout trauma and neurological condition.

Moreover, its expression timing in astrocytes is essential to determine the influence of hypoxia-induced signalling on stroke volume. Furthermore, in addition to the impacts of hypoxia-signalling in astrocytes on neuron viability, it seems necessary to consider how such alterations will affect astrocyte viability. We must fully comprehend how to lessen the harm caused by stroke if we can better define the various consequences of hypoxia signalling in astrocytes.

Funding

The research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interests

The authors have declared no competing interests.

Ethical approval

The study does not require any ethical approval.

Availability of data and materials

No data was generated in the current study.

Author details

Farwa Munir[1], Nida Islam[2], Muhammad Hassan Nasir[1], Zainab Anis[2], Shahar Bano[2], Shahzaib Naeem[3,4], Atif Amin Baig[1*] and Zaineb Sohail[3,4]

1 Universiti Sultan Zainal Abidin, Malaysia

2 School of Food and Agriculture sciences, University of Management and Technology, Lahore, Pakistan

3 Surriya Azeem Teaching Hospital, Pakistan

4 Department of Life Sciences, University of Management and Technology, Lahore, Pakistan

*Address all correspondence to: atifameen01@gmail.com

References

[1] Sofroniew MV, Vinters HV. Astrocytes: Biology and pathology. Acta Neuropathologica. 2010;**119**(1):7-35

[2] Verkhratsky A, Nedergaard M, Hertz L. Why are astrocytes important? Neurochemical Research. 2015;**40**(2):389-401

[3] Lawal O, Ulloa Severino FP, Eroglu C. The role of astrocyte structural plasticity in regulating neural circuit function and behavior. Glia. Aug 2022;**70**(8):1467-1483. DOI: 10.1002/glia.24191. Epub 2022 May 10. PMID: 35535566; PMCID: PMC9233050

[4] Herrmann JE, Imura T, Song B, Qi J, Ao Y, Nguyen TK, et al. STAT3 is a critical regulator of astrogliosis and scar formation after spinal cord injury. Journal of Neuroscience. 2008;**28**(28):7231-7243

[5] Puspitasari V, Gunawan PY, Wiradarma HD, Hartoyo V. Glial fibrillary acidic protein serum level as a predictor of clinical outcome in ischemic stroke. Open Access Macedonian Journal of Medical Sciences. 2019;**7**(9):1471

[6] Hashimi SR, Hashimi S. Anticholinergic Burden and Risk of Cognitive Impairment In Older Adults. Virginia Commonwealth University. 2020. DOI: 10.25772/CMQ2-4A23

[7] Kortebi I. Understanding Cortical Astrocyte Distribution through Perinatal Birth Dating [Doctoral dissertation]. University of Toronto Canada; 2021

[8] Pekny M, Wilhelmsson U, Pekna M. The dual role of astrocyte activation and reactive gliosis. Neuroscience Letters. 2014;**565**:30-38

[9] Sofroniew MV. Astrogliosis. Cold Spring Harbor Perspectives in Biology. 2015;**7**(2):a020420

[10] Verkhratsky A, Rodríguez JJ, Steardo L. Astrogliopathology: A central element of neuropsychiatric diseases? The Neuroscientist. 2014;**20**(6):576-588

[11] Lanciotti A, Brignone M, Bertini E, Petrucci T, Aloisi F, Ambrosini E. Astrocytes: Emerging stars in leukodystrophy pathogenesis. Translational Neuroscience. 2013;**4**(2):144-164

[12] Bedner P, Dupper A, Hüttmann K, Müller J, Herde MK, Dublin P, et al. Astrocyte uncoupling as a cause of human temporal lobe epilepsy. Brain. 2015;**138**(5):1208-1222

[13] Combes V, Guillemin GJ, Chan-Ling T, Hunt NH, Grau GE. The crossroads of neuroinflammation in infectious diseases: Endothelial cells and astrocytes. Trends in Parasitology. 2012;**28**(8):311-319

[14] Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. Brain, Behavior, and Immunity. 2007;**21**(2):153-160

[15] Yin Z, Milatovic D, Aschner JL, Syversen T, Rocha JB, Souza DO, et al. Methylmercury induces oxidative injury, alterations in permeability and glutamine transport in cultured astrocytes. Brain Research. 2007;**1131**:1-10

[16] Struys-Ponsar C, Guillard O, de Aguilar PVDB. Effects of aluminum exposure on glutamate metabolism: A possible explanation for its toxicity. Experimental Neurology. 2000;**163**(1):157-164

[17] Zhao Y, Rempe DA. Targeting astrocytes for stroke therapy. Neurotherapeutics. 2010;**7**(4):439-451

[18] Oide T, Yoshida K, Kaneko K, Ohta M, Arima K. Iron overload and antioxidative role of perivascular astrocytes in aceruloplasminemia. Neuropathology and Applied Neurobiology. 2006;**32**(2):170-176

[19] Sanacora G, Banasr M. From pathophysiology to novel antidepressant drugs: glial contributions to the pathology and treatment of mood disorders. Biological Psychiatry. 2013;**73**(12):1172-1179

[20] Büttner A, Weis S. Neuropathological alterations in drug abusers. Forensic Science, Medicine, and Pathology. 2006;**2**(2):115-126

[21] Marina N, Kasymov V, Ackland GL, Kasparov S, Gourine AV. Astrocytes and Brain Hypoxia. Advances in Experimental Medicine and Biology. 2016;**903**:201-207. DOI: 10.1007/978-1-4899-7678-9_14. PMID: 27343098

[22] Ranaivo HR, Hodge JN, Choi N, Wainwright MS. Albumin induces upregulation of matrix metalloproteinase-9 in astrocytes via MAPK and reactive oxygen species-dependent pathways. Journal of Neuroinflammation. 2012;**9**(1):1-12

[23] Qu Yi, Duan Z, Zhao F, Wei D, Zhang J, Tang B, et al. Telomerase reverse transcriptase upregulation attenuates astrocyte proliferation and promotes neuronal survival in the hypoxic–ischemic rat brain. 2011;**42**:3542-3550. DOI: 10.1161/STROKEAHA.111.626325Stroke

[24] Wang Z, Xu J, Geng X, Zhang W. Analysis of DNA methylation status of the promoter of human telomerase reverse transcriptase in gastric carcinogenesis. Archives of Medical Research. Jan 2010;**41**(1):1-6. DOI: 10.1016/j.arcmed.2009.11.001. Epub 2010 Jan 29. PMID: 20430247

[25] Hamby ME, Sofroniew MV. Reactive astrocytes as therapeutic targets forCNS disorders. Neurotherapeutics. 2010;**7**:494-506

[26] Michaluk P, Wawrzyniak M, Alot P, Szczot M, Wyrembek P, Mercik K, et al. Influence of matrix metalloproteinase MMP-9 on dendritic spine morphology. Journal of Cell Science. 2011;**124**:3369-3380

[27] Barr TL, Latour LL, Lee KY, Schaewe TJ, Luby M, Chang GS, et al. Blood–brain barrier disruption in humans is independently associated with increased matrix metalloproteinase-9. Stroke. 2010;**41**:e123-e128

[28] Hill MD, Martin RH, Palesch YY, Tamariz D, Waldman BD, Ryckborst KJ, et al. The albumin in acute stroke part 1 trial: An exploratory efficacy analysis. Stroke. 2011;**42**(6):1621-1625

[29] Kou Z, VandeVord PJ. Traumatic white matter injury and glial activation: from basic science to clinics. Glia. 2014;**62**:1831-1855. DOI: 10.1002/glia.22690

[30] Blagodatski A, Poteryaev D, Katanaev VL. Targeting the Wnt pathways for therapies. Molecular Cell Therapy. 2014;**2**:28. DOI: 10.1186/2052-8426-2-28

[31] Munji RN, Choe Y, Li G, Siegenthaler JA, Pleasure SJ. Wnt signaling regulates neuronal differentiation of cortical intermediate progenitors. The Journal of Neuroscience. 2011;**31**:1676-1687. DOI: 10.1523/JNEUROSCI.5404-10.2011

[32] Lee P, Chandel NS, Simon MC. Cellular adaptation to hypoxia through hypoxia inducible factors and beyond. Nature Reviews Molecular Cell Biology. 2020;**21**(5):268-283

[33] Semenza GL. Hypoxia-inducible factors in physiology and medicine. Cell. 2012;**148**(3):399-408

[34] Yeo EJ. Hypoxia and aging. Experimental & Molecular Medicine. 2019;**51**(6):1-15

[35] Caravagna C, Seaborn T. Oxygen sensing in early life. Lung. 2016;**194**:715-722

[36] Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet. 2014;**383**:736-747

[37] Antikainen H, Driscoll M, Haspel G, Dobrowolski R. TOR-mediated regulation of metabolism in aging. Aging Cell. 2017;**16**:1219-1233

[38] Taylor CT, Kent BD, Crinion SJ, McNicholas WT, Ryan S. Human adipocytes are highly sensitive to intermittent hypoxia induced NF-kappaB activity and subsequent inflammatory gene expression. Biochemical and Biophysical Research Communications. 2014;**447**:660-665

[39] Prabhakar NR, Semenza GL. Adaptive and maladaptive cardiorespiratory responses to continuous and intermittent hypoxia mediated by hypoxia-inducible factors 1 and 2. Physiological Reviews. 2012;**92**:967-1003

[40] Nanduri J et al. HIF-1alpha activation by intermittent hypoxia requires NADPH oxidase stimulation by xanthine oxidase. PLoS One. 2015;**10**:e0119762

[41] Shay JE, Celeste SM. Hypoxia-inducible factors: Crosstalk between inflammation and metabolism. Seminars in Cell & Developmental Biology. 2012;**23**(4):389-394

[42] Adams J, Difazio L, Rolandelli R, Luján J, Haskó G, Csóka B, et al. HIF-1: A key mediator in hypoxia (Review). Acta Physiologica Hungarica. 2009;**96**(1):19-28

[43] Fan X, Heijnen CJ, van der Kooij MA, Groenendaal F, van Bel F. The role and regulation of hypoxia-inducible factor-1α expression in brain development and neonatal hypoxic–ischemic brain injury. Brain Research Reviews. 2009;**62**(1):99-108

[44] Sharp FR, Bernaudin M. HIF1 and oxygen sensing in the brain. Nature Reviews Neuroscience. 2004;**5**(6):437-448

[45] Lacerte M, HSA, Mesfin FB. Hypoxic Brain Injury. StatPearls; 2022

[46] Lu N, Li X, Tan R, An J, Cai Z, Hu X, et al. HIF-1α/Beclin1-mediated autophagy is involved in neuroprotection induced by hypoxic preconditioning. Journal of Molecular Neuroscience. 2018;**66**(2):238-250

[47] Wang X, Cui L, Ji X. Cognitive impairment caused by hypoxia: From clinical evidences to molecular mechanisms. Metabolic Brain Disease. 2022;**37**(1):51-66

[48] Ciuffreda L, Falcone I, Incani UC, Del Curatolo A, Conciatori F, Matteoni S, et al. PTEN expression and function in adult cancer stem cells and prospects for therapeutic targeting. Advances in Biological Regulation. 2014;**56**:66-80

[49] Zhang Z, Yao L, Yang J, Wang Z, Du G. PI3K/Akt and HIF-1 signaling pathway in hypoxia-ischemia (Review). Molecular Medicine Reports. 2018;**18**(4):3547-3554

[50] Sarode P, Schaefer MB, Grimminger F, Seeger W, Savai R. Macrophage and tumor cell cross-talk is fundamental for lung tumor progression: We need to talk. Frontiers in Oncology. 2020:10

[51] Hirai K, Furusho H, Hirota K, Sasaki H. Activation of hypoxia-inducible factor 1 attenuates periapical inflammation and bone loss. International Journal of Oral Science. 2018;**10**(2):12

[52] Yoshida T, Okumura T, Matsuo Y, Okuyama T, Michiura T, Kaibori M, et al. activation of transcription factor HIF inhibits IL-1β-induced NO production in primary cultured rat hepatocytes. Nitric Oxide. 2022;**124**:1-14

[53] Brant KA, Fabisiak JP. Role of hypoxia-inducible factor 1, α subunit and cAMP-response element binding protein 1 in synergistic release of interleukin 8 by prostaglandin E2 and nickel in lung fibroblasts. American Journal of Respiratory Cell and Molecular Biology. 2013;**49**(1):105-113

[54] Khalil SM, Bernstein I, Kulaga H, Gour N, Rowan N, Lajoie S, et al., editors. Interleukin 13 (IL- alters hypoxia-associated genes and upregulates CD73). International Forum of Allergy & Rhinology; 2020: Wiley Online Library.

[55] Heurteaux C, Lauritzen I, Widmann C, Lazdunski M. Essential role of adenosine. Adenosine.

[56] Heurteaux C, Lauritzen I, Widmann C, Lazdunski M. Essential role of adenosine, adenosine A1 receptors, and ATP-sensitive K+ channels in cerebral ischemic preconditioning. Proceedings of the National Academy of Sciences. 1995;**92**(10):4666-4670

[57] Prass K, Scharff A, Ruscher K, Lowl D, Muselmann C, Victorov I, et al. Hypoxia-induced stroke tolerance in the mouse is mediated by erythropoietin. Stroke. 2003;**34**:1981-1986

[58] Semenza GL, Agani F, Booth G, Forsythe J, Iyer N, Jiang B-H. Structural and functional analysis of hypoxia-inducible factor 1. Kidney International. 1997;**51**(2):553-555. ISSN: 0085-2538. DOI: 10.1038/ki.1997.77

[59] Barker AJ, Ullian EM. Astrocytes and synaptic plasticity. The Neuroscientist. 2010;**16**(1):40-50

[60] Halassa MM, Haydon PG. Integrated brain circuits: Astrocytic networks modulate neuronal activity and behavior. Annual Review of Physiology. 2010;**72**:335

[61] Chung WS, Allen NJ, Eroglu C. Astrocytes control synapse formation, function, and elimination. Cold Spring Harbor Perspectives in Biology. 2015;7(9):a020370

[62] Bernardinelli Y, Muller D, Nikonenko I. Astrocyte-synapse structural plasticity. Neural Plasticity. 2014:2014