ADVANCED SCIENCE
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Supporting Information

for *Adv. Sci.*, DOI 10.1002/advs.202104136

Medical Gas Therapy for Tissue, Organ, and CNS Protection: A Systematic Review of Effects, Mechanisms, and Challenges

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Supporting Information

Table S1

Summary of Articles Exhibiting Adverse Effects or No Discernible Therapeutic Benefits of Medical Gases

Author/Year	Gas	Model	Findings
Lopez, I. 2003[1]	CO	In vivo: 8-day old rat pups	Mild chronic CO exposure hindered cochlea development.
Cheng, Y. 2012[2]	CO	In vivo: 10-day old CD-1 mouse pups	Three-hour exposure to 5 ppm or 100 ppm CO mitigated developmental apoptosis in neocortex and hippocampus, increasing neuronal numbers to trigger megalencephaly with impaired memory, learning, and socialization.
Cheung, N. S. 2007[3]	H_2S	In vitro: murine primary cortical neurons	H_2S induced neuronal death and apoptosis through activating ionotropic glutamate receptors.
Kim, D. S. 2020[4]	H_2S	In vivo: mouse after acute exposure to H_2S	H_2S caused lesions in the inferior colliculus (IC) and thalamus (TH) via modulation of multiple biological pathways including unfolded protein response, neurotransmitters, oxidative stress, hypoxia, calcium signaling, and inflammatory response in the IC and TH.
Matchett, G. A. 2009[5]	H_2	In vivo: neonatal hypoxia-ischemia rat model	H_2 (2.9%) did not ameliorate neural damage of moderate to severe neonatal hypoxia-ischemia insults.
Takeuchi, S. 2016[6]	H_2	In vivo: intracerebral hemorrhage rat model	H_2 did not attenuate brain water content or improve functional outcome.
Badr, A. E. 2001[7]	O_2	In vivo: MCAO rat model	HBO therapy for ≥12 h significantly exacerbated the cerebral infarct area.
Veltkamp, R. 2006[8]	O_2	In vivo: rat transient and permanent MCAO model	O_2 was not effective in reducing neural lesion after permanent MCAO.
Hjelde, A. 2002[9]	O_2	In vivo: rat permanent MCAO model	HBO did not reduce neutrophil infiltration into the infarct brain tissue and did not mitigate tissue damage in rats after 4h of permanent focal ischemia, relative to control treatment.
David, H. N. 2012[10]	Ag	Ex vivo: OGD injury in brain slices In vivo: MCAO rat model	Post-ischemic argon exposure worsened MCAO-caused subcortical brain damage and did not improve neurologic outcome, compared to control animals.
Harris, K. 2013[11]	He	Ex vivo: mechanical trauma in the organotypic hippocampal brain slices	Helium, neon, and krypton did not result in neuroprotection.
Aehling, C. 2018[12]	He	In vivo: rat cardiac resuscitation model	The combined helium pre/post-conditioning did not benefit neurofunctional outcome.
Rizvi, M. 2010[13]	Ag & He	In vitro: OGD injury in human tubular kidney cells	Neon, argon, and krypton did not protect cells from OGD. Helium worsened cell injury.
Brosnan, H. 2013[14]	Xe	Ex vivo: organotypic hippocampal cultures	Xenon causes neuronal cell death in an in vitro model of the developing rodent brain.

Abbreviations: HBO, hyperbaric oxygen therapy; MCAO, middle cerebral artery occlusion; OGD, oxygen glucose deprivation.

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Table S2

Analysis of Experimental Models and Medical Gas Dosages in Studies Exhibited in Table 2

Gases	Therapeutic Agents	Study Subjects/Materials	Injury/Lesion Types	Safe and/or Effective Dosage	Toxic Dosage
	Biological Gases				
CO	In vitro: CORM-2 In vivo: CO Gas, CORM ALF-186, CORM-2, CORM-3, and Methylene Chloride	In vitro: Human Umbilical Cord Vein Endothelial Cells, Primary Human Brain Astrocytes, and Human Brain Microvascular Endothelial Cells In vivo: Male Wistar rats, Male/Female Sprague Dawley rats, and Male C57BL/6 mice	In vitro: Excitotoxicity, oxidative stress, hypoxia, and OGD In vivo: Retinal, kidney or cardiac I/R injury, optical nerve crush, MCAO, cerebral hypoxia-ischemia, neurotrauma, myocardial infarction, heat shock-induced lung injury, acetaminophen-triggered liver lesion, and hepatectomy	**CO gas**: 250 ppm CO gas inhalation for 1 h post-injury [6] **CORM-2**: 5-20 μM RuCO added to culture media for 2-6 h [1a], 100 μM CORM-2 added to culture media for 8 h [2a], 5-100 μM CORM-2 added to culture media for 2-12 h [4], 30 mg/kg i.p. CORM-2 pretreatment for 2 h pre-injury [5b], and 0.1/1.0/10 mg/kg i.v. SMA/CORM-2 injected 24 h pre-BLM injections for 33 d [5c] **CORM-3**: 4 mg/kg or 8 mg/kg dissolved in distilled water, i.v., CORM-3 injected post-injury [1b] 4 mg/kg body weight dissolved in saline, i.p. CORM-3 injected 1 h post-injury [6] **CORM ALF-186**: 10 mg/kg body weight i.v. dissolved in water injected 0-3 h post-injury [5a] **Methylene Chloride**: 500 mg/kg p.o. 3 h pre-injury [3]	All medical gas dosages were well tolerated and safe in the experimental models investigated (see *Left Columns)*. For the purposes of the cited studies (**Table 2**), no toxic doses (gases in further higher concentrations) were evaluated
H_2S	In vitro: NaHS, and Diallyl Trisulfide (DATS) In vivo: NaHS, Na_2S, H_2S Donor (NaGYY), and H_2S Donor (PTA-NO-NPs)	In vitro: Primary Astrocytes (from cerebral cortices of Sprague-Dawley rats), and Human Umbilical Cord Vein Endothelial Cells In vivo: Male APP/PS1 (APPswe PS1dE9) transgenic mice, Male Wistar rats, Male C57BL/6J mice, B6.129P2-Nos3tm1Unc/J (eNOS-knockout) mice, 3xTg-AD mice, and Male Sprague–Dawley rats	In vitro: Excitotoxicity, cytotoxicity, and hypoxia/reoxygenation In vivo: TBI, PD, chronic restrain stress, brain toxicity, SAH, intracranial hemorrhage, MCAO, vascular dementia, AD model, spinal cord lesion, retinal, liver, or cardiac I/R, ischemia, cardiac arrest, heart failure, and hypertension	**NaHS:** 50 μmol/kg, i.p. NaHS once daily for 4 weeks post-injury [7a], 5.6 mg/kg, i.p. NaHS once daily for 3 weeks post-injury [7b, 10a], 50 μmol/kg, i.p. NaHS pre-surgery/once daily for 5 d post-surgery [9b], 3 mg/kg NaHS i.p 5 min post-surgery [11a], 50 and 100 μmol/kg intracerebral injection NaHS daily for 8 weeks post-injury [11b], 200–800 μM NaHS added to culture media 1 h pre-injury [12a], and 56 μmol/kg i.p. NaHS 30 min pre-closure of surgical incision [12b] **Diallyl Trisulfide (DATS):** 200 μg/kg retro-orbital injection, DATS once during study [9a] **Na_2S:** 0.5-1.0 mg/kg retro-orbital injection, Na_2S twice daily [8a], and 6-12 mg/kg, i.p. Na_2S once daily 6 d pre-injury [10b] **H_2S donor (NaGYY):** 100 mg/kg, i.p. NaGYY once daily for 12 weeks post-injury [8b] **H_2S donor (PTA-NO-NPs):** 0.5-1 mg/mL PTA-NO-NPs added to culture media [13b]	Same as above
NO	In vitro: NO donors: SNAP, Spermine NONOate, PTA-NO-NPs, and NOC-18 In vivo: NO Donor ($NaNO_2$), NO Gas, and NO Synthesis Stimulator (L-arginine)	In vitro: Human Epidermal Stem Cells, Human Umbilical Cord Vein Endothelial Cells, and Human Embryonic Kidney 293 cells In vivo: Male Sprague–Dawley rats, Neonatal Sprague–Dawley rats, Infant Yorkshire piglets, and Male Wistar rats	In vitro: Excitotoxicity, OGD, endothelial oxidative stress, mechanical nerve injury, and angiogenesis In vivo: Excitotoxicity, DHCA, cerebral malaria, acute kidney injury, skin burn, liver, and lung transplant or I/R	**NO donors (SNAP, spermine NONOate)**: 100 μM SNAP/10 μM spermine NONOate added to culture media for 48 h post-injury [13a] **NO donor (PTA-NO-NPs)**: 0.05-1 mg/mL PTA-NO-NPs added to culture media [13b] **NO donor ($NaNO_2$):** 4 μmol, i.v. $NaNO_2$ 5 min post-injury [14] **NO donor (NOC-18):** 300 μM bath perfusion Noc-18 added to culture media [15] **NO gas:** 5-20 ppm inhalation NO and <1 ppm NO_2 for 7 d [16a], and 20 ppm inhalation NO for 3 h post-injury [16b] **NO stimulator (L-arginine):** 50 mg/kg L-arginine i.v. in the anhepatic phase [17]	**NO donors (SNAP/spermine NONOate)**: 5000μM SNAP/100 μM NONOate for 48 h post-injury **NO donor (PTA-NO-NPs:** ≥1 mg/mL added to culture media

H_2	In vitro: H_2 Gas In vivo: H_2 Gas, and Hydrogen-rich Saline	In vitro: Primary Hepatocytes (from Male C57BL/6 (B6) mice), and Hippocampal neurons (from newborn Sprague-Dawley rats) In vivo: Pregnant ICR (CD-1) mice, Male C57BL/6 (B6) mice, Male Sprague-Dawley, and Neonatal BALB/c mice	In vitro: OGD/reoxygenation, oxidative stress, and hypoxia and/or reoxygenation In vivo: Spinal cord, cardiac, hepatic, retinal and cerebral I/R, cardiac arrest, birth asphyxia, MCAO, SAH, SCI, toxicity, and STZ-induced diabetes	**Hydrogen-rich saline:** 0.4 mM hydrogen-rich water 200 ml/kg/d x 14 [18a], 1 mL 7 ppm hydrogen-rich saline spread on directly on liver pre-injury [18b], 0.16 mol/kg, i.p. hydrogen-rich saline post-surgery [20a], 3 µmol/kg, i.p. hydrogen-rich saline daily 5 d pre-surgery [20b], and 5 ml/kg, i.p. hydrogen saline 3 d post-injury [22] **H_2 gas:** 21% O_2, 5% CO_2, 3.8% H_2, and N_2 gas mixture added to culture media for 10 h [18b], 67% H_2-33% O_2 mixed gas (1 h inhalation/d x 1, 3 or 7) [19a, 19b], 2% H_2 gas inhalation for 1-2 h post-injury [20c], 1-3% H_2 gas inhalation 10 min pre-injury and 130 min post-injury [20d], and 60% H_2, 10% O_2, 5% CO_2, and 25% N_2 gas mixture inhalation for 24 h post-injury [21]	All medical gas dosages were well tolerated and safe in the experimental models investigated (see *Left Columns)*. For the purposes of the cited studies (**Table 2**), no toxic doses (gases in further higher concentrations) were evaluated
O_2	In vitro: Hyperbaric O_2 In vivo: Hyperbaric O_2	In vitro: Human Umbilical Cord Vein Endothelial Cells, and Spinal cord neurons (from embryonic Sprague-Dawley rats) In vivo: Male Sprague-Dawley rats, C57B and SV129 mice, and Male Wistar rats	In vitro: Osteoarthritic chondrocytes, dermal fibroblasts, and muscle progenitor cells In vivo: Nerve injury, SCI, AD model, MCAO, TBI, cerebral I/R, hepatectomy, muscle injury, ischemic, and tumor model	**Hyperbaric O_2:** 2.5 atmospheres 100% O_2 inhalation (1 h/d x 5 post-surgery) [23a], 2 atmospheres 95% O_2 inhalation (1 h/b.i.d. in first 3 d and q.d. x 11 d post-surgery) [23b], 1-2.5 atmospheres 98% O_2 added to culture media for 2-8 h [23c], 280 kPa HBO added to culture media for 60 min [24], 2.0 atmospheres 100% O_2 1 h inhalation x 4/d pre-injury [25], and 2.5 atmospheres 100% O_2 inhalation (2 h/d x 5 post-injury) [26]	Same as above
O_3	In vitro: None In vivo: Ozone Gas, and Ozone Oil	In vitro: None In vivo: C57B/L6 mice, and Male Sprague-Dawley rats	In vitro: Endothelial cells In vivo: Pam3CYS inflammatory induction in the lungs, streptozotocin-induced diabetic model, and skin wound model	**Ozone gas:** 2 ppm ozone for 3 h pre-injury [27], 50 µg/ml ozone (q.d. x 15 post-injury) [28] **Ozone oil:** 400 µl ozone oil applied once every 2 d x 12 post-lesion [29]	Same as above
	Noble Gases				
Xenon (Xe)	In vitro: Xe Gas In vivo: Xe Gas, Xe-ELIP	In vitro: Mixed cortical glial-neuronal cocultures (from BALB/c mice), Midbrain cultures (from embryos of female Wistar rats), and hearts (from Male New Zealand rabbits) In vivo: Sprague-Dawley rats, Male Wistar rats, and C57BL/6J mice	In vitro: OGD, hypoxia, excitotoxicity, and mechanical trauma In vivo: TBI, I/R of spinal cord, MCAO, neonatal hypoxic-ischemic injury, and cardiac I/R	**Xe gas:** 12.5-70% Xe gas inhalation for 90 min post-injury [30a], 12.5-70% Xe gas added to culture media [30a], 70-75% Xe gas for 1 h post-injury [30b], 75% Xe gas applied to culture media for 3 d [31], 70% Xe gas inhalation for 3 h pre-injury [33], and 75% Xenon gas for 1 h pre-injury [34] **Xe-ELIP:** 7-14 mg/kg (in 200 µL; i.a./intra-common carotid artery) of Xe-ELIP administered at 2, 3, or 5 h post-injury) [32]	Same as above
Argon (Ar)	In vitro: Ar Gas In vivo: Ar Gas	In vitro: Human Neuroblastoma Cells, and Human Cardiac Myocyte-like Progenitor Cells In vivo: Sprague-Dawley rats, and Male New Zealand rabbits	In vitro: Rotenone-induced apoptosis, LPS induction of microglia, OGD, OGD-reperfusion. In vivo: MCAO, retinal I/R, kidneys, transplant, and multiorgan failure	**Ar gas:** 25-75% Ar gas inhalation for 2-4 hours post-injury [35a] 75% Ar gas inhalation for 60 min post-injury [35b], 75% Ar gas added to culture media for 2 h post-injury [35], 30-50% Ar gas added to culture media for 90 min pre-injury [36], 70% Ar gas inhalation 30 min pre-injury to 300 min post-injury [37a], and 2.06-2.14 MPa Ar gas [37b]	Same as above
Helium	In vitro: None	In vitro: None	In vivo: Brain hypoxic-	**He gas:** 70% He gas inhalation for 5 min x 3 periods pre-	Same as above

(He)	In vivo: He Gas	In vivo: Rat pups (7 d/o), Male Wistar rats, C57BL/6J mice, Male and New Zealand white rabbits	ischemic injury, cardiac arrest, and cardiac I/R	injury[38], 70% He gas inhalation for 5, 15, or 30 min post-injury [39], 70% He gas inhalation for 30 min pre-injury [40], and 70% He gas inhalation for 5 min x 1, 3, or 5 times post-injury [41]

Table S2: (1) Abbreviations and reference citations (same as **Table 2**) in Section S3. (2) For citation numbers representing more than one references, citation of the number only (e.g., [20] versus [20a] or [20d]) indicated that all references under that number (e.g., all 4 papers under [20]) were included.

Table S3

Analysis of Statistical Methods Used in All Medical Gas Studies Exhibited in Table 2

Gases	Data Presentation	Model and Sample Size	Power Analysis	Statistical Test	*Post-hoc* Analysis	Significance Level	Statistical Software
Biological Gases							
CO	Mean ± SD [1, 2, 4, 5a, 6] Mean ± SEM [3, 5b & c]	**In vitro:** n = 3 [1a] n = 3-4 [2] n = 4 [5b & c] n = 3-6 [4] n = 5-6 [6] n = 7 [5c] n = 6-8 [5b] **In vivo:** n = 3-7 [6] n = 6 [1b] n = 8 [5a] n = 5-10 [3] n = 10-13 [6] n = 9-15 [6]	1 [6]/8 (12.5%)* *Percentage of studies that conducted power analysis	One way ANOVA [1-3, 5, 6] Two way ANOVA [6] Kruskal-Wallis test [3, 5a] Student's *t*-test [4, 5c]	Bonferroni test [1a] Scheffé test [1a] Tukey's test [1b-3, 6] Mann-Whitney U test [3] Holm-Sidak test [5a, 6] Fisher's exact test [5b] Newman-Keuls test [5c] Paired *t*-test [6]	*p*-value ($p < 0.005$-0.05) [1-6] α-value ($\alpha = 0.05$) [6] β-value ($\beta = 0.2$) [6]	GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA) [2, 6] GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA) [1b] SigmaPlot 11.0 (Systat Software Inc., San Jose, CA, USA) [5a] SPSS 22.0 (IBM, Armonk, NY, USA) [5c]
H_2S	Mean ± SD [12a] Mean ± SEM [7a-11b, 12b]	**In vitro:** n = 3 [12a] n = 3-4 [8b] n = 4 [7b, 9a] n = 4-5 [9b] n = 7 [9b] n = 12 [12b] **In vivo:** n = 4-12 [8a] n = 5 [7a] n = 6 [7b, 8b, 10-11b] n = 8 [10b] n = 12 [11b] n = 18 [10a]	0/12 (0%)	One way ANOVA [7, 8b-12a] Two way ANOVA [7b, 9a, 11, 12b] Mann-Whitney U test [8a, 9a] Kruskal-Wallis test [8a, 9a] Student's *t*-test [7a, 8b, 9a] Two-tailed independent *t*-test [10a]	Bonferroni test [7b, 9b, 10a, 11, 12b] Tukey's test [7b, 8b, 9a, 10b] Dunn's test [8a, 9a] Games-Howell test [10a] Fisher's LSD [11a] Newman-Keuls test [12a] Dunnett's test [12a]	*p*-value ($p < 0.001$-0.05) [7-12b]	SPSS 13.0 (IBM, Armonk, NY, USA) [9b] SPSS 16.0 (IBM, Armonk, NY, USA) [7b, 11a, 12b] SPSS 19.0 (IBM, Armonk, NY, USA) [9b, 10a, 12a] SPSS 20.0 (IBM, Armonk, NY, USA) [11b] SPSS 22.0 (IBM, Armonk, NY, USA) [10b] GraphPad Prism (GraphPad Software, San Diego, CA, USA) [8a, 9a]
NO	Mean ± SD [13a, 14] Mean ± SEM [13b, 15-17]	**In vitro:**	0/7 (0%)	One way ANOVA [13, 14, 16a] Two way ANOVA [14]	Newman-Keuls test [16a] F-test [17]	*p*-value ($p < 0.001$-0.05) [13-17]	GraphPad Prism (GraphPad Software, San Diego, CA,

		n = 3 [13a] n = 3-4 [13b] n = 3-8 [15] n = 6-8 [15] n = 12-16 [14] **In vivo:** n = 3-5 [14] n = 4-5 [14] n = 4-9 [14] n = 5 [16b] n = 6-10 [14] n ≥ 12 [16a] n = 18-19 [14] n = 22 [17]		Mann-Whitney U test [14, 16b] Kruskal-Wallis test [14] Student's *t*-test [13a, 15] Two-tailed unpaired *t*-test [16b] Two-tailed Chi-squared test [17]			USA) [13b] GraphPad Prism 4.0 (GraphPad Software, San Diego, CA, USA) [16a] GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA) [16b] GraphPad Prism 6.05 (GraphPad Software, San Diego, CA, USA) [14]
H_2	Mean ± SD [19b-20a, 20c-21] Mean ± SEM [18-19a, 20b] Median [20d]	**In vitro:** n = 3 [18b, 21] n = 5-7 [18a] n = 6 [20b] n = 8 [20b] **In vivo:** n = 3-4 [20c, 22] n = 4 [20a] n = 5-7 [18b] n = 6 [19a, 20c & d, 22] n = 14 [20a] n = 16-23 [19b] n = 20 [18a]	1 [20d]/10 (10%)	One way ANOVA [18a-22] Two way ANOVA [20d] Mann-Whitney U test [18a] Kruskal-Wallis test [18a] Student's *t*-test [18a] Bivariate analysis [20a] Chi-squared test [18a]	Bonferroni test [20c] Tukey's test [18a, 19a, 20b, 20d, 22] Dunn's test [18a] Student's *t*-test [18b] Dunnett's test [20a] F-test [20c] Fisher's LSD test [21]	*p*-value ($p < 0.001$-0.05) [18-22] α-value ($\alpha = 0.01$) [20d]	GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA) [18a] SPSS 13.0 (IBM, Armonk, NY, USA) [20a, 20b] SPSS 16.0 (IBM, Armonk, NY, USA) [19b] SPSS 19.0 (IBM, Armonk, NY, USA) [19a, 21] EZAnalyze (Microsoft, Redmond, WA, USA) [20c] Statflex 6.0 (ARTECH Co, LTD, Osaka, Japan) [20d] Sigmaplot 13.0 (Systat Software Inc., San Jose, CA, USA) [20d]
O_2	Mean ± SD [23-25] Mean ± SEM [26]	**In vitro:** n ≥ 3 [24] **In vivo:** n = 3 [23c] n = 5 [23a] n = 5-6 [26] n = 6 [23b] n = 6-8 [25] n = 6-13 [26]	0/6 (0%)	One way ANOVA [23-26] Two way ANOVA [26] Kruskal-Wallis test [18a] Student's *t*-test [23a, 26] Independent *t*-test [23b] Welch's *t*-test [26]	Bonferroni test [26] Newman-Keuls test [25] Fisher's LSD test [23c, 24]	*p*-value ($p < 0.01$-0.05) [23-26]	SPSS 17.0 (IBM, Armonk, NY, USA) [23b, 25] SPSS 18.0 (IBM, Armonk, NY, USA) [24] SPSS 23.0 (IBM, Armonk, NY, USA) [26]
O_3	Mean ± SD [28-29]	**In vitro:**	0/3 (0%)	One way ANOVA [29]	N/A	*p*-value	GraphPad Prism

	Mean ± SEM [27]	n ≥ 3 [29] **In vivo:** n = 4 [27] n = 6 [28] n = 10-15 [27] n = 24 [29]		Mann-Whitney U test [27] Student's *t*-test [28, 29]		(p < 0.001-0.05) [27-29]	(GraphPad Software, San Diego, CA, USA) [27] GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA) [29] SPSS 18.0 (IBM, Armonk, NY, USA) [28]
Noble Gases							
Xenon (Xe)	Mean ± SD [30a, 31, 32, 34] Mean ± SEM [33] Mean [30b]	**In vitro:** n = 4 [30a, 33] n = 6-16 [31] **In vivo:** n = 4 [32] n = 4-5 [30b] n = 4-6 [30a, 33] n = 8-9 [32] n = 10-20 [34]	0/6 (0%)	One way ANOVA [30, 31, 33, 34] Two way ANOVA [34] Kruskal-Wallis test [31, 32] Kaplan-Meier test [30a] Wilcoxon rank sum test [32]	Bonferroni test [34] Newman-Keuls test [30a, 31, 33] Unpaired *t*-test [30a] Mann-Whitney U test [30a] *Post-hoc t*-test [34]	*p*-value (p < 0.0005-0.01) [30-34]	Sigmastat 3.1 (Systat Software Inc., San Jose, CA, USA) [30b] SigmaPlot 12.5 (Systat Software, San Jose, CA, USA) [31] Statistica (Statsoft Inc., Tulsa, OK, USA) [32] SPSS 16.0 (IBM, Armonk, NY, USA) [34]
Argon (Ar)	Mean ± SD [35, 36] Mean ± SEM [37] Median [37a]	**In vitro:** n = 3 [36] n = 4-8 [37b] n = 5-8 [35a] n = 6 [35b] **In vivo:** n = 4-8 [35b] n = 7 [37a]	0/5 (0%)	One way ANOVA [35] Two way ANOVA [36-37a] Student's *t*-test [36, 37a] Mann-Whitney U test [37b] Kruskal-Wallis test [35, 37a]	Bonferroni test [36] Holm-Sidak test [35, 37a] Mann-Whitney U test [37a] Newman-Keuls test [35a]	*p*-value (p < 0.0001-0.05) [35-37b]	SigmaPlot 11.0 (Systat Software, San Jose, CA, USA) [35, 37b] GraphPad Prism 6.0 (GraphPad Software, San Diego, CA, USA) [36]
Helium (He)	Mean ± SD [38, 40, 41] Mean ± SEM [39]	**In vitro:** N/A **In vivo:** n = 4-8 [39] n = 4-9 [40] n = 6-7 [41] n = 7-16 [38] n = 6 [41] n = 7 [39-40] n = 16 [38]	1[41]/4 (25%)	One way ANOVA [38, 40, 41] Two way ANOVA [40] Kruskal-Wallis test [39] Welch's *t*-test [40] Mann-Whitney U test [40]	Bonferroni test [40, 41] Dunn's test [39] Newman-Keuls test [38]	*p*-value (p < 0.01-0.05) [38-41] α-value (α = 0.05) [41] β-value (β = 0.2) [6]	SPSS 16.0 (IBM, Armonk, NY, USA) [38] GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA) [39] GraphPad Prism 5.01 (GraphPad Software, San Diego, CA, USA) [40]

Table S3: (1) Abbreviations: ANOVA, analysis of variance; SD, standard deviation; SEM, standard error of mean; N/A, not available. (2) Reference citations (same as **Table 2**) in Section S3. (3) For citation numbers representing more than one references, citation of the number only

(e.g., [20] versus [20a] or [20d]) indicated that all references under that number (e.g., all 4 papers under [20]) were included. (4) All research papers enrolled in **Table 2** (n = 62; see Section S3) were systematically evaluated regarding statistical methods utilized, which included data presentation format, sample size, utilization of power analysis, specific statistical methods, *post-hoc* analysis, significance level setting, and statistical software used for computation.

Table S4

Data Pre-Processing in Medical Gas Studies Exhibited in Table 2

Gases	Data Pre-processing	Method of Data Quality Analysis
Biological Gases		
Carbon Monoxide (CO)	Normalization [1-6] Percentage [1a, 3, 4] Ratio [5a]	Shapiro-Wilk test for normality [1b] Levene's test to assess the equality of variances for a variable calculated for two or more groups [1b]
Hydrogen (H_2)	Normalization [18, 19b, 20d, 22] Percentage [18a, 19a, 20a, 21-22] Ratio [19a, 22] Transformation [20d]	Shapiro-Wilk test [20d] Brown-Forsythe test for the equality of group variances based on performing an ANOVA on a transformation of the response variable [20d]
Hydrogen Sulfide (H_2S)	Normalization [8a, 10] Percentage [7-8a, 10a, 11a] Ratio [8a, 10a] Homoscedasticity [10a]	Shapiro-Wilk test [10a] Levene's test [10a]
Nitric Oxide (NO)	Normalization [13a, 14-16a] Percentage [14, 15] Ratio [13a, 14, 16a]	Not specified
Oxygen (O_2)	Normalization [23a, 23c, 26] Percentage [26] Ratio [23b & c, 26] Homoscedasticity [26]	Shapiro-Wilk test [26] Levene's test [26]
Ozone (O_3)	Normalization [27, 29] Log2-transformation [27] Ratio [28, 29]	Quantile Normalization to eliminate or minimize technical variability [27]
Noble Gases		
Argon (Ar)	Normalization [35, 36] Percentage [35, 36, 37b] Ratio [35]	Kolmogorov-Smirnov test, a nonparametric goodness-of-fit test used to determine if two distributions differ, or an underlying probability distribution differs from a hypothesized one [36]
Helium (He)	Normalization [38-40] Percentage [41] Ratio [38-40]	D'Agostino and Pearson test to assessing normality of data using skewness and kurtosis [40]
Xenon (Xe)	Normalization [30a & b, 32-33] Percentage [30-32, 34] Ratio [30a, 32] Rank [32] Transformation [32]	Not specified

Table S4: (1) Reference citations (same as **Table 2**) in Section S3. (2) For citation numbers representing more than one references, citation of the number only (e.g., [20] versus [20a] or [20d]) indicated that all references under that number (e.g., all 4 papers under [20]) were included. (3) All research papers enrolled in **Table 2** (n = 62; see Section S3 for reference citations) were assessed for methods of data pre-processing to evaluate data quality. Normalization, transformation, and homoscedasticity were data pre-processing procedures that were utilized in 34/62 (55%) of the reports reviewed in **Table 2**. Methods applied for data quality analysis were Brown-Forsythe test, D'Agostino and Pearson test, Kolmogorov-Smirnov test, Levene's test, Quantile Normalization, and Shapiro-Wilk test (see more details in the table above). However, the cited studies on CO (n = 8), NO (n = 4, and Xe (n = 4) did not specify statistical methods used in data normalization.

Figure S1

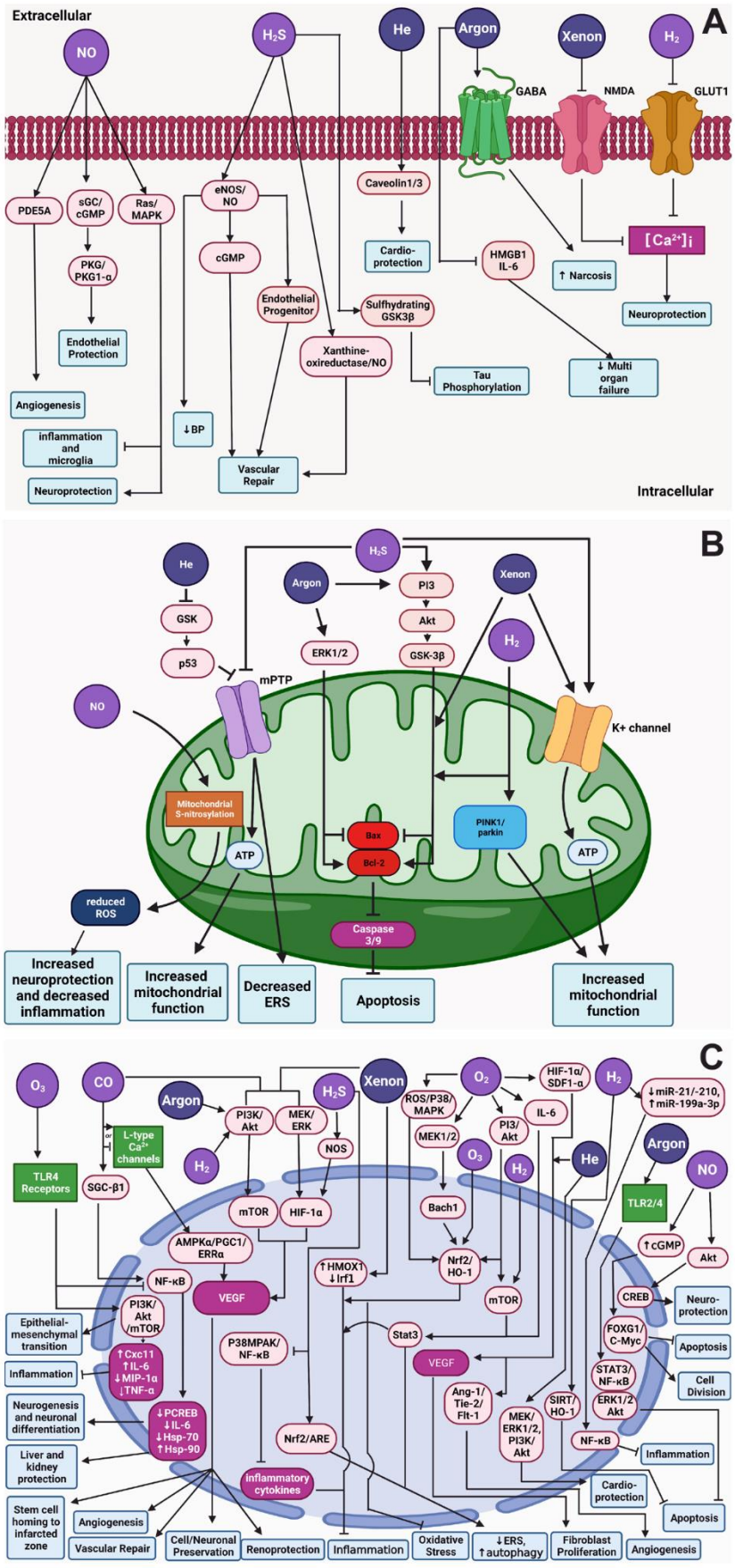

Figure S1. The key signal transduction pathways and molecular mechanisms underlying the primary tissue protective effects of the medical gases reviewed. **Figure S1** illustrated the main signal transduction pathways, cell signalling convergence, divergence and crosstalk, and key messenger, effector or target molecules underlying the primary tissue protective mechanisms of the medical gases reviewed in **Table 2**. To avoid redundancy with **Figures 4** and **5**, only the therapeutic mechanisms of 3 biological gases (H_2, H_2S, and NO) and 3 noble gases (Argon/Ar, Helium/He, and Xenon/Xe) were detailed at cytoplasmic (**A**) and mitochondrial (**B**) levels; primary nuclear level mechanisms for tissue protection of all six biological gases (CO, H_2, H_2S, NO, O_2, and O_3) and 3 noble gases (Ar, He, and Xe) were shown in **C** (note: for summaries on tissue protective mechanisms of medical gases, see **Table 2**; abbreviations, acronyms, and reference citations, see Section S3; for cytoplasmic and mitochondrial mechanisms of CO, O_2 and O_3, see **Figures 4** and **5**; **Figure S1** plotting was assisted by BioRender.com).

Section S1: Supporting Information

Database Search Strategies

I. Limitation for all database: (1) publications from January 1, 2000 to July 31, 2021

(2) literature published in English

II. Search Criteria for Ovid MEDLINE, using Medical Subject Headings (MeSH)

1. Tissue preservation/

2. Tissue preservation.mp.

3. Tissue repair.mp.

4. Tissue protection.mp.

5. Neuroprotection/

6. Neural Protection.mp.

7. Regeneration/

8. Neuroregeneration.mp.

9. Neural Regeneratiom.mp.

10. Spinal cord regeneration/

11. Angioplasty/

12. Bone regeneration/

13. Bone protection.mp.

14. Liver regeneration/

15. Nerve regeneration/

16. Brain regeneration/

17. Neural Repair.mp.

18. Brain repair.mp.

19. Spinal cord repair.mp.

20. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19

21. Medical gas.mp.

22. Gases/

23. Oxygen/

24. Hydrogen/

25. Hydrogen Sulfide/

26. Carbon Monoxide/

27. Nitric Oxide/

28. Nitrous Oxide/

29. Ozone/

30. Noble gas/

31. Noble gas.mp.

32. Helium/

33. Xenon/

34. Krypton/

35. Argon/

36. 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35

37. Signal transduction/

38. Signal transduction.mp.

39. Mechanism.mp.

40. Pathway.mp.

41. Signaling.mp.

42. 37 OR 38 OR 39 OR 40 OR 41

43. 20 AND 36 AND 42

III. The same search criteria was utilized for EMBASE for performing a focused search using MeSH

VI. Search Criteria for Scopus and Google Scholar

(Tissue AND Preservation) OR ("Tissue protection") OR (Tissue AND Repair)

AND

("Medical gas") OR (Oxygen AND Therapy) OR (Hydrogen AND Therapy) OR ("Hydrogen sulfide") OR ("Carbon monoxide") OR ("Nitrous Oxide") OR ("Nitric Oxide") OR (Ozone) OR ("Noble gas") OR (Helium) OR (Xenon) OR (Krypton) OR (Argon)

AND

("Signal transduction") OR (Mechanism) OR (Pathway)

Section S2: Supporting Information

Publications Qualified for Systematic Review Enrollment

(note: articles are listed in alphabetical order under each medical gas molecule)

- Biological gases

1. Carbon Monoxide [1-48]
2. Hydrogen [29, 49-74]
3. Hydrogen sulfide [75-129]
4. Nitric oxide [130-147]
5. Oxygen [148-172]
6. Ozone [173-180]

- Noble gases

1. Argon [181-191]
2. Helium [191, 192-197]
3. Xenon [191, 198-212]

- Reports on findings of adverse effects or no significant therapeutic impact of medical gases on some or all outcome measures [192, 199, 211, 213-223]

Biological Gases

Carbon Monoxide (CO)

1. Bai, J., Bai, Y., Wang, X.-P., Zheng, W.-C. & Zhang, L.-M. Carbon Monoxide-Releasing Molecule-3 Ameliorates Acute Lung Injury in a Model of Hemorrhagic Shock and Resuscitation: Roles of p38MAPK Signaling Pathway. *Shock* **55**, 816-826, doi: 10.1097/SHK.0000000000001684 (2021).
2. Biermann, J., Lagreze, W. A., Dimitriu, C., Stoykow, C. & Goebel, U. Preconditioning with inhalative carbon monoxide protects rat retinal ganglion cells from ischemia/reperfusion injury. *Invest Ophthalmol Vis Sci* **51**, 3784-3791, doi:http://dx.doi.org/10.1167/iovs.09-4894 (2010).
3. Carraway, M. S. *et al.* Carbon monoxide promotes hypoxic pulmonary vascular remodeling. *Am J Physiol Lung Cell Mol Physiol* **282**, L693-702, doi:10.1152/ajplung.00211.2001 (2002).
4. Choi, Y. K. *et al.* Carbon monoxide promotes VEGF expression by increasing HIF-1alpha protein level via two distinct mechanisms, translational activation and stabilization of HIF-1alpha protein. *J Biol Chem* **285**, 32116-32125, doi:10.1074/jbc.M110.131284 (2010).
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9. Dreyer-Andersen, N. *et al.* Intermittent, low dose carbon monoxide exposure enhances survival and dopaminergic differentiation of human neural stem cells. *PLoS ONE* **13**, e0191207,

doi:10.1371/journal.pone.0191207 (2018).
10. Han, Y. *et al.* Carbon monoxide offers neuroprotection from hippocampal cell damage induced by recurrent febrile seizures through the PERK-activated ER stress pathway. *Neurosci Lett* **585**, 126-131, doi:http://dx.doi.org/10.1016/j.neulet.2014.11.040 (2015).
11. Horvat, A., Vardjan, N. & Zorec, R. Targeting Astrocytes for Treating Neurological Disorders: Carbon Monoxide and Noradrenaline-Induced Increase in Lactate. *Curr Pharm Des* **23**, 4969-4978, doi:10.2174/1381612823666170622112734 (2017).
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13. Jamal Uddin, M. *et al.* IRG1 induced by heme oxygenase-1/carbon monoxide inhibits LPS-mediated sepsis and pro-inflammatory cytokine production. *Cell Mol Immunol* **13**, 170-179, doi:10.1038/cmi.2015.02 (2016).
14. Joshi, H. P. *et al.* Nanocarrier-mediated Delivery of CORM-2 Enhances Anti-allodynic and Anti-hyperalgesic Effects of CORM-2. *Mol Neurobiol* **56**, 5539-5554, doi:10.1007/s12035-019-1468-7 (2019).
15. Józkowicz, A. *et al.* Heme oxygenase and angiogenic activity of endothelial cells: stimulation by carbon monoxide and inhibition by tin protoporphyrin-IX. *Antioxid Redox Signal* **5**, 155-162, doi:10.1089/152308603764816514 (2003).
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19. Kim, J. H. *et al.* Hypoxia-responsive microRNA-101 promotes angiogenesis via heme oxygenase-1/vascular endothelial growth factor axis by targeting cullin 3. *Antioxid Redox Signal* **21**, 2469-2482, doi:10.1089/ars.2014.5856 (2014).
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Hydrogen (H_2)

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Hydrogen Sulfide (H_2S)

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Noble Gases

Argon (Ar)

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Reports on Findings of Adverse Effects or No Significant Therapeutic Impact of Medical Gases on Some or All Outcome Measures

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- Noble Gases:

Argon (Ar)

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Section S3: Supporting Information

Abbreviations and References of Tables 2-4

Table 2. Representative Tissue Protective Effects of Medical Gases

Abbreviations:

AD, Alzheimer's disease; Akt, protein kinase B; AMPKα, adenosine monophosphate-activated protein kinase α subunit; AP-1, activating protein-1; ATP, adenosine triphosphate; Bax, BCL2 Associated X: a protein coding gene regulating apoptosis; Bach1, BTB And CNC Homology 1/basic leucine zipper transcription factor 1; Bcl2, B-cell lymphoma 2: a protein coding gene regulating apoptosis; Cav-1/3, caveolin-1/3; cGMP, cyclic guanosine monophosphate; c-Myc, cellular Myc proto-oncogene (Myc: abbreviation for myelocytoma); CO, carbon monoxide; CORM, carbon monoxide releasing molecule; CREB, cAMP response element-binding protein; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; ERK1/2, extracellular regulated kinase 1/2; ERRα, estrogen-related receptor alpha; ERS, endoplasmic reticulum stress; FOXG1, Forkhead Box G1: a protein coding gene; Fyn: a proto-oncogene tyrosine-protein kinase that belongs to the Src family kinases; GABA, gamma-aminobutyric acid; GSK, glycogen synthase kinase; GSK3β, glycogen synthase kinase 3β; HIF1α, hypoxia-inducible factor 1-alpha; HMGB1: high mobility group box 1 protein; HMOX1, a human gene encoding for the heme oxygenase 1; HO-1, heme-oxygenase 1; I/R, ischemia/reperfusion; Irf1, interferon regulatory factor 1; IL, interleukin; L-type Ca^{2+} channels, long-lasting calcium channels; M2 macrophages: M2 subtype-polarized macrophages mainly produce Arginase-I, IL-10 and TGF-β and other anti-inflammatory cytokines to promote tissue repair and wound healing; MAPK, mitogen-activated protein kinase; MCAO, middle cerebral artery occlusion; MEK, MAP kinase/ERK kinase or mitogen-activated protein kinase kinase; MIP-1α, macrophage inflammatory protein 1; miR, microRNA; MPa, megapascal (1 MPa = 10 bar or ~145 PSI/ pounds per square inch); mPTP, mitochondrial permeability transition pore; mTOR, the mammalian target of rapamycin: a kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NMDA receptor, N -methyl-D-aspartate receptor; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; Nrf2, the nuclear factor erythroid 2–related factor 2; NSCs, neural stem cells; OGD, oxygen-glucose deprivation; PD, Parkinson's disease; PDE5A, phosphodiesterase-5A; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1α; PI3K, phosphoinositide 3-kinase; PINK1, PTEN-induced kinase 1 that is a mitochondrial serine/threonine-protein kinase; PKG, cyclic GMP–dependent protein kinase; p-p38MAPK, phosphorylated p38 mitogen-activated protein kinases; Ras, Ras (rat sarcoma) proteins belonging to small GTPase family; RISK, the reperfusion injury salvage kinase; ROS, reactive oxygen species; SAH, subarachnoid hemorrhage; SCI, spinal cord injury; sGC, soluble guanylyl cyclase; SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription 3; STZ, streptozotocin; TBI, traumatic brain injury; TLR, the toll-like receptor family; VEGF, vascular endothelial growth factor; and Xe-ELIP, xenon containing echogenic liposomes.

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Table 3. Neuroprotective Mechanisms of Carbon Monoxide (CO)

Abbreviations:

Akt, protein kinase B; AIF1, allograft inflammatory factor 1; AMPKα, adenosine monophosphate-activated protein kinase α subunit; Bax, BCL2 Associated X: a protein coding gene regulating apoptosis; Bcl2, B-cell lymphoma 2: a protein coding gene regulating apoptosis; BV2 cell line, a type of microglial cell derived from C57/BL6 murine that was immortalized by v-raf /v-myc carrying J2 retrovirus; CaMKKβ, Ca^{2+}/calmodulin-dependent protein kinase kinase β; cGMP, cyclic guanosine monophosphate; CHOP, C/EBP homologous protein; CO, carbon monoxide; CORM, carbon monoxide releasing molecule; CREB, cAMP response element-binding protein; elF2, eukaryotic initiation factor 2; eNOS, endothelial nitric oxide synthase; ERK1/2, extracellular regulated kinase 1/2; ERRα, estrogen-related receptor alpha; ERS, endoplasmic reticulum stress; GFAP, glial fibrillary acidic protein; GRP78, glucose-regulated protein 78; HBMEC, human brain microvascular endothelial cells; HIF1α, hypoxia-inducible factor 1-alpha; HO-1, heme-oxygenase 1; HSF1, heat shock factor 1: a transcription factor; Hsp-70 or 90, heat shock protein 70 KD or 90 KD; IL, interleukin; I/R, ischemia/reperfusion; ICAM-1, intercellular adhesion molecule 1; IRE1, the ER-resident transmembrane kinase-endoribonuclease inositol-requiring enzyme 1; Kv2.1, potassium voltage gated channel, Shab-related subfamily, member 1; L-type Ca^{2+} channels, long-lasting calcium channels; MAP2, microtubule-associated protein 2; MAPK, mitogen-activated protein kinase; MCAO, middle cerebral artery occlusion; MEK, MAP Kinase/ERK Kinase or mitogen-activated protein kinase kinase; mitoKATP, mitochondrial adenosine triphosphate-dependent potassium channel; MMP, matrix metalloproteinase; mTOR, the mammalian target of rapamycin: a kinase; NAMPT, nicotinamide phosphoribosyl transferase 1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; nNOS, neuronal nitric oxide synthase; Nrf2, the nuclear factor erythroid 2–related factor 2; NSCs, neural stem cells; OGD, oxygen-glucose deprivation; p-p38, phosphorylated-p38 mitogen-activated protein kinase; pCREB, phosphorylated CREB; PERK, the protein kinase R (PKR)-like endoplasmic reticulum kinase; PI3K, phosphoinositide 3-kinase; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1α; PKG, cyclic GMP–dependent protein kinase; Ras, Ras (rat sarcoma) proteins belonging to small GTPase family; RGC, retinal ganglion cells; RISK, the reperfusion injury salvage kinase; ROS, reactive oxygen species; SCI, spinal cord injury; sGC, soluble guanylyl cyclase; SIRT1, sirtuin 1;TBI, traumatic brain injury; TNFα, tumor necrotic factor α; VEGF, vascular endothelial growth factor; and XBP1, the X-box binding protein 1: a transcription factor.

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Table 4. Neuroprotective Mechanisms of Xenon (Xe)

Abbreviations:

Akt, protein kinase B that was originally identified as the oncogene in the transforming retrovirus, AKT8; Ar, argon; ATM, standard atmosphere, unit of pressure, equal to the mean atmospheric pressure at sea level (i.e., 14.7 pounds per square inch; it is used to describe relative pressure); Bax, BCL2 Associated X: a protein coding gene regulating apoptosis; Bcl2, B-cell lymphoma 2: a protein coding gene regulating apoptosis; BDNF, brain-derived neurotrophic factor; CREB, cAMP response element-binding protein; DA, dopamine; E, embryonic day; ERK, extracellular regulated kinase; HIF1α, hypoxia-inducible factor 1-alpha; Irf1, interferon regulatory factor 1; LDH, lactate dehydrogenase; MAPK, mitogen-activated protein kinase; MCAO, middle cerebral artery occlusion; NMDA, N-methyl-D-aspartate; OGD, oxygen-glucose deprivation; p-Akt, phosphorylated Akt; PC12, a cell line derived from a pheochromocytoma of the rat adrenal medulla, with an embryonic origin from

the neural crest (a mixture of neuroblastic cells and eosinophilic cells); PDC, l-trans-pyrrolidine-2,4-dicarboxylic acid: an synthetic analog of glutamate; p-ERK, phosphorylated ERK; PI3K, phosphoinositide 3-kinase; PND, postnatal day; TBI, traumatic brain injury; TREK1, Twik-related K^+ channels (TREK) 1; Twik, tandem of P domains in weakly inward rectifier K^+ channels; Xe, xenon; Xe-ELIP, Xe-containing echogenic liposomes.

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Section S4: Supporting Information

Abbreviations, Acronyms, and Nomenclatures in the Text

Akt: protein kinase B that is the oncogene in the transforming retrovirus, AKT8

AMPKα: 5'-AMP-activated protein kinase catalytic subunit alpha-1

ARDS: acute respiratory distress syndrome

ATA: atmospheres absolute (1 ATA = 14.7 pounds per square inch that is the average atmospheric pressure exerted at sea level; it is used to describe the total ambient pressure on the system)

ATM: standard atmosphere, unit of pressure, equal to the mean atmospheric pressure at sea level (i.e., 14.7 pounds per square inch; it is used to describe relative pressure: e.g., 33' of water is 1 ATM of water but it is 2 ATA because of the 1 atmosphere of air above it)

BACH1: BTB and CNC homology 1 or basic leucine zipper transcription factor 1

Bax: Bcl-2-associated X protein

BBB: the blood-brain barrier

Bcl-2: B cell lymphoma 2

Bcl-xL: B-cell lymphoma-extra large

BSCB: the blood-spinal cord barrier

CA: the cornu ammonis

Cav-1 and Cav-3: caveolin-1 and caveolin-3

CDC: centers for disease control and prevention

C/EBP homologous protein: the UPR-regulated CCAAT/enhancer-binding protein (C/EBP) homologous protein

CF: concentration factor (CF = theoretical distribution/actual distribution)

cGMP: cyclic guanosine monophosphate

c-Myc: cellular Myc, with homology to an oncogene of the Avian virus, Myelocytomatosis, v-Myc

COPD: chronic obstructive pulmonary disease

CORM: carbon monoxide-releasing molecule

COVID-19: the coronavirus disease 2019

CREB: cAMP response element-binding protein

CSE: cystathionine γ-lyase, the endogenous biosynthetic enzyme of H_2S

CST: the corticospinal tract

CXCL: cysteine-X-cysteine motif chemokine ligand

d/o: day(s) old

d.p.i.: day(s) post injury

DTDP: 2,2′-dithiodipyridine

ELISA: enzyme-linked immunosorbent assay

eNOS: endothelial nitric oxide synthetase

ER: endoplasmic reticulum

ERK: extracellular signal-regulated kinase

ERRα: estrogen-related receptor alpha

FDA: food and drug administration

FOXG1: forkhead box G1

Fyn: a proto-oncogene tyrosine-protein kinase that belongs to the Src family kinases

GAP-43: growth associated protein 43

GRP78: the 78-kDa glucose-regulated protein

GSK-3: glycogen synthase kinase 3

GSK3β: glycogen synthase kinase 3β

HBO: hyperbaric oxygen

HIBI: hypoxic-ischemic brain injury

HIF-1α: hypoxia inducible factor-1α

hiPSCs: human inducible pluripotent stem cells

HK II: hexokinase II

HMGB1: high-mobility group box protein 1

HMOX1: a human gene encoding for the heme oxygenase 1

HO: heme oxygenase

HSF-1: heat shock factor 1

HSP: heat shock protein

HSP-70: heat shock protein 70

HSP-90: heat shock protein 90

i.a.: intraarterial

ICAM-1: intercellular adhesion molecule-1

IL: interleukin

iNOS: inducible nitric oxide synthetase

Interleukin: IL

IRE1: inositol-requiring enzyme-1

Irf1: interferon regulatory factor 1

IRG1: immune responsive gene 1

IRI: ischemia-reperfusion injury

i.t.: intrathecal

i.v.: intravenous

LC: lethal concentration

LSP: lipopolysaccharides

$_{L}$-trans-2,4-PDC: $_{L}$-trans-pyrrolidine-2,4-dicarboxylic acid

m/o: month(s) old

MACO: middle cerebral artery occlusion

MAP2: microtubule associated protein 2

MAPK: the mitogen-activated protein kinase

MBP: myelin basic protein

MDA: malondialdehyde

MEK-1/2: mitogen-activated protein kinase kinase-1/2

MeSH: medical subject headings

MGT: medical gas therapy

MIP-1α: macrophage inflammatory protein 1

Mitophagy: selective degradation of mitochondria by autophagy.

MPa: megapascal pressure unit

mPTP: the mitochondrial permeability transition pore

mTOR: mechanistic target of rapamycin for cell proliferation

NADH-TR: nicotinamide adenine dinucleotide dehydrogenase-tetrazolium reductase

NF-κB: nuclear factor-κB

NIH: the national institutes of health

NMDA: N-methyl-D-aspartate

nNOS: neuronal nitric oxide synthetase

NOS: nitric oxide synthetase

NPAS2: neuronal PAS (prostate specific antigen) domain protein 2

NQO1: NAD(P)H quinone oxidoreductase 1

Nrf2: nuclear factor erythroid 2-related factor 2

OGD: oxygen-glucose deprivation

pAkt: phosphorylated Akt (phospho-Akt)

PDE5A: phosphodiesterase-5A that specifically degrades cGMP, an important signaling molecule

p.i.: post injury

p38MAPK: p38 mitogen-activated protein kinases

p-p38MAPK: phosphorylated p38 mitogen-activated protein kinases

Parkin: an E3 ubiquitin ligase

PBN: N-tert-butyl-a-phenylnitrone

PD: Parkinson's disease

pERK: phosphorylated ERK

PERK: protein kinase R (PKR)-like ER kinase

PGC-1α: peroxisome proliferators-activated receptor (PPAR) gamma coactivator 1-alpha that induces the expression of several members of the mitochondrial ROS detoxification system

PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha

PI3K: phosphoinositide 3-kinases

PINK1: PTEN-induced kinase 1 (PTEN: phosphatase and tensin homolog deleted on chromosome 10)

PKG: protein kinase G

PND: postneonatal day

pO_2: partial pressure of oxygen

ppm: parts per million

Ras: a class of small GTPase

RISK: the reperfusion injury salvage kinase

RNS: reactive nitrogen species

ROS: reactive oxygen species

rRT-PCR: real-time reverse transcription polymerase chain reaction

scRNA-seq: single-cell RNA (ribonuclear acid) sequencing

SDF-1: stromal cell-derived factor-1α and -1β

SDF-1α: stromal cell derived factor-1α

SIRT1: NAD-dependent protein deacetylase sirtuin-1

S-nitrosylation: the addition of one NO group to the thiol side chain of cysteine residues within a protein or a peptide to form an *S*-nitrosothiol

SOD: superoxide dismutase

Stat3: signal transducer and activator of transcription 3

Tau: a microtubule-associated protein that normally stabilizes neuronal microtubules

TGF- β1: transforming growth factor- β1

TLRs: toll-like receptors, a class of receptors that play a key role in regulating the innate immune system

TNFα: tumor necrosis factor-α

TNFα: tumor necrosis factor-α

tPA: tissue plasminogen activator

VEGF-B: vascular endothelial growth factor-B

vol: volume

XBP1: X-box binding protein 1

Xe-ELIP: Xe-containing echogenic liposomes

y/o: year(s) old