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Original Research Article

The Role of Astrocyte-Mediated Neurovascular Coupling in the Regulation of Blood–Brain Barrier Permeability and Cerebral Hemodynamics under Ischemic Hypoxia

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Abstract:

Background: Ischemic hypoxia disrupts cerebral blood flow and compromises the integrity of the blood–brain barrier (BBB), leading to neuronal injury and neurological dysfunction. Astrocytes play a central role in neurovascular coupling by linking neuronal activity with vascular responses and maintaining BBB homeostasis through interactions with endothelial cells and pericytes. Understanding astrocyte-mediated mechanisms under ischemic hypoxia may identify novel therapeutic targets for stroke and other cerebrovascular disorders.

Objective: To investigate the role of astrocyte-mediated neurovascular coupling in regulating blood–brain barrier permeability and cerebral hemodynamics under ischemic hypoxia conditions.

Methods: A prospective experimental study was conducted using ischemic hypoxia models. BBB permeability was evaluated using Evans blue dye extravasation and immunohistochemical analysis of tight junction proteins (occludin, claudin-5, and ZO-1). Cerebral hemodynamics were assessed by laser Doppler flowmetry and cerebral perfusion imaging. Astrocyte activation was quantified by glial fibrillary acidic protein (GFAP) expression, while inflammatory cytokines and oxidative stress markers were analyzed using enzyme-linked immunosorbent assay (ELISA). Statistical analysis was performed using appropriate parametric and non-parametric tests, with $p < 0.05$ considered statistically significant.

Conclusion: Astrocyte-mediated neurovascular coupling is a critical regulator of blood–brain barrier integrity and cerebral hemodynamics during ischemic hypoxia. Targeting astrocyte signaling pathways may represent a promising therapeutic strategy to preserve BBB function, improve cerebral perfusion, and reduce neurological damage following ischemic brain injury.

Keywords: Astrocytes; Neurovascular coupling; Blood–brain barrier; Ischemic hypoxia; Cerebral hemodynamics; Cerebral blood flow; Blood–brain barrier permeability; Stroke; Tight junction proteins.

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Introduction

Ischemic hypoxia is a major cause of neurological injury and is commonly observed in conditions such as ischemic stroke, cardiac arrest, traumatic brain injury, and cerebral vascular insufficiency. Reduced oxygen and glucose delivery to the brain initiates a cascade of pathological events, including energy failure, excitotoxicity, oxidative stress, inflammation, and neuronal cell death. These processes not only impair neuronal function but also disrupt the integrity of the blood–brain barrier (BBB) and cerebral microcirculation, contributing to poor neurological outcomes. Despite advances in acute stroke management, the mechanisms regulating BBB permeability and cerebral hemodynamics during ischemic hypoxia remain incompletely understood.

The neurovascular unit (NVU), comprising neurons, astrocytes, endothelial cells, pericytes, vascular smooth muscle cells, and the extracellular matrix, plays a fundamental role in maintaining cerebral homeostasis. Within the NVU, astrocytes are uniquely positioned to coordinate communication between neurons and cerebral blood vessels through their extensive end-feet, which envelop more than 90% of the cerebral microvasculature. This anatomical arrangement enables astrocytes to regulate cerebral blood flow, maintain ion and water balance, and preserve BBB integrity under physiological conditions. Neurovascular coupling is

the process by which neuronal activity is matched with local cerebral blood flow to meet metabolic demands. Astrocytes are central mediators of this process by sensing neurotransmitter release and generating intracellular calcium signals that stimulate the release of vasoactive molecules, including prostaglandins, epoxyeicosatrienoic acids, nitric oxide, and potassium ions. These signaling pathways regulate vasodilation or vasoconstriction of cerebral arterioles, thereby ensuring adequate oxygen and nutrient delivery to active neuronal tissue. During ischemic hypoxia, however, astrocyte signaling becomes dysregulated, leading to impaired neurovascular coupling and abnormal cerebral perfusion. Astrocytes also play a critical role in preserving BBB integrity through direct interactions with endothelial cells and pericytes. They regulate the expression of tight junction proteins, including occludin, claudin-5, and zonula occludens-1 (ZO-1), which are essential for maintaining selective BBB permeability. Under ischemic conditions, astrocyte activation is accompanied by excessive production of inflammatory cytokines, reactive oxygen species, matrix metalloproteinases, and vascular endothelial growth factor, all of which contribute to BBB disruption, vasogenic edema, and secondary neuronal injury. Recent experimental studies have demonstrated that modulation of astrocytic calcium signaling, aquaporin-4 expression, and inflammatory pathways can preserve BBB function and improve cerebral blood flow following ischemic injury. These findings suggest that astrocytes are not merely passive supporting cells but active regulators of cerebrovascular physiology and potential therapeutic targets for reducing ischemic brain damage. However, the precise relationship between astrocyte-mediated neurovascular coupling, BBB permeability, and cerebral hemodynamics during ischemic hypoxia has not been fully elucidated.

Materials and Methods

This prospective experimental study was conducted in the Department of Physiology, at Darbhanga Medical College and Hospital Darbhanga Laheriasarai, Bihar. and collaboration with the Department of Neuroscience at a tertiary care research institute over a period of 15 months. The study was designed to investigate the role of astrocyte-mediated neurovascular coupling in regulating blood–brain barrier (BBB) permeability and cerebral hemodynamics under ischemic hypoxia conditions. Institutional Ethics Committee approval was obtained before study initiation, and all experimental procedures complied with national guidelines for the care and use of laboratory animals. A total of 56 healthy adult male Wistar rats (weighing 220–280 g and aged 8–10 weeks) were included in the study. Animals were housed under standard laboratory conditions with a 12-hour light/dark cycle, controlled temperature (22 ± 2°C), and free access to standard pellet diet and water.

Group Allocation

The animals were randomly divided into two groups:

- Group I (Control group): 28 rats maintained under normoxic conditions.
- Group II (Ischemic hypoxia group): 28 rats subjected to transient focal cerebral ischemia followed by hypoxic exposure.

Induction of Ischemic Hypoxia: Transient focal cerebral ischemia was induced by the middle cerebral artery occlusion (MCAO) technique for 60 minutes, followed by reperfusion. Hypoxic conditions were maintained using a controlled hypoxia chamber with reduced oxygen concentration according to the experimental protocol. Physiological parameters, including body temperature, heart rate, and oxygen saturation, were continuously monitored throughout the experiment.

Assessment of Astrocyte Activation: Astrocyte activation was evaluated by immunohistochemical staining for glial fibrillary acidic protein (GFAP). Brain tissue sections from the ischemic cortex and hippocampus were analyzed using light microscopy, and GFAP-positive cells were quantified in randomly selected microscopic fields.

Assessment of Blood–Brain Barrier Permeability: BBB permeability was assessed using Evans blue dye extravasation. Following intravenous administration of Evans blue, brain tissues were harvested, and dye leakage was quantified spectrophotometrically. Tight junction protein expression (occludin, claudin-5, and ZO-1) was evaluated by immunohistochemistry and Western blot analysis.

Assessment of Cerebral Hemodynamics: Cerebral blood flow was measured using laser Doppler flowmetry before ischemia, during occlusion, and after reperfusion. Mean cerebral perfusion values were recorded and expressed as percentages of baseline blood flow.

Biochemical Analysis: Brain tissue homogenates were analyzed for oxidative stress markers, including malondialdehyde (MDA), superoxide dismutase (SOD), and reduced glutathione (GSH). Inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), were measured using enzyme-linked immunosorbent assay (ELISA).

Histopathological Examination: Brain specimens were fixed in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin (H&E). Histopathological evaluation focused on neuronal degeneration, cerebral edema,

vascular congestion, and inflammatory cell infiltration.

The primary outcome measures were:

- Changes in BBB permeability.
- Cerebral blood flow.
- Astrocyte activation (GFAP expression).

Secondary outcome measures included:

- Tight junction protein expression.
- Oxidative stress markers.
- Inflammatory cytokine levels.
- Histopathological changes in brain tissue.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using SPSS version 26.0. Continuous variables were expressed as mean ± standard deviation (SD). Comparisons between groups were performed using the independent Student's t-test, while categorical variables were analyzed using the Chi-square test. Correlations between astrocyte activation, BBB permeability, and cerebral blood flow were assessed using Pearson's correlation coefficient. A p-value of <0.05 was considered statistically significant.

Results

A total of 56 experimental subjects completed the study, with 28 animals in the control group and 28 in the ischemic hypoxia group. No animals were excluded from the final analysis. Astrocyte activation, assessed by glial fibrillary acidic protein (GFAP) expression, was significantly higher in the ischemic hypoxia group compared with the control group ($p < 0.001$). Increased GFAP immunoreactivity was predominantly observed in the ischemic cortex and hippocampal regions, indicating marked reactive astrogliosis following ischemic injury. Blood–brain barrier (BBB) permeability was significantly increased in the ischemic hypoxia group, as demonstrated by greater Evans blue dye extravasation ($p < 0.001$). This increase was accompanied by a significant reduction in the expression of the tight junction proteins occludin, claudin-5, and ZO-1, suggesting disruption of BBB integrity. Cerebral hemodynamic assessment showed a significant reduction in cerebral blood flow in animals subjected to ischemic hypoxia compared with controls ($p < 0.001$). Laser Doppler flowmetry demonstrated persistent impairment of cerebral perfusion despite reperfusion, indicating defective neurovascular coupling. Oxidative stress was significantly increased in the ischemic hypoxia group, with higher malondialdehyde (MDA) levels and lower superoxide dismutase (SOD) and reduced glutathione (GSH) concentrations than those observed in the control group ($p < 0.05$ for all comparisons). Inflammatory cytokines, including TNF-α, IL-1β, and IL-6, were significantly elevated following ischemic hypoxia ($p < 0.001$), reflecting an enhanced neuroinflammatory response. Histopathological examination revealed neuronal degeneration, cerebral edema, vascular congestion, and inflammatory cell infiltration in the ischemic hypoxia group, whereas normal brain architecture was preserved in the control group. Correlation analysis demonstrated a significant positive correlation between GFAP expression and BBB permeability ($r = 0.69$, $p < 0.001$), while cerebral blood flow showed a significant negative correlation with BBB permeability ($r = –0.65$, $p < 0.001$). These findings indicate that increased astrocyte activation is associated with impaired neurovascular coupling, disruption of BBB integrity, and reduced cerebral perfusion under ischemic hypoxia conditions.

Table 1: Baseline Characteristics of Experimental Animals

Parameter	Control (n = 28)	Ischemic Hypoxia (n = 28)	p-value
Body weight (g)	248.6 ± 15.2	250.1 ± 14.8	0.71
Age (weeks)	9.1 ± 0.8	9.2 ± 0.7	0.65
Heart rate (beats/min)	352 ± 18	349 ± 20	0.54
Oxygen saturation (%)	98.2 ± 0.9	98.0 ± 1.0	0.48

Table 2: Astrocyte Activation and Blood–Brain Barrier Permeability

Parameter	Control (n = 28)	Ischemic Hypoxia (n = 28)	p-value
GFAP-positive cells (%)	21.5 ± 4.2	56.8 ± 7.1	<0.001
Evans blue extravasation (µg/g tissue)	5.3 ± 1.2	16.9 ± 3.4	<0.001
Occludin expression (%)	94.2 ± 5.4	58.6 ± 8.1	<0.001
Claudin-5 expression (%)	91.8 ± 6.2	55.4 ± 7.8	<0.001
ZO-1 expression (%)	93.5 ± 5.8	57.2 ± 8.0	<0.001

Table 3: Cerebral Hemodynamics and Biochemical Markers

Parameter	Control (n = 28)	Ischemic Hypoxia (n = 28)	p-value
Cerebral blood flow (% of baseline)	99.2 ± 3.5	58.9 ± 9.2	<0.001
MDA (nmol/mg protein)	2.5 ± 0.6	5.9 ± 1.1	<0.001
SOD (U/mg protein)	18.6 ± 2.4	10.8 ± 2.0	<0.001
GSH (µmol/g tissue)	8.9 ± 1.2	4.6 ± 0.9	<0.001
TNF-α (pg/mL)	24.8 ± 5.6	61.7 ± 10.4	<0.001
IL-1β (pg/mL)	18.3 ± 4.5	46.8 ± 8.3	<0.001
IL-6 (pg/mL)	16.9 ± 3.8	42.5 ± 7.9	<0.001

Table 4: Correlation Between Astrocyte Activation, Blood–Brain Barrier Permeability, and Cerebral Blood Flow

Variables	Correlation coefficient (r)	p-value
GFAP expression vs. BBB permeability	0.69	<0.001
GFAP expression vs. Cerebral blood flow	–0.61	<0.001
BBB permeability vs. Cerebral blood flow	–0.65	<0.001
MDA vs. BBB permeability	0.58	<0.001
TNF-α vs. GFAP expression	0.63	<0.001

Discussion

The present study investigated the role of astrocyte-mediated neurovascular coupling in regulating blood–brain barrier (BBB) permeability and cerebral hemodynamics under ischemic hypoxia conditions. The findings demonstrated that ischemic hypoxia resulted in marked astrocyte activation, disruption of BBB integrity, impaired cerebral blood flow, increased oxidative stress, and enhanced neuroinflammatory responses. These observations highlight the central role of astrocytes in maintaining neurovascular homeostasis and suggest that dysfunction of astrocyte-mediated signaling contributes significantly to the pathophysiology of ischemic brain injury. A major finding of this study was the significant increase in glial fibrillary acidic protein (GFAP) expression in the ischemic hypoxia group, indicating reactive astrogliosis. Astrocytes normally regulate neuronal metabolism, extracellular ion balance, and vascular tone through close interactions with endothelial cells and pericytes. Under ischemic conditions, however, excessive astrocyte activation alters intracellular calcium signaling and the release of vasoactive mediators, resulting in impaired neurovascular coupling and reduced cerebral perfusion. These findings are consistent with previous experimental studies demonstrating that astrocyte dysfunction contributes to inadequate cerebral blood flow following ischemic injury.

The present study also demonstrated a significant increase in BBB permeability, accompanied by reduced expression of the tight junction proteins occludin, claudin-5, and ZO-1. Astrocytic end-feet play a critical role in maintaining BBB integrity by regulating endothelial tight junctions and water transport. During ischemic hypoxia, inflammatory cytokines, reactive oxygen species, and matrix metalloproteinases released from activated astrocytes disrupt these junctional proteins, leading to increased vascular permeability, cerebral edema, and secondary neuronal damage. Similar observations have been reported in experimental models of cerebral ischemia, emphasizing the importance of preserving BBB function to improve neurological outcomes. Cerebral hemodynamic assessment revealed a significant reduction in cerebral blood flow following ischemic hypoxia. Impaired neurovascular coupling limits the ability of cerebral vessels to respond appropriately to neuronal metabolic demands, thereby exacerbating tissue hypoxia and infarct progression. The observed negative correlation between BBB permeability and cerebral blood flow suggests that vascular dysfunction and barrier breakdown occur simultaneously during ischemic injury. Restoration of astrocyte-mediated signaling has been shown in previous studies to improve microvascular perfusion and reduce ischemic tissue damage. The study further demonstrated significantly elevated levels of oxidative stress markers and pro-inflammatory cytokines in the ischemic hypoxia group. Oxidative stress promotes lipid peroxidation and mitochondrial dysfunction, while inflammatory mediators such as TNF-α, IL-1β, and IL-6 amplify endothelial injury and BBB disruption. These molecular events further impair astrocyte-endothelial communication, creating a vicious cycle of inflammation, vascular dysfunction, and neuronal loss. The positive correlations observed between astrocyte activation, oxidative stress, and inflammatory markers support this mechanism. Histopathological examination confirmed the biochemical findings by demonstrating neuronal degeneration, vascular congestion, inflammatory cell infiltration, and cerebral edema in animals exposed to ischemic hypoxia. These structural alterations are characteristic of ischemic brain injury and reflect the combined effects of reduced cerebral

perfusion, BBB disruption, oxidative damage, and neuroinflammation. The present study has certain limitations. The relatively modest sample size and the use of a single experimental model may limit the generalizability of the findings. In addition, long-term neurological recovery and behavioral outcomes were not evaluated. Future studies involving larger sample sizes, multiple ischemic models, and targeted interventions directed at astrocyte signaling pathways are warranted to validate these findings and explore their translational potential. Overall, the findings indicate that astrocyte-mediated neurovascular coupling plays a fundamental role in preserving BBB integrity and regulating cerebral hemodynamics during ischemic hypoxia. Therapeutic strategies aimed at modulating astrocyte function, reducing oxidative stress, and suppressing neuroinflammation may help preserve cerebral microvascular function and improve neurological recovery following ischemic brain injury.

Conclusion

The present study demonstrates that astrocyte-mediated neurovascular coupling is a key determinant of blood–brain barrier integrity and cerebral hemodynamics during ischemic hypoxia. Ischemic injury was associated with marked astrocyte activation, increased blood–brain barrier permeability, reduced expression of tight junction proteins, impaired cerebral blood flow, elevated oxidative stress, and enhanced neuroinflammatory responses. These alterations collectively contribute to neuronal damage and deterioration of cerebral function.

The significant correlations between astrocyte activation, blood–brain barrier disruption, and reduced cerebral perfusion emphasize the pivotal role of astrocytes in maintaining neurovascular homeostasis under pathological conditions. Preservation of astrocyte function may help limit vascular leakage, reduce inflammatory injury, and improve cerebral perfusion following ischemic hypoxia. Overall, the findings suggest that therapeutic strategies targeting astrocyte-mediated signaling pathways have the potential to protect the neurovascular unit, preserve blood–brain barrier integrity, and improve neurological outcomes in ischemic stroke and other hypoxic brain disorders. Further experimental and clinical studies are warranted to validate these mechanisms and translate them into effective therapeutic interventions.

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