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Neuroprotective gases – Fantasy or reality for clinical use?

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ABSTRACT

The neuroprotective properties for certain medical gases have been observed for decades, leading to extensive research that has been widely reported and continues to garner interest. Common gases including oxygen, hydrogen, carbon dioxide and nitric oxide, volatile anesthetics such as isoflurane, sevoflurane, halothane, enflurane and desflurane, non-volatile anesthetics such as xenon and nitrous oxide, inert gases such as helium and argon, and even gases classically considered to be toxic (*e.g.*, hydrogen sulfide and carbon monoxide) have all been supported by the evidence alluding to their use as potential neuroprotective agents. A wide range of neural injury types such as ischemic/hemorrhagic, stroke, subarachnoid hemorrhage, traumatic brain injury, perinatal hypoxic–ischemic brain injuries, neurodegenerative disease as well as spinal cord ischemia have been used as platforms for studying the neuroprotective effects of these gases, yet until now, none of the gases has been widely introduced into clinical use specifically for protection against neural injury. Insufficient clinical data together with contradictory paradigms and results further hinders the clinical trials. However, pre-clinical models suggest that despite the various classes of gases and the broad range of injuries to which medical gases confer, protection, several underlying mechanisms for their neuroprotective properties are similar. In this review, we summarize the literature concerning the neuroprotective effect of each gas and its underlying mechanisms, extract common targets reported for the neuroprotective effects of different gases, highlight the conflicting observations from clinical trials and further discuss the possible hindrances impeding clinical applications in order to propose future research perspectives and therapeutic exploitations.

Contents

Abbreviations: AD, Alzheimer's disease; AMPA, alpha-amino-D-hydroxy-5-methyl-4-isoxazole-propionate; Ar, argon; ATA, absolute atmosphere; ATP, adenosine triphosphate; BBB, blood–brain barrier; CAT, catalase; CO, carbon monoxide; CO_2, carbon dioxide; COHb, carboxyhemoglobin; CPB, cardiopulmonary bypass; $CMRO_2$, cerebral metabolic rate of oxygen; Des, desflurane; EAAT1 (2, 3), excitatory amino acid transporter 1 (2, 3); ERK, extracellular signal-regulated kinase; FiO_2, fraction of inspiration O_2; GABA, gamma-aminobutyric acid; GCL, glutamate-cysteine ligase; GCS, Glasgow Coma Scale; GFAP, glial fibrillary acidic protein; GOS, Glasgow Outcome Scale; H_2, hydrogen; H_2S, hydrogen sulfide; HBO, hyperbaric oxygen; He, helium; HIE, hypoxic–ischemic encyphalophathy; HO-1, heme oxygenase-1; HSP, heat shock protein; Iba-1, ionized calcium-binding adapter molecule 1; ICP, intracranial pressure; IL-1β, interleukin-1β; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; Iso, isoflurane; JNK1, c-Jun N-terminal kinase1; K_{ATP}, ATP-sensitive K^+ channel; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinases; MCAO, middle cerebral artery occlusion; MDA, malondialdehyde; mGluR, metabotropic glutamate receptors; Mito-K_{ATP}, mitochondrial ATP-sensitive potassium channel; MMP-9, matrix metalloproteinase-9; MPTP, mitochondrial permeability transition pore; NBO, normobaric oxygenation; NE, norepinephrine; NIHSS, National Institutes of Health Stroke Scale; NMDA, N-methyl-D-aspartic acid; NO, nitrous oxide; O_2, oxygen; OGD, oxygen and glucose deprivation; PI3k-Akt, phosphoinositide-3-kinase-protein-kinase-B; PaO_2, arterial oxygen partial pressure; PD, Parkinson's disease; PO_2, partial oxygen pressure; POCD, postoperative cognitive dysfunction; $PtiO_2$, brain tissue oxygen; PTSD, post-traumatic stress syndrome disease; ROS, reactive oxygen species; Sevo, sevoflurane; SOD, superoxide dismutase; TACE, tumor necrosis factor-alpha converting enzyme; TBI, Traumatic brain injury; TNF-alpha, tumor necrosis factor-alpha; TnI, troponin I; TnT, troponin T; tPA, tissue plasminogen activator; TREK-1, two-pore-domain K^+ channels; Xe, xenon.

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1. Introduction

Central nervous system (CNS) injury is a major cause of death and disability in developed countries, and represents a major economic burden in the world (Lopez et al., 2006). In the US and China, stroke is one of the most prevalent neurological injuries, striking approximately 800,000 and 2 million people per year, respectively (Roger et al., 2011). In addition, traumatic brain injury (TBI) has increased over time due to modern motor transportation and the persistence of wars. According to a meta-analysis, 12% of 25,134 adults investigated had a history of traumatic brain injury (Frost et al., 2013). Combining the incidence of stroke and TBI with other types of central nervous system injury such as spinal cord injury, perinatal hypoxia ischemia brain injury, as well as