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Free Radical Biology & Medicine 38 (2005) 979–988

www.elsevier.com/locate/freeradbiomed

Serial Review: Heme oxygenase in human diseases
Serial Review Editor: Phyllis A. Dennery

HO in pregnancy☆,☆☆

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Received 22 June 2004; revised 20 October 2004; accepted 1 November 2004
Available online 31 December 2004

Abstract

The enzyme heme oxygenase (HO) has been implicated in several physiological functions throughout the body including control of vascular tone and regulation of the inflammatory and apoptotic cascades as well as contributing to the antioxidant capabilities in several organ systems. These various properties attributed to HO are carried out through the catalytic products of heme degradation, namely carbon monoxide (CO), biliverdin, and free iron (Fe^{2+}). As the newly emerging roles of HO in normal organ function have come to light, researchers in several disciplines have assessed the role of this enzyme in various physiological and pathological changes taking place in the human body over a lifetime. Included in this new wave of interest is the involvement of HO, and its by-products, in the normal function of the vital organ of pregnancy, the placenta. In this review the role of HO, and its catalytic products, will be examined in the context of pregnancy. The different isoforms of the HO enzyme (HO-1, HO-2, HO-3) have been localized throughout placental tissue, and have been shown to be physiologically active. The HO protein and more specifically its catalytic by-products (CO, biliverdin, and Fe^{2+}) have been postulated to be involved in the maintenance of uterine quiescence throughout gestation, regulation of hemodynamic control within the uterus and placenta, regulation of the apoptotic and inflammatory cascades in trophoblast cells, and the maintenance of a balance of the oxidant-antioxidant status within the placental tissues. The association between this enzyme system, and its above-noted roles throughout pregnancy, with the hypertensive disorder of pregnancy preeclampsia (PET), will also be examined. It is hypothesized that a decrease in HO expression and/or activity throughout gestation would be capable of initiating several pathological processes involved in the etiology of PET. This hypothesis has led to further discussion emphasizing the possibility of novel therapeutic designs targeting this enzyme system for the treatment of PET.

Keywords: Heme oxygenase; HO; HO-1; HO-2; Carbon monoxide; CO; Bilirubin; Biliverdin; Ferritin; Pregnancy; Placenta; Placental perfusion; Antioxidants; Preeclampsia; Free radicals

Contents

Abbreviations: HO, heme oxygenase; CO, carbon monoxide; NO, nitric oxide; ROS, reactive oxygen species; RT-PCR, real-time polymerase chain reaction; ODQ, 1*H*-(1,2,4)oxadiazole(4,3-1)quinoxalin-1-one; YC-1, 3-(5-hydroxymethyl-2′-furyl)-1-benzylindazole; NOS, nitric oxide synthase; PET, preeclampsia.

☆ Sources of financial support: Strategic Training Initiative in Research in Reproductive Health Sciences (STIRRHS), CIHR.
☆☆ This article is part of a series of reviews on "Heme oxygenase in human disease." The full list of papers may be found on the home page of the journal.
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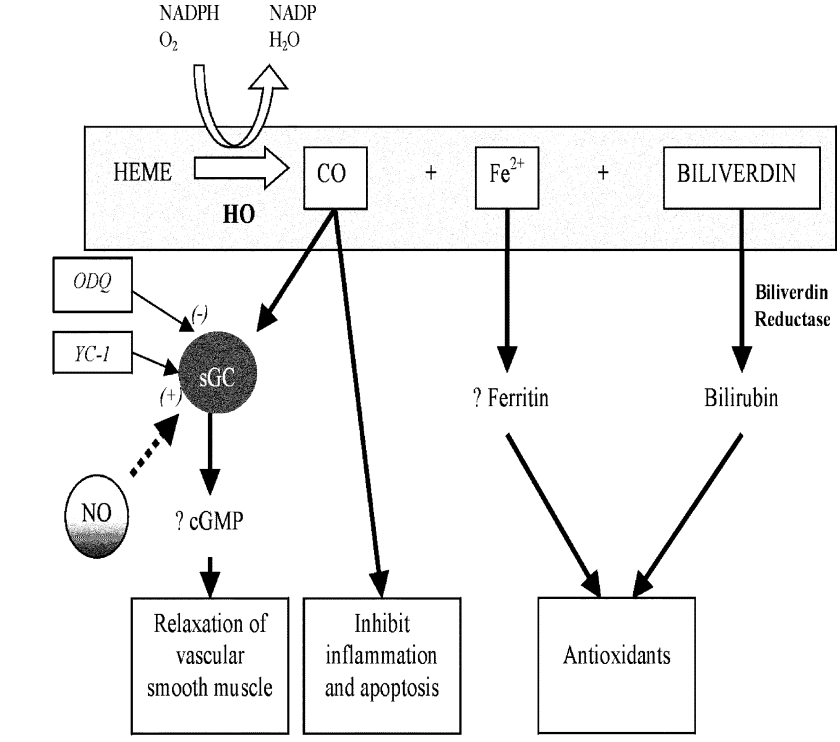
doi:10.1016/j.freeradbiomed.2004.11.002

Introduction

The enzyme heme oxygenase (HO) was originally characterized in 1968 by Tenhunen, and was described as the only mediator of heme metabolism in a cell [1]. This led to the notion that this enzyme was a housekeeping protein, strictly involved in maintaining homeostasis of the heme pool. Since then, great strides have been made in the areas of research surrounding heme metabolism in general and HO in particular. It is now recognized that HO is involved in the control of vascular tone [2–4], regulating anti-inflammatory [5–7] and antiapoptotic [6–9] responses as well as reducing oxidative stress and subsequent tissue damage in several organ systems [10–12]. These various properties attributed to HO are carried out through the catalytic products of heme degradation, namely carbon monoxide (CO), biliverdin, and free iron (Fe^{2+}) (Fig. 1).

Three isoforms of the HO protein have been identified. HO-1 is a 32-kDA inducible form of the enzyme; HO-2 is a 36-kDa constitutive form of the enzyme while HO-3 is the



Healthy Pregnancy	Maintenance of adequate blood flow through uterine and placental blood vessels	Inhibition of excessive activation of inflammatory and apoptotic cascades in placental tissue	Maintenance of a healthy oxidant-antioxidant balance within the placenta
PET Pregnancy	Decreased and oscillating blood flow through placental blood vessels	Heightened activation of inflammatory and apoptotic cascades in placental tissue	Increased levels of ROS coupled with a decrease in antioxidant capacity within the placenta

Fig. 1. Heme degradation pathway and physiological roles of its breakdown products CO, Fe^{2+}, and biliverdin during a healthy and PET pregnancy.