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REVIEW

Obstructive Sleep Apnea Syndrome and Ischemic Stroke: Investigating Inflammatory Mechanisms

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Abstract: Obstructive Sleep Apnea Syndrome (OSAS) is characterized by repeated episodes of complete (apnea) or partial (hypopnea) collapse of the upper airway during sleep, leading to chronic intermittent hypoxia and/or hypercapnia, and sleep fragmentation. This review systematically examines the mechanisms linking OSAS and ischemic stroke, with particular emphasis on the roles of the PI3K/Akt signaling pathway, Toll-like receptor signaling pathway, and NLRP3 inflammasome in OSAS-related inflammatory responses, and their contributions to the pathogenesis and progression of ischemic stroke. We also explore how OSAS affects stroke recovery through impaired sleep quality and increased cardiovascular stress, potentially worsening prognosis. This article discusses potential anti-inflammatory therapeutic strategies, underscores the importance of early OSAS intervention in reducing recurrence and improving outcomes, and offers new perspectives on OSAS-related ischemic stroke mechanisms and clinical management.

Keywords: obstructive sleep apnea syndrome, ischemic stroke, inflammatory mechanisms, signalling pathways

Introduction

Obstructive Sleep Apnea Syndrome (OSAS) is a prevalent sleep disorder characterized by recurrent partial or complete upper airway collapse, apnea episodes, and hypoventilation. This condition typically results in intermittent hypoxia, hypercapnia, sleep disruption, and daytime fatigue.[1] Epidemiological data indicate that approximately 936 million individuals worldwide aged 30–69 years have moderate to severe OSAS, with about 425 million classified as moderate to severe cases. China reports the highest prevalence rates, followed by the United States, Brazil, and India. The global burden of OSAS continues to rise.[2] OSAS significantly impacts daily functioning and overall health, highlighting the need to understand its fundamental mechanisms for improved prevention and treatment strategies. Substantial evidence demonstrates a strong association between OSAS and ischemic stroke (IS).

Ischemic stroke represents a major global health challenge, presenting complex prognostic and therapeutic difficulties. Common manifestations include hemiparesis, speech articulation deficits, aphasia, sensory disturbances, and visual impairment. Currently affecting at least 77.19 million people worldwide, the incidence of IS is projected to increase.[3] This review employs current experimental evidence to explore the inflammatory mechanisms connecting OSAS and IS, with the aim of providing valuable insights for future research in this field.

Search Strategy and Selection Criteria

This article is a narrative review focusing on the inflammatory mechanisms linking OSAS and ischemic stroke. We conducted a comprehensive literature search in major databases including PubMed, Web of Science, and Embase up to December 2024. The search strategy employed combinations of the following keywords: "Obstructive Sleep Apnea",

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"Ischemic Stroke", "Inflammation", "PI3K/Akt signaling", "Toll-like receptor", "NLRP3 inflammasome", and "Intermittent Hypoxia". We primarily selected original research articles, systematic reviews, and meta-analyses published in English. Studies were included if they provided mechanistic insights into the inflammatory pathways connecting sleep apnea and stroke pathologies. We excluded abstracts without full text, case reports, and studies with insufficient relevance to the specific signaling pathways discussed.

The Pathogenesis of OSAS

The pathogenesis of OSAS involves both anatomical and functional components. Anatomical factors encompass upper airway collapse and morphological abnormalities, while functional elements include nocturnal rostral fluid displacement, reduced respiratory threshold, and increased loop gain.

Anatomic Factors Leading to OSAS

Most OSAS patients present varying degrees of anatomical abnormalities in the upper respiratory tract.[4] These structural variations are strongly influenced by BMI, age,[5] and gender.[6] Respiratory failure in OSAS can be categorized as active or passive. Active collapse relates to impaired neuromuscular control of airway dilator muscles, while passive collapse involves the anatomical structure of the upper airway. Characteristic morphological abnormalities include elongation of the soft palate, mandibular positioning issues, facial structural variations, and increased volume of peripharyngeal soft tissues.[7,8] These anatomical alterations compromise upper airway patency and contribute significantly to OSAS development.

Functional Factors Contributing to OSAS

Functional factors affecting OSAS incidence and severity primarily involve upper respiratory tract dynamics. Nocturnal rostral fluid transfer plays a crucial role in OSAS severity, particularly following IS.[9] During daytime hours, gravitational forces cause fluid accumulation in the lower extremities. Upon assuming a recumbent position at night, this fluid redistributes from the legs to the neck region, resulting in upper airway narrowing that may precipitate or exacerbate OSAS. Reducing daytime leg fluid accumulation may consequently ameliorate OSAS severity.[9,10]

The Respiratory Arousal Threshold (AT), representing the physiological measure of respiratory effort required to initiate sleep arousal, represents another relevant factor.[11] Hyperventilation following arousal events can induce central sleep apnea, affecting vagus and hypoglossal nerve output, decreasing airway sphincter activity, and increasing OSAS susceptibility.[12] This mechanism affects approximately half of patients with moderate to severe OSAS, contributing to daytime sleepiness and attentional deficits.[13]

Loop gain, quantifying respiratory stability and central apnea susceptibility, constitutes an additional important factor.[14] Elevated loop gain in OSAS may reflect heightened sensitivity to CO2 fluctuations, potentially decreasing upper airway dilator activity and promoting recurrent respiratory events.[15]

Emerging research suggests associations between gut microbiota alterations and OSAS, with microbiota fluctuations linked to intermittent hypoxia and sleep fragmentation.[16] In summary, OSAS represents a complex interplay between anatomical and functional factors, with sleep fragmentation and upper respiratory failure serving as key drivers. Future investigations should integrate multi-omics approaches to further elucidate molecular networks and identify novel targets for precision interventions.

Pathogenesis of Ischemic Stroke

Ischemic stroke constitutes an acute, focal neurological disorder resulting from inadequate cerebral blood flow. This may occur when blood clots obstruct circulation, either through local thrombus formation (thrombotic stroke) or embolic migration from distant sites (embolic stroke). Additionally, IS can arise from structural or functional abnormalities in cerebral vasculature that impair adequate blood supply.[17]

The pathophysiology of IS involves complex cascade reactions including energy metabolism impairment and excitotoxicity, oxidative stress and free radical injury, and inflammation with immune activation.

Energy Metabolism Impairment and Excitotoxicity

Cerebral ischemia reduces neuronal NAD+, an essential cofactor in mitochondrial respiratory chain function and DNA repair enzymes (including PARP1 and Sirtuins), leading to energy depletion and mitochondrial respiratory chain blockade. During ischemia, neurons shift from the pentose phosphate pathway (PPP) to glycolysis, reducing NADPH and increasing oxidative stress. In excitotoxicity, cerebral ischemia triggers glutamate release from neurons and astrocytes, with subsequent glutamate receptor overactivation causing excessive calcium influx that initiates downstream toxic signaling pathways.[18]

Oxidative Stress and Free Radical Damage

Both ROS and RNS contribute to oxidative stress injury in IS, with ROS serving as the primary mediators. Mitochondrial dysfunction following ischemia and reperfusion increases ROS production. Pathological ROS effects manifest through three major categories: lipid peroxidation, protein oxidation, and DNA damage. ROS also induce neuronal apoptosis via mitochondrial and death receptor pathways (such as Fas/FasL). Under inflammatory conditions with intact blood-brain barrier, ROS activate specific signaling pathways that promote protease and inflammatory mediator release, ultimately leading to blood-brain barrier disruption.[17]

Inflammation and Immune Activation

Local cerebral blood flow disruption following IS can induce hypoxic neuronal death and activate both microglia and peripheral immunity. Microglia release proinflammatory factors through activation of related signaling pathways and recruit neutrophils and monocytes for infiltration. Neutrophils produce matrix metalloproteases (MMP-9) that damage the blood-brain barrier and generate neutrophil extracellular traps (NETs) that exacerbate ischemia; Th1/Th17 cells produce IFN-γ and IL-17, activating astrocytes and amplifying inflammation. Concurrently, regulatory T cells (Treg) inhibit excessive immune responses and promote repair through IL-10 and PD-1 mechanisms.[19]

The pathological cascade centers on disturbances in energy metabolism, oxidative stress, and inflammation. Targeting these components (for instance, through ROS production inhibition or microglial polarization modulation) may represent crucial strategies for minimizing neuronal injury.

Mechanisms of OSAS-Induced and Exacerbated Ischemic Stroke

Although the association between OSAS and IS has been extensively investigated, the precise causal relationships remain incompletely elucidated.[20,21] Nevertheless, substantial evidence confirms that OSAS significantly contributes to IS development and progression, with varying OSAS severity conferring differential IS risk. Patients with moderate or severe OSAS face elevated IS risk compared to those with mild or no OSAS.[22]

OSAS is known to promote IS through cerebral hemodynamic alterations and atherosclerosis, with established evidence demonstrating that OSAS dramatically increases stroke risk independent of other risk factors.[23] Research indicates that OSAS induces oxidative stress and inflammation via intermittent hypoxia and sleep fragmentation, characterized by reactive oxygen species activation resulting from oxidative stress and inflammation triggered by activated hypoxia-inducible factors (HIFs).[24,25]

OSAS-Induced IS

Inflammation links both cerebral hemodynamics and atherosclerosis in OSAS-related IS pathogenesis. Regarding cerebral blood flow, severe OSAS affects cerebral circulation through cyclic vasodilation and constriction, sympathetic nervous system activation, and impacts on cerebral autoregulatory mechanisms. Inflammation itself may alter cerebral hemodynamics. OSAS induces transient cerebral blood flow changes that can result in cerebral tissue ischemia.[25]

Concerning atherosclerosis, OSAS can induce vascular endothelial disorders that exacerbate atherosclerosis in major arteries, potentially leading to cerebral blood flow disruptions and subsequent IS.[26,27] Importantly, OSAS-induced IS does not operate through isolated mechanisms but rather involves intermittent hypoxia and inflammatory responses that both directly impair cerebrovascular function and activate the NLRP3 inflammasome, which associates with

atherosclerotic pathological processes. Inflammasome activation in atherosclerotic plaques may promote plaque instability, thereby increasing cardiovascular event risk. According to the "inflammatory aging" theory linking aging with inflammation, inflammatory markers may predict atherosclerotic stroke risk.[28]

It should be emphasized that OSAS-induced IS involves multiple interconnected pathways, with intermittent hypoxia and inflammatory responses triggered by OSAS directly impairing cerebrovascular function while indirectly facilitating atherosclerotic plaque development and rupture through activation of molecular pathways such as the NLRP3 inflammasome. Furthermore, research indicates that activation of these inflammatory pathways contributes not only to stroke onset but also plays crucial roles in post-stroke injury amplification. For example, intermittent hypoxia exacerbates neuronal death through mitochondrial dysfunction and oxidative stress, while persistent inflammasome activation aggravates blood-brain barrier disruption and neuroinflammatory infiltration.

OSAS Exacerbates IS Injury

Based on the aforementioned mechanisms, the aggravating effects of OSAS on IS injury primarily manifest in three domains: energy metabolism disturbance, oxidative stress, and immune activation.

Regarding energy metabolism and excitotoxicity, OSAS worsens post-ischemic injury; intermittent hypoxia in IS parallels post-ischemic conditions, leading to mitochondrial dysfunction. Intermittent hypoxic preconditioning has been found to exacerbate mitochondrial permeability transition pore opening, accelerating neuronal dysfunction.[29]

Concerning oxidative stress and free radical damage, intermittent hypoxia promotes excessive ROS and RNS release, exacerbating ischemic perfusion injury after IS and leading to neuronal death and infarct expansion. Animal studies demonstrate that severe intermittent hypoxia (6% O2) significantly increases brain tissue levels of malondialdehyde and 8-hydroxydeoxyguanosine.[30] Concurrently, antioxidant enzyme activities are suppressed, suggesting that OSAS contributes to stroke injury amplification.

Regarding inflammation and immune activation, intermittent hypoxia upregulates pro-inflammatory factors and promotes neutrophil infiltration by activating specific inflammatory signaling pathways. Clinical studies reveal direct correlations between inflammatory markers in OSAS patients and stroke severity, with certain inflammatory responses reversible through treatment, as indicated in reference[31] suggesting that inflammation represents a key pathway through which OSAS exacerbates brain injury in IS.

Influence of Age and Sex on Inflammatory Mechanisms

The inflammatory landscape linking OSAS to ischemic injury is fundamentally altered by biological variables, particularly sex and age. While OSAS is traditionally characterized by male predominance, the risk profile shifts dramatically in females following menopause. This surge suggests that the withdrawal of estrogen compromises its established anti-inflammatory and neuroprotective barriers, thereby increasing susceptibility to stroke.[32,33] Furthermore, the aging process introduces "inflammaging"—a baseline state of chronic, low-grade inflammation. This pre-existing condition likely lowers the threshold for neuroinflammatory cascades triggered by intermittent hypoxia.[34] This mechanistic vulnerability is substantiated by clinical evidence confirming that severe OSAS remains a potent independent predictor of stroke in the elderly, countering earlier assumptions that this risk attenuates with age.[35] Consequently, distinguishing the specific roles of pathways such as TLR4 and NLRP3 requires rigorous stratification by demographic factors to avoid generalized conclusions that mask subgroup-specific mechanisms.[36]

Effects of Sleep Apnea on Ischemic Brain Injury in Animal Models

Intermittent hypoxia represents the most prominent sleep apnea feature, and researchers have frequently utilized this characteristic to model sleep apnea, more often analyzing respiratory control instability in OSAS patients and intermittent hypoxia effects on systemic physiology than simulating upper airway collapse through surgical means.[37]

Two similar experiments investigated intermittent hypoxia in ischemic brain injury. The first found that OSAS significantly increased MCAO-induced brain damage after ischemia-reperfusion in MCAO model mice (subjected to obstructive sleep apnea with AHI ≥15 for 3 days and 3 hours), suggesting that OSAS adversely affects brain damage recovery following IS episodes.[38] The second experiment revealed significantly increased MCAO-induced brain damage

after ischemia-reperfusion in male rats treated with intermittent hypoxia compared to non-hypoxic controls, with the intermittent hypoxia group exacerbating overall neurological injury from cerebral ischemia-reperfusion in rats.[39] Both experiments concluded that intermittent hypoxia contributes to ischemic brain injury, with the first experiment additionally employing a 3D model to develop a novel experimental OSAS model using an OSAS device.

While intermittent hypoxia (IH) models effectively mimic oxygen desaturation, they fundamentally fail to reproduce the mechanical airway obstruction defining human OSAS. Consequently, these models lack critical pathophysiological features such as profound negative intrathoracic pressure swings and the specific autonomic fragmentation seen in patients.[40] This discrepancy likely simplifies the inflammatory landscape, potentially explaining why neuroprotective agents that show promise in rodent IH paradigms often fail to translate into clinical efficacy for stroke patients. Future translational success depends on developing models that incorporate actual airway occlusion to simulate the full hemodynamic and inflammatory syndrome.[20]

Regulatory Mechanisms of Signaling Pathways in OSAS-Induced and Exacerbated IS

In this review, we specifically prioritize the PI3K/Akt, Toll-like receptor (TLR), and NLRP3 inflammasome pathways due to their extensively validated roles at the intersection of intermittent hypoxia and cerebral ischemic injury. Current evidence suggests these three pathways represent the primary signaling hubs linking OSAS-induced oxidative stress to the neuroinflammatory cascade in ischemic stroke. While other signaling mechanisms, such as the JAK/STAT and MAPK pathways, are also implicated in inflammatory regulation, the direct crosstalk between intermittent hypoxia and the specific triad of PI3K/Akt, TLR, and NLRP3 offers the most robust translational evidence to date.

PI3K/Akt Signaling Pathway

The PI3K/Akt signaling pathway comprises Akt and serine/threonine kinase PI3K. Human cells express three PI3K classes, with Class I PI3Ks particularly relevant to IS. In this pathway, PI3K activation occurs through receptor-coupled tyrosine kinases and heterotrimeric G proteins. Akt activation typically occurs downstream of PI3K, with Akt phosphorylation serving as a PI3K activation marker.

PI3K activation promotes conversion of phosphatidylinositol-4,5-bisphosphate (PI(4,5)P2) to phosphatidylinositol-3,4,5-trisphosphate (PI(3,4,5)P3), also termed PIP3. PIP3 functions as a second messenger mediating Akt and other effector protein activation. Akt activation proves crucial for various physiological processes including cell growth, survival, metabolism, and migration.[41]

The PI3K/Akt signaling axis can activate immune cells such as macrophages to regulate inflammation. In macrophages, this pathway transduces signals from cytokines and Toll-like receptors.[42] Beyond macrophages, the PI3K/Akt pathway plays important roles in microglial transformation, promoting polarization from pro-inflammatory M1 to anti-inflammatory M2 phenotypes. Inhibition of this pathway may impede this transition, resulting in increased inflammation.[43]

The PI3K/Akt pathway has been implicated in various diseases including obesity, type 2 diabetes, spinal cord injury, idiopathic pulmonary fibrosis, cancer, and neurodegenerative disorders, where its dysregulation may either contribute to disease pathogenesis or offer therapeutic potential.[44–48]

OSAS Influences the PI3K/Akt Signaling Pathway in IS

The interaction between ROS and the PI3K/Akt pathway is complex and context-dependent. Emerging evidence suggests a biphasic response: while physiological or transient levels of ROS may function as signaling molecules to activate Akt and promote cell survival during early hypoxic stress, the pathological scenario differs significantly. In the context of severe OSAS, the chronic and excessive accumulation of ROS overwhelms antioxidant defenses, leading to the oxidative modification of key signaling proteins. This sustained oxidative stress predominantly inhibits the PI3K/Akt axis—often through the inactivation of PTEN or direct oxidation of Akt kinases—thereby abrogating its neuroprotective capacity and shifting the cellular fate toward apoptosis and inflammation.[49,50] PI3K/Akt pathway activation induces NF-κB pathway expression, leading to TNF-α, IL-8, IL-6 and CRP production.[51] Simultaneously, reduced GSK3β expression decreases anti-inflammatory factor expression (such as CD206, TGFβ),[52] as illustrated in Figure 1, promoting inflammation.

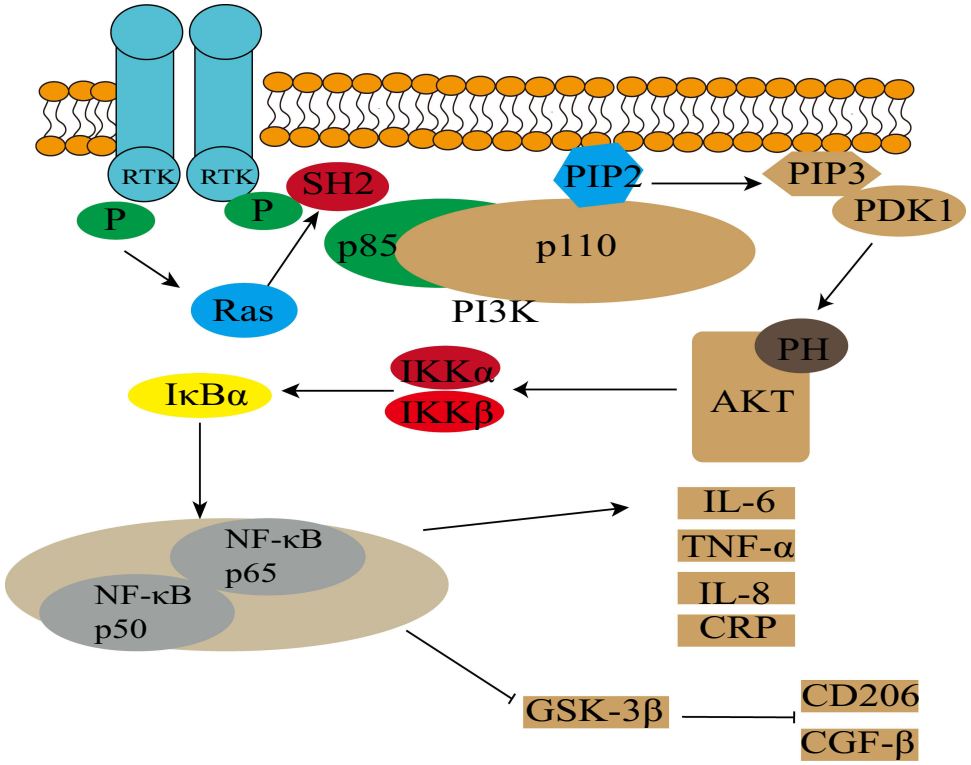

Figure 1 The figure illustrates that chronic intermittent hypoxia (CIH) activates the PI3K/Akt signaling pathway, which stimulates the release of pro-inflammatory factors (e.g., TNF-α, IL-6, IL-8) through the NF-κB signaling pathway. Additionally, it suppresses GSK-3β expression, thereby intensifying neuroinflammation. In the figure, t-arrows denote inhibition, while solid arrows denote activation.

Conversely, the PI3K/Akt signaling pathway inhibits M1 to M2 microglial conversion, with M1 microglia and macrophage activation resulting in neuroinflammation. Neuroinflammation associates with acute stroke, blood-brain barrier disruption, neuronal damage, and other critical neurological outcomes. Blood-brain barrier damage following IS intensifies inflammation, permitting peripheral immune cell migration (eg., macrophages) into the brain, thereby worsening neuroinflammation.[53–55]

Toll-Like Receptor Signaling Pathway

Toll-like receptors (TLRs) constitute type I transmembrane proteins consisting of multiple extracellular leucine-rich repeats and a Toll/IL-1 receptor structure.[56] The TLR family represents a crucial component of innate immunity by recognizing molecular markers of microbial pathogens. TLR activation can induce diverse inflammatory gene expression through signaling pathway activation, with cellular responses influenced by pathogens and intracellular adapter proteins.[57]

Based on findings from Daniel Fische and colleagues, the myddosome (a signaling complex containing MyD88) operates throughout the TLR pathway and regulates its activity, representing a critical TLR signaling component. Myddosome disruption or inhibition may diminish TLR signaling pathway contributions to inflammation and autoimmune diseases.[58] Similarly, targeting the myddosome or suppressing its expression could reduce Toll-like receptor pathway impacts in these contexts.

The TLR4 pathway, similar to the PI3K/Akt pathway, demonstrates dual functionality: it can both induce inflammation leading to cell death and regulate inflammation.[59] TLRs associate with diverse diseases including infection, autoimmunity, chronic inflammation, cancer, diabetes, neuroimmunity, and lifestyle disorders.[60] Reviewing TLR signaling pathways may prove beneficial for treating or alleviating these.

OSAS Affects the Signaling Pathway of Toll-Like Receptor in IS

OSAS can damage central nervous system cells (such as neurons), leading to damage-associated molecular pattern (DAMP) release including Heat Shock Protein (HSP60) and High Mobility Group Box 1 (HMGB1). These DAMPs activate through Toll-like receptor interactions on microglial cells, inducing inflammation.[61]

Research by Javier R. Caso's team demonstrated that TLR4-deficient mice exhibited reduced infarcts and less severe inflammation following ischemia, suggesting TLR4 involvement in ischemia-induced brain damage and inflammation.[62] Similar to the PI3K/Akt signaling pathway, TLR2/MyD88 or TLR4/NF-κB signaling pathway activation promotes associated inflammatory mediator production. TLR2/MyD88 activation results in neuroinflammation.[63,64]

Comparable to PI3K/Akt signaling, the TLR4 signaling pathway demonstrates dual roles, either promoting inflammatory responses causing cell death or regulating inflammation.[59] TLR4 plays significant roles in atherosclerosis, with TLR4 promoting adhesion molecule expression and inflammatory cell invasion that accelerate plaque progression. Low-dose TLR ligands induce ischemic tolerance and reduce infarct volume.[65] Notably, TLR2 effects on IS primarily drive inflammatory responses, though under certain circumstances may provide neuroprotection through neurosteroid modulation.[66]

NLRP3 Inflammasome

Inflammasomes represent intracellular multimeric protein complexes that activate inflammatory caspase-1, with inflammasome activation constituting a primary inflammatory pathway.[67] Inflammasomes serve as crucial innate immunity components, regulating inflammatory responses through inflammatory cysteine protease activation.[68] Among these complexes, the NLRP3 inflammasome has been most extensively studied.

The NLRP3 inflammasome comprises three proteins: NLRP3, ASC (apoptosis-associated speck-like protein containing a CARD domain), and the effector protein procaspase-1.[69] NLRP3 activation mechanisms include potassium, calcium, and chloride efflux; reactive oxygen species generation; mitochondrial dysfunction; large nonspecific pore formation; and lysosomal rupture.[70] Activation pathways divide into classical and non-classical routes that promote pro-inflammatory cytokine maturation and release (such as IL-1β and IL-18).[71]

Hypoxia induces HIF-1α production, which can co-localize with NLRP3,[72] potentially enhancing NLRP3 inflammasome activation through this interaction.[73] Classical pathway activation requires two distinct signals: a "priming" signal triggered by pattern recognition receptors such as TLR4, and an activation signal facilitating NLRP3, ASC, and procaspase-1 assembly.[74] The non-classical pathway detects cytoplasmic lipopolysaccharide and bacterial mRNA, directly activating the NLRP3 inflammasome without NLRP3 involvement.

The NLRP3 inflammasome has been implicated in various disorders including Ehrlichiosis, sepsis, metabolic diseases, neurodegenerative conditions, autoinflammatory syndromes, cancer, and atherosclerosis.[75,76]

OSAS Regulates NLRP3 in IS

OSAS-induced intermittent hypoxia causes mitochondrial dysfunction and excessive mtROS production. Excessive ROS can damage mitochondria and induce mitochondrial membrane potential loss and cellular component release, such as mtDNA. This mtDNA can activate the NLRP3 inflammasome, thereby promoting inflammasome assembly and inflammatory factor production,[77] as shown in Figure 2.

The NLRP3 inflammasome also activates through OSAS's Toll-like receptor signaling pathway.[77] Chronic intermittent hypoxia in the NLRP3 inflammasome elevates NLRP3, cleaved caspase-1, and caspase-1 levels, leading to cellular pyroptosis.[78]

The NLRP3 inflammasome plays pivotal roles in IS pathogenesis, with its activation closely linked to inflammation exacerbation. The NLRP3 inflammasome constitutes a multiprotein complex that monitors cellular damage and regulates various signaling pathways including AMPK/Nrf2/NLRP3, TAK1/JNK/NLRP3, DRP1/NLRP3, ROS/TXNIP/NLRP3, TLR4/NF-κB/NLRP3, and others. These pathways enhance pro-inflammatory cytokine release such as IL-1β and IL-18, thereby driving inflammatory responses following ischemic injury.[79,80]

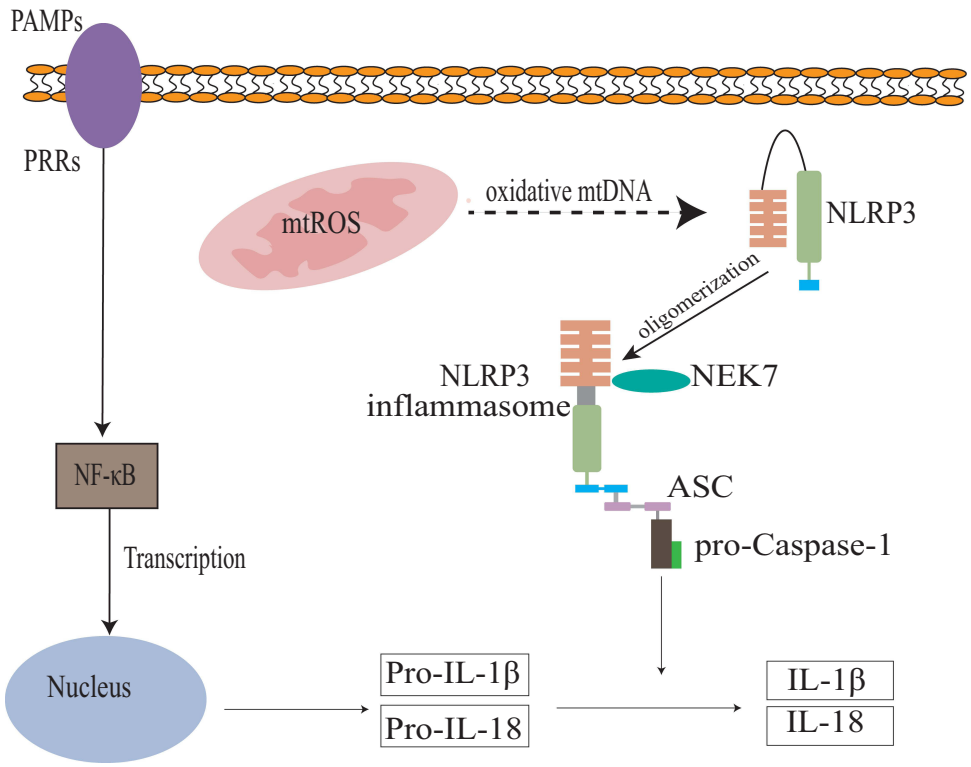

Figure 2 Intermittent hypoxia triggers mitochondrial ROS (mtROS) leakage, which activates the NLRP3 inflammasome. This activation promotes the caspase-1-mediated maturation and release of IL-1β and IL-18, ultimately inducing cellular pyroptosis.

Therapeutic Strategies Targeting Signaling Pathways in IS

As summarized in Table 1, all experimental interventions targeting inflammatory signaling pathways in middle cerebral artery occlusion rats ultimately yielded favorable outcomes. Beneficial effects in IS treatment were achieved through modulation of these signaling pathways.

Table 1 Summary of Potential Therapeutic Agents Targeting Inflammatory Signaling Pathways in OSAS-Related Ischemic Stroke

Signaling Pathway	Intervention/ Agent	Study Model	Key Mechanisms & Effects	Ref.
PI3K/Akt	2-Acetylacteoside	Mouse MCAO	Promotes neurogenesis and neural stem cell proliferation via PI3K/Akt pathway activation.	[81]
PI3K/Akt/NF-κB	Quercetin	Rat MCAO	Inhibits inflammatory cytokines and promotes microglia polarization toward anti-inflammatory M2 phenotype.	[82]
PI3K/Akt/mTOR	Piperine	Rat MCAO	Reduces ischemic injury and enhances neurologic recovery by inhibiting autophagy via PI3K/Akt/mTOR.	[83]
PI3K/Akt/mTOR	Aloe-emodin; Resveratrol	Rat MCAO	Upregulates anti-inflammatory factors, suppresses oxidative stress and prevents nerve injury.	[84]
JAK2/STAT3/PI3K/ AKT/mTOR	Resveratrol	Rat MCAO	Provides neuroprotection by regulating the JAK2/STAT3/PI3K/AKT/mTOR signaling pathway.	[85]
TLR4	TLR4 Deficiency	Mouse (TLR4-/-)	Enhances neurogenesis and suppresses acute inflammation, leading to improved functional recovery.	[86]
TLR4/NF-κB	Meisoindigo	Mouse MCAO	Inhibits NLRP3 inflammasome activation and regulates microglia/macrophage polarization (M1 to M2)	[87]
NLRP3 (via CSF1R)	Ki20227	Mouse MCAO	Inhibits CSF1R to block Microglia M1 polarization and NLRP3 inflammasome pathway activation.	[88]

Abbreviations: AHI, apnea-hypopnea index; CSF1R, colony-stimulating factor 1 receptor; MCAO, middle cerebral artery occlusion; NF-κB, nuclear factor kappa B; NLRP3, NOD-like receptor protein 3; OSAS, obstructive sleep apnea syndrome; PI3K/Akt, phosphatidylinositol 3-kinase/protein kinase B; TLR4, Toll-like receptor 4.

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In the PI3K/Akt signaling pathway, pathway activation promotes neural stem cell proliferation and neurogenesis while reducing M1 microglia numbers to minimize neuroinflammation. By interfering with PI3K/Akt/mTOR and PI3K/Akt/NF-κB signaling, inflammation prevention and IS-related neuroinflammation reduction become possible. Tanshinone modulation may exert neuroprotective effects.[89]

Novel approaches include Qilong Capsule, a Chinese herbal compound that inhibited the TLR4/NF-κB signaling pathway, alleviating brain ischemia/reperfusion inflammation and promoting nerve recovery.[90] Therapeutic targeting of Toll-like receptors may effectively reduce IS-associated inflammation and neurological damage.

Regarding therapeutic strategies, NLRP3 inflammasome inhibition has been proposed as a potential treatment approach. Numerous inhibitors have demonstrated efficacy in preclinical models, including small molecule compounds, type I interferons, microRNAs, nitric oxide, and nuclear factor erythroid 2 (Nrf2).[91] For instance, MCC950, a small molecule inhibiting NLRP3 inflammasome assembly by blocking caspase-1 activation, reduces IL-1β maturation and release, thereby mitigating ischemic brain injury in animal models.[92]

Furthermore, various natural products and herbs including artemisinin, curcumin, ginsenosides Rd, paeoniflorin, and metformin demonstrate NLRP3 inflammasome modulatory effects and have shown efficacy in reducing IS damage.[93,94] Modulation of IS-related signaling pathways may positively influence OSAS outcomes, suggesting that OSAS therapy could prove beneficial in IS management.

Clinical Research Perspectives

Impact of OSAS in Recovery from IS

Timely and consistent implementation of effective secondary prevention strategies in patients experiencing first stroke or transient ischemic attack could reduce stroke burden by up to 25%.[95]

Consequently, intervention in post-stroke patients proves significant.OSAS occurs in 67.5% of IS patients,[96] indicating broad OSAS effects in IS populations. OSAS significantly negatively impacts IS recovery time. OSAS patients experience fragmented sleep architecture and recurrent nocturnal apnea, resulting in impaired sleep quality during post-stroke recovery. This may influence nerve function recovery and cognitive improvement. OSAS has been found to worsen cognitive impairment, delay recovery, and affect patients' functional independence and physical recovery.[97]

Additionally, OSAS negatively affects cardiovascular systems in stroke patients. Intermittent hypoxemia and sleep fragmentation due to OSAS may cause blood pressure variability and increased cardiovascular workload.[98] In conclusion, OSAS exerts comprehensive and profound impacts on stroke recovery. Therefore, OSAS recognition and treatment in stroke patients proves essential for optimizing recovery outcomes and reducing long-term stroke burden.

Prognostic Results of Treatment of OSAS for IS

Clinical OSAS treatment with continuous positive airway pressure ventilation is associated with reduced recurrence rates in IS patients with OSAS demonstrating greater impact than in cardiovascular disease. This effect relates to OSAS treatment duration, with earlier CPAP administration yielding better outcomes.[99] CPAP may similarly reduce the incidence of new vascular events and for patients unable to undergo CPAP treatment, CPAP therapy absence can increase new cerebrovascular event probability five-fold.[100]

For IS patients with OSAS, CPAP therapy has been linked to reduced mortality in observational cohorts.[101] In older adults, CPAP therapy adherence reduces stroke recurrence rates, with adherence associated with recurrence frequency. CPAP treatment efficacy was mitigated by poor treatment adherence, with many patients responding poorly to CPAP. OSAS intervention in IS patients requires alternative therapies, potentially achieved through bilevel positive airway pressure ventilation, automatic adjustable continuous positive airway pressure ventilation, and oral appliances.[99]

Multiple research groups have examined CPAP therapy effects on OSAS in stroke patients, as well as differences between CPAP and other therapies. Stroke patient studies, summarized in Table 2, demonstrate various treatment outcomes.

As evident from Table 2, CPAP remains the current OSAS treatment mainstay. However, other modalities can treat OSAS with comparable efficacy in cases of poor patient compliance, highlighting the importance of demonstrating high-quality experiment feasibility regarding CPAP effects on stroke in OSAS.

Table 2 Clinical Evaluation of OSAS Interventions in Patients with Ischemic Stroke

Treatment Method	Study Design	Sample Size (Treated/ Control)	Patient AHI	Key Outcomes & Results	Ref.
CPAP	Observational	28/70	Avg 26	Positive: CPAP treatment was associated with a significant reduction in 5-year mortality (Adjusted HR = 0.24).	[101]
CPAP	RCT (Pilot)	25/25	32.2 ± 25.3	Feasibility: Early CPAP initiated immediately after stroke is feasible but showed no significant short-term functional benefit.	[102]
CPAP	Observational	15/36	≥ 20	Positive: Effective in reducing stroke recurrence when compliance is high.	[100]
CPAP	RCT	20/20	44.4 vs 34.9	Positive: CPAP treatment (≥4 h/night) improves cognitive function, sleep quality, and daytime sleepiness.	[103]
HFNC/CPAP	Cohort Study	115/63	Median 14	Alternative: HFNC and CPAP showed consistent prognostic improvements; HFNC is a viable alternative for CPAP-intolerant patients.	[104]
CPAP	RCT (Multicenter)	1346/1341	Moderate-Severe	Neutral (SAVE Trial): CPAP improved mood and quality of life but did not prevent recurrent cardiovascular events (stroke/MI).	[105]
CPAP	RCT (Acute)	63/63	≥ 20	Positive: Early CPAP (within 48h) significantly improved neurological recovery (NIHSS scores) and delayed cardiovascular events.	[106]
Oropharyngeal Exercises	RCT (Feasibility)	15/15	Mean 24	Alternative: Oropharyngeal muscle strengthening is feasible and reduced OSAS severity (AHI) in post-stroke patients.	[107]
CPAP	Retrospective Cohort	845/440	Moderate-Severe	Mixed: CPAP significantly reduced long-term all-cause mortality (HR=0.75) but had no significant effect on stroke recurrence rates.	[108]

Abbreviations: AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula; HR, hazard ratio; IS, ischemic stroke; NIHSS, National Institutes of Health Stroke Scale; OSAS, obstructive sleep apnea syndrome; RCT, randomized controlled trial.

Alternative Therapeutic Strategies:CPAP into lerance is frequent among stroke survivors secondary to facial paresis, aphasia, or cognitive deficits, necessitating alternative interventions. Mandibular advancement devices (MADs) offer a viable strategy for mild-to-moderate OSAS by mechanically enlarging the upper airway, subject to adequate dentition and motor function.[109] Positional therapy serves as a cost-effective, non-invasive adjunct specifically for position-dependent OSAS phenotypes.[110] Additionally, High-Flow Nasal Cannula (HFNC) therapy delivers positive airway pressure with superior comfort profiles compared to traditional masks.[104] Despite their physiological benefits, the specific efficacy of these non-CPAP modalities in reducing post-stroke inflammatory markers remains to be validated in rigorous randomized trials.

Impact of Comorbidities on Inflammatory

Risk Obesity, type 2 diabetes, and hypertension fundamentally alter the pathogenic landscape of OSAS-related stroke. In obesity, adipose tissue functions as an endocrine organ, releasing basal IL-6 and TNF-α to "prime" the immune system.[111] This chronic inflammatory state synergizes with intermittent hypoxia, amplifying endothelial injury beyond the effects of either condition alone. Concurrently, hyperglycemic conditions in diabetes trigger NLRP3 inflammasome activation.[112] On this primed background, OSAS acts as a critical "second hit," where intermittent hypoxia accelerates neurovascular damage beyond what either condition causes alone.[113]

Conclusion and Future Perspectives

Current evidence suggests that OSAS may exacerbate ischemic stroke outcomes via the PI3K/Akt, TLR, and NLRP3 inflammatory pathways. Clinically, variable CPAP adherence underscores the potential value of adjunctive anti-inflammatory strategies and early OSAS screening. Future research should prioritize developing specific NLRP3/TLR4 inhibitors, identifying prognostic biomarkers, and conducting large-scale longitudinal cohorts to further investigate the association between OSAS endotypes and stroke severity.Observational studies have consistently linked CPAP therapy to improved neurological recovery and reduced recurrence of vascular events in stroke patients with OSAS. Conversely, the large-scale multicenter SAVE trial found that CPAP did not significantly reduce the composite endpoint of cardiovascular events, despite improvements in mood and quality of life. This discrepancy is widely attributed to suboptimal treatment adherence in the trial cohort (mean usage < 3.3 hours/night), suggesting that higher compliance is essential for achieving prognostic cardiovascular benefits.Additionally, common stroke medications such as statins and ARBs may also mitigate inflammation in OSAS patients, warranting further investigation.

Conclusion

This review examines OSAS and IS mechanisms and their interactions, primarily through inflammatory pathways. Animal experiments demonstrate that early OSAS identification and management prove important for reducing IS risk. However, limited experimental data necessitate further investigation into specific OSAS damage mechanisms and pathways in IS. In OSAS and IS contexts, OSAS treatment may reduce relapse and death risks, though more treatment options remain needed. Although current research provides important insights into OSAS-IS relationships, further exploration is required to elucidate their specific molecular mechanisms and other interaction pathways.

Abbreviations

AHI, Apnea-Hypopnea Index; IS, Ischemic Stroke; BBB, Blood-Brain Barrier; CPAP, Continuous Positive Airway Pressure; DAMPs, Damage-Associated Molecular Patterns; HIF-1α, Hypoxia-Inducible Factor 1 Alpha; HMGB1, High Mobility Group Box 1; IL-1β, Interleukin-1 Beta; IL-6, Interleukin-6; IL-8, Interleukin-8; IL-10, Interleukin-10; IL-17, Interleukin-17; IL-18, Interleukin-18; MMP-9, Matrix Metalloproteinase-9; mtROS, Mitochondrial Reactive Oxygen Species; NF-κB, Nuclear Factor Kappa B; NLRP3, NOD-like Receptor Protein 3; OSAS, Obstructive Sleep Apnea Syndrome; PI3K/Akt, Phosphatidylinositol 3-Kinase/Protein Kinase B; ROS, Reactive Oxygen Species; RNS, Reactive Nitrogen Species; TLR, Toll-like Receptor; TNF-α, Tumor Necrosis Factor Alpha; Treg, Regulatory T Cells.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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