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REVIEW ARTICLE

Role of Heme Oxygenases in Cardiovascular Syndromes and Co-morbidities

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Abstract: Cardiovascular Diseases (CVD), are the leading cause of human mortality worldwide and the focus of the intensive investigation is to characterize their pathogenesis. This review examines contribution to CVD of heme oxygenases (HOs), heat shock protein enzymes, comprising 3 isoforms: HO-1 (inducible), HO-2 (constitutively expressed) and HO-3 (function presently undefined), which constitute a primary endogenous countermeasure to oxidative tissue damage. Their role as CVD countermeasures is considered in the context of atherosclerosis, consequences of which are the leading cause of CVD deaths and from which 5 major syndromes may develop, namely: coronary artery disease and stroke, peripheral artery disease, kidney disease, cardiopulmonary disease and cerebrovascular disease. Over 75% of CVD deaths result from Coronary artery disease and stroke, with the severity of these conditions correlating with a systemic increase of the endogenous antioxidant bilirubin, produced by HO degradation of heme. Peripheral artery disease, (PAD) resulting from constricted arteries of the extremities is a painful and disabling condition, the severity of which correlates with elevated serum HO. Whether this represents an adaptive response or the enzyme is a contributor to PAD, remains to be determined. CVD symptoms, particularly hypertension, damage the vasculature and filtering structures of the kidneys and may be ameliorated by HO inducers. Interestingly, constitutive renal expression of HO-2 indicates that the enzyme is vital for healthy kidney function. Right ventricular hypertrophy and increased vascular resistance in blood vessels of the lungs exhibit mutually reinforcing positive feedback to result in cardiopulmonary heart disease, with morbidity and mortality resulting from associated inflammation and may be decreased with HO-1 inducers. Cerebrovascular disease, a major CVD complication affecting brain vasculature, with resulting susceptibility to stroke, maybe potently ameliorated by HO-1 inducers.

***Conclusion*:** Each of the six major categories of CVD exhibit features of pathogenesis that hold potential as future therapeutic targets, for modulated heme oxygenase activity.

Keywords: Heme oxygenase, cardiovascular disease, atherosclerosis, stroke, endothelium, kidney.

1. INTRODUCTION: CARDIOVASCULAR DISEASES: MAJOR FEATURES OCCURRENCE AND CURRENT TREATMENTS

Cardiovascular diseases (CVD) are disorders that affect the functionality of blood vessels and the heart [1]. This class of pathologies is comprised prominently of coronary artery disease (CAD - which includes ischemic heart disease), myocardial infarction (commonly called heart attack), with associated cardiac pain (angina); and other CVD syndromes, including rheumatic, hypertensive congenital and valvular, heart disease, heart failure, thromboembolic disease, venous thrombosis, aortic aneurysms, cardiomyopathy and carditis stroke, heart failure, hypertensive heart disease, cardiomyopathy, cardiac arrhythmia, congenital heart disease, valvular heart disease, carditis, peripheral artery disease (PAD – a CVD form featuring impairment of blood flow to extremities), cerebrovascular disease, in which blood flow to the brain is impaired – and includes stroke, stenosis (narrowing with occlusion of vessel diameter) of the renal arteries and resulting kidney failure, along with many related syndromes [2]. Mechanisms contributing to the types of CVD listed above are varied. For example, PAD, CAD and stroke, may occur as a result of high alcohol intake, smoking, elevated cholesterol and blood pressure, poor diet, obesity and sedentary lifestyle, to name some of the conditions that may lead to CVD [3]. The nature of these factors means that approximately 90% of all CVD is avoidable through the practice of heart-healthy behavior [4]. Cardiovascular diseases are the major cause of human mortality worldwide [2]. This is partly a consequence of the fact that cells of cardiovascular tissue exhibit significantly greater sensitivity than other cells to oxidative stress that develops normally during the normal aging process, particularly as a consequence of progressive age-dependent accumulation of senescent cell phenotypes that express inflammatory cytokines and advanced glycation end products (AGEs) that trigger release of reactive oxygen species (ROS), when interacting with their cognate receptors (RAGEs) [5, 6]. Moreover, CVD mortality is very high particularly among affluent populations – although decreasing in these societies with increased public education on prevention, but increasing in the developing world, with increasing affluence and resulting lifestyle changes [7], with initial diagnosis occurring on average 7-10 years earlier for males than females [3]. CVD pathophysiology has been the subject of intensive investigation for many years at the time of this writing and its major features are fairly well documented. Atherosclerosis is the major degenerative syndrome leading to CVD, with approximately 1 in 3 people dying from its effects. It features progressive occlusion of the arteries beginning in childhood, (as early as 7-9 years of age) with deposits of cholesterol, cells and proteinaceous material called atheromas, or atherosclerotic plaques impeding blood flow and occasionally initiating clots that may break loose as thrombi, resulting in stroke [8, 9]. The influence of plaques on CVD progression is accompanied and exacerbated by a buildup of calcium phosphate in the extracellular matrix of cardiovascular tissue, which significantly stiffens blood vessels and reduces the functional efficiency of the heart [8]. Several major pharmacological approaches to CVD are currently available for clinical use. A major example is the use of medication for treatment of high blood pressure, which has proven generally valuable in reducing the likelihood of CVD onset and symptom severity, regardless of baseline blood pressure, cardiovascular risk levels or age and gender [10]. The most commonly used treatments include statins, which may slow the progress of CVD in

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persons diagnosed with one of the component syndromes – with therapeutic response to this class of drug, being more easily monitored in men than in women [11]. Risk and CVD symptom severity may also be lessened with some blood glucose-lowering medications useful in the management of Type 2 Diabetes, although some debate remains as to the effectiveness of these drugs in mitigating CVD severity [12]. Investigations into the benefits of regular aspirin intake, revealed that this is of only limited benefit for persons at low risk of developing a cardiovascular syndrome, since the benefits are offset by increased occurrence of gastrointestinal bleeding, which is a side effect of aspirin for some people, particularly with sustained intake and/or high dose ranges [13].

2. HEME OXYGENASES: MAJOR PHYSIOLOGICAL ACTIVITIES

Heme oxygenases (HOs) are heat shock protein enzymes that use tissue heme as a substrate and function as an essential antioxidant adaptive response by all vertebrate cells studied at the time of this writing - and are essential for preservation of normal cellular and tissue homeostasis in response to oxidative stress imposed by a wide range of influences, including injuries, and disease. Three HO isoforms have been described: HO-1, an inducible form which is up-regulated I n response to oxidative stress. HO-2 which is produced constitutively at a basal level by all cells and HO-3, which also metabolizes heme, but is not well characterized at the time of this writing. A major putative function of HOs is clearance of heme deposits that accumulate in tissues due to normal erythrocyte turnover. The enzymatic process mediated by these proteins, degrade heme to biliverdin, ferrous iron, and carbon monoxide (CO) according to the following reaction sequence: Heme + NADPH + H+ + 3 O2 → biliverdin + Fe2+ + CO + NADP+ + H2O [14]. Potential toxicity of the free iron released by this reaction is prevented by its sequestration by ferritin, a physiological regulator of iron levels – and biliverdin is subsequently converted by biliverdin reductase to bilirubin, a potent endogenous antioxidant, which contributes substantially to control of inflammation by inhibition of NADPH oxidase [15]. CO is produced by this reaction at levels in which it acts as a highly efficient second messenger that augments cellular resistance to oxidative stress by increasing intracellular cyclic nucleotides, particularly cGMP, according to the general reaction: CO-> guanylate cyclase ->increased cGMP [16]. These HO-mediated processes additionally stabilize membrane ionic balance preventing mitochondrial calcium overload-induced tissue damage [17]. Some evidence suggests that elevated systemic levels of its activity may be used as diagnostic predictors of meta-inflammation associated with insulin resistance and metabolic syndrome [18]. For the past several years at the time of this writing, rapidly evolving insight into HO-mediated cytoprotective mechanisms, has stimulated interest in approaches pharmacological modulation of these enzymes to in clinical settings. This is a particularly attractive objective given the powerful protective capacity of this enzyme for many tissues, particularly cells of the cardiovascular system, lungs, brain and kidneys [19].

3. INVOLVEMENT OF HEME OXYGENASE ACTIVITY IN ADAPTIVE RESPONSES TO CVD

The remainder of the present review examines the involvement of heme oxygenases in the adaptive response to and therapeutic approaches for 6 major CVD categories. These include: atherosclerosis, coronary artery disease and stroke, peripheral artery disease, kidney disease, cardiopulmonary disease and cerebrovascular disease.

3.1. Atherosclerosis

Atherosclerosis is a CVD category which has emerged as the number one cause of disability and death in the developed world [20]. The condition results from a buildup of plaque deposits within the arteries, which progressively restricts blood flow to tissues and also may form thrombi as a result of blood clotting at the site of plaques, which may break loose to cause stroke [21]. In humans, atherosclerotic arterial plaque accumulation may begin in early childhood, but not manifest as obvious symptoms until middle age. As the condition worsens, it may progress into a debilitating and life-threatening phase of the disorder that that may also transition into one or more of the 5 CVD syndromes named above (coronary artery disease/stroke, peripheral artery disease, kidney disease, cardiopulmonary disease and cerebrovascular disease) stroke [21].

The role of heme oxygenase in these syndromes and atherosclerosis, will be considered below. The etiology of atherosclerosis is presently not clearly defined, however major risk factors for its development and severity are well known and include obesity, smoking, high blood pressure and diabetes, along with a family history of the condition [22]. The pathogenesis of the disease occurs as a primary result of formation of plaques composed of blood proteins, cholesterol, fat and calcium deposits, into which macrophages typically migrate and mature into “foam cells” as a result of ingestion of plaque material – which express high levels of inflammatory cytokines, this compounding the effects of blood flow restriction with inflammatory tissue damage [23]. Recent clinical evaluations of approaches to slow the progression of atherosclerotic symptoms have demonstrated the efficacy of this objective by intake of dietary compounds that amplify HO activity. For example, sustained consumption of docosahexaenoic acid (DHA), present in many fish, augments systemic HO production through the endothelial free fatty acid receptor 4, and Nrf2 signaling, significantly abates inflammation associated with atherosclerotic plaques [24]. This encouraging observation is bolstered by recent findings described in a 2017 *Current Pharmaceutical Design* report demonstrating that HO-mediated induction by dietary curcumin, a bioactive component of turmeric significantly abates major features of atherosclerotis, by reducing the incidence of thrombus formation and stabilizing vascular tone and vascular endothelial cell (VEC) growth. The underlying anti-atherosclerotic mechanisms in which HO activity is involved, appears to result from improved regulation of VEC expression of P-selectin, STAT-3, p38, intercellular adhesion molecule (ICAM)-1, and (especially) the pro-inflammatory transcription factor NFκB and JNK [25]. These and other studies are increasingly revealing HO amplification n to be an increasingly promising countermeasure to atherosclerosis.

3.2. Coronary Artery Disease and Stroke

These two syndromes are together responsible for 80% of CVD mortality in males and 75% in females [3]. Outcomes of a very exciting human clinical investigation, reported in 2014, showed that increased levels of serum bilirubin, a major endogenous antioxidant produced by HO-mediated heme degradation, correlated with significant improvement in prognostic profiles of CVD patients, especially coronary artery calcification (CAC) and thrombus formation [26].

3.3. Peripheral Artery Disease

Peripheral artery disease (PAD) is characterized prominently by constriction of peripheral arteries, that is, those which are not blood supply conduits for the brain, pathologies of which are called cerebrovascular disease, or heart (coronary arterial disease) occurring most frequently in arteries of the legs [27], with symptoms that in the affected leg notably include walking-associated-pain (intermittent claudication), along with reduced hair growth skin ulceration and discoloration [27]. Stroke, tissue necrosis and enhanced susceptibility to infections constitute major PAD complications – although approximately half of all PAD cases are asymptomatic [27]. Based on the known adaptive effects of HO in many forms of tissue trauma, it may be intuitively speculated that influences that ameliorate PAD effects might also promote elevated expression of the enzyme. Indeed, future analysis of PAD pathogenesis may reveal this to be

the case as an understanding of the disorder evolves. Nevertheless, it is interesting to note that an initial characterization of HO activity in human PAD patients, showed that a standard exercise used clinically to suppress intermittent claudication also exhibited strong positive correlation with decreased circulating leukocyte expression of HO which occurred along with improved pain-free walking time and changes in immune parameters suggesting lessening of PAD symptom severity [28]. The significance of these observations with respect to the role of HOs on PAD is unclear at the time of this writing, but is likely to become better defined with increased understanding of PAD pathogenesis.

3.4. CVD-associated Kidney Disease

Kidney disorders are a major complication of many CVDs, most often associated with impaired blood filtering capacity resulting from damage to kidney tissues involved in this activity which are delicate and sensitive due to excessive blood pressure. Moreover, since hypertension/high blood pressure is a major feature of many CVDs, some degree of kidney impairment is present in almost all hypertensive patients – very often debilitating to an extent that lifetime dialysis treatments are required [29]. Heme oxygenase activity mediates several well-known protective effects on the kidney – and has been identified as a major physiologic mechanism for the preservation of renal tissue function [19]. A major mechanism by which this enzyme protects the organ appears to be the interaction of CO generated by HO-mediated heme degradation. This protective activity may be induced by oxidative stressors and other insult to kidney tissue, which results in HO-1 up-regulation. An added measure of protection against both acute and chronic renal injury occurs as a consequence of constitutive HO-2 expression – a phenomenon that underscores the capacity of the 2 isoforms of the enzyme to combine activities in preservation of a tissue which is particularly sensitive to trauma [30]. Interestingly, HO activity is not absolutely necessary for protection of renal tubules and vasculature. Indeed, CO administered at subtoxic dose as an inhalant, is also demonstrated to limit oxidative renal tissue injury [30].

3.5. Cardiopulmonary Heart Disease

Disease states that affect cardiovascular tissue engender feedback processes with significantly adverse effects on the respiratory system. The resulting syndromes are known as cardiopulmonary disease. A prominent symptom and anatomical feature of this class of disorder is right ventricular hypertrophy resulting from effects of elevated blood pressure and pulmonary blood vessel stenosis and increased vascular resistance [31]. Such ventricular hypertrophy and related effects are promoted by sustained exposure of heart tissue to high blood pressure – resulting in expansion of muscle fibers due to increased workloads, which in turn result in a cluster of potentially fatal effects, including cardiac arrhythmias [32]. Classification of a particular CVD syndrome as pulmonary heart disease, is based on it major etiologic contributors having an origin within the pulmonary circulation. Two major triggers of this class of pathologies, include damage to vascular tissue resulting from chronic hypoxic pulmonary vasoconstriction and hypoxic injury resulting from oxygen deprivation – a process often observed in preeclamptic females experiencing cardiopulmonary complications to pregnancy [33]. At the time of this writing, few descriptions have been published describing the effects of varying levels of heme oxygenase activities on the major pathological features of cardiopulmonary heart disease. Nevertheless, some research has been accomplished that suggest that HO inducers such as some plant polyphenols will exert a general beneficial effect on respiratory tissue homeostasis in these syndromes and other disorders of the lungs [19]. A specific application of these effects in the clinical management of cardiopulmonary disease is suggested by intriguing outcomes of a 2015 study that demonstrated suppression of inflammatory tissue damage resulting from cardiopulmonary bypass surgery as a result of systemic treatment with propofol, an anesthetic with potent HO-1-inducing properties [34].

3.6. Cerebrovascular Disease

These disorders are characterized by pathological alteration of the brain's vasculature, typically involving disruptions to circulation within the organ, resulting from damage to its afferent arteries with resulting disruption of cerebral circulation. CNS-affecting stroke is the most common manifestation of such conditions and may be ischemic in nature, resulting from blockage of a vessel with resulting oxygen deprivation to the tissue it is serving – or alternatively, hemorrhagic stroke which occurs when a blood vessel ruptures [35]. The most significant contributing risk factor for the development of cerebrovascular disease is hypertension, which over long time periods, adversely alters blood vessel structure – particularly if compounded by the presence of atherosclerotic plaques which inhibit cerebral perfusion through the narrowing of blood vessel diameter and predispose an afflicted person to stroke [35]. Since heme oxygenase activity is known to be strongly neuroprotective [19], persons afflicted with cerebrovascular diseases are likely to substantially benefit from approaches to amplifying HO activity, particularly at sites within the brain where blood vessel damage may set the stage for stroke, dementia or other consequences of vascular disorders that trigger neurodegenerative processes. Some intriguing insight into contributing mechanisms that might in the future be manipulated with drugs or selective exercise routines, was described in a January 2018 report, published in *Biomedical Research International*, that evaluated heme oxygenase-1 (HO-1) effects on neuroanatomical pathological abnormalities and impairment of spatial memory imaging by exercise-induced HO-1 expression in a (mixed gender) Wistar rat model of Alzheimer's disease – which exhibits crebrovascular alterations in brain structure and function with similarity to humans [36]. The investigators observed that increased HO-1 activity exhibited a strong positive correlation with abatement of adverse neuropathological changes, along with improved spatial memory. These outcomes confirm previous studies demonstrating HO-mediated benefits to both neurologic and cardiovascular tissue [19] – and suggest novel directions for use of amplified HO activity in the management of cerebrovascular disease [36].

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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