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Forum Editorial

The Heme Oxygenase System: Past, Present, and Future

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THE MICROSOMAL HEME OXYGENASE (HO) SYSTEM is the most effective mechanism in the cell for α-isomer-specific cleavage of Fe-protoporphyrin IX (heme b, hematin, hemin) and production of carbon monoxide (CO), and the open tetrapyrrole, biliverdin (for review, see 26). In the course of this catalysis, the chelated iron is released, with its subsequent reutilization for maintenance of iron homeostasis and gene regulation. The mechanism of heme cleavage involves a mixed-function oxidase type of reaction, *i.e.,* molecular oxygen is used to generate oxidized products and water; the concerted activity of NADPH-cytochrome P450 (cytP450) reductase is required for transfer of electrons to the heme–oxygen complex and activation of oxygen. Reduction of biliverdin to bilirubin by the dual pH/cofactor-dependent soluble enzyme, biliverdin reductase, terminates the multistep process of heme metabolism (37).

In the last decade, there has been an impressive expansion in the number of reports dealing with the HO system that exceeds, by severalfold, the collective number of publications of the prior three decades. In particular, much progress has been made toward elucidating functions mediated by one of the HO products, CO, and many studies have convincingly demonstrated that CO functions in parallel with nitric oxide (NO) as a signal molecule in the cell (for review, see 28). The developments are uncanny, considering the long-held view of CO and bile pigments solely as cellular toxins that, respectively, cause fatal poisoning and kernicterus in the newborn. Some key events of the past that have led to the present standing of the HO system, which in turn form the foundation of the future of the field, are noted in the following.

PAST

Early on, research interest in the HO system was modest and limited to a handful of laboratories (30, 58, 68). The system was presumed to consist of a single cytP450-dependent enzyme, and to be of physiological significance solely in the context of catalysis of heme, primarily that of hemoglobin. In the years that followed, the identification of the HO system as a distinct microsomal enzyme pathway that controls cytP450 levels and oxidative metabolism of drugs and chemicals (31, 68) increased its visibility in the research community.

A fundamental observation about the mechanism of HO activity that proved to be the key in revealing the multifaceted dimension of its function in the cell was finding that all metalloporphyrins bind to an evolutionarily conserved domain of the HO protein, the "heme pocket" (25, 45), now known also as the "heme binding domain" and "HO signature" (GenBank). Defining the inability of the "pocket" to recognize the metal chelated within the porphyrin ring was fundamental to the evolvement of the HO system to its current prominent standing in science and medicine. In principle, enzyme activity is blocked by metalloporphyrins that do not activate molecular oxygen, such as tetrapyrrole complexes of Zn, Sn, and others through competition with Fe-protoporphyrin IX for binding to the heme pocket (24, 32). This finding formed the basis, first, for the experimental use of nonphysiological metalloporphyrins in the treatment of newborn jaundice (19), and a decade later proved crucial for exploring the function of CO generated by HO activity as a signal molecule in the cell (16, 61, 69).

Concurrent with defining the independence of the HO system from cytP450 was the discovery that metal ions are potent inducers of HO activity (31, 33). This identified the HO system as the first stress-inducible gene/enzyme. Later, it was shown that the elicited response was not specific to metals, but extended to a host of unrelated environmental chemicals with one feature in common, *i.e.,* the ability to cause oxidative stress (for review, see 26), and hence recognition of the HO system as an HSP32 family of proteins (11, 20, 50). The ensuing comprehensive work in defining the molecular mechanisms for HO regulation by different types of stimuli served to extend the reach of the system to divergent disciplines (for review, see 2).

The increase in HO activity in response to the systemic stress was detected in all tissues except testes and brain. Exploring the cellular and molecular basis for the unexpected and "novel" tissue response to metals (34) led to the discovery of the second and the constitutive form of HO, referred to as HO-2, with the stress-inducible form designated as HO-1

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(35). The two forms were shown to present different gene products with disparate mechanisms of regulation and pattern of tissue distribution, with the adrenal glucocorticoids being the effective inducers of HO-2 gene expression (49, 64). An intriguing property of HO-2 uncovered was the direct interaction of the "heme regulatory motifs" of the protein with NO radicals (7). This suggested the possible role of HO-2 as an intracellular "sink" for NO radicals and the potential to function as an intracellular oxygen sensor (7, 28). Later, an HO-2-related form, HO-3, was described in the rat brain (39). Because the presence of this protein has not been established in the human and it has negligible heme catabolism activity in the rat tissue, HO-3 has been marginalized to HO-1 and HO-2.

A most unexpected outcome of the effort to characterize HO-2 was the finding that the brain had an unexpectedly high level of HO-2 (54) that was concentrated in neurons in those regions of the brain associated with memory and learning (hippocampus), sensory tracts, and locomotion (12). Deliberating a physiological basis for the high-level expression of HO-2 in the brain led to the proposal that "heme oxygenase in the brain has functions other than heme degradation" (54). This proposal was validated by the subsequent demonstration of the function of CO generated by HO (HO-2) activity as a signal molecule in the brain and linking generation of cycle GMP in the brain and other tissues to CO and HO activity (15, 16, 27, 61, 69). As such, the *in vitro* studies demonstrating activation of guanylate cyclase by CO (3) were extended to tissue levels.

Meanwhile, another "toxic" product of HO activity, bilirubin, and to a lesser extent biliverdin, were characterized for their potent intracellular antioxidant activity (53). Collectively, those findings were instrumental in setting in motion a radical change in our perception of CO and bile pigments, and identified them as the most unexpected components of cell signaling pathways and defense mechanisms.

PRESENT

The answer to the question "why heme needs to be degraded to iron, biliverdin, and CO" (47) can be found in the volley of publications that have culminated in the now commonly accepted concept that increase in HO-1 activity is a desirable cellular response that can positively influence a variety of pathophysiological events, including the outcome of organ transplantation, ischemic stroke, and untoward effects of exposure to tissue-damaging oxidative stimuli (5, 18, 38, 48, 51, 55, 56, 60, 65, 67). Also, persuasive arguments for the involvement of abnormal activity of HO isozymes in neurodegenerative disorders, including stress-induced neuronal deficits such as Alzheimer's disease (57), and angiogenesis have been be made (8).

In support of the now firmly established role of bilirubin as an effective intracellular antioxidant (52) is the finding that low serum bilirubin levels correlate with the risk of early familial coronary disease (17). In addition, bilirubin is now also known to modulate immune effector functions and suppress inflammatory response (9, 42, 66).

Not only does generation of CO and biliverdin denote the significance of the HO system, but the vital role of the system in the maintenance of iron homeostasis in all forms of life, as well as intimate interactions of the HO system with other signaling pathways, is increasingly acknowledged (4, 10, 14, 60, 63). Also, because heme itself, not iron, is the most effective catalyst for formation of reactive oxygen species, the basic act of degrading heme is now realized to be important component of the role of the HO system in protection against oxidative stress (36).

A reflection of the many ways that increased HO activity can be of benefit to the cell is the current interest in manipulation of HO gene expression. In experimental settings, HO-1 gene transfer and amplification have been used to prolong allograft survival time in systemic organs, to inhibit injury-induced neointima formation, to protect endothelial cells and lungs against oxidant-induced injury, and to promote angiogenesis (6, 43, 44, 59).

Of course, it would be ingenuous to consider that in all instances an increase in heme degradation activity would promote a positive outcome. Indeed, the unresponsiveness of HO-2 to oxidative stress, plus the fact that HO-1 is only transiently induced by any stimuli, attests to the importance of a tightly regulated ability to degrade heme and is consistent with the assessment that excess levels of HO activity in a protracted time span may not be compatible with the normal physiology of the cell.

FUTURE

Gene transfer and silencing are now considered promising approaches to the therapy of various disorders in both systemic organs and the CNS. The sum of the new developments in the field bears the promise of further exploration of the beneficial outcome of HO gene transfer in a therapeutic approach to systemic organ malfunctions and neurodegenerative disorders, including Parkinson's disease. It is imminent that in the future, genetic and pharmacological manipulations of the HO system will be routinely used in clinical settings. To date, the prospect of HO-1 gene therapy in the nervous system for treatment of neurological disorders, or HO-2 gene therapy in any organ, has not been examined. HO-2 gene therapy, however, would appear to be a most promising approach for the treatment of vascular and neurological disorders, whereby both the antioxidant and CO signaling activities of its products would be realized (23, 40), and the protein itself could serve to inactivate free radicals of O_2 and NO.

Indeed, further exploration of the significance of HO-2 interaction with NO radicals and the potential role of HO-2 as an intracellular sink for free radicals and/or oxygen sensor may offer a new perspective and understanding of the mechanism by which cellular homeostasis of gaseous molecules is maintained.

It is most likely that recent discoveries about the heme degradation pathway enzymes will expand the reach of the HO system in a yet wider range of disciplines. The emergence of bile pigments as a new class of cell signaling entities (13, 29), and the discovery of kinase and transcriptional activities of biliverdin reductase (1, 21, 46) are certain to figure prominently in the future direction of research and likely will expand the reaches of the HO system far beyond what was once unthinkable. The future direction of research into the regula-

tion and function of the HO system could include the potential utility of biliverdin reductase gene therapy to increase bilirubin production and to increase expression of HO-1 (21).

In addition, in-depth investigation of interactions between the HO, NO, and cyclooxygenase pathways, which are linked by certain common criteria, including having constitutive and oxidative stress-inducible forms and an intimate link to the heme molecule, would be crucial to further understanding of the intricacies of processes that govern cell functions (10, 41, 62).

Based on the past developments and the present understanding, the prospect of the HO system to continue "mesmerizing investigators" (22) for the foreseeable future is strong.

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ABBREVIATIONS

CO, carbon monoxide; cytP450, cytochrome P450; HO, heme oxygenase; NO, nitric oxide.

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