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Medicinal gases for treating central nervous system injuries☆

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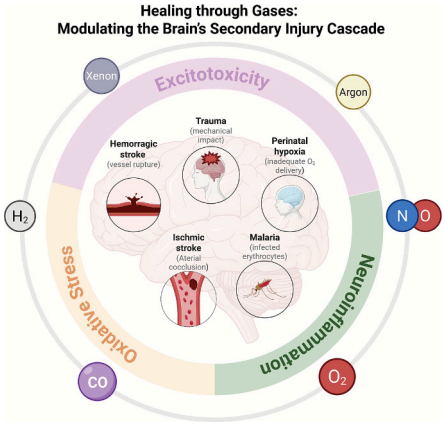
GRAPHICAL ABSTRACT



ABSTRACT

Central nervous system (CNS) injuries—such as stroke, traumatic brain injury, and perinatal hypoxia—trigger complex secondary cascades involving oxidative stress, inflammation, and apoptosis that limit recovery and therapeutic efficacy. Recent advances in medical gas delivery offer a novel, multifaceted approach to modulate these pathological processes. Gases including hydrogen, nitric oxide, carbon monoxide, xenon, and argon demonstrate potent neuroprotective, anti-inflammatory, and vasomodulatory properties in preclinical models. This review synthesizes current evidence on gas-based interventions across CNS pathologies, elucidates their molecular mechanisms, and evaluates translational challenges related to timing, dosing, and delivery technologies. Gas therapeutics represent a promising frontier in neurocritical care with potential to transform outcomes in otherwise intractable neurological injuries.

1. Introduction

Central nervous system (CNS) injuries—including traumatic brain injury, stroke, and spinal cord injury—are among the leading causes of death and long-term disability worldwide [1,2]. Primary insults can result from mechanical trauma, systemic hypoxia, ischemia, or hemorrhage, all of which impair oxygen and nutrient delivery and often lead to rapid and irreversible loss of neural function [3,4]. Across these

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conditions, the initial insult is characteristically followed by a cascade of secondary injury mechanisms—including excitotoxicity, mitochondrial dysfunction, oxidative stress, neuroinflammation, and apoptosis—that evolve over minutes to weeks and have been described in ischemic stroke, traumatic brain injury, and spinal cord injury, where they substantially exacerbate tissue loss and functional deficits [3–8].

Despite extensive research, effective clinical treatments remain limited, and most patients experience only partial recovery—especially when interventions are delayed beyond the critical window for neuroprotection [9,10]. Conventional strategies such as pharmacotherapy, cell-based therapies, and rehabilitation have shown promise in preclinical studies but have generally failed to demonstrate consistent efficacy in clinical trials, underlining the urgent need for alternative therapeutic approaches [11–14]. Among emerging strategies, therapeutic gas delivery has garnered increasing interest for its ability to modulate secondary injury mechanisms. Gases such as hydrogen (H_2), carbon monoxide (CO), hydrogen sulfide (H_2S), oxygen (O_2), nitric oxide (NO), and xenon (Xe) have demonstrated anti-inflammatory, antioxidant, anti-apoptotic, and neuroprotective effects in preclinical models [15–17]. By acting on components of the neurovascular unit and promoting neuroplasticity, gas-based therapies offer a novel and potentially transformative approach to CNS repair. However, the clinical translation of gas therapeutics remains challenged by issues related to targeted delivery, dose control, and timing. This review explores the current state of therapeutic gas delivery for CNS injuries, focusing on their mechanisms of action, delivery technologies, and translational prospects in the broader context of neuroprotective and regenerative medicine.

2. The role of gases in CNS physiology

Several gaseous molecules, both endogenously produced and exogenously administered, play pivotal roles in maintaining central nervous system (CNS) homeostasis. Endogenous gases such as nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S), alongside externally delivered gases like oxygen (O_2) and xenon (Xe), contribute to essential neurophysiological processes [18,19]. Oxygen is fundamentally critical for CNS functionality due to its indispensable involvement in mitochondrial respiration and neuronal energy metabolism. Adequate cerebral oxygenation ensures effective ATP production via oxidative phosphorylation, supporting neuronal activity, neurotransmission, and synaptic plasticity [20]. Precise regulation of oxygen homeostasis occurs through neurovascular coupling mechanisms, wherein astrocytes sense neuronal activity and coordinate corresponding adjustments in cerebral blood flow to match metabolic demands [21]. Oxygen also modulates intracellular signaling pathways integral to neuronal differentiation, neurogenesis, and survival, largely through hypoxia-inducible factors (HIFs), which dynamically respond to fluctuations in tissue oxygenation [22]. Even minor disturbances in cerebral oxygen levels can significantly compromise neuronal viability, underscoring oxygen's vital physiological role [23]. Nitric oxide, produced in neurons by neuronal nitric oxide synthase (nNOS), functions primarily as a retrograde neurotransmitter, critically modulating synaptic plasticity, learning, and memory. Additionally, endothelial-derived NO (via endothelial NOS or eNOS) regulates cerebral blood flow through vasodilation, thus facilitating optimal oxygen and nutrient delivery to neural tissues [24]. Carbon monoxide, another endogenous gas produced by heme oxygenase enzymes, exerts neuromodulatory actions, including anti-inflammatory and anti-apoptotic effects. It thereby helps maintain neuronal signaling and provides protective mechanisms against oxidative stress [25]. Hydrogen sulfide, synthesized by enzymes such as cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE), modulates synaptic transmission and neuronal excitability. Its neuroprotective properties arise from antioxidant activity, which mitigates oxidative injury within the CNS [26]. Finally, xenon, an inert noble gas administered exogenously, possesses anesthetic and neuroprotective properties largely through antagonism of N-methyl-D-aspartate (NMDA) receptors. This interaction attenuates excitotoxic neurotransmission and is actively explored for therapeutic neuroprotection in clinical contexts [27]. Collectively, these gases profoundly influence neurotransmission, vascular tone regulation, and cellular protection, thus representing integral components of CNS physiology.

2.1. Pathophysiology of CNS Injuries

Central nervous system (CNS) injuries originate from diverse primary insults, each defined by distinct initial pathological triggers [6]. In ischemic stroke, abrupt arterial occlusion interrupts cerebral perfusion, leading to rapid oxygen-glucose deprivation, metabolic failure, and neuronal energy depletion, ultimately causing acute ischemic necrosis in the core region of the affected vessel and delayed neuronal death within surrounding penumbral tissue [28]. Hemorrhagic stroke caused by blood vessel rupture, leads to intracranial bleeding and immediate mechanical tissue damage by the expanding hematoma, subsequently exacerbated by hemoglobin degradation products such as free heme and iron, which catalyze reactive oxygen species (ROS) generation and promote severe neuroinflammation [29]. In traumatic brain injury (TBI), the initial mechanical impact induces direct cellular disruption, diffuse axonal injury (DAI), and vascular compromise, immediately impairing neuronal integrity and cerebral perfusion [7]. Perinatal hypoxia, characterized by inadequate oxygen delivery during labor or birth, disrupts critical developmental neurogenesis and oligodendrocyte maturation, causing profound metabolic dysfunction and impaired white matter development via cellular energy failure, oxidative stress, excitotoxicity, inflammation, and impaired vascular function [30]. Finally, in cerebral malaria, infected erythrocytes (*Plasmodium falciparum*) obstruct cerebral microvessels, triggering endothelial activation, localized hypoxia, vascular leakage, and inflammatory cytokine release, rapidly leading to cerebral edema and neuronal injury [31].

Regardless of the initiating insult, these primary events universally trigger secondary injury cascades, which are characterized by a complex interplay of biochemical, cellular, and immunological responses. Key pathological mechanisms include excitotoxicity, oxidative stress, and neuroinflammation, all of which contribute to the progression of neuronal damage and functional decline. Excitotoxicity is driven by the excessive release of glutamate from depolarized pre-synaptic vesicles leading to sustained activation of NMDA and AMPA receptors. This results in a pathological influx of calcium ions, which may result in immediate cell death or in mitochondrial calcium overload followed by disruption of oxidative phosphorylation. The consequent energy failure exacerbates ROS production and activates both caspase-dependent and independent apoptotic pathways [32]. Concurrently, mitochondrial dysfunction, NADPH oxidase activity, and uncoupled nitric oxide synthase (NOS) drive the generation of ROS and reactive nitrogen species (RNS), which damage cellular lipids, proteins, and DNA [33–35].

These oxidative insults further activate inflammatory signaling networks, notably nuclear factor-kappa B (NF-κB), mitogen-activated protein kinases (MAPKs), and inflammasome complexes, resulting in robust microglial activation and peripheral immune cell infiltration [8]. While these responses initially serve to clear debris and promote repair, they frequently become dysregulated and chronic, thereby perpetuating neurotoxicity, edema, and BBB disruption [36,37].

Despite these shared secondary mechanisms, notable differences exist across CNS injury types. In ischemic stroke, abrupt focal arterial occlusion creates a steep gradient of cerebral blood flow with an irreversibly injured ischemic core surrounded by metabolically compromised but still viable penumbral tissue. Within this penumbra, persistent hypoperfusion, oxygen–glucose deprivation, failure of ion homeostasis, peri-infarct depolarizations, and glutamate-mediated excitotoxicity evolve over hours to days, so that neurons remain structurally intact yet functionally impaired; this core–penumbra architecture and its time-limited progression define a particularly well-characterized

therapeutic window for neuroprotection and reperfusion, even though partially salvageable regions also exist in other CNS disorders [3,28,32,38]. Hemorrhagic stroke is distinct in its cytotoxic response to heme and iron breakdown products, which intensify oxidative damage and perihematomal edema [39]. In TBI, chronic neurodegeneration arises from diffuse axonal injury and prolonged microglial activation [40], while perinatal hypoxia is marked by arrested oligodendrocyte maturation and white matter injury, exacerbated by the immature brain's limited antioxidant capacity [41]. In cerebral malaria, sequestration of Plasmodium falciparum-infected erythrocytes within the cerebral microvasculature leads to cytoadherence-mediated microvascular obstruction and a distinct pattern of immune-mediated endothelial activation. These events contribute to blood-brain barrier dysfunction, cerebral edema, and elevated intracranial pressure. While endothelial inflammation, cerebral edema, and raised intracranial pressure are also features of other CNS injuries such as traumatic brain injury and stroke, the parasite-induced vascular occlusion and the specific sequestration-driven immune interactions in cerebral malaria constitute a unique and defining aspect of its neuropathology [42,43].

Importantly, neuronal regeneration following injury is limited in the CNS. Endogenous repair mechanisms in the central nervous system (CNS), including neural progenitor cell proliferation, axonal sprouting, and angiogenesis, are hindered by the formation of a glial scar. This scar is predominantly composed of reactive astrocytes and extracellular matrix molecules, notably chondroitin sulfate proteoglycans (CSPGs), which create a non-permissive environment for neural regeneration by inhibiting axonal growth and remodeling [44,45]. This hostile microenvironment, combined with ongoing inflammation and deficient neurotrophic support, constrains axonal regrowth and synaptic integration [46]. Moreover, restoration of the BBB, while essential for homeostasis, limits the entry of neuroprotective therapeutics, thereby reducing treatment efficacy and complicating clinical interventions [47].

In summary, secondary injury responses in CNS pathologies are complex and multifactorial, involving overlapping mechanisms such as inflammation, oxidative stress, and excitotoxicity, which are further shaped by the nature of the initial insult. Advancing our understanding of these interconnected yet injury-specific cascades is essential for the development of targeted therapeutic strategies aimed at mitigating progressive tissue damage and promoting regeneration. Among emerging approaches, the use of medical gases has garnered increasing attention for their neuroprotective, anti-inflammatory, and vasomodulatory properties, offering a novel avenue for intervention in the acute and subacute phases of CNS injury

3. Therapeutic use of gases in CNS injury

3.1. Ischemic stroke

Over the past decade, medical gases have gained attention as potential neuroprotective agents in ischemic stroke, with several showing efficacy in both experimental and clinical contexts. Oxygen therapy, primarily aimed at improving tissue oxygenation in hypoxic regions such as the ischemic penumbra, includes approaches like supplemental oxygen, normobaric hyperoxia (NBO), and hyperbaric oxygen therapy (HBOT). By restoring oxygen availability, supplemental oxygen may in principle support mitochondrial oxidative phosphorylation and prevent excessive anaerobic glycolysis (and lactate accumulation), which otherwise aggravates energy failure during ischemia; however, direct experimental evidence for this effect in ischemic stroke remains limited. [48] While oxygen supplementation remains essential for hypoxemic patients, clinical trials have not consistently demonstrated benefits for non-hypoxemic individuals, and current guidelines do not support routine use in such cases [49] In the quasi-randomized trial by Rønning and Guldvog, non-hypoxemic stroke patients received 100% oxygen via nasal catheter at 3 L/min for 24 hours, initiated within 24 hours of symptom onset, without improvement in survival or disability, illustrating that low-flow continuous oxygen over the first day after stroke is not beneficial in unselected patients [49]. NBO, although promising in preclinical and early-phase clinical studies—especially when combined with reperfusion therapies—has yet to show consistent efficacy in randomized trials, and concerns remain about ROS-mediated toxicity [50]. Mechanistically, NBO has been shown to temporarily improve penumbral oxygenation, reduce glutamate-driven excitotoxicity, and suppress early depolarization events. In animal models, NBO also decreases matrix metalloproteinase-9 (MMP-9) activity and mitigates early blood–brain barrier disruption, thereby limiting vasogenic edema. [51–53] Recent endovascular trials typically apply NBO as 100% oxygen delivered by face mask at approximately 10 L/min for 2–6 hours around mechanical thrombectomy in patients randomized within a 6-hour time window, highlighting that clinically tested NBO protocols involve short-term high-flow oxygen closely coupled to reperfusion therapy [50]. HBOT has demonstrated neuroprotective effects in animal models by attenuating oxidative stress and inflammation and preserving blood-brain barrier integrity [54,55]; however, clinical evidence is inconclusive, and HBOT remains experimental due to logistical challenges and risk of oxygen toxicity. [56,57] These protective effects arise from HBOT's ability to increase dissolved oxygen content in plasma, enhance diffusion into ischemic tissue, and upregulate antioxidant defenses such as superoxide dismutase and catalase [58]. Experimental stroke protocols most often use 100% oxygen at 1.5–3.0 atmospheres absolute (ATA) for 60–120 minutes per session, started during ischemia or within a few hours of reperfusion and sometimes repeated daily, which defines a relatively narrow therapeutic window and exposure range in preclinical HBOT studies. [54,58] HBOT further suppresses NF-κB–mediated inflammatory signaling [59], reduces leukocyte adhesion [60], and modulates apoptosis by inhibiting caspase activation and stabilizing Bcl-2 family protein expression. [61]

Molecular hydrogen (H_2) has shown compelling antioxidant, anti-inflammatory, and anti-apoptotic effects in ischemic stroke. Beyond its well-established ability to selectively scavenge highly cytotoxic reactive oxygen species such as hydroxyl radicals, H_2 also neutralizes peroxynitrite and reduces lipid peroxidation, thereby preserving mitochondrial membrane potential and sustaining cellular integrity during ischemia–reperfusion injury [62–64]. In addition to these antioxidant effects, H_2 suppresses neuroinflammation by inhibiting the TLR4/NF-κB signaling pathway, which reduces pro-inflammatory cytokine release and microglial activation [65,66]. H_2 further promotes neuronal survival by restoring the Bcl-2/Bax ratio, reducing caspase activation, and enhancing protective autophagy, including PINK1/Parkin-mediated mitophagy [65,67]. Another key mechanism is the preservation of blood–brain barrier integrity, which contributes to reduced cerebral edema and smaller infarct volumes [63,65]. Consistent with these molecular actions, numerous preclinical models demonstrate that H_2—administered via inhalation, injection, or hydrogen-rich water—reduces infarct size, improves neurological outcomes, and enhances survival across diverse stroke paradigms, including diabetic models where benefits appear circadian-independent [68]. In these experimental studies, neuroprotection is typically achieved with low-concentration H_2 (≈1–4%) inhaled for 30–60 minutes during ischemia or shortly after reperfusion, or with single bolus injections of hydrogen-rich saline at 5–10 mL/kg given at or soon after vessel occlusion, indicating that effective regimens use modest concentrations delivered in the early ischemia–reperfusion period. [62–65,68] Initial clinical trials report accelerated neurological recovery without adverse effects in patients treated with low-concentration hydrogen gas or hydrogen-enriched solutions [69]. In the randomized controlled trial by Ono et al., patients with acute cerebral infarction (NIHSS 2–6) inhaled 3% H_2 gas for 1 hour twice daily over 7 days, initiated 6–24 hours after stroke onset, which was safe and associated with improvements in MRI and functional indices. [70] Its excellent safety profile supports ongoing trials aimed at optimizing dosing and delivery. [70]

Nitric oxide (NO) exhibits dual roles in ischemic stroke: endothelial

NOS (eNOS)-derived NO is neuroprotective, enhancing perfusion and reducing platelet aggregation and inflammation, while overproduction from nNOS and iNOS exacerbates injury through oxidative stress and mitochondrial dysfunction [71]. Mechanistically, eNOS-derived NO activates soluble guanylate cyclase and elevates cGMP levels in cerebral microvessels, leading to vasodilation, improved collateral flow to the ischemic penumbra, and reduced leukocyte–endothelial adhesion [72,73]. In contrast, nNOS- and iNOS-generated NO rapidly combines with superoxide to form peroxynitrite, which nitrates proteins, inhibits mitochondrial respiratory chain complexes, and triggers neuronal apoptosis and necrosis [74,75]. Clinical trials using NO donors, such as glyceryl trinitrate (GTN), demonstrated functional benefits only with early administration, likely due to blood pressure and perfusion modulation [33,76]. In ENOS and related studies, GTN was usually given as a 5-mg/24-h transdermal patch (sometimes preceded by 0.4-mg sublingual GTN), started within 48 hours of stroke onset and continued for up to 7 days, whereas the RIGHT-2 prehospital trial applied a 5-mg GTN patch in the ambulance within 4 hours of symptom onset for 3 days, underscoring that tested regimens use low-dose continuous transdermal delivery in the hyperacute to early subacute phase. [33,76] While early, ultra-acute administration —defined as delivery of treatment within the first 3 hours after symptom onset— of GTN (as in prehospital trials) has been proposed to improve cerebral perfusion and functional outcome, the largest prehospital randomized trial (RIGHT-2) failed to show a benefit; earlier smaller studies and pooled analyses hint at possible benefit when GTN is begun within 6 h of onset, but evidence remains conflicting [77]. Inhaled nitric oxide (iNO) has shown promise in experimental models by selectively improving perfusion to ischemic areas without systemic hypotension, as iNO preferentially dilates collateral arterioles supplying hypoxic regions and enhances microvascular oxygen delivery while maintaining systemic hemodynamic stability. In rodent middle cerebral artery occlusion models, iNO is typically administered at 5–50 ppm (most often around 50 ppm) in an oxygen/air mixture, starting at reperfusion or within the first hour thereafter and continued for several hours, which improves collateral flow, limits infarct growth, and does not significantly alter systemic blood pressure. In rodent middle cerebral artery occlusion (MCAO) models, iNO also reduces ICAM-1 expression, limits microglial activation, and lowers pro-inflammatory cytokine production, indicating a direct anti-inflammatory role. Targeted NO bioactivity in hypoxic tissue is further supported by hemoglobin- and nitrite-dependent NO signaling, which allows vasodilatory NO species to form preferentially under low-oxygen conditions. [78–80] While safe in clinical use for other indications, iNO remains experimental in stroke, with further trials needed.

Carbon monoxide (CO), though historically toxic, demonstrates strong neuroprotective effects at low concentrations or when administered via carbon monoxide-releasing molecules (CORMs). In animal models of transient middle cerebral artery occlusion (tMCAO), CO—especially via CORM-3—reduced infarct size, cerebral edema, and neurological deficits through anti-inflammatory, anti-apoptotic, and antioxidant mechanisms, notably via Nrf2/HO-1 pathway activation [81,82]. In the tMCAO mouse model, a single intravenous injection of the water-soluble donor CORM-3 at 4 mg/kg given at the time of reperfusion significantly reduced infarct volume, brain edema, and blood–brain barrier leakage, whereas vehicle had no effect, indicating a narrow but clearly defined effective dose and timing window in vivo. [81] CO additionally suppresses microglial activation and pro-inflammatory cytokines while preserving blood–brain barrier integrity by maintaining tight-junction proteins and limiting MMP-9 activity. At the mitochondrial level, CO promotes cytoprotective signaling by modulating cytochrome-c oxidase activity, generating low-level redox signals, and preventing cytochrome c release and caspase-3 activation [83–85]. However, the narrow therapeutic window and risk of toxicity hinder its clinical application, emphasizing the need for safe delivery strategies and further human studies.

Xenon, a noble gas with NMDA receptor antagonism and potassium channel modulation properties, reduces excitotoxicity and preserves white matter in stroke models. By competitively inhibiting the glycine co-activation site of the NMDA receptor, xenon limits calcium influx, suppresses downstream calpain activation, and prevents mitochondrial depolarization—key drivers of ischemia-induced excitotoxic injury [86,87]. In rodent focal ischemia models, xenon has been applied at 50–70% (balanced with oxygen and nitrogen) for 1–3 hours, started either shortly before ischemia or within minutes after reperfusion, consistently reducing infarct size and improving neurological outcomes. [86,87] It rapidly crosses the blood-brain barrier and offers synergy with therapeutic hypothermia with combined treatment showing enhanced suppression of apoptotic pathways and improved neurobehavioral outcomes compared with either therapy alone [88,89]. Delivery innovations, such as xenon-loaded liposomes, are under development to improve targeting and efficacy [90,91]. Xenon has demonstrated neuroprotection in cardiac arrest patients and is being studied in stroke contexts. In post–cardiac arrest trials, xenon was typically administered at 40–50% in combination with therapeutic hypothermia for approximately 24 hours, demonstrating feasibility and acceptable safety in a clinical neurocritical care setting. [92] However, its high cost, logistical barriers, and interference with tPA activity limit its widespread use, although it remains a promising candidate for adjunctive neuroprotection [17,92].

3.2. Hemorrhagic stroke

Oxygen therapy, particularly through hyperbaric oxygen therapy (HBOT), is being actively investigated as a supportive intervention for hemorrhagic stroke due to its capacity to mitigate secondary brain injury and facilitate neurological recovery. HBOT involves administering 100% oxygen at pressures above atmospheric levels, thus increasing soluble O_2 in blood plasma. Thereby, HBTO substantially enhances oxygen diffusion into brain tissues compromised by hemorrhage [93]. Preclinical studies indicate that early HBOT reduces cerebral edema, suppresses neuroinflammation, and limits neuronal death, with moderate hyperbaric pressures and timely intervention offering the most pronounced benefits. In rodent ICH models, very early (within 30 min of ICH induction) oxygen therapy (including HBOT) helps preserve the blood–brain barrier (BBB) by preventing occludin degradation and suppressing MMP-9 activation, while also lowering HIF-1α expression. [94] HBOT preconditioning reduces perihematomal edema in parallel with downregulation of astrocytic aquaporin-4 (AQP4) expression. [95] HBOT preconditioning further dampens innate immune activation by decreasing the number of activated microglia and shifting microglial polarization toward anti-inflammatory states with reduced TNF-α levels. [96,97] In addition, HBOT preconditioning activates p70 ribosomal S6 kinase (p70S6K)—a translation regulator linked to stress-response signaling—which has been associated with reduced brain swelling after ICH. [98] Mechanistically, HBOT supports repair of damaged vasculature, promotes synaptogenesis and neuroplasticity, and may improve outcomes by fostering neural circuit reorganization [99]. Clinical evidence from subacute and chronic stroke phases suggests improved cognitive and motor function following repeated HBOT sessions, with some studies indicating greater cognitive gains in hemorrhagic versus ischemic stroke patients [100]. However, HBOT remains experimental, with challenges including the need to define optimal treatment windows, dosing regimens, and efficacy confirmation through large-scale randomized trials [54].

Hydrogen (H_2) and hydrogen sulfide (H_2S) have also shown neuroprotective promise in hemorrhagic stroke, including subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH), due to their antioxidant, anti-inflammatory, and anti-apoptotic effects. For H_2, a core molecular action is selective quenching of the most cytotoxic oxidants—hydroxyl radicals (•OH) and peroxynitrite ($ONOO^-$)—thereby limiting radical chain reactions in neural tissue [101]. H_2 reduces

oxidative stress, inhibits microglial activation, and attenuates neuronal apoptosis, resulting in reduced brain edema and improved neurological outcomes in preclinical SAH and ICH models [102,103]. Mechanistically in SAH, brief H_2 inhalation lowers astroglial injury marker S100B and p-JNK signaling, dampens reactive astrogliosis, and lessens early brain injury with downstream mitigation of delayed brain injury—effects observed without directly altering large-artery vasospasm [102]. In parallel, hydrogen-rich saline suppresses NF-κB/NLRP3 inflammasome activation and pro-inflammatory cytokines during early brain injury after SAH [104]. In ICH models, H_2 inhalation reduces TNF-α/IL-1β expression, decreases cleaved caspase-3, and limits BBB leakage/edema with accompanying neurological improvement. [105] Clinical observations, including randomized trials, report that hydrogen-enriched solutions can enhance consciousness recovery and functional outcomes without adverse effects, with one study showing benefit when H_2 was combined with intracisternal magnesium sulfate post-SAH [106]. Specifically, a small randomized trial in poor-grade SAH ($n = 37$) found that adding intravenous H_2 solution to intracisternal $MgSO_4$ reduced vasospasm/DCI and improved functional scores (e.g., Barthel Index). [106] For H_2S, exogenous donors (e.g., NaHS) curb microglial TLR4/NF-κB signaling and thereby reduce neuroinflammation and cognitive impairment after SAH. [107] H_2S also preserves the BBB and reduces edema by down-modulating MMP-9–associated tight-junction injury and regulating AQP4 expression [108]. Anti-apoptotic signaling has been demonstrated via L-type Ca^{2+}-channel–dependent increases in Bcl-2 with reductions in Bax and cleaved caspase-3 in SAH models [107]. In ICH, H_2S attenuates edema and neuronal injury while suppressing autophagy (↓LC3-II/Beclin-1, ↑p62) and apoptosis; notably, protection is dose-dependent (e.g., ~25 μmol/kg effective, ≥50–100 μmol/kg not protective), underscoring a narrow therapeutic window [109]. H_2S, though similarly protective in preclinical settings, has a narrow therapeutic window, with neurotoxic effects at higher doses limiting its clinical potential [109,110]. This constraint is biologically plausible because supraphysiologic H_2S inhibits mitochondrial cytochrome-c oxidase, precipitating histotoxic hypoxia [111]. To date, no head-to-head comparisons directly contrasting H_2 and H_2S have been reported in hemorrhagic stroke models; however, the combination of a narrow safety window and lack of clinical data means that H_2S remains at an earlier, preclinical stage of development. In contrast, H_2 has shown a broader preclinical safety profile and is already supported by early clinical feasibility and safety data in SAH, so at present it should be regarded as the more advanced candidate for clinical translation rather than intrinsically superior in neuroprotective efficacy.

Nitric oxide (NO) plays a context-dependent role in hemorrhagic stroke, exhibiting both protective and harmful effects based on source, concentration, and timing. NO derived from endothelial NOS (eNOS) preserves neurovascular function by promoting vasodilation, regulating blood flow, inhibiting platelet aggregation, and suppressing leukocyte adhesion [112]. These eNOS-dependent actions are mediated via endothelial soluble guanylate cyclase–cGMP–PKG signaling and are neurovascular-protective in SAH models; in mice, eNOS-dependent preconditioning prevents vasospasm and neurological deficits [113]. These actions help mitigate secondary injury and oxidative stress, particularly early post-hemorrhage. However, overproduction of NO from neuronal and inducible NOS (nNOS and iNOS) can generate peroxynitrite, exacerbating oxidative and nitrosative stress and leading to neuronal death. After ICH, NOS upregulation drives $ONOO^-$ formation that disrupts BBB tight junctions (claudin-5/ZO-1), increases brain edema, and correlates with neurological deficits, as evidenced by 3-nitrotyrosine accumulation. [114] Consistently, selective iNOS inhibition in experimental SAH reduces M1 microglia, neuroinflammation, edema, and neuronal injury [115]. Therapeutic approaches seek to enhance eNOS-derived NO while limiting nNOS/iNOS activity. Inhaled nitric oxide (iNO), already approved for other indications, has demonstrated selective vasodilation in hypoxic cerebral regions in experimental models without systemic hypotension, making it a candidate for enhancing perfusion in hemorrhagic stroke. [116] In mouse SAH, iNO reduces early pial microvasospasms, improves microcirculatory perfusion, lowers brain injury and mortality, while sparing systemic arterial pressure [112]. Mechanistically, iNO can be exported from the lung as bioactive carriers (e.g., S-nitrosohemoglobin and nitrite) that deliver NO activity to cerebral microvessels. [78] Moreover, inhaled ethyl nitrite, an NO donor, has shown neuroprotective effects in SAH models, suggesting further translational potential [117]. Inhaled ethyl nitrite (≈20 ppm) augments S-nitrosohemoglobin, increases cortical tissue PO_2 and red-blood-cell flow velocity, reduces vasospasm and brain water, and does not lower systemic blood pressure in SAH mice [118]. Human pilot trials further support this approach: a 2022 prospective study of SAH patients with delayed cerebral ischemia demonstrated that iNO (40 ppm) achieved pre-specified physiologic improvement thresholds across modalities—>10% dilation on DSA in a subset, >5 mmHg $PtiO_2$ increases at multiple time-points, and reductions in CT-perfusion mean-transit-time–defined perfusion deficits in most evaluated cases—without treatment-limiting hypotension [119]

Low-dose carbon monoxide (CO) is also under investigation as a neuroprotective agent in SAH and ICH. Although toxic at high concentrations, controlled low-dose CO or CO-releasing molecules (CORMs) have shown efficacy in preclinical studies by reducing neuroinflammation, suppressing pro-inflammatory cytokines, and attenuating neuronal apoptosis [82,120]. In a rat ICH model, the water-soluble donor CORM-3 reduced inflammatory responses (including leukocyte/microglial activation) and lessened brain injury versus inactive CORM, supporting CO's anti-inflammatory/anti-injury actions in hemorrhagic stroke [120]. CO also mitigates vasospasm—a common post-SAH complication—and facilitates heme clearance via upregulation of the HO-1 pathway, while also restoring circadian gene expression patterns [121,122]. Experimentally, brief low-dose CO inhalation (~250 ppm, 1 h) after SAH attenuates large-artery vasospasm and improves neurobehavioral outcomes [122]. Mechanistically, CO engages the microglial HO-1/CO axis to accelerate erythrophagocytosis and blood clearance; microglia-specific HO-1 is required to limit neuronal death and vasospasm after SAH, and exogenous CO inhalation rescues the HO-1–deficient phenotype [123]. CO also preserves/normalizes clock-gene oscillations (e.g., Per2/Clock) after SAH, linking restoration of circadian transcriptional rhythms to reduced brain injury [121]. In animal models, CORMs significantly reduced brain edema and improved functional and cognitive outcomes [120]. Consistently, CORM-3 reduced perihematomal brain water and improved neurologic scores in rat ICH compared with inactive CORM [120]. However, premature or high-dose administration can be detrimental, underscoring the need for strict control over therapeutic timing and dosage. Therapeutic CO has a narrow dose–response and must be delivered under protocols that cap carboxyhemoglobin (COHb); human phase-I dose-escalation trials (100–200 ppm for 90 min/day) targeted COHb ≈6–8% to demonstrate feasibility and safety, emphasizing careful dosing for translation [124].

Lastly, noble gases—argon, helium, and xenon—have been evaluated for their neuroprotective effects in hemorrhagic stroke, with varied efficacy. Argon has shown promising results in vitro and in vivo by reducing neuronal death, infarct size, and inflammation, primarily via Toll-like receptor inhibition and activation of Nrf2-mediated antioxidant responses. [125–127] Consistent with these mechanisms, argon suppresses TLR2/4-dependent pro-apoptotic signaling upstream of ERK1/2 in neuronal injury models [128]. In experimental SAH, argon post-conditioning (≈50% for 1 h begun ~1 h post-ictus) reduced early mortality and hippocampal neuronal loss in a randomized controlled animal study, with follow-up work suggesting attenuation of microglial activation [126]. Helium has yielded inconsistent results and lacks defined mechanisms of action, limiting its translational value [129]. Evidence for helium neuroprotection is model-dependent (e.g., neonatal hypoxia–ischemia preconditioning) and has not translated convincingly to hemorrhagic stroke [130]. Xenon, the most extensively studied, acts through NMDA receptor antagonism and modulation of potassium

channels, reducing excitotoxicity, neuroinflammation, and neuronal apoptosis [131]. Mechanistically, xenon competitively inhibits the NMDA receptor at the glycine co-agonist site, and reviews identify background two-pore-domain K^+ channels as additional xenon targets relevant to neuroprotection. [87] Preclinical models of ICH and SAH confirm xenon's ability to preserve hippocampal neurons and improve functional outcomes [132]. In SAH, xenon (≈50% for 1 h, ~1 h after hemorrhage) reduced hippocampal neuronal damage and dampened post-hemorrhagic microglial neuroinflammation; targeted xenon delivery via echogenic liposomes likewise lessened early brain injury and mortality [131]. Xenon, clinically approved as an anesthetic in Europe, offers a favorable safety profile, though high costs and limited availability remain barriers to widespread use despite advanced delivery/recycling systems [133].

3.3. Traumatic brain injury (TBI)

Oxygen therapy remains a cornerstone in the management of traumatic brain injury (TBI), aiming to maintain adequate cerebral oxygenation and limit secondary injury. In contemporary care, brain tissue oxygen ($PbtO_2$)–guided protocols are used to detect and treat parenchymal hypoxia that can persist despite normal arterial oxygenation; phase-II randomized data (BOOST-II) demonstrate reduced brain hypoxia burden and have informed the ongoing phase-III BOOST-3 trial [134]. Standard supplemental oxygen is routinely administered, although excessive oxygen exposure may be detrimental [135]. Early hyperoxemia (supraphysiologic PaO_2 in the first 24 h) has been associated with worse functional outcomes and higher mortality after TBI—mechanisms likely include vasoconstriction-mediated reductions in cerebral blood flow and reactive-oxygen-species–driven injury [136]. Conversely, when applied judiciously, short-term normobaric hyperoxia can acutely improve cerebral metabolism in pericontusional tissue (lower lactate/pyruvate ratio, lactate, and glutamate) and raise $PbtO_2$ [137]. Hyperbaric oxygen therapy (HBOT), has shown promise in improving neurological outcomes, cognitive performance, and long-term recovery in patients with moderate to severe TBI, particularly when applied early [138]. Mechanistically in TBI, HBOT increases dissolved plasma O_2 and augments oxidative metabolism and mitochondrial function (↑ATP, improved electron-transport activity), lowers intracranial pressure and edema, promotes a shift of microglia from pro-inflammatory M1 to reparative M2 phenotypes, and attenuates apoptosis (↓caspase-3, favorable Bcl-2/Bax signaling) [139]. While generally well-tolerated, rare adverse effects such as pulmonary barotrauma have been reported [140], and clinical outcomes remain variable due to differences in treatment timing, pressure protocols, and duration across studies. In practice, the most common complication of HBOT is middle-ear barotrauma; oxygen-toxicity seizures and pulmonary barotrauma are uncommon with modern protocols [141].

Among gaseous interventions, hydrogen (H_2) and hydrogen sulfide (H_2S) have garnered attention for their neuroprotective properties in TBI. H_2 acts as a potent antioxidant, scavenging reactive oxygen species, reducing lipid peroxidation, and suppressing inflammation through inhibition of microglial activation and the NLRP3 inflammasome [142]. In controlled-cortical-impact (CCI) models, early low-concentration H_2 inhalation (≈2–4%) limits blood–brain barrier (BBB) disruption, brain edema, and lesion volume and improves neurological scores, effects accompanied by reduced oxidative products and increased endogenous antioxidant enzyme activities [143] and by promotion of an M1→M2 microglial shift with suppression of pro-inflammatory cytokines. [144] Hydrogen also engages cytoprotective transcriptional programs in TBI by activating Nrf2 signaling, consistent with decreases in oxidative stress markers in injured cortex. [145]It also preserves blood-brain barrier integrity, attenuates neuronal apoptosis, and reduces cerebral edema. Concordantly, hydrogen-rich water/saline and drinking-water formulations reproduce these benefits in vivo (reduced BBB permeability and edema; improved sensorimotor and cognitive outcomes) [143,146,147]. In animal models, administration of hydrogen gas or hydrogen-enriched solutions has been shown to reduce lesion volume, improve survival, and enhance functional outcomes [148]. Clinical data, although limited, support its safety and potential efficacy; in perioperative neurosurgical patients (glioma), a randomized prospective study found that short-term H_2/O_2 inhalation reduced postoperative brain edema and improved early neurological scores without safety signals [149]. H_2S has also demonstrated neuroprotective effects in preclinical models, mitigating oxidative stress, neuroinflammation, and neuronal death, though its therapeutic window is narrow due to neurotoxicity at higher doses [150]. In TBI mice, the H_2S donor NaHS reduced brain edema, improved motor performance and spatial memory, and inhibited both apoptosis and autophagy (↓LC3-II, ↓Beclin-1, restored p62) [151]. Mechanistically, H_2S protection involves activation of mitochondrial ATP-sensitive K^+ (mitoKATP) channels and reduction of oxidative stress in CCI-TBI rats [152]. Dose–response studies demonstrate a narrow therapeutic window in TBI: low NaHS doses (~1 mmol/kg) are protective, whereas higher doses (e.g., 45 mmol/kg) can exacerbate injury, underscoring the need for careful dosing and timing. [151]

Nitric oxide (NO) exhibits a dual role in TBI pathophysiology, with its effects dictated by concentration, timing, and the source isoform. Early NO release from endothelial and neuronal nitric oxide synthase (eNOS and nNOS) is associated with improved cerebral blood flow and synaptic function, whereas delayed and excessive NO production from inducible NOS (iNOS) contributes to oxidative damage, neuroinflammation, and apoptosis [153–155]. Consistent with this isoform-specific physiology, eNOS supports maintenance of cerebral blood flow after controlled cortical impact (CCI); eNOS knockout mice show impaired post-traumatic perfusion [156], and eNOS-dependent augmentation of CBF has been demonstrated during erythropoietin-mediated vascular responses after CCI [157]. Preclinical studies have shown that NO donors, such as DETA/NONOate, enhance neurogenesis, angiogenesis, and functional recovery post-TBI [158]. In particular, DETA/NONOate administered for 7 days after CCI increased BrdU-labeled neurogenesis and improved behavioral recovery [158]. Innovative delivery strategies now enable sustained, spatially controlled NO release: a mussel-inspired NO micro-reservoir that simultaneously scavenges ROS promoted angiogenesis and neurogenesis while attenuating neuroinflammation in murine TBI. [159] Inhaled NO (iNO) has shown promise in animal models by improving perfusion, lowering intracranial pressure, and reducing edema without systemic toxicity [160]. In a mouse CCI model, 24-h iNO increased CBF and reduced intracranial pressure, brain edema, and blood–brain barrier disruption with no systemic hypotension. [160] Additionally, isoform-specific NOS inhibition represents a viable strategy; for instance, the selective inhibitor VAS203 has shown efficacy in reducing brain edema and improving outcomes in both animal models and early clinical trials, although nephrotoxicity at high doses remains a concern [161,162]. Preclinically, 4-amino-tetrahydrobiopterin (VAS203) reduced edema and intracranial hypertension after TBI [162]; in a placebo-controlled Phase IIa TBI trial, VAS203 improved 6-month eGOS but the highest dose was associated with transient, dose-dependent acute kidney injury. [161] Dedicated renal-hemodynamic work in healthy volunteers further characterizes reversible renal effects of VAS203 [163].

Carbon monoxide (CO), at low doses or delivered via carbon monoxide-releasing molecules (CORMs), has emerged as a potential neuroprotective agent in TBI. Mechanistically, CO enhances neurogenesis by preserving pericyte viability and promoting communication with neural stem cells, by limiting perivascular pericyte loss after injury and increasing phosphorylated neuronal NOS within neural stem cells—changes that are required for the pro-neurogenic effect of CORM-3 [164–166] Beyond this pericyte–neural stem cell axis, canonical CO signaling engages hemoprotein targets to tune cell fate—most notably mitochondria (mild, signaling ROS; cytochrome-c oxidase modulation) and the cGMP pathway—providing upstream routes to anti-apoptotic, anti-inflammatory, and pro-repair programs. [167] CO's pericyte-

directed actions also intersect white-matter repair: pericyte AKAP12 signaling is required for OPC→oligodendrocyte differentiation and central myelination in adult white matter, supporting a plausible mechanism by which CO-preserved pericytes could facilitate oligodendrogenesis/remyelination after TBI [168]. In vivo, CO delivered as CORM-3 dampens inflammasome activity and cytokine release in TBI settings (↓caspase-1/GSDMD, ↓serum IL-1β/IL-18), preserves intestinal barrier structure, and ameliorates ventromedial prefrontal cortex injury with improved learning/memory—evidence for gut–brain protection in TBI+hemorrhagic shock models [165]. Complementary work shows that CORM-3 reduces amygdala pyroptosis/apoptosis and improves anxiety-/depression-like behavior in combined TBI+hemorrhagic shock, consistent with a central anti-inflammatory/anti-cell-death mechanism [169]. Systemically, CORM-3 also mitigates TBI-induced cardiac dysfunction by inhibiting myocardial pyroptosis (GSDMD-N) and apoptosis, extending CO's protective profile to heart–brain crosstalk after TBI [170]. Finally, CO's benefits are strictly dose-dependent: clinical dose-escalation studies of inhaled CO in critical illness have established algorithms to achieve target carboxyhemoglobin levels (~6–8%) while maintaining safety—an important translational constraint for any future TBI application [124].

Among noble gases, xenon and argon show significant neuroprotective potential in TBI. Xenon functions as a low-affinity NMDA receptor antagonist, attenuating glutamate-induced excitotoxicity—a key mechanism of secondary neuronal injury [171,172]. More specifically, xenon competitively inhibits the NMDA receptor at the glycine co-agonist site, confirming direct target engagement underlying its anti-excitotoxic action [86]. It also modulates neuroinflammatory pathways, preserves neuronal viability, and improves both motor and cognitive functions in experimental models [173,174]. In controlled cortical impact (CCI) models, xenon reduced reactive astrogliosis (GFAP) and microglial proliferation (Iba1), preserved hippocampal neurons and callosal white matter, and improved long-term survival and cognition [175]; similar benefits with early microglial/astrocytic responses were observed after severe TBI in rats [173]. Notably, xenon retains efficacy when administered within a clinically feasible window of up to three hours post-injury [175,176] —in mice, xenon reduced contusion volume when delivered ≤3 h after CCI [176]. Clinical experience also supports translational feasibility and safety: in a multicenter randomized trial of cardiac surgery patients, xenon anesthesia was non-inferior to sevoflurane and appeared safe [177], consistent with prior feasibility/safety studies of xenon-balanced anesthesia. In contrast, argon—though less extensively studied—has shown neuroprotective effects in TBI models through anti-inflammatory and anti-apoptotic mechanisms, potentially mediated by modulation of Toll-like receptor and oxidative stress pathways [178]. Mechanistically, argon activates a TLR2/4 → ERK1/2 axis to suppress pro-apoptotic signaling and inflammatory mediators, providing cell-survival benefits in neuronal systems [128,179]. Preclinical studies report that argon reduces neuronal loss, alleviates cerebral edema, and improves neurological function [180]. In a mouse CCI model, 70% inhaled argon started 10 min post-injury (for 24 h) accelerated sensorimotor recovery, reduced pericontusional vasogenic edema and inflammatory markers, and lessened white-matter damage [180]; however, results are mixed—other paradigms (e.g., closed-head injury with 24 h argon) showed no improvement in longer-term outcomes [181]. Its affordability, non-anesthetic properties, and simple delivery make it a compelling candidate for further development, although clinical validation is still pending. Collectively, these gaseous agents represent a promising frontier in TBI therapy, with ongoing research focused on optimizing safety, efficacy, and delivery strategies.

3.4. Perinatal hypoxia

Xenon is a promising investigational adjunct to therapeutic hypothermia (TH), the current standard of care for neonatal hypoxic-ischemic encephalopathy (HIE), owing to its potent neuroprotective properties and demonstrated synergism with TH [182]. Acting as a non-competitive antagonist of NMDA receptors, xenon attenuates glutamate-mediated excitotoxicity—a major contributor to hypoxic-ischemic brain injury [183]. Mechanistically, xenon competitively antagonizes the NMDA receptor at the glycine co-agonist site, which is considered the principal driver of its anti-excitotoxic action [86]. Preclinical studies in neonatal rodent and piglet models have shown that xenon, at concentrations between 40–70%, significantly reduces brain injury and improves neurological outcomes, particularly when combined with TH [89,184]. In newborn pigs and rats, 50% xenon given with TH (typically 12–24 h of TH) produced additive benefit vs either therapy alone and improved early metabolic markers (e.g., reduced thalamic lactate/NAA on MRS) [185,186]. This combined effect is attributed to the complementary modulation of excitotoxicity, inflammation, and metabolic stress [187]. Preclinically, the therapeutic window appears clinically plausible: combining TH with xenon remained effective even when both were started 5 h after the insult in neonatal rats [188]. Early-phase clinical work also supports feasibility and hemodynamic stability: in cooled neonates, 50% xenon for up to 18 h was tolerated without blood-pressure instability, and piglet studies likewise showed stable cardiovascular profiles during 50% xenon with/without TH. [185,189] However, randomized controlled trials remain inconclusive. In the TOBY-Xe proof-of-concept RCT, 30% xenon for 24 h (started >6 h after birth) did not improve early MRI biomarkers versus TH alone, underscoring the likely importance of dose and timing [190]. Ongoing/next-stage studies (e.g., CoolXenon/CoolXenon3) have aimed to test earlier initiation and higher concentrations with closed-circuit delivery systems (ClinicalTrials.gov NCT02071394). Despite inconclusive clinical efficacy, xenon's strong safety profile and mechanistic rationale continue to support its evaluation in clinical trials for neonatal neuroprotection.

Argon is another emerging neuroprotective gas with substantial preclinical support for use in perinatal HIE. Although it has not yet entered clinical trials in neonates, rodent and piglet studies consistently show that argon reduces brain infarction, oxidative stress, inflammation, and neuronal cell death following hypoxic-ischemic injury [191,192]. In neonatal rats, brief post-insult exposure to ~70% argon reduced infarct volume and TUNEL-positive cells and lowered oxidative stress/inflammation markers, with parallel improvements in neuronal viability [193]. In neonatal piglets, adding 45–50% argon from 2–26 h post-insult to therapeutic hypothermia (TH) improved brain energy metabolism on MRS, accelerated EEG recovery, and decreased histologic cell death without physiological instability. [192] A meta-analysis reported an estimated neuroprotective efficacy of 70.3% for argon, surpassing xenon's 39.7% in similar models. Mechanistically, argon activates the Nrf2 antioxidant pathway, upregulates cytoprotective enzymes such as NQO1 and SOD1, and enhances glutathione levels, while its efficacy is attenuated by PI3K or ERK1/2 pathway inhibition, suggesting a critical role for these signaling cascades [193]. Specifically in neonatal HI, argon increased p-mTOR and nuclear Nrf2, upregulated NQO1 and SOD1, raised the brain GSH/GSSG ratio, and its protection was blunted by PI3K (wortmannin) or ERK1/2 (U0126) inhibitors and by Nrf2 knockdown [193]. Safety studies in newborn piglets show that argon ventilation at 30–80% is well-tolerated, even when combined with TH, without adverse effects on cardiovascular parameters or brain histology [194]. In a piglet safety study, ventilation with 30%, 50%, and 80% argon—plus a hypoxia ± TH arm with 50% argon—did not change heart rate, mean arterial pressure, cerebral saturation, EEG, or blood gases; histology showed no toxicity [194]. Argon's abundance, low cost, and compatibility with standard ventilators make it a practical and scalable therapeutic candidate. Unlike xenon, argon is not anesthetic at normobaric pressure (requires hyperbaric conditions), facilitating continuous neurological monitoring during administration [195]. Though limited to preclinical settings, these findings provide a compelling rationale for advancing argon to early-phase clinical trials as a potential adjunct therapy in neonatal HIE [196].

Inhaled nitric oxide (iNO) is an established therapeutic in

neonatology, primarily used to treat hypoxic respiratory failure associated with persistent pulmonary hypertension of the newborn (PPHN), a common complication of perinatal hypoxia [197]. As a selective pulmonary vasodilator, iNO improves pulmonary blood flow and systemic oxygenation without inducing systemic hypotension, indirectly supporting oxygen delivery to the brain and other hypoxia-sensitive organs [198]. Mechanistically, iNO diffuses to pulmonary arterial smooth muscle and activates soluble guanylate cyclase to raise cGMP, relaxing vascular smooth muscle; rapid scavenging by hemoglobin confines vasodilation to ventilated lung units and minimizes systemic hypotension [199]. Although not directly neuroprotective, iNO significantly reduces the need for extracorporeal membrane oxygenation (ECMO) in term and near-term infants, according to multiple clinical trials and meta-analyses, without increasing neurodevelopmental or behavioral abnormalities at two years of age. [200] Large randomized trials demonstrated reduced ECMO use—for example, the CINRGI study (NEJM 2000) reported 38% vs 64% ECMO (iNO vs placebo) with improved oxygenation [201], and the earlier NINOS trial (NEJM 1997) showed improved oxygenation without systemic hypotension [199]; 2-year follow-up of NINOS found no excess neurodevelopmental impairment [202]. These trial results align with Cochrane meta-analysis conclusions in term/near-term infants [201]. Furthermore, preclinical studies suggest that iNO may mitigate long-term pulmonary complications, including right ventricular hypertrophy and endothelial dysfunction, reinforcing its utility in broader neonatal cardiopulmonary stabilization [203]. In neonatal models, continuous low-dose iNO during chronic hypoxia attenuated pulmonary arterial muscularization and prevented right-ventricular hypertrophy [204]; iNO also reduced pathologic pulmonary artery remodeling in injured infant lungs. [205] In chronically ventilated preterm lambs, iNO preserved endothelial NO synthase levels and enhanced alveolar development, supporting improved pulmonary vascular/airway structure. [206] While its role in direct brain protection is unclear, iNO remains a vital adjunct for optimizing systemic oxygenation in the management of neonatal hypoxic injury.

Oxygen therapy, both as conventional supplementation and as hyperbaric oxygen therapy (HBOT), is foundational in managing perinatal hypoxia and neonatal HIE. Conventional oxygen remains a cornerstone of neonatal resuscitation and early stabilization, ensuring adequate oxygen delivery and preventing exacerbation of hypoxic damage (guided by AHA/AAP neonatal resuscitation recommendations to titrate O_2 to target saturations rather than use fixed 100% O_2) [207]. However, current consensus is that oxygen supplementation itself is supportive (for cardiorespiratory stabilization) rather than directly neuroprotective; in term/near-term HIE, therapeutic hypothermia remains the only intervention with proven neuroprotective efficacy to date [208,209]. In contrast, HBOT shows disease-modifying mechanisms in neonatal hypoxia–ischemia models: it suppresses apoptosis via reduced TUNEL-positive cells and down-regulation of caspase-3/-9 activity [210]; promotes endogenous repair by increasing subventricular-zone neural stem/progenitor-cell proliferation and their differentiation into neurons and oligodendrocytes [211]; and engages canonical developmental pathways (Wnt3/β-catenin and BMP2) linked to neurogenesis/oligodendrogenesis [212]. At the transcriptional/antioxidant level, hyperbaric oxygen preconditioning activates Nrf2 and downstream effectors (e.g., HO-1), attenuating oxidative injury in neonatal HI brain [213]. Functionally, these mechanisms correlate with improved sensorimotor and cognitive outcomes in neonatal rodent HI models [214]. Clinically, pooled randomized trials—predominantly from China—suggest improved composite neurological outcomes and fewer sequelae when HBOT is added to usual care for neonatal HIE, though heterogeneity and risk of bias warrant cautious interpretation and demand high-quality multicenter RCTs [215]. Across reported trials, HBOT was typically delivered at ~0.15–0.17 MPa (1.5–1.7 ATA) for 60–120 minutes, one to three sessions per day [216], and experimental work indicates a therapeutic window within hours of the hypoxic–ischemic insult (≤6 h confers the largest benefit; effects wane after ~24–48 h) [217]. Safety remains paramount: excessive oxygen dose (higher partial pressures or prolonged exposures) can precipitate central nervous system oxygen toxicity (including seizures) and pulmonary toxicity, necessitating careful pressure–time dosing and monitoring in neonates [218].

3.5. Malaria

Inhaled nitric oxide (iNO) has been investigated as an adjunctive therapy for severe and cerebral malaria in pediatric populations, based on the hypothesis that diminished nitric oxide (NO) bioavailability contributes to endothelial dysfunction and worsened disease severity [219]. Mechanistically, severe and cerebral malaria are characterized by reduced endothelial NO production due to low plasma L-arginine (the NOS substrate), accumulation of endogenous NOS inhibitors, and scavenging of NO by cell-free hemoglobin, which together impair NO-mediated vasodilation and antithrombotic signaling [219,220]. While severe malaria is marked by systemic inflammation and microvascular obstruction, the resulting decrease in NO exacerbates vascular leakage and endothelial activation. At the endothelial level, low NO fails to suppress Weibel–Palade body exocytosis and angiopoietin-2 (Ang-2) release, thereby promoting upregulation of adhesion molecules (e.g., ICAM-1, VCAM-1), enhanced sequestration of parasitized erythrocytes, and disruption of the blood–brain barrier—key steps in the pathogenesis of cerebral malaria [220]. Preclinical work in experimental cerebral malaria provides direct mechanistic support for this concept: in murine models, prophylactic or early iNO exposure reduced systemic TNF, IFN-γ, and MCP-1 levels, decreased soluble ICAM-1 and von Willebrand factor, increased Ang-1, limited parasite accumulation and ICAM-1 expression in cerebral microvessels, preserved blood–brain barrier integrity, and improved survival when combined with artesunate [221]. Clinical trials conducted in African children demonstrated that iNO, administered at 80 ppm via non-rebreather mask for up to 72 hours alongside standard intravenous artesunate therapy, is safe and well-tolerated, showing no significant increase in adverse events, mortality, or neurological deficits compared to placebo [222]. However, therapeutic efficacy has been limited. Key endothelial biomarkers such as angiopoietin-2 (Ang-2) remained unchanged, and no significant improvements were observed in clinical recovery, parasite clearance, or mortality [223]. Although neurocognitive outcomes were largely unaffected, one study reported a significant reduction in fine motor impairment at six months post-treatment among children receiving iNO. [223] In a complementary pediatric cerebral malaria trial, iNO similarly failed to modify Ang-1/Ang-2 or inflammatory cytokine trajectories, yet produced clear pharmacodynamic effects—blood methemoglobin and plasma nitrate levels increased significantly in the NO arm—confirming effective NO delivery without translating into better survival or reduced neurological sequelae. [222]

In contrast, carbon monoxide (CO) has shown promise as a neuroprotective and anti-inflammatory adjunctive agent in experimental cerebral malaria. Generated endogenously via heme oxygenase-1 (HO-1) during hemolysis, CO mitigates oxidative damage and inflammation by neutralizing toxic free heme and stabilizing endothelial function [224]. In murine models, HO-1–derived CO is essential for disease tolerance: susceptible mice that fail to upregulate HO-1 develop severe blood–brain barrier disruption and fatal experimental cerebral malaria (ECM), whereas pharmacologic induction of HO-1 or administration of low-dose CO gas prevents ECM and reduces vascular leakage and brain inflammation [225]. In preclinical models, CO reduced blood-brain barrier disruption, neuroinflammation, and endothelial injury—key mechanisms in cerebral malaria pathology. These protective effects are linked to CO-mediated sequestration/detoxification of free heme, reduced endothelial activation and leukocyte adhesion, and improved microvascular integrity in both ECM and malaria-associated acute lung injury (ALI) models. [226] A novel CO-releasing molecule, ALF492, provided

complete protection against experimental cerebral malaria (ECM) and malaria-associated acute lung injury (ALI) in mice, without impairing hemoglobin's oxygen transport—an advantage over inhaled CO, which poses risks of hypoxia in anemic patients. ALF492 enabled controlled systemic CO delivery, prevented neurological signs and mortality from ECM, abrogated ALI, and did not increase carboxyhemoglobin or impair arterial oxygen content, thereby separating CO's cytoprotective signaling from its classical gas-exposure toxicity. Protection persisted

Table 1
Medical gases across CNS injuries

	Gas	Main mechanisms	Representative dose / timing	Clinical CNS status
Ischemic stroke	O_2 / NBO / HBOT	↑ penumbral O_2, modulates ROS, MMP-9, BBB, inflammation/apoptosis [48,51–61]	NBO: 100% O_2 ~2–6 h around thrombectomy [50]; HBOT: 100% O_2, 1.5–3.0 ATA, 60–120 min, early after ischemia [54,58]	Supportive only if hypoxemic; NBO/HBOT experimental [49,50,56,57]
	H_2	Scavenges •OH/$ONOO^-$, ↓ NF-κB/NLRP3, ↑ Bcl-2/Bax, preserves BBB [62–67]	1–4% H_2 30–60 min during ischemia/early reperfusion; H_2-saline 5–10 mL/kg at/soon after occlusion [62–65,68]	Early clinical trial (3% H_2 1 h BID ×7 d) safe, promising [69,70]
	NO (GTN / iNO)	eNOS-NO vasodilation; excess nNOS/iNOS-NO → $ONOO^-$, mitochondrial injury [71–75]	GTN patch 5 mg/24 h (±0.4 mg SL) within 4–48 h [33,76,77]; iNO 5–50 ppm at reperfusion for several h [78–80]	Mixed GTN results; RIGHT-2 neutral; iNO preclinical only [33,76–80]
	CO (CORM-3)	Nrf2/HO-1, ↓ microglia/cytokines, BBB protection [81–85]	CORM-3 4 mg/kg i.v. at reperfusion in tMCAO [81]	Preclinical only; toxicity window limits direct CO use [81–85]
	Xe	NMDA glycine-site antagonism, ↓ excitotoxic Ca^{2+}, preserves mitochondria/WM [86–89]	50–70% Xe 1–3 h, peri-ischemic or early post-reperfusion [86,87]	Clinical neuroprotection data mainly post–cardiac arrest; stroke use limited [17,92]
Hemorrhagic stroke (SAH/ICH)	O_2 / HBOT	↓ edema, neuroinflammation, BBB injury; modulates AQP4, microglia [93–99]	Early HBOT at 1.5–3.0 ATA, 60–120 min in rodent SAH/ICH [93–98]	Subacute/chronic HBOT trials suggest benefit but remain experimental [99,100]
	H_2	Scavenges ROS/RNS, ↓ astro/microgliosis, ↓ NF-κB/NLRP3, preserves BBB [101–105]	Brief H_2 inhalation and H_2-rich saline early after SAH/ICH (protocols model-dependent) [102–105]	Small SAH RCT: i.v. H_2 + intracisternal $MgSO_4$ improved vasospasm/DCI and function [106]
	H_2S	↓ TLR4/NF-κB, ↓ MMP-9 BBB damage, AQP4 modulation, ↓ apoptosis/autophagy [107–109]	NaHS ~25 μmol/kg protective in ICH; ≥50–100 μmol/kg not protective [109]	Preclinical only; narrow window and mitochondrial toxicity at high doses [109–111]
	NO / iNO / ethyl nitrite	Vasodilation, improved perfusion, ↓ microvasospasm, ↓ inflammation [112–119]	iNO ~40–50 ppm post-SAH; ethyl nitrite ≈20 ppm in SAH models [116–118]; 40 ppm iNO in SAH DCI patients [119]	Experimental; small SAH series physiologically positive, efficacy unproven [112,116–119]
	CO / CORM-3	↓ inflammation, vasospasm, edema; HO-1/CO-mediated heme clearance, circadian reset [82,120–123]	CORM-3 in ICH rats; inhaled CO ~250 ppm ×1 h after SAH [120,122]	Only preclinical in CNS; safety guided by non-CNS CO studies [124]
	Xe, Ar	Ar: Nrf2/TLR modulation; Xe: NMDA antagonism [87,125–128,131]	≈50% Xe or Ar 1 h ~1 h post-SAH; Xe-ELIP i.v. + US in SAH/ICH [126,131,132]	Xe: anesthetic with preclinical hemorrhagic data; Ar: experimental only [125–128,131–133]
TBI	O_2 / HBOT	↑ $PbtO_2$, improved metabolism, ↓ ICP/edema, mitochondrial support [134,137–139]	HBOT 1.5–2.5 ATA, 60–90 min, repeated; normobaric hyperoxia guided by $PbtO_2$ [137–139]	BOOST-3 ongoing; HBOT/O_2 still investigational [134–136,138–141]
	H_2	↓ ROS, NLRP3, microglial activation; preserves BBB, ↓ edema/apoptosis [142–146]	2–4% H_2 early after CCI; H_2-rich saline/water in acute phase [143–147]	Limited human peri-neurosurgical data; no TBI RCTs yet [149]
	H_2S	↓ oxidative stress/inflammation, ↓ apoptosis/autophagy [150–152]	NaHS ~1 mmol/kg protective; high-dose (~45 mmol/kg) harmful [151]	Preclinical only; narrow therapeutic window [150–152]
	NO (donors, iNO, VAS203)	Early NO: supports CBF/synaptic function; delayed iNOS: damage [153–157]; DETA-NONOate: ↑ neuro/angiogenesis; MINOR: local NO reservoir [158,159]; iNO: ↑ perfusion, ↓ ICP/edema [160]	DETA-NONOate for 7 d; iNO 24 h; VAS203 tested in rodents and phase-IIa TBI [158–162]	VAS203: improved outcome but AKI at higher dose [161–163]; others preclinical [158–160]
	CO / CORM-3	Pericyte/NSC support, oligodendrogenesis, anti-inflammatory, gut–brain and cardioneuroprotection [164–170]	CORM-3 via gut or i.v. in TBI+hemorrhagic shock models [165,169,170]	No CNS clinical trials; CO safety data from other indications [124]
	Xe	↓ excitotoxicity/inflammation; preserves tissue, improves motor/cognitive outcomes [86,171–175]	Effective when given ≤3 h post-CCI (50–70% Xe for several h) [175,176]	Only indirect clinical data (anesthesia, cardiac); TBI neuroprotection trials lacking [177]
	Ar	Anti-inflammatory/anti-apoptotic, ↓ edema/WM damage via TLR2/4–ERK1/2 and Nrf2 [178–180]	70% Ar from 10 min post-CCI for up to 24 h in rodent models [180,181]	Preclinical, mixed long-term benefit [178–181]
	Xe	NMDA antagonism; synergy with TH [86,89,184–187]	40–70% Xe for 12–24 h with TH, started ≤5 h post-insult in animals; 30% Xe for 24 h in TOBY-Xe trial [89,184–190]	50% Xe for 18 h with TH safe [185,189]; TOBY-Xe neutral; further trials ongoing [190]
Perinatal HIE	Ar	Nrf2–NQO1/SOD1 activation, ↑ GSH, ↓ oxidative stress/apoptosis [191–193]	~70% Ar post-HI in rats; 45–50% Ar 2–26 h post-insult with TH in piglets [192,193]	Piglet studies show safety up to 80% Ar [194]; no neonatal trials [191–196]
	O_2 / HBOT	HBOT: ↓ apoptosis, ↑ neuro/oligodendrogenesis, Wnt/Nrf2 activation [210–214]	0.15–0.17 MPa (1.5–1.7 ATA), 60–120 min, 1–3×/day, early post-HI [215–217]	RCTs (mostly Chinese) suggest benefit but with bias; dosing and toxicity concerns remain [215–218]
Perinatal hypoxia	iNO	Selective pulmonary vasodilator, ↑ oxygenation, ↓ ECMO, no worse 2-y neurodevelopment [197–202]	5–20 ppm iNO in term/near-term infants with PPHN [197–202]	Established standard of care for PPHN [197–202]
Cerebral malaria	iNO	Restores NO bioactivity, targets endothelial dysfunction [219–221]	80 ppm iNO up to 72 h plus artesunate in children [222,223]	Safe but no improvement in Ang-2, parasite clearance, or mortality [222,223]
	CO / ALF492	HO-1/CO detoxifies free heme, stabilizes endothelium, ↓ BBB disruption and neuroinflammation [224–227]	Inhaled CO ~250 ppm; ALF492 systemically, effective even when delayed and with artesunate [225,227]	Preclinical only; CO-RMs allow controlled CO delivery [227–229]

when ALF492 was started after onset of neurological symptoms and when combined with artesunate, supporting its potential as a late-stage adjunct rather than only a prophylactic intervention. [227]

Inhaled CO has also demonstrated protective effects in ECM models, reinforcing its mechanistic plausibility. Pamplona et al. showed that low-dose inhaled CO (≈250 ppm) significantly reduced ECM incidence and brain inflammation in susceptible mice, phenocopying HO-1 induction and supporting CO as a key effector downstream of HO-1 in cerebral malaria. [225]Nonetheless, toxicity concerns remain central, as high systemic CO levels can compromise oxygen delivery. The use of CO-releasing molecules offers a promising alternative, allowing for controlled, targeted delivery with reduced systemic risk [228]. Contemporary CO-RM reviews highlight that appropriately designed CORMs can deliver CO in a tissue-restricted and triggerable fashion, limiting peak carboxyhemoglobin and enabling safer clinical translation than inhaled CO gas. [229] Despite encouraging preclinical data, clinical trials in human malaria are lacking, and further studies are essential to evaluate the safety, dosing strategies, and therapeutic efficacy of CO-based treatments in severe malaria.

A concise overview of the medicinal gases discussed across CNS indications, their predominant mechanisms, representative dosing regimens, and clinical status is provided in Table 1. (See Figs. 1–3.)

3.6. Advanced delivery strategies for medicinal gases

A major bottleneck in translating medicinal gases to the clinic is the difficulty of delivering short-lived, low-solubility molecules to the injured CNS in a controlled, tissue-selective manner. Conventional systemic or inhalational administration often results in subtherapeutic CNS exposure, off-target effects, or dose-limiting toxicity. Recent work in drug delivery has therefore focused on engineering carriers and devices that provide spatiotemporally controlled gas delivery, aligning closely with the scope of advanced drug delivery research. Selected advanced delivery platforms for medicinal gases are summarized in **Table 2**.

3.7. Nanocarrier-based systems: liposomes, nanobubbles and microbubbles

Echogenic liposomes and related gas-loaded vesicles are among the most advanced platforms for CNS gas delivery. In a seminal proof-of-concept study, Britton et al. encapsulated xenon into echogenic liposomes (Xe-ELIP) using a pressurization–freeze method (~15–20 μL Xe per mg lipid; gas mixture 70% Xe/30% Ar) and showed that intravenous or intra-arterial Xe-ELIP combined with low-power ultrasound over the carotid artery reduced infarct volume by ~48% with Xe-ELIP alone and up to ~75% when ultrasound-triggered release was applied in a rat MCAO model. [230] Building on this, Peng et al. systematically defined the therapeutic time window and dose dependence for Xe-ELIP in focal ischemia: Xe-ELIP administered at 2–5 h after a 2-h MCAO significantly reduced infarct size, with an optimal dose range of 7–14 mg/kg at 3 h post-occlusion, accompanied by activation of Akt/MAPK signaling and increased BDNF expression. [231]

The same Xe-ELIP platform has been adapted to other cerebrovascular injuries. In a subarachnoid hemorrhage model, intravenous Xe-ELIP followed by carotid ultrasound reduced early brain injury,

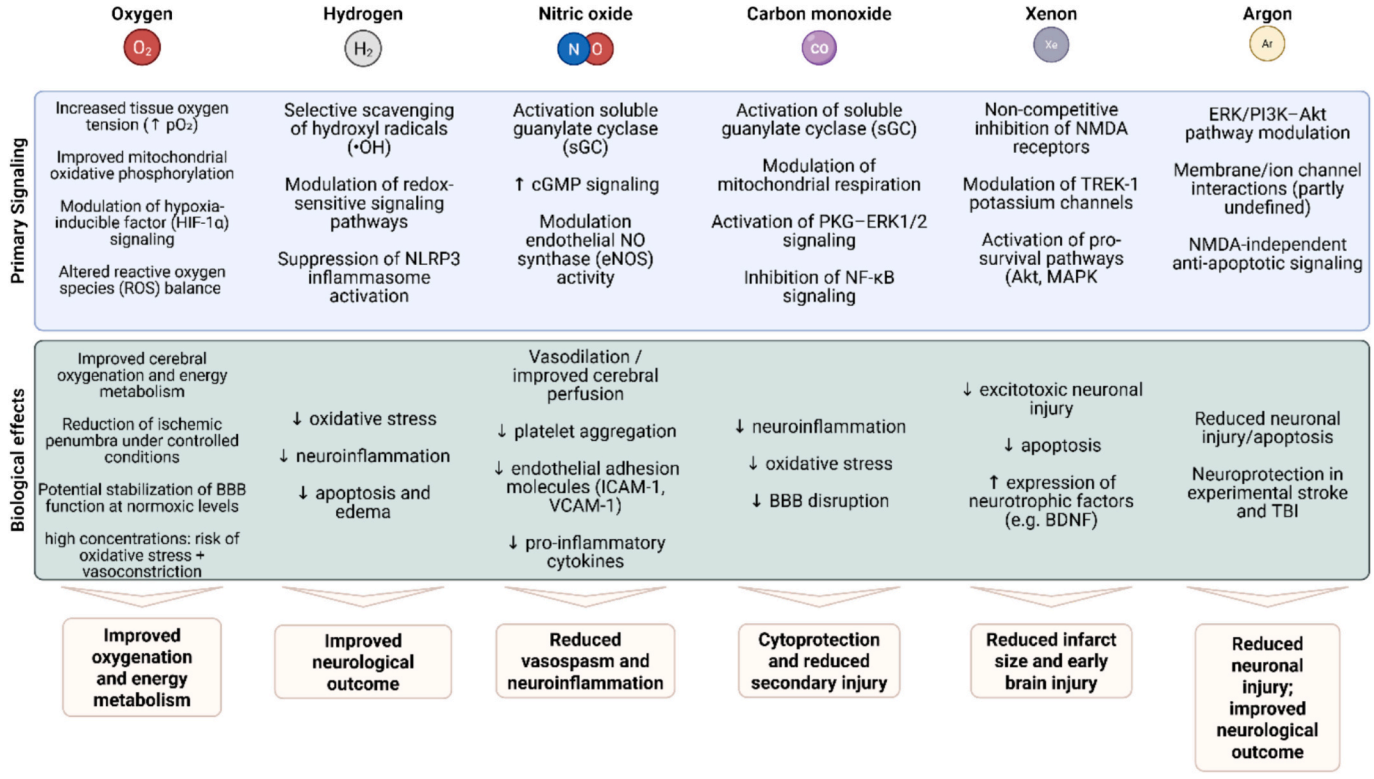

Fig. 1. Gas-specific molecular mechanisms and downstream effects relevant to CNS injury. The schematic summarizes the principal molecular and cellular signaling pathways through which medicinal gases exert neuroprotective or cytoprotective effects in CNS injury. For each gas, primary signaling targets are shown together with the dominant biological effects and resulting pathophysiological outcomes. Nitric oxide activates soluble guanylate cyclase and cGMP signaling, leading to vasodilation, reduced vasospasm, and attenuation of neuroinflammation. Xenon primarily inhibits NMDA receptors and modulates potassium channels while activating pro-survival signaling pathways, thereby reducing excitotoxic injury and apoptosis. Carbon monoxide modulates sGC-, PKG–ERK1/2-, and NF-κB-dependent signaling, resulting in anti-inflammatory and cytoprotective effects. Hydrogen reduces oxidative stress and inflammasome activation through selective radical scavenging and redox modulation. Argon induces NMDA-independent pro-survival signaling, whereas oxygen improves tissue oxygenation and energy metabolism in a dose-dependent manner. The figure highlights dominant mechanistic themes rather than exhaustive signaling cascades and provides a conceptual framework linking gas-specific molecular actions to key therapeutic outcomes (created with biorender.com).

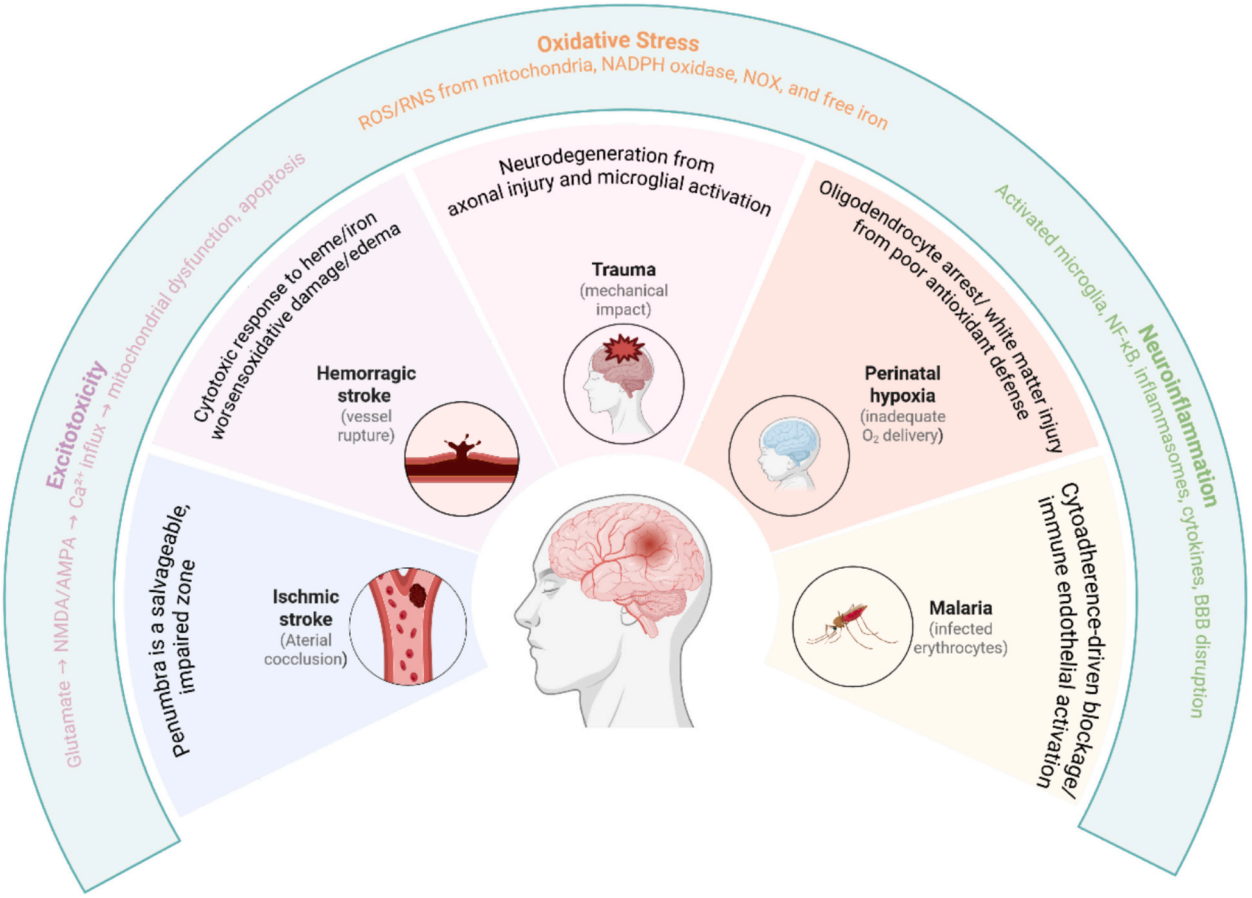

Fig. 2. Convergence and divergence of pathophysiological mechanisms in central nervous system (CNS) injuries. This schematic summarizes the primary etiologies and distinct injury patterns of five major CNS insults—ischemic stroke, hemorrhagic stroke, traumatic brain injury (TBI), perinatal hypoxia, and cerebral malaria. The outer ring delineates three core secondary injury cascades that are commonly activated across these diverse primary insults. This integrative depiction highlights the mechanistic overlap between CNS pathologies and underscores shared targets for neuroprotective therapeutic intervention (created with biorender.com).

apoptosis, and mortality, indicating that ultrasound-responsive Xe carriers can also target hemorrhagic pathologies [132]. More recently, xenon-loaded liposomes have been combined with reperfusion therapy: in an embolic stroke model, Peng et al. administered Xe-liposomes (20 mg/kg i.v. at 2 h after stroke onset) together with rtPA (10 mg/kg at 2 or 4 h), achieving improved neurological outcome, reduced TUNEL-positive cells, and attenuation of rtPA-associated hemorrhagic transformation. [232] These studies illustrate how nanocarrier-based xenon delivery can be synchronized with reperfusion therapies and tuned in terms of dose and timing.

Beyond xenon, echogenic liposomes and microbubbles have been used as generic platforms for gasotransmitters such as nitric oxide and hydrogen sulfide. NO-loaded echogenic liposomes (NO-ELIP) enable ultrasound-triggered, site-specific NO release to cerebral arteries, providing vasodilation in models of subarachnoid hemorrhage-related vasospasm while limiting systemic exposure. [233] A broader review of therapeutic gas delivery via microbubbles and liposomes highlights that these acoustically active carriers can encapsulate noble gases, NO, and H_2S, and be imaged and triggered by diagnostic-range ultrasound, thereby integrating diagnostics and therapy (theranostics) in a single platform [234]. Such systems are particularly attractive for stroke and TBI, where ultrasound is already used for vascular imaging and clot lysis.

3.8. Controlled-release systems for gasotransmitters

In parallel, chemically defined gas-releasing prodrugs extend the concept of controlled gas delivery beyond physical carriers. Carbon monoxide-releasing molecules (CORMs) provide a controllable source of CO with tunable pharmacokinetics. In rodent models of traumatic brain injury complicated by hemorrhagic shock, intestinal administration of the water-soluble CO donor CORM-3 attenuated neurodegeneration in the amygdala, improved anxiety- and depression-like behavior, and reduced gut and brain inflammation, effects linked to modulation of the PKG–ERK1/2 pathway. [165] Other preclinical studies in cardiac arrest and radiation brain injury similarly show that CORM-3 can limit neuronal death and microglial activation, supporting its role as a systemically administered, organ-protective CO source [165,235].

Analogously, sustained-release NO systems have been engineered to provide long-lasting local NO signaling in the injured brain. A recent "mussel-inspired nitric oxide-release microreservoir" (MINOR) combines ROS-scavenging with controlled NO generation; after implantation into TBI lesions, MINOR supports angiogenesis, neurogenesis, and functional recovery over extended periods, illustrating how solid-state reservoirs can deliver gasotransmitters in a temporally programmed fashion. [159] Long-acting H_2S donors and multi-gas–releasing hybrids illustrate how gasotransmitter pharmacology can be refined by chemical design rather than simple inhalation. Slow-release H_2S donors such as GYY4137 achieve sustained, low-level H_2S exposure and have shown cytoprotective effects in multiple ischemia–reperfusion and inflammatory models. [236] Hybrid NO/H_2S-releasing "NOSH" non-steroidal anti-inflammatory drugs (e.g., NOSH-aspirin, NOSH-naproxen) further demonstrate that dual gasotransmitter delivery from a single prodrug can enhance anti-inflammatory and chemopreventive efficacy while reducing gastrointestinal toxicity in vivo. [237,238] Although these systems have been developed mainly in inflammatory, cardiovascular,

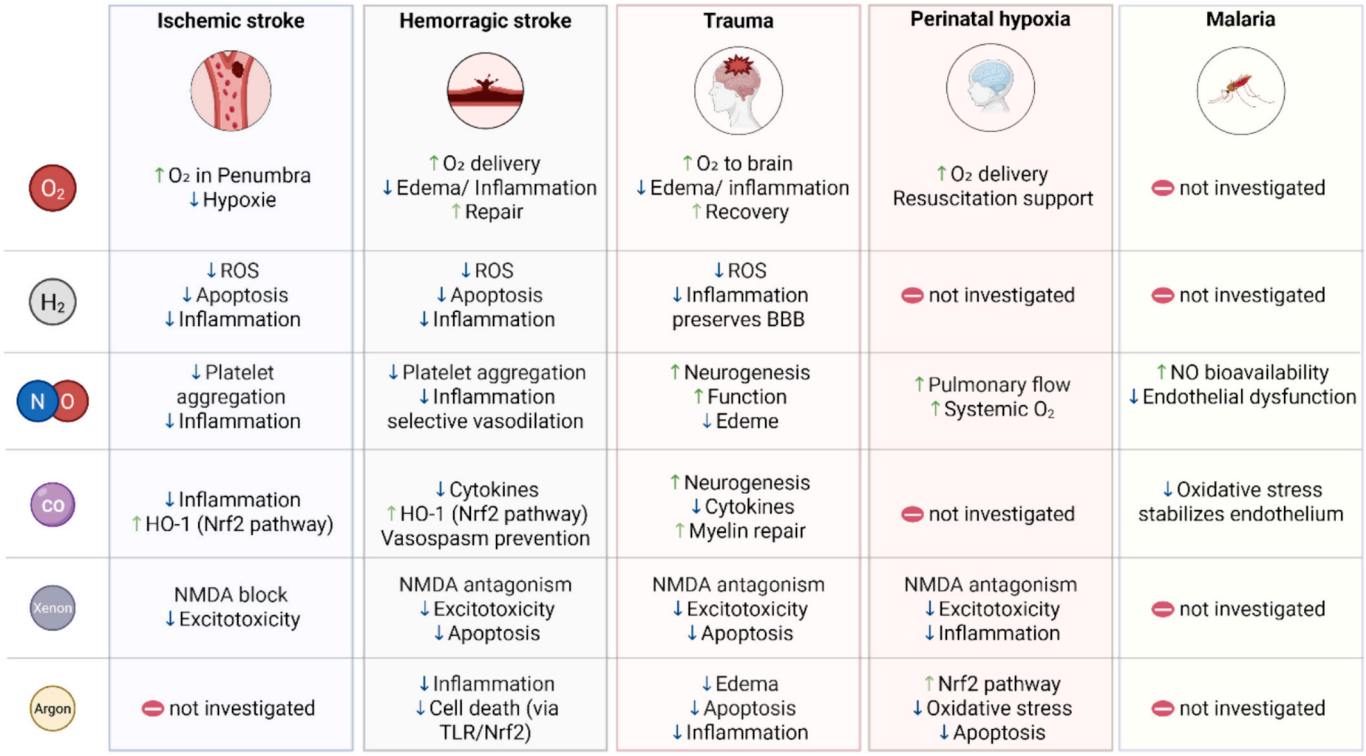

Fig. 3. Medical gas therapies across CNS injury types. Overview of selected medical gases—oxygen (O_2), hydrogen (H_2), nitric oxide (NO), carbon monoxide (CO), xenon, and argon—and their reported or proposed therapeutic effects in major CNS injuries: ischemic stroke, hemorrhagic stroke, traumatic brain injury (TBI), perinatal hypoxia, and cerebral malaria. Filled cells indicate reported or proposed efficacy in experimental or clinical models for the corresponding pathology (created with biorender.com).

and cancer models rather than CNS injury, they provide a proof of principle for controlled, multi-gas delivery platforms that could be adapted for stroke or TBI in the future. Collectively, these donor systems represent a chemical counterpart to nanocarriers, enabling programmable gas release based on hydrolysis, enzymatic activation, or redox conditions.

3.9. Optimization and personalization of inhaled delivery

Finally, advanced inhalation systems seek to overcome the practical limitations of continuous gas administration—particularly for expensive or potent gases such as xenon and NO. For xenon, closed-circuit delivery devices equipped with real-time gas analyzers and automated controllers have been developed for prolonged neuroprotective administration in large animals. In a neonatal piglet model of hypoxic–ischemic encephalopathy, Dingley et al. showed that an automated ambient-pressure closed-circuit system could maintain 50% inhaled xenon for 72–78 h in combination with hypothermia, at a relatively low gas cost and without inducing lung injury. [239]Earlier feasibility work in newborn pigs demonstrated that similar systems can deliver xenon for up to 16 h with or without concurrent cooling, providing a technical basis for prolonged neonatal xenon therapy. [240] These approaches illustrate how feedback-controlled, gas-recycling circuits enable precise targeting of therapeutic xenon concentrations, minimize wastage, and facilitate individualized dosing.

Comparable optimization has occurred for inhaled NO, where ventilator-coupled delivery systems and continuous chemiluminescence monitoring of NO and NO_2 (together with routine methemoglobin measurements) enable accurate ppm-level titration across a wide range of ventilator modes, while limiting systemic hypotension and oxidant toxicity in conditions such as PPHN and ARDS. [241–244] Conceptually, these closed-loop inhalation strategies are directly transferable to other therapeutic gases (e.g., H_2, CO_2, O_2 at supra-atmospheric fractions) and provide a framework for integrating bedside physiological monitoring with personalized gas dosing.

Together, these nanocarrier-based formulations, controlled-release donors, and optimized inhalation systems move medicinal gases squarely into the realm of advanced drug delivery. They provide a unifying technological framework across ischemic stroke, hemorrhagic stroke, TBI, and perinatal hypoxia, and directly address the reviewers' request for a more systematic and forward-looking discussion of gas delivery technologies within the review.

3.10. Combination and multi-gas strategies

Although most preclinical and clinical work has evaluated single gases, several studies already illustrate the potential of combination or multi-gas strategies. In neonatal hypoxic–ischemic brain injury, xenon shows additive neuroprotection when combined with therapeutic hypothermia: in a rat model, 50% xenon plus mild hypothermia (32 °C) given after hypoxia–ischemia produced greater long-term functional and histopathologic protection than either treatment alone, supporting the concept of combining a medicinal gas with a non-gaseous neuroprotectant. [245] Translational evidence comes from comatose survivors of out-of-hospital cardiac arrest, where a phase II randomized trial found that 40–50% inhaled xenon administered for 24 h on top of targeted temperature management (33 °C) reduced diffusion tensor MRI white-matter damage compared with hypothermia alone, although functional outcomes were not significantly improved at 6 months. [246] Dual-gas approaches are also emerging: in aneurysmal subarachnoid hemorrhage, a randomized controlled trial protocol is evaluating early inhalation of a hydrogen–oxygen gas mixture as an adjunct to standard care, aiming to attenuate early brain injury and delayed cerebral ischemia. [247] Beyond inhaled mixtures, multi-gasotransmitter donors such as NOSH-aspirin—which releases both nitric oxide and hydrogen sulfide—demonstrate in vivo that simultaneous NO/H_2S delivery can

Table 2
Advanced delivery strategies for medical gases

Gas	Delivery strategies (as discussed in this review)	Main CNS-related models / indications	Key effects (very condensed)	Translation notes
Xenon (Xe)	• **Nanocarriers:** xenon-containing liposomes / echogenic liposomes (Xe-ELIP) with ultrasound-triggered release • **Optimized inhalation:** closed-circuit, gas-recycling Xe systems for prolonged administration	Focal and embolic ischemic stroke (± rtPA), SAH, TBI (preclinical); neonatal HIE (large animals, early clinical)	Xe-ELIP: i.v. Xe + carotid ultrasound enhances local delivery, reduces infarct/early brain injury and, with rtPA, lowers hemorrhagic transformation. Closed-circuit systems maintain 30–50% Xe for many hours with hypothermia at acceptable gas cost and stable cardio-respiratory parameters.	Nanocarriers enable spatiotemporal targeting but are preclinical and require ultrasound and i.v. access. Closed-circuit inhalation is technically mature and provides a basis for individualized Xe neuroprotection, but cost/logistics and tPA interference limit acute stroke use.
Carbon monoxide (CO)	• **Systemic CO-releasing molecules (CORMs)** such as CORM-3 • **Next-generation CO-releasing molecules/ materials** (e.g., ALF492 in malaria models)	tMCAO, ICH, TBI with hemorrhagic shock, experimental cerebral malaria (ECM/ALI)	Systemic CO-RMs given around reperfusion or disease onset reduce infarct size, edema, BBB disruption and neuroinflammation, protect gut–brain and heart axes, and in ECM/ALI models prevent fatal disease even with delayed administration.	CO-RMs decouple cytoprotective CO signaling from inhaled-gas toxicity and allow controlled dosing. All CNS applications are preclinical; translation is constrained by the narrow CO safety window and the need for well-tolerated CO-RMs.
Nitric oxide (NO)	• **Local depots / hydrogels** (e.g., NO-releasing microreservoirs) • **Liposomal / ultrasound-triggered NO carriers** (NO-ELIP) • **Optimized inhalation systems (iNO)** integrated into ventilators with continuous NO/NO_2/metHb monitoring	TBI and SAH (preclinical); PPHN and critical care (established cardiopulmonary use)	Solid NO depots implanted in TBI lesions enable sustained, localized NO release, promoting angiogenesis/neurogenesis and improving functional recovery. NO-ELIP permit ultrasound-triggered, focal vasodilation in SAH-related vasospasm. Modern iNO systems allow precise ppm-level titration and selective pulmonary vasodilation, improving oxygenation without major systemic hypotension.	Local depots and NO-ELIP illustrate spatially and temporally controlled NO delivery but remain preclinical. Ventilator-integrated iNO is clinically established in neonatology and serves as a template for personalized inhaled delivery of other medicinal gases.
Hydrogen (H_2)	• **Inhalation** via standard ventilator/respiratory circuits (low-concentration H_2 or H_2/O_2 mixtures) • **Hydrogen-rich solutions** (saline or water, i.v. or oral)	Ischemic and hemorrhagic stroke, TBI, perinatal HIE, post–cardiac arrest (preclinical and early clinical)	Inhaled H_2 and H_2-rich solutions reduce oxidative stress, neuroinflammation, apoptosis and edema, leading to smaller lesion volumes and better neurological outcomes. Early protocols in stroke and SAH patients (e.g., low-% H_2 inhaled for several days, or i.v. H_2 solution as adjunct) have shown feasibility and good tolerability.	Uses existing ventilator and infusion platforms; non-explosive at clinically used concentrations. Optimal concentration, timing and treatment duration in CNS patients are under investigation in ongoing and planned clinical trials.
H_2S and NO/H_2S hybrids	• **Slow-release H_2S donors** (e.g., GYY4137) • **Dual-gasotransmitter prodrugs** (e.g., NOSH-NSAIDs releasing NO + H_2S)	Ischemia–reperfusion and inflammatory models (non-CNS in this review; discussed as platforms)	Slow-release donors provide sustained, low-level H_2S exposure with improved tolerability compared with bolus NaHS. NOSH-NSAIDs deliver NO and H_2S from a single scaffold, enhancing anti-inflammatory and chemopreventive effects while lowering GI toxicity.	Not yet applied to CNS injury in the studies reviewed here, but they exemplify chemically programmable single- and multi-gas delivery systems that could be adapted to overcome H_2S's narrow therapeutic window and enable dual-gas strategies in neuroprotection.

enhance anti-inflammatory efficacy and reduce gastrointestinal toxicity compared with aspirin alone. [238] Although NOSH-aspirin has been studied mainly outside the CNS, these examples collectively support the rationale for rationally designed combination and multi-gas strategies in neuroprotection and motivate future work specifically in stroke, TBI, and other CNS injuries.

3.11. *Clinical translation of medicinal gases*

Several of the gases discussed have now progressed beyond proof-of-concept animal work into early human trials, but their translational pathways are at very different stages. Supplemental oxygen is routine in neurocritical care, yet randomized trials of normobaric or hyperbaric oxygen as neuroprotectants in stroke, TBI and HIE remain small and heterogeneous, so these approaches are still considered experimental in non-hypoxemic patients. Molecular hydrogen has advanced to first-in-patient studies: in acute cerebral infarction, low-concentration H_2 inhalation (3%, 1 h twice daily for 7 days, started 6–24 h after onset) was safe and showed signals of reduced infarct progression and improved NIHSS scores, [70] and more recently the multicentre HYBRID II trial demonstrated the feasibility and safety of 2% H_2 for 18 h in comatose out-of-hospital cardiac arrest patients, with improved secondary clinical outcomes but a neutral primary endpoint. [248] Inhaled NO is fully translated as a selective pulmonary vasodilator for persistent pulmonary hypertension of the newborn, but CNS-directed trials—such as adjunctive iNO in severe pediatric malaria or phase-II studies measuring cerebral blood flow responses in acute ischemic stroke—have so far shown safety without clear efficacy on mortality or functional outcome. [220] Xenon is already approved as an anesthetic and has entered neuroprotection trials: in neonatal hypoxic–ischemic encephalopathy, the TOBY-Xe trial confirmed feasibility and hemodynamic stability of 30% Xe for 24 h in combination with hypothermia, but did not demonstrate a significant MRI benefit, [190] and a similar picture emerges from post–cardiac arrest studies, where xenon reduced white-matter injury on MRI but has not yet translated into robust functional benefit. [246] By contrast, carbon monoxide and hydrogen sulfide remain confined to preclinical CNS models: low-dose inhaled CO has reached early clinical testing in non-CNS indications, and CO-releasing molecules or slow-release H_2S donors are viewed as promising delivery platforms, but no CO- or H_2S-based neuroprotective trials in humans have been reported. Argon and helium likewise remain at the preclinical stage. Overall, clinical translation is most advanced for xenon, hydrogen and inhaled NO, intermediate for CO (via systemic CO-releasing strategies), and still purely experimental for H_2S and argon, underscoring the need for carefully designed early-phase trials that integrate optimized delivery systems, dosing and patient selection (Table 3).

Table 3
Clinical translation status of medicinal gases in CNS indications

Gas	Main CNS indication(s) tested in humans	Example protocol / phase	Current status
O_2 / HBOT	Ischemic stroke, TBI, HIE	Small phase II trials, mixed results	Supportive O_2 routine; NBO/HBOT neuroprotection experimental
H_2	Ischemic stroke, OHCA, SAH (ongoing)	3% H_2 1 h BID ×7 d in AIS; 2% H_2 18 h in OHCA	Phase I/II–type, safe, efficacy signals, larger trials needed
Xe	Neonatal HIE, OHCA	30–50% Xe with TH, 18–24 h	Licensed anesthetic; neuroprotection trials feasible but efficacy not yet proven
iNO	PPHN, severe malaria, AIS (CBF studies)	5–20 ppm (PPHN); 80 ppm up to 72 h (malaria)	Standard in PPHN; CNS benefit unproven, mechanistic/neutral trials
CO	None (CNS); ARDS, sepsis, transplant (non-CNS)	100–200 ppm for 60–90 min, COHb ≈6–8%	Early clinical safety data outside CNS; CNS use preclinical only
H_2S, Ar, He	CNS indications	–	Preclinical only

4. Summary and conclusion: Challenges and future directions in gas-based therapies for CNS injuries

The therapeutic application of medical gases has emerged as a promising strategy in the treatment of central nervous system (CNS) injuries, including ischemic and hemorrhagic stroke, traumatic brain injury (TBI), perinatal hypoxia, and cerebral malaria. Gases such as oxygen (O_2), hydrogen (H_2), nitric oxide (NO), carbon monoxide (CO), xenon, and argon have demonstrated diverse neuroprotective properties in preclinical studies, with several progressing to early-phase clinical trials. These gases exert multifaceted actions including antioxidant, anti-inflammatory, anti-apoptotic, vasodilatory, and metabolic effects, allowing them to intervene at multiple points in the secondary injury cascade following CNS insult. In some contexts, such as the use of inhaled NO for neonatal pulmonary hypertension or xenon for anesthesia, their clinical use is already established, providing a foundation for broader neurological applications.

Despite encouraging results, significant challenges remain before gas therapies can be widely adopted in clinical neurology. One of the foremost obstacles is the narrow therapeutic window within which many gases exert their beneficial effects. Timing is critical; early-phase administration often determines the balance between neuroprotection and toxicity, as is particularly evident with nitric oxide and carbon monoxide, which can transition from protective to harmful depending on dose and enzymatic source. This temporal sensitivity complicates clinical implementation, especially in acute settings where delays are common.

Moreover, precise dosing and delivery remain complex. While some gases like hydrogen are safe over a broad range of concentrations, others such as CO and NO demand tightly regulated delivery to avoid systemic side effects. The development of novel delivery systems—such as carbon monoxide-releasing molecules (CORMs), liposomal gas carriers, and sustained-release formulations—is crucial to ensure targeted and controlled exposure. However, these technologies are still in preclinical or experimental phases, and their translational readiness must be further validated.

The clinical evidence base for many gas therapies is heterogeneous. Hyperbaric oxygen therapy (HBOT), for example, has yielded inconsistent outcomes across studies due to variability in treatment protocols, timing, and patient selection. These inconsistencies hinder the establishment of standardized clinical guidelines and highlight the need for more rigorously designed trials. Additionally, logistical and economic barriers limit the feasibility of certain gases in clinical practice. Xenon, although highly effective in preclinical studies and approved for anesthesia in some countries, remains prohibitively expensive and requires complex closed-circuit delivery systems, reducing its accessibility and scalability. Conversely, gases such as argon and hydrogen offer logistical advantages due to their abundance, cost-effectiveness, and compatibility with conventional ventilator systems, yet lack robust clinical data to support their routine use.

Adding to the complexity is the mechanistic diversity and context-dependent nature of gas actions. For example, nitric oxide derived from endothelial nitric oxide synthase (eNOS) promotes vasodilation and neuroprotection, while excessive NO from inducible or neuronal sources may drive neurotoxicity through oxidative and nitrosative stress. Understanding the interplay of these pathways, and how they shift over time following CNS injury, is essential for designing effective and safe interventions. This complexity underscores the potential value of biomarker-guided approaches that allow for real-time monitoring and personalized modulation of gas therapy.

Future research should prioritize large, multicenter clinical trials to evaluate efficacy, safety, and optimal treatment protocols, particularly for gases with favorable preclinical profiles such as hydrogen, xenon, and inhaled nitric oxide. Integration of gas therapies with existing standards of care, such as therapeutic hypothermia, reperfusion therapies, or neurorehabilitation protocols, may enhance therapeutic outcomes through synergistic mechanisms. Continued innovation in delivery technologies, combined with biomarker-informed dosing strategies, will be instrumental in translating these therapies from bench to bedside.

In conclusion, medical gases represent a novel and versatile class of therapeutics for CNS injuries, capable of targeting key pathological mechanisms with temporal precision. While several candidates show compelling preclinical and early clinical promise, overcoming challenges related to timing, delivery, standardization, and scalability is essential. With sustained research efforts and technological advancement, gas-based interventions may ultimately become integral components of neurocritical care, improving functional outcomes and quality of life across a spectrum of neurological conditions.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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