Similar to nitric oxide (NO), produced by a family of nitric oxide synthases (NOSs), carbon monoxide (CO) is also endogenously generated from heme by the catalytic reaction of heme oxygenase (HO) (Fig. 1). CO is endogenously produced, and three isoforms of HO (e.g., HO-1, HO-2, and HO-3) have been identified. These isoforms of HO differ in their tissue distributions and molecular properties. HO-1, induced in response to a broad spectrum of stimuli, was first identified as a stress protein and acted as cytoprotective agents (Wu et al., 2011). The second isoform, HO-2, is constitutively expressed (Traksheil and Maines, 1989). The third isoform, HO-3, is highly homologous to HO-2 but possesses significantly lower catalytic activity. These enzymes, both HO-1 and HO-2, catalyze the oxidative conversion of heme to ferrous iron, CO, and biliverdin. Biliverdin is reduced to bilirubin by biliverdin reductase (reviewed in Kim et al., 2011) (Fig. 1).

HO is expressed in the brain; however, the relative distributions of the three isoforms varies greatly depending on injury and age (Maines, 1997). Inducible HO-1 is not normally detectable in the healthy brains, and its expression is detected in glia and macrophages 24 hours after trauma rat brains (Fukuda et al., 1995). HO-1 is also induced in astrocytes of the peri-infarct regions 48 hours after macular cerebral artery occlusion (MCAO) in the mouse brain (Choi et al., 2017). HO-2 is highly expressed in brain cells, astrocytes, cerebral endothelial cells (ECs) and neurons (Scapagnini et al., 2002; Parfenova et al., 2006). HO-2 appears to protect against lipid peroxidation-mediated cell loss and impaired motor recovery after traumatic brain injury (Chang et al., 2003), whereas its deletion exacerbated cerebral hemorrhage-induced brain edema (Wang and Dore, 2008). HO-2 is abundantly expressed in the cerebellum and hippocampus (Ewing and Maines, 1992; Maines, 1997; McCoubrey, 1997). In the hippocampus, HO-2 is highly expressed in hippocampal granule cells and pyramidal neurons of the CA1 and CA3 regions (Verma et al., 1993), suggesting its role in memory function.

The beneficial or detrimental effects of CO may depend on its concentration. Higher than 500 ppm may lead to toxic effects. Rats exposed to CO at 500 ppm showed cardiac function abnormalities via the induction of the late Na+ current (Dallas et al., 2012). CO inhalation of 3 mg/kg for one hour can lead to critical concentrations at the upper limit of 14.3% carboxyhemoglobin in human blood; therefore, clinical trials have used up to 250 ppm (Motterlini and Otterbein, 2010;
Peers, 2012). The protective effects of 250 ppm CO in the CNS have been demonstrated in ischemic brain injury such as stroke and traumatic brain injury in animal models (Wang et al., 2011; Choi et al., 2016a).

The development of safe and efficient CO-releasing molecules (CORMs) for therapy, as well as therapeutic use of CO gas in treatment of neurovascular diseases, is of great current interest. These CORMs possess transition metal carriers that require stringent characterization from a metabolic and toxicological states. Several CORMs have been synthesized as therapeutic agents aimed at delivering controlled amounts of CO to tissues and organs (Motterlini et al., 2002). CORM-A1 (Na₂(H₃BCO₂)) is soluble and stable in water and decomposes to release CO under physiological conditions with slow kinetics (t½=21 min) (Motterlini et al., 2003). CORM-2 ([Ru(CO)₃Cl₂]₂) is soluble in dimethyl sulfoxide and releases CO with fast kinetics (t½=1 min) (Motterlini et al., 2002). CORM-3 ([Ru(CO)₃Cl(glycinate)]) is a water-soluble CO-releasing agent with fast kinetics (t½=1 min) (Clark et al., 2003). A newly synthesized CO-releasing agent, CORM-401 ([Mn(CO)₃(S₂CNMeCH₂CO₂H)]), contains a manganese metal center and releases up to 3 CO/mole of compound (Fayad-Kobeissi et al., 2016). Most of the beneficial cellular effects of CORMs were demonstrated at concentrations of 10-200 μM (Hettiarachchi et al., 2014; Choi et al., 2016a).

A protective role for low-dose CO in vascular and neuronal systems in the central nervous system (CNS) has been reported, implying its beneficial effects on neurovascular diseases such as traumatic brain injury, Alzheimer’s disease, and stroke (Yabluchanskiy et al., 2012; Hettiarachchi et al., 2014; Choi et al., 2016b). It may be involved in improving angiogenesis, neurogenesis, and memory functions. This review highlights the therapeutic effects of CO/HO on CNS diseases involved in neurogenesis, synaptic plasticity and angiogenesis. Moreover, the cellular mechanisms and interactions by which CO/HO are exploited for therapeutic applications in traumatic brain injury, Alzheimer’s disease, and stroke are also discussed.

THE ROLE OF CO/HO IN THE NEUROVASCULAR UNIT

Brain ECs closely interact with other types of cells, including pericytes, astrocytes, microglia, and neurons, to form a functional ‘neurovascular unit (NVU)’, which maintains proper brain homeostasis. The NVU is a highly dynamic multicellular structure capable of integrating and responding to both neuronal and vascular systems. Miscommunication and malfunction in members of the NVU are important in many neurologic diseases.

CO may provide neuroprotective mechanisms via direct binding with heme proteins or by indirectly inducing HO-1 (Chun and Kim, 2016; Han et al., 2016). HO-1 is a neuroprotective factor that is upregulated by an array of conditions including elevated CO. Bursts of physiological intracellular reactive oxygen species (ROS) levels activates the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway and induces HO-1, leading to CO production (Kim et al., 2012; Jeong et al., 2016; Jin et al., 2016). These results imply that there is positive circuit between the HO-1/CO and ROS/Nrf2 pathways, resulting in the continuous production of CO. CO/CORMs protect cells from cytotoxicity induced by pathological levels of ROS, which may be a crucial factor in the pathogenesis of human ischemic diseases by providing anti-inflammation, anti-apoptosis, and anti-oxidative injury mechanisms. This review focuses on the possible role of CO/HO in neurovascular repair processing in terms of neurogenesis, synaptic plasticity, and angiogenesis in neurologic diseases (e.g., traumatic brain injury, Alzheimer’s disease, and stroke).

The effects of CO/HO on neurogenesis

Cerebral ischemia and neurodegenerative diseases lead to impairment or death of neurons in the CNS. Regeneration of functional neurons from stem cell-based therapies is a promising strategy currently under investigation. Neurogenesis is the process by which neural stem cells (NSCs) generate newly synthesized neurons to replace damaged neurons or maintain brain functions. NO promotes adult neurogenesis after brain damage (Zhang et al., 2001). Similar to NO, low doses of CO may induce endogenous neurogenesis, providing a potential therapeutic strategy for neurodegenerative diseases. In the traumatic brain injury mouse model, 4 mg/kg CORM-3 rescues pericyte-NSC crosstalk, possibly promoting neurorecovery during the chronic phase (Choi et al., 2016a). Inhibition of HO by tin-protoporphyrin significantly blocked CORM-3-mediated neurogenesis and neuroscore improvements after traumatic brain injury, suggesting reciprocal signaling between CO and HO (Choi et al., 2016a). Moreover, inhibition of NOS with L-NAME blocked CORM-3-mediated neurogenesis and migration of NSCs (Choi et al., 2016a), suggesting that CO may activate NOS to boost neurogenesis. In this study, CO could not induce conversion of pericytes into NSCs in in vitro or in vivo models (Choi et al., 2016a); instead, conditioned medium from cultured oxygen-glucose deprived pericytes treated with CORM-3 enhanced the differentiation of NSCs into mature neurons. These findings suggest that no direct pericyte-to-NSC conversion was taking place; instead, the effects on neurogenesis may be indirectly mediated by the ability of CORM-3
to modulate pericyte-NSC crosstalk (Choi et al., 2016a).

In the MCAO mouse models, HO-1−/− mice had fewer positive cells for both the axon migrating marker netrin and 5-Bromo-2′-deoxyuridine (BrdU; a marker for proliferating cells), as compared to vehicle (Nada et al., 2014). In addition, the MCAO mice brains showed upregulation of nicotinamide phosphoribosyltransferase (Nampt) levels compared with levels in the sham mice, and this effect was significantly blocked in the brains of the HO-1−/− mice (Choi et al., 2017). Nampt-transgenic mice showed an increased number of NSCs and improved neural functional recovery compared with those in wild-type mice after MCAO (Zhao et al., 2015), suggesting that the HO-1/Nampt axis may be involved in neuronal recovery after ischemic stroke. For neuronal differentiation, combinatorial treatment of CORM-A1 with retinoic acid induced the neuronal marker TuJ1 in the human neuroblastoma SH-SYSY cell line, human teratocarcinoma NT2 cell line and organotypic hippocampal slice cultures (Almeida et al., 2016). Recently, the beneficial effects of the CORM-2 and HO-1 pathways on the reduction of neuronal cell death (SH-SYSY cells and hippocampal neurons) against amyloid β peptide toxicity has been reported (Heitlarachchi et al., 2014). More investigation, however, will be necessary to ascertain whether CO/HO can induce neurogenesis to rescue the cognitive functions in Alzheimer’s diseases. Taken together, these findings suggest that the CO/HO pathway may induce neurogenesis in several neurovascular diseases.

The effects of CO/HO on synaptic plasticity

Synapses are the basic structural and functional component for neural communication in the brain. A neuron may receive information via neurotransmitters from hundreds of other neurons connecting thousands of synaptic terminals, as well as from cellular crosstalk. The inputs are highly varied because each transmitting neuron may secrete a different quantity or kind of neurotransmitter in various pathophysiological conditions (Fig. 2A). Endogenous CO production occurring at comparatively low concentrations is thought to have a role at the synapse leading to long-term potentiation (LTP) (Verma et al., 1993; Zhuo et al., 1993). CO can release glutamate from synaptosomes and has a role in LTP, possibly resulting in memory processing (Shinomura et al., 1994) (Fig. 2B). Poss et al. (1995) noted that although brain HO activity was markedly reduced in HO-2-deficient mice compared to those in wild-type (Poss et al., 1995), both groups demonstrated an equal ability for synaptic potentiation, suggesting that direct CO or HO-1 may be important for synaptic potentiation. In particular, high expression levels of HO-1 in the hippocampus may provide further evidence linking endogenous CO with cognitive processing; however, more investigation is required to determine the role of HO-1 on cognitive functions.

The growth-associated protein (GAP-43) is associated with presynaptic neuronal outgrowth and neuronal plasticity in general (Snipes et al., 1987). Transgenic overexpression of GAP-43 can result in the formation of new synapses, neurite outgrowth, and synaptogenesis after injury (Routenberg et al., 2000). The expression of GAP-43 is restricted in neurons, and its expression is stabilized by HuD, a neuronal-specific RNA-binding protein (Mobarak et al., 2000). Recently, we reported that conditioned media from pericytes exposed to CORM-3 during oxygen-glucose deprived conditions induce the production of GAP-43 protein in embryonic and adult rat neural stem cells (Choi et al., 2016a), suggesting that pericyte-NSC crosstalk may induce neuronal regeneration, presynaptic outgrowth and plasticity (Fig. 2B).

The effects of CO/HO on angiogenesis

Blood vessel development is a regulated process involving the proliferation, migration, and remodeling of ECs from adjacent pre-existing blood vessels (angiogenesis) or following differentiation of endothelial progenitor cells (EPCs) from mesodermal precursors (vasculogenesis). Because expression of HO-1 can protect EPCs from oxidative injury and stimulate EPC homing to injured regions to promote angiogenesis, this positive feedback may be beneficial for EPC function (Li et al., 2012). Vascular endothelial growth factor (VEGF), a potent angiogenic and permeability factor, induces pathologic vessel formation in neurovascular diseases; therefore, anti-VEGF (bevacizumab) therapy has been used to prevent vision loss in patients with eye diseases such as diabetic retinopathy and retinopathy of prematurity (Spaida and Fisher, 2006; Mintz-Hittner et al., 2011). Secretion of VEGF by astrocytes is increased in response to low oxygen tension (Stone et al., 1995). In a mouse model of multiple sclerosis, astrocytic VEGF expression was a key driver of blood-brain barrier (BBB) permeability, lymphocyte infiltration and neuropathology in inflammation and demyelinating lesions (Argaw et al., 2012).

Ischemia insults or ROS results in the upregulation of hypoxia-inducible factor-1 alpha (HIF-1α), which regulates several target genes including VEGF, with functions ranging from EC fate decisions to vasculogenesis and angiogenesis (Semenza, 2003). Overexpression of HO-1 or 100 μM CORM-2 stabilizes the HIF-1α protein in astrocytes, leading to up-
regulation of VEGF expression (Choi et al., 2010). HIF-1α can also activate the transcription ofstromal cell-derived factor 1 (SDF-1) in ECs, resulting in increased adhesion, migration and homing of circulating C-X-C chemokine receptor type 4 (CXCR4, a cognate receptor for SDF-1)-positive progenitor cells to ischemic tissue (Ceradini et al., 2004). Mice exposed to 250 ppm CO gas for 2 h per day had enhanced vasculogenesis after vascular injury through increased circulating EPCs and elevated serum SDF-1 levels (Lin et al., 2009). SDF-1 also promoted angiogenesis via an HO-1-dependent mechanism in EPCs and aortic ECs isolated from wild-type, but not from HO-1−/− mice (Deshane et al., 2007). Similar to CO, NO is a gaseous signaling molecule that plays an important role in homeostatic vascular health. Interestingly, NO induces angiogenesis by upregulating pro-angiogenic mediators, such as HO-1, VEGF and interleukin (IL)-8 (Pae et al., 2005), suggesting NO crosstalk with HO-1/CO for angiogenic pathway regulation. Endothelial nitric oxide synthase (eNOS) is involved in SDF-1/CXCR4-mediated bone marrow stem cell recruitment following injury (Li et al., 2009).

Overexpression of HO-1 or pretreatment of 100 μM CORM-2 followed by recovery stabilizes peroxisome proliferator-activated receptor-γ (PPAR-γ) coactivator-1α (PGC-1α) protein in astrocytes, leading to upregulation of VEGF expression in an HIF-1α-independent manner (Choi et al., 2017). CO stimulates angiogenesis and energy metabolism via the induction of metabolic modulators such as PPAR-γ and PGC-1α (Bilban et al., 2006; Suliman et al., 2007). In addition, CO elicits a mild oxidative stress response that stimulates mitochondrial energy metabolism, PGC-1α protein expression and mitochondrial DNA copy number (Lancel et al., 2009). Adenosine monophosphate protein kinase (AMPK) can enhance sirtuin 1 (SIRT1, an NAD+-dependent class III histone deacetylase) activity by increasing cellular NAD+ levels, resulting in the deacetylation and modulation of downstream SIRT1 targets, including PGC-1α (Canto et al., 2009). Therefore, CO/HO pathway may promote angiogenesis and vasculogenesis.

THE EFFECTS OF CO/HO ON CELLULAR NETWORK IN PATHOLOGIC CONDITIONS

Coordinated regulation of vascular and neuronal systems in the CNS is associated with normal brain functions. Knowledge of the neurovascular crosstalk among endothelial cells, pericytes, astrocytes, and neurons is important to understanding the molecular basis of neurological disease (Lo et al., 2004). Recently, a link between pericyte loss and neurologic disease has gained interest (Winkler et al., 2010). Pericytes in the NVU are a key effector for the regulation of BBB permeability (Armulk et al., 2010; Daneman et al., 2010), cerebral blood flow (Bell et al., 2010), and neuronal morphology and behavior (Bell et al., 2010). Astrocytes are also involved in neurovascular coupling. Astrocytes play a critical role in the maintenance of the BBB through vasoactive endothelial growth factor signaling mechanisms and interactions with extracellular matrix proteins (Lee et al., 2003; Argaw et al., 2012).

There is an abundance of preclinical evidence in both large and small animals demonstrating the beneficial effects of CO, administered either as CO gas or CORMs, in neurodegenerative diseases such as traumatic brain injury, Alzheimer’s disease and stroke (Bauer and Pannen, 2009; Motterlini and Otterbein, 2010; Choi et al., 2016a). The possible therapeutic roles of CO in neurovascular diseases are discussed as follows.

CO/HO in traumatic brain injury

Primary injury is the immediate mechanical and ischemic damage that occurs at the time of the traumatic event, while secondary injury evolves over a period of days to months following the initial injury. Oxidative-nitrative stress is one of the important mechanisms underlying secondary injury following traumatic brain injury (Lynch and Dawson, 1994). Another result of traumatic brain injury is long-term cognitive dysfunction, memory loss and altered motor skills (Xiong et al., 2013). The restoration of high-level cognitive and motor functions requires mature neural circuitry through the induction of angiogenesis, the process by which EPCs may induce new blood vessels to support glucose and oxygen supply. Therefore, therapeutic agents for the treatment of neurodegenerative diseases may require multifunctional mechanisms to reduce oxidative-nitrative stress, and enhance neurorestorative processes, including neurogenesis, synaptogenesis, and angiogenesis, consequently contributing to the recovery of cognitive and motor functions. The beneficial role of CO in traumatic brain injury has been reported, leading to neurogenesis which may be influenced by rescued pericyte-derived factors, consequently activating the neuronal NOS/NO axis (Choi et al., 2016a) (Fig. 3). It is increasingly recognized that pericytes are a critical neurovascular target cell in stroke and neurodegeneration (Yemisci et al., 2009; Winkler et al., 2011). Consistent with these data, widespread pericyte cell death occurs after traumatic brain injury, and the ability to prevent pericyte drop-out with CO suggests that its potential role as a neurovascular target. Interestingly, cleaved caspase 3 (apoptotic marker) expression coincides with that of pericyte marker, and ROS/HIF-1α axis may act as the pro-apoptotic initiator for pericyte

https://doi.org/10.4062/biomolther.2017.144

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cell death (Choi et al., 2016a) (Fig. 3). Rescuing pericytes also amplified the endogenous recovery response, suggesting that pericyte-NSC crosstalk may be a mechanism for the regulation of neurogenesis in the recovering brain. These cell-cell interactions reinforce the importance of help-me signaling between multiple cell types in the CNS (Xing and Lo, 2016), and may provide novel opportunities for amplifying endogenous pathways for remodeling injured brain tissue.

**CO/HO in Alzheimer’s diseases**

A form of mental deterioration, or dementia, Alzheimer’s disease is characterized by confusion and memory loss. Its incidence is usually age-related; however, traumatic brain injury and cerebral vascular diseases are factors conferring increased risk for late-onset Alzheimer’s disease (reviewed in Ikonomovic et al., 2017). Alzheimer’s disease results in a characteristic brain pathology: neurons die in large areas of the brain, and brain tissue often shrinks. It is diagnosed based on postmortem findings of two features—neurofibrillary tangles (bundles of tau protein), and senile plaques—in the remaining brain tissue is diagnostic. Senile plaques are aggregates of beta-amyloid, an insoluble peptide of 40 to 42 amino acids that is cleaved from a membrane protein normally present in neurons. Apoptosis contributes to the neuronal loss associated with amyloid-β-peptide toxicity in Alzheimer’s disease. 10 μM CORM-2 protects against amyloid-β-induced toxicity in the human neuroblastoma SH-SY5Y, and in rat hippocampal neurons (Hettiarachchi et al., 2014). In Alzheimer’s disease, molecular signaling is compromised between pericytes and other cell components of the NVU (Winkler et al., 2014) and pericyte loss is accelerated. An association between pericyte loss and the accumulation of soluble Aβ was demonstrated in transgenic APPSwe mice (Sagare et al., 2013). Therefore, the link between CO and pericytes requires investigation in the Alzheimer’s disease model.

This perspective is changing with the growing realization that glia actively crosstalk with neurons and influence synaptic development, transmission, and plasticity through an array of secreted and contact-dependent signals. Elevated astrocyte Ca²⁺ can trigger the release of gliotransmitters, which modulate neuronal activity as well as synaptic transmission and plasticity (Araque, 2008). 100 μM CORM-2 pre-treatment or HO-1 overexpression in astrocytes secretes VEGF, an angiogenic and neurogenic factor, through an L-type Ca²⁺ channel activation-mediated signaling cascade (Choi et al., 2017). Disruptions in neuron-glia signaling may contribute to synaptic and cognitive impairment in Alzheimer’s disease (Chung et al., 2015). Age results in increased astrocyte expression of glial fibrillary acidic mRNA and a shift to a pro-inflammatory phenotype, as well as signs of oxidative damage and expression of the senescence-associated secretory phenotype (reviewed in Garwood et al., 2017). The possible role of CO/HO in the promotion of cellular network requires further investigation.

**CO/HO in stroke**

Stroke is a clinical condition in which the blood supply to the brain is limited or severed by embolism and blood clotting, or by the rupture of blood vessels and subsequent cerebral hemorrhage. Ischemic stroke resulting from vascular disorders induces several biochemical and cellular reactions such as increased calcium overload, ROS production, inflammatory response, and impairment of BBB. During reperfusion, ROS concentration peaks, which causes cytotoxicity through lipid peroxidation, protein oxidation, and DNA fragmentation (Nelson et al., 1992; Gursoy-Ozdemir et al., 2004). The potential efficacy of CO therapy in neurovascular diseases may be consistent with past attempts to utilize CO for ischemia-reperfusion injury in other organs (Fujita et al., 2001). Interestingly, 4 mg/kg CORM-3, administered either before or three days after intracerebral hemorrhage, altered the inflammatory response and reduces brain damage in a rat model of hemorrhagic stroke (Yabluchansky et al., 2012). Astrocytes isolated from HO-1-deficient animals were more vulnerable to hemoglobin and to hemin toxicity than were wild-type cells (Chen-Roetling et al., 2005; Chen-Roetling and Regan, 2006). HO-1 may be essential for astrocyte resistance to hemoglobin, but it has no protective effect in neurons. As a consequence of the differential effects of HO-1 in neurons and in astrocytes, it is important to selectively induce HO-1 overexpression in astrocytes. An interesting approach has been utilized to selectively express HO-1 in astrocytes using the glial fibrillary acidic protein promoter. Exclusive overexpression of HO-1 in astrocytes, but not in neurons, resulted in reduced hemin-induced cell death (Benvenisti-Zarom and Regan, 2007). HO-1 induction is generally considered an adaptive cytoprotective response against the toxicity of oxidative stress. Overexpression of HO-1 in the mouse brain revealed a reduction in infarct volumes induced by MCAO (Panahian et al., 1999). Challenged with glutamate, an acute excitotoxic amino acid, resulted in reduced viability of primary neuronal cells from HO-1-knockout mice, compared with those of the wild-type mice (Ahmad et al., 2006). Therefore, the CO/HO pathway may be useful for the therapeutic treatment of stroke.

**PERSPECTIVES**

The various involvements of the CO/HO system have received considerable attention as targets for therapeutic interventions against neurovascular diseases in the CNS. CO/CORMs may offer a novel therapeutic approach for neurovascular diseases by preventing cell death and promoting cellular networks to boost regeneration for functional recovery. The results of this and other studies suggest that CO/CORMs may be a translationally viable and novel approach for CNS disorders. CO/CORMs may modify both aspects of CNS pathology, thus providing proof-of-concept that it is feasible to pursue dual-effect therapies to prevent apoptosis and brain damage during the acute phase of brain injury as well as enhance neurogenic responses to restore cognitive and motor function during the recovery phase.

**CONFLICT OF INTEREST**

There is no conflict of interest.

**ACKNOWLEDGMENTS**

YKC is thankful to Dr. Eng H Lo (Massachusetts General Hospital, Harvard Medical School, USA) for his useful discussion. This research was supported from a grant of the Korea Health Technology R&D Project through the Korea Health...
Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI17C2160).

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https://doi.org/10.4062/biomolther.2017.144