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Heme Oxygenase and Carbon Monoxide: Medicinal Chemistry and Biological Effects
Guest Editor: Yuji Naito

Introduction to Serial Review: Heme Oxygenase and Carbon Monoxide: Medicinal Chemistry and Biological Effects

Yuji Naito*

Medical Proteomics, Kyoto Prefectural University of Medicine, Kyoto 602-8566, Japan

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Heme oxygenase (HO) exists as constitutive (HO-2, HO-3) and inducible isoforms (HO-1), the latter which responds to regulation by multiple stress-stimuli [*1*]. Several signaling molecules (e.g., mitogen-activated protein kinases), transcriptional regulators (activator protein-1, NF-E2-related factor-2, hypoxia-inducible factor-1, Bach-1), as well as two enhancer regions in the *ho-1* 5' regulatory region, participate in the regulation of the *ho-1* gene [*2*]. Recent progress indicates that carbon monoxide (CO), a gaseous second messenger, exerts novel anti-inflammatory and anti-apoptotic effects (Table 1), although little is known about the precise molecular mechanism of these actions. There has been many reports that inhalation of CO could be protective against acute ischemia-reperfusion injury in intestine, lung, kidney, and liver (Table 2). More recent report indicates that inhalation of 100–125 ppm CO by patients with chronic obstructive pulmonary disease is feasible and leads to trends in reduction of sputum eosinophils and improvement of responsiveness to methacholine [*3*]. In addition to beneficial effects of CO, further studies need to confirm the safety of this gas, especially in the cardiac function [*4*, *5*]. In this serial review, we invited several outstanding researchers in this field to summarize their work, to review their peers' activity, and to encourage us their opinions. I thank all the anonymous reviewers of these articles for their insightful comments.

Table 1. Mechanisms of anti-inflammatory and cytoprotective effects of carbon monoxide

Inhibition of chemokines and chemokine receptors
Inhibtion of ICAM-1
Inhibition of iNOS expression and NO production
Inhibition of Th1 type cytokines (IL-2, IFNγ)
Inhibition of proinflammatory mediators (IL-1β, TNFα, IL-6, COX-2)
Augmentation of IL-10
Heme oxygenase-1-dependent pathway
Nuclear factor-κB-independent pathway
Soluble guanylyl cyclase (sGC)-dependent pathway
p38MAPK pathway-dependent
Akt-eNOS pathway-dependent

*To whom correspondence should be addressed.
Tel: +81-75-251-5508 Fax: +81-75-252-3721
E-mail: ynaito@koto.kpu-m.ac.jp

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Table 2. Effects of inhalated carbon monoxide on experimental disease models in rodents

Animal	Organ	Model	Carbon monoxide		Efficacy	Year	Authors
			Conc.	Duration			
Rat	Lung	Hyperoxic injury	250 ppm	56 h	Effective	1999	Otterbein *et al.*
Mouse	Lung	Inflammation by aeroallergen	250 ppm	48 h	Effective	2001	Chapman *et al.*
Rat	Lung	Hyperoxic lung injury	50–500 ppm	60 h	No change	2001	Clayton *et al.*
Rat	Intestine	Ischemia/Reperfusion	250 ppm	1 h	Effective	2003	Nakao *et al.*
Rat	Intestine	Graft motility	250 ppm	25 h	Effective	2003	Nakao *et al.*
Mouse	Intestine	Postoperative ileus	250 ppm	24 h	Effective	2003	Moore *et al.*
Mouse	Lung	Airway Hyperesponsiveness	250 ppm	1 h/day, 5 day	Effective	2003	Ameredes *et al.*
Rat	Heart	Ischemia/Reperfusion	1000 ppm	30 min	Effective	2004	Fujimoto *et al.*
Rat	Kidney	Ischemia/Reperfusion	250 ppm	25 h	Effective	2004	Neto *et al.*
Mouse	Lung	Acute injury, ARDS	500 ppm	1 h	No change	2005	Ghosh *et al.*
Rat	Liver	Ischemia/Reperfusion	100 ppm	25 h	Effective	2005	Kaizu *et al.*
Rat	Intestine	Necrotizing enterocolitis	250 ppm	1h/day, 3day	Effective	2005	Zuckerbraun *et al.*
Mouse	Multiple organ	Hemorrhagic shock	250 ppm	1 h	Effective	2005	Zuckerbraun *et al.*
Rat	Intestine	Postoperative ileus	250 ppm	24 h	Effective	2005	Moore *et al.*
Mouse	Intestine	IL-10-deficient colitis	250 ppm	24 h	Effective	2005	Hegazi *et al.*
Rat	Heart	Myocardial infarction	500 ppm	3 week	Worse	2005	Mirza *et al.*
Mouse	Liver	Ischemia/Reperfusion	250 ppm	1 h	Effective	2005	Ott *et al.*
Pig	Lung	Endotoxin shock	250 ppm	1 h	Effective	2005	Mazzola *et al.*
Rat	Heart	Allograft survival	20 ppm	14–100 days	Effective	2006	Nakao *et al.*
Rat	Kidney	Allograft nephrophathy	20 ppm	30 days	Effective	2006	Neto *et al.*
Rat	Lung	Donors/recipients	250 ppm	pre (1 h)/after	Effective	2006	Kohmoto *et al.*
Rat	Heart	Dysfunction/hypoxia	100 ppm	90 min	Worse	2006	Favory *et al.*
Swine	Vein	Intinal hyperplasia	100/250 ppm	pre/intraope.	Effective	2007	Ramlawi *et al.*
Mouse	Liver	Fulminant hepatitis	250 ppm	1 h	Effective	2007	Tsui *et al.*
Rat	Heart	Dysfunction/hypoxia	50 pm	1 week	Worse	2007	Gautier *et al.*
Rat	Lung	Ischemia/Reperfusion	250 ppm	2 h	Effective	2007	Boutros *et al.*
Rat	Multiple organ	LPS-induced MOF	250 ppm	3 h	Effective	2007	Liu *et al.*
Rat	Liver	Transplantation	20–250 ppm	pre (1 h)/after (24 h)	Effective	2007	Kaizu *et al.*