Review Article

Therapeutic Approach to Neurodegenerative Diseases by Medical Gases: Focusing on Redox Signaling and Related Antioxidant Enzymes

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Oxidative stress in the central nervous system is strongly associated with neuronal cell death in the pathogenesis of several neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. In order to overcome the oxidative damage, there are some protective signaling pathways related to transcriptional upregulation of antioxidant enzymes, such as heme oxygenase-1 (HO-1) and superoxide dismutase (SOD)-1/-2. Their expression is regulated by several transcription factors and/or cofactors like nuclear factor-erythroid 2 (NF-E2) related factor 2 (Nrf2) and peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α). These antioxidant enzymes are associated with, and in some cases, prevent neuronal death in animal models of neurodegenerative diseases. They are activated by endogenous mediators and phytochemicals, and also by several gases such as carbon monoxide (CO), hydrogen sulphide (H2S), and hydrogen (H2). These might thereby protect the brain from severe oxidative damage and resultant neurodegenerative diseases. In this paper, we discuss how the expression levels of these antioxidant enzymes are regulated. We also introduce recent advances in the therapeutic uses of medical gases against neurodegenerative diseases.

1. Introduction

The brain consumes 20 to 50% of total body oxygen (O2) consumption, although it only accounts for 2% of the body weight, meaning that brain function is largely dependent on constitutive supply of O2 [1]. Compared to the normal physiological condition, in which 2 to 5% of total oxygen consumed by cells is converted into reactive oxygen species (ROS) as a byproduct of mitochondrial respiration, excessive and unregulated production of ROS can occur in pathological conditions [2, 3]. Therefore, scavenging and regulating the amount of ROS in the brain is important to maintain normal brain activity.

Although aberrant production of ROS in the central nervous system (CNS) is critically linked to several neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), a set of antioxidant defense system can save the brain from severe injuries [4–8]. Oxidative stress activates a stress response, and adaptation against ROS-derived cellular injury maintains the redox balance and protects cells from lethal damage [9]. This adaptive response often requires upregulation of endogenous antioxidant enzymes, and their expression levels can be regulated by several transcription factors. To date, the importance of transcriptional regulation of antioxidant enzymes is recognized as a route to the discovery of neuroprotective strategies. In this paper, we highlight two major transcriptional regulation factors, nuclear factor-erythroid 2 (NF-E2) related factor 2 (Nrf2) and peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α). Also, we focus on the role of heme oxygenase-1 (HOlinebreak and superoxide dismutase (SOD)
in neurodegenerative diseases, because these are the key components of antioxidant mechanism Figure 1. Finally, we would like to introduce recent research on several gases such as CO, H₂, and H₂S (now called medical gases), suggesting a new therapeutic approach against oxidative damage and resultant neurodegenerative diseases, most notably PD.

2. Nrf2: a Master of Redox Homeostasis

Nuclear factor-erythroid 2 (NF-E2) related factor 2 (Nrf2) is an important transcription factor and is recognized as a major contributor to the upregulation of multiple antioxidant defense system in response to oxidative stress. Nrf2 belongs to the cap’n’collar (CNC) family of basic region-leucine zipper (bZip)-type transcription factors [10]. NF-E2 is a heterodimeric protein which contains a large p45 and small p18 subunit [11]. Cloning of its cDNA revealed that p45 contains a cap’n’collar-(CNC-) type bZip domain [12]. The p45 subunit utilizes its CNC-bZip domain to form a heterodimer with p18; the latter has been identified as MaFK, one of the small musculoaponeurotic fibrosarcoma oncogene (Maf) transcription factors [12, 13]. The heterodimer binds to an NF-E2 motif; the small Maf protein p18 confers DNA-binding activity to p45, while p45 activates transcription via its transactivation domain [13, 14]. Nrf2 binds to the antioxidant-responsive element (ARE) or the electrophile-responsive element (EpRE) [15, 16]. ARE has been detected in the promoter or upstream promoter regions of the genes encoding Phase II antioxidant enzymes including glutathione S-transferase subunits (GST-ß, GST-P, GST-M1/M3, etc.), glutamate-cysteine ligase catalytic (GCLC) and glutamate-cysteine ligase modifier (GCLM) subunits, the thioredoxin (TRX) and peroxiredoxin (PRX) families, and NAD(P)H:quinone oxidoreductase (NQO-1) [17–21]. Heme oxygenase-1 (HO-1) is also one of the Nrf2-ARE pathway-derived upregulated factors [22, 23], and its transcriptional upregulation is also mediated by some other transcription factors such as AP-1, CREB, and NF-κB [24]. In the CNS, genetic or pharmacological activation of Nrf2-ARE pathway can confer resistance against neurodegenerative disease insults such as AD, PD, HD, and ALS. A lentiviral vector encoding human Nrf2 reduced spatial learning deficits in aged APP/PS1 mice, a mouse model of AD [25]. Compared to neurons, astrocytes have a much greater ability to increase Nrf2-ARE pathway-derived gene expressions, as shown by a study using cortical neuronal cultures obtained from ARE-human placental alkaline phosphatase (hPAP) reporter mice [26], grown under condition where the mixed cortical cultures consist of 50% astrocytes and 70% neurons. Genetic-overexpression of Nrf2 in astrocytes using the glial fibrillary acidic protein (GFAP) promoter (GFAP-Nrf2) has shown protective effects against several animal models of neurodegeneration, for example, motor neuron degeneration produced by expressing mutant human superoxide dismutase 1 in ALS model mice [27], and dopaminergic neuronal loss by a neurotoxin (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP) in PD model mice [28]. Transplantation of astrocytes infected with adenovirus-Nrf2 protects striatal medium-spiny neuron degeneration by a mitochondrial complex II inhibitor (3-nitropropionic acid or malonate) in HD model mice [29].

HO-1, one of the antioxidant enzymes upregulated by Nrf2, is thought to be highly associated with AD pathology. In AD brain, HO-1 is expressed both in neurons and in astrocytes; 86% of GFAP-positive astrocytes in AD hippocampus exhibit HO-1 immunoreactivity, whereas those in age-matched normal tissues are in the range of only 6–7% [30]. HO-1 overexpression in astrocyte by transient transfection of HMOX1 cDNA significantly decreased intracellular cholesterol concentrations and increased the level of at least four oxysterol species compared to untreated control cultures [30]. In mild cognitive impairment or early AD, enhanced HO-1 expression stimulated astrocyte cholesterol biosynthesis, oxysterol formation, and cholesterol efflux (to sites of neuronal repair and for egress across the blood-brain barrier). Gliarial cholesterol efflux exceeds biosynthesis, and total cholesterol levels in affected brains are normal or diminished. Regulation of sterol homeostasis is important in AD pathology because a massive increase in the free cholesterol pool saturates the sterol efflux mechanism, which results in an increase in brain cholesterol levels and exacerbates amyloid deposition and neurodegeneration in advanced AD. Uregulation of HO-1 has another therapeutic potential for clearance of tau protein by the ubiquitin-proteasome system (UPS) [30]. Proteasome activity is reduced in AD brain and amyloid beta (Aβ) inhibits the UPS in cultured cells [31, 32]. This influence on UPS, for which heme-derived iron and CO are responsible, promotes intracellular degradation of α-synuclein as observed in HMOX1-transfected M17 cells [33]. Therefore, HO-1 is highly associated with the therapeutic approach not only by its antioxidant function but also by its influence on proteasomal degradation of tau and α-synuclein.

3. The Role of PGC-1α in Neurodegenerative Diseases

Since its discovery over a decade ago, peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) has been implicated in energy homeostasis, adaptive thermogenesis, β-oxidation of fatty acids, and glucose metabolism [34]. The activity of PGC-1α depends on its ability to form heteromeric complexes with a variety of transcription factors including nuclear respiratory factor 1 and 2 (NRF-1 and NRF-2), and the nuclear hormone receptors [35]. In particular, NRF-1 and NRF-2 are transcriptional regulators that act on nuclear genes encoding for constituent subunits of the oxidative phosphorylation system including cytochrome c, complex I-V, and mitochondrial transcription factor A (Tfam) [36]. Tfam, a transcription factor that acts on the promoters within the D-loop region of mitochondrial DNA and regulates the replication and transcription of the mitochondrial genome, contains consensus-binding sites for both NRF-1 and NRF-2 [37].

Mice lacking PGC-1α show a profound spongiform pattern of lesions in the striatum together with hyperactivity,
Figure 1: The transcriptional upregulation of antioxidant enzymes in neurodegenerative diseases. Both neurons and astrocytes can increase several antioxidant enzymes including heme oxygenase-1 (HO-1), copper and zinc-containing SOD (Cu/ZnSOD), manganese-containing SOD (MnSOD), and glutathione peroxidase (GPx). By drug application or genetic overexpression of transcription factor, the transcriptional responses via NF-κB (p50/p65), AP-1 (c-Jun/c-Fos), Nrf2/sMaf, and NRF1/PGC-1α in response to oxidative stress and related neurodegenerative disease are activated.
protects against the in vitro neurotoxicity induced by Aβ [59]. In vivo, coexpression of hSOD1 with an APP transgene protects against the lethal effects of APP [60]. SOD2 is enriched around amyloid plaques [61, 62] and brain microvessels [63] in hAPP transgenic mice but decreased in AD brains overall [64]. Esposito et al. has shown that partial reduction in the main mitochondrial superoxide scavenger SOD2 using SOD2+/− mice accelerates the onset of hAPP/Ab-dependent behavioral abnormalities and worsens a range of AD-related molecular and pathological alterations [65]. On the other hand, overexpression of SOD2 reduces hippocampal superoxide and prevents memory deficits in the Tg2576 mouse model of AD that overexpresses the hAPP carrying the Swedish mutation (K670N:M671L) [66].

4. Reducing ROS by Medical Gases

The generation of ROS and related oxidative damage are believed to be involved in the pathogenesis of neurodegenerative diseases. The main ROS involved in the pathogenesis of neurodegeneration are O₂•−, H₂O₂, and the highly reactive hydroxyl radical (HO•). Recently, there have been increasing reports showing that medical gases, such as carbon monoxide (CO), nitric oxide (NO), and hydrogen sulfide (H₂S) as well as molecular hydrogen (H₂), might overcome the harmful damage produced by oxidative stress [67, 68]. These gases directly eliminate ROS, or induce resistant proteins and antioxidant enzymes to antagonize oxidative stress Table 1.

4.1. Carbon Monoxide. CO is a diatomic molecule and is soluble in aqueous media and organic solvents [69]. Not only exogenous environmental exposure but also endogenous production during heme metabolism are major sources of CO from primitive prokaryocytes to human [69, 70]. Endogenous production of CO is highly associated with HO-1 activity which induces enzymatic degradation of heme. HO breaks the alpha-methylene carbon bond of the porphyrin ring using NADPH and molecular O₂ in a reaction that releases equimolar amount of biliverdin, iron, and CO [71, 72].

Recent studies have revealed that CO serves as an intrinsic signaling molecule and shows anti-inflammatory and antiapoptotic effects. These effects of CO are mediated by p38 mitogen-activated protein kinase (MAPK) signaling, which is activated in response to physical and chemical stress inducers including oxidative stress, UV light, ischemia, and proinflammatory cytokines [73]. Activation of p38 also mediates the induction of heat shock protein (Hsp72) via its transcriptional factor, heat shock factor-1, leading to the cytoprotective effects [74].

Exogenous CO also activates Nrf2 pathway and decreased infarct size in an ischemia/reperfusion model [75]. Nrf2 activation can coordinately upregulate expression of several antioxidative enzymes recognized to play important roles in combating oxidative stress, including HO-1. Endogenous CO, which is produced by heme degradation, induces ROS-dependent signal transduction in the mitochondrial SOD2 and in HO-1 itself [76].

4.2. Hydrogen Sulfide. H₂S is a flammable, water-soluble gas with a smell of rotten eggs and is known as a toxic gas and as an environmental hazard. The production of H₂S from L-cysteine is catalysed primarily by two enzymes, cystathionine γ-lyase (CSE) and cystathionine β-synthase (CBS). Although exposure to higher levels (∼μM) of H₂S is cytotoxic (free radical generation, glutathione depletion, intracellular iron increase, and mitochondrial cell death signal), lower concentration (∼μM) of H₂S shows cytoprotective (antinecrotic and antiapoptotic) effects.

Biochemical analysis has revealed that sulphide shows a direct antioxidant reaction with one- or two-electron molecules (one-electron molecules: •NO₂, •OH, CO₂•−, two-electron molecules: peroxynitrite, hydrogen peroxide, hypochlorite, taurine, and chloramine) as well as other low-molecular-weight thiol molecules such as cysteine and glutathione. Although sulphide is not a preferential target for radicals or oxidants due to its low concentration in vivo, it can serve as a direct antioxidant [77, 78]. H₂S can also induce upregulation of transcription for anti-inflammatory and cytoprotective genes including HO-1 [79, 80]. By upregulating HO-1 expression, H₂S can trigger the production of CO, which shows anti-inflammatory and antiapoptotic effects.

4.3. Hydrogen. Since the first striking evidence indicating that molecular hydrogen acts as an antioxidant and inhalation of hydrogen-containing gas reduces ischemic injury in brain [81], there have been increasing numbers of reports which support the therapeutic properties of hydrogen against oxidative stress-related diseases and damages in brain [82, 83], liver [84], intestinal graft [85], myocardial injury [86, 87], and atherosclerosis [88]. Hydrogen can be taken up by inhalation of hydrogen-containing air (hydrogen gas) or drinking hydrogen-containing water (hydrogen water). One hour after the start of inhalation of hydrogen gas, hydrogen can be detected in blood, at levels of 10 μM in arterial blood [81]. The content of hydrogen can be measured even after intake of hydrogen water by a catheter, which yields 5 μM in arterial blood calculated after 3 min of hydrogen water incorporation [82]. Taking into account its continuous intake, it is easier and safer to drink hydrogen water than inhaling hydrogen gas.

We have previously showed that H₂ in drinking water reduced the loss of dopaminergic neurons in MPTP-induced Parkinson’s disease (PD) mice [89]. The therapeutic effects of H₂ water were observed in another PD model, 6-OHDA-treated rats [90]. In these animal models, administration of neurotoxins decreased the number of dopaminergic neurons in the substantia nigra pars compacta (SNpc), as well as dopaminergic nerve terminal fibers in the striatum. However, taking H₂ water significantly reduced the loss of both neuronal cell bodies and fibers compared with the controls drinking normal water. Mice chronically treated with MPTP using an osmotic pump also showed behavioral impairments observed by open-field test [91], and rats administered with 6-OHDA showed behavioral impairments assessed by the rotarod test. Hydrogen improved these
behavioral impairments in both of these animal models of PD.

In the first report [81], H2 selectively reduced cytotoxic •OH radicals, whereas the production of other radicals such as superoxide, hydrogen peroxide, and nitric oxide was not altered. This selectivity was verified in a cell-free system, and in particular, the preference for scavenging •OH rather than superoxide was confirmed in PC12 cell culture system. According to Setsukinai et al. [92], both •OH and peroxynitrite (ONOO−) are much more reactive than other ROS. This would explain why H2 shows a selective reaction with only the strongest radicals, both in the cell-free system and in PC12 cells.

Especially, •OH overproduction in oxidative and neurotoxic reaction by MPTP leads to lipid peroxidation in nigral dopaminergic neurons prior to cell death, observed by 4-hydroxynonenal (4-HNE) immunostaining, the markers of membrane lipid peroxidation. Immunoreactivity of 4-HNE in MPTP-treated mice is increased by three times compared to that in saline-treated mice [89], which is similar to the previous report of 4-HNE protein levels in substantia nigra observed at the same time after MPTP administration using HPLC [93]. H2 water significantly reduces the formation of 4-HNE in dopaminergic neurons in substantia nigra to the level of control [89]. MPTP-induced loss of dopaminergic neuron is associated with the accumulation of 8-oxo-7, 8-dihydroguanine (8-oxoG) in the dopaminergic neurons. H2 water significantly decreased this accumulation in the striatum [89]. 8-oxoG is the major oxidized form of guanine in DNA, RNA and nucleotide pool by •OH and is accumulated in both mitochondrial and nuclear DNA; their nomenclature are mt8oxo-G and nu8-oxoG, respectively. Mt8oxoG accumulates in the striatum which is rich in mitochondria in nerve terminals of dopaminergic neurons projecting from the substantia nigra. Although nu8oxoG was not detected in the nigral cell nucleus, H2 water might prevent the mt8oxoG-induced cellular apoptotic signals, not just reduce •OH in the dopaminergic nerve terminal. On the other hand, the increase in O2•−, which was detected by the O2•− indicator, dihydroethidium (DHE), was not significantly decreased by H2 water [89]. Although H2 prevented superoxide formation in brain slices in hypoxia/reperfusion injury [94], H2 water might show a preferential reduction of •OH during the protection of dopaminergic neurons.

Initial evidence suggests that H2 protects cells and tissues against strong oxidative stress by scavenging •OH [81]. Also, H2 was effective when it was inhaled during reperfusion; when H2 was inhaled just during the initial ischemia (not in the reperfusion stage), infarct volume was not significantly decreased. It was shown that hydrogen in the brain decreased immediately after stopping inhalation and completely disappeared within 10 min [89], indicating that the effect of hydrogen can be observed only during the period when the oxidative insults occur. According to a previous report [82], H2 could be detected in the blood 3 minutes after administration of H2 water into the stomach. However, unpublished data showed that the half-life of H2 in the muscle in rats was approximately 20 minutes after the administration of H2 gas. Taking these reports into consideration, H2 in the brain and other tissues does not stay long enough to exert its ability as an antioxidant to ROS directly. Therefore, it is unlikely that direct reaction of H2 itself with ROS plays a major role in the neuroprotection, especially with H2 in drinking water, even though H2 itself has the ability to reduce •OH preferentially. In accordance with this hypothesis, previous reports from Nakao et al. has demonstrated that drinking hydrogen water increased the amount of antioxidant enzyme, superoxide dismutase (SOD) [95], an endogenous defensive system against ROS-induced cellular damage. It was also reported that H2-water increases total bilirubin for four to eight weeks compared to baseline. Bilirubin is produced by the catalytic reaction of HO-1, and degradation of heme generates bilirubin as well as CO and free iron. Therefore, taking these observations into consideration, there seem to be other mechanisms for protective effect of H2 in drinking water, different from that exerted by H2 inhalation. It is possible that drinking H2 water has not only the ability to reduce cytotoxic radicals,

| Medical gases       | Direct reaction to ROS | Reference | Endogenous cytoprotective protein induction | Reference |
|---------------------|------------------------|-----------|------------------------------------------|-----------|
| Hydrogen (H2)       | Radical scavenging     | [67]      | Increase superoxide dismutase (SOD)      | [81]      |
|                     | HO• + H2 → H2O + H•    |           | Increase bilirubin                       | [81]      |
| Carbon monoxide (CO)|                        |           | Activation of p38 MAPK signaling         | [59]      |
|                     |                        |           | p38 → HSF1 → Hsp72                       |           |
| Hydrogen sulphide (H2S)| Radial scavenging  | [64]      | Activation of Nrf2 pathway               | [61]      |
|                     | 2O2•− + H2S → HS–SH + O2 + 2OH• | [63] | Induce superoxide dismutase (SOD)         | [62]      |
|                     |                        |           | and HO-1                                 |           |
|                     |                        |           | Upregulation of cytoprotective genes     | [65]      |
|                     |                        |           | including HO-1                           | [66]      |
but also brings into play novel mechanisms which are related to antioxidative defense system.

5. Conclusion

Recent advance in understanding of the regulation of antioxidant enzyme expression by transcriptional factors has given us the possibility that we can overcome several diseases mediated or induced by oxidative stress. As discussed above, transcriptional upregulation of several antioxidant enzymes like HO-1 and SOD might be beneficial for several neurodegenerative diseases such as AD, PD, HD, and ALS. Several phytochemicals (resveratrol, curcumin, flavonoids, carnosol, etc.) and endogenous mediators (15-deoxy-Δ12,14-PGJ2) can upregulate the antioxidants via transcription factors such as Nrf2, NF-E2, and AP-1 [24]. Surprisingly, HO-1 and SOD are increased by CO, H2 and H2S, although we cannot say whether these gases accelerate the stress response signaling or some transcriptional regulation system mediated by Nrf2 and PGC-1α. Together with the fact that H2S itself has the ability to react with ROS directly, we strongly suggest that these gases can buffer the ROS and in addition might prevent and/or protect the neurons from oxidative stress damages in neurodegenerative diseases.

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