Review

Iron and nitric oxide play key roles in the development of cardiovascular disorder

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Iron (Fe) is an essential but potentially harmful nutrient. On the other hand, nitric oxide (NO) is an inorganic free-radical gaseous molecule which has been implicated to play an unprecedented variety of roles in biological systems. Although complex relationships between Fe and NO have been demonstrated, there are still controversies as to what are the influences of Fe on NO balance in the development of cardiovascular disorder. Both Fe and NO have dual but unique roles in the prevention and/or development of cardiovascular complications such as atherosclerosis and/or myocardial infarction. Sustained increase in the concentration of both Fe and NO has been associated with generation of free radical species, promoting oxidation of low density lipoproteins (LDL) which strongly correlated with cell oxidative damage. Moreover, the oxidation of LDL has been implicated as a risk factor in the genesis of cardiovascular disorders. In this light, the mechanistic interactions between Fe and NO in the development of and/or predisposition to cardiovascular disorder are discussed.

Key words: Iron, nitric oxide, oxidative damage, cardiovascular disorder.

INTRODUCTION

Myocardial infarction (MI) or acute myocardial infarction (AMI), commonly known as a heart attack is the interruption of blood supply to part of the heart, causing some heart cells to die. This is most commonly due to occlusion (blockage) of a coronary artery, following the rupture of a vulnerable atherosclerotic plaque, which is an unstable collection of lipids (fatty acids) and white blood cells (especially macrophages) in the wall of an artery. The resulting ischemia (restriction in blood supply) and oxygen shortage, if left untreated for a sufficient period of time, can cause damage or death (*infarction*) of heart muscle tissue (*myocardium*). Moreover, several investigators have studied the relationship between reactive oxygen species and various diseases, and it has been revealed that many of the reactions that involve reactive oxygen species often require the presence of a transition metal such as iron (Sengoelge et al., 2005; Orimadegun et al., 2007; Tavora et al., 2009).

Perhaps it is noteworthy to know that both iron and nitric oxide play important but opposite roles in the development of cardiovascular disorder. While an increased iron status may promote free hydroxyl radical generation in cellular systems and thus potentiate cellular damage and atherosclerosis, production of nitric oxide. However, a continuous and sustained production of nitric oxide could contribute to oxidative damage through the formation of peroxynitrite, a very reactive free radical which could promote lipid peroxidation. Because of the crucial roles that iron and nitric oxide play in cellular systems and the strong link that has been demonstrated between the duo (Richardson and Ponka, 1996; Richardson and Lok, 2008), it will not be out of place to emphasis that a delicate homeostatic balance exist between iron and nitric oxide in biological systems such that any disruption or perturbation to this strictly regulated balance could be catastrophic to the cellular system. Inspite of this, investigations may be required to elucidate and bring to light the outcome of iron and nitric oxide mechanistic interaction as relate to development of cardiovascular disorders. This will put to rest curiosity and questions relating to the likely consequences of a

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sustained high iron status and nitric oxide levels against the background that increased iron and nitric oxide could trigger generation of free radical species which may spell doom for the biological system if exposure is long enough. This article is an attempt aimed at discussing the probable roles of iron and/or nitric oxide toward development of cardiovascular disorder.

IRON (FE) AND NITRIC OXIDE (NO) IN LIVING CELLS

Iron is an essential but potentially harmful nutrient. It contributes to many important physiologic functions in the body and as well may increase biological markers of oxidative stress, cytotoxicity, and lipid peroxidation in biological systems. Iron not only affects the functions of leukocytes, endothelial cells and cytokine production but also causes oxidative stress and support microbial growth. More than 2 decades ago, it was proposed that iron depletion protects against ischemic heart disease and that this effect may explain the remarkably low incidence of cardiovascular disorders in menstruating women (Sullivan, 1981, 1989, 2003). Studies have been able to show that increase in cellular iron plays a major role in the formation of hydroxyl radicals which potentially contribute to cell damage and atherosclerosis (Sengoelge et al., 2005; Tavora et al., 2009). Free iron has been implicated in lipid peroxidation and ischemic myocardial damage, and it was reported that iron is an independent risk factor for myocardial infarction (Klipstein-Grobusch et al., 1999; Orimedegun et al., 2007). Though it was suggested that the availability of catalytic iron may be more important than overall body iron stores (Lauffer, 1990; Sengoelge et al., 2005) nevertheless an independent relationship between coronary heart disease and the level of serum iron status as a risk factor has been demonstrated (Salonen et al., 1992). Thus the question being asked is "how safe is stored iron?" (Sullivan, 2004). In a separate study, Ascherio et al. (1994) reported a link between an increased risk of fatal coronary heart disease and heme iron intake. This is even as indirect evidence that iron is involved in reperfusion injury after an ischemic event has been provided from animal studies (Klipstein-Grobusch et al., 1999).

This study revealed that free radicals were generated after blood flow was restored to ischemic myocardium, thus contributing to the subsequent myocardial injury (Klipstein-Grobusch et al., 1999). Events such as blood donation, which depletes iron stores in the donors, has been associated with reduced risk of myocardial infarction (Klipstein-Grobusch et al., 1999; Zheng et al., 2005) and cardiovascular disease (Orimadegun et al., 2007). Meanwhile it has been observed that maximum protection exists among iron deficient subjects since iron status affects the modification of LDL cholesterol and myocardial reperfusion injury (Sullivan, 1992; Facchini

and Saylor, 2002). More recent studies have also shown that men with moderately elevated ferritin level have a significantly worse coronary artery disease risk profile than men with lower level (Ramakrishnan et al., 2002).

The endothelium secretes a nitric oxide (NO) of vascular-relaxing substances as well as several vaso-constricting agents. However, one of the most potent endogenous vasodilators is endothelial-derived NO. NO is a critical modulator of blood flow and blood pressure (Vallance et al., 1989) and opposes the vaso-constricting effects of endothelin, angiotensin II, serotonin, and nor-epinephrine (Luscher et al., 1993). NO also suppresses the proliferation of vascular smooth muscle (Annuk et al., 2003). Deficiency of NO contributes not only to increased vascular resistance but to blood vessel medial thickening and/or myointimal hyperplasia, which may alter the structure of the vascular bed. Oxidative stress is one process that has been shown to decrease the expression of endothelial nitric oxide synthase (eNOS) (Luscher et al., 2003). eNOS limits monocyte/macrophage-endothelial cell interaction, therefore its loss or decreased expression may lead to the formation of a macrophage-rich atheroma. This results in a soft plaque that increases the risk of unstable angina, thrombosis, and acute myocardial infarction (Annuk et al., 2003). It has been demonstrated that excess number react with the superoxide anion to produce peroxynitrite, a very aggressive free radical species that contribute to lipid peroxidation and oxidative stress (Torreilles et al., 1999). Moreso a decreased production of number, or reduced sensitivity to the action of number, has consistently been shown to impair endothelial-dependent vasodilation, contributing to the pathogenesis of atherogenesis (Luscher et al., 1993).

POSSIBLE MECHANISMS BY WHICH IRON AND/OR NITRIC OXIDE MAY PREDISPOSE TO DEVELOPMENT OF CARDIOVASCULAR DISORDER

(1) Increased iron status may lead to the generation of free hydroxyl radicals which promotes oxidation of low-density lipoprotein (LDL). The importance of oxidized LDL in atherosclerosis (Orimadegun et al., 2007), and the potential for iron to act as a catalyst in processes leading to cellular oxidative damage (Reif, 1992; Silva and Aust, 1993; Satoh and Tokunaga, 2002), has been reported. This supports a potential role of iron in coronary heart disease. Previous studies have demonstrated that an association exist between iron and increased oxidation of LDL cholesterol with the former catalysing production of tissue-damaging free hydroxyl radicals (Klipstein-Grobusch et al., 1999). Moreso, that it has been established that LDL oxidation plays an important role in the pathogenesis of atherosclerosis and cardiovascular disease (Sengoelge et al., 2005). Oxidized LDL causes lipids to accumulate in macrophages and foam cells

(Ramakrishnan et al., 2002), and this process has been shown to be cytotoxic to many cell types and chemotactic for monocyte macrophages.

(2) High iron status may result in endothelial cell dysfunction. Experimental evidence have revealed that increase in cellular iron could down-regulate the expression of nitric oxide synthase (NOS) (Kim and Ponka, 2002; Richardson and Lok, 2008) through a strictly controlled mechanism. The enzyme NOS is responsible for the formation of NO starting from L-arginine. NO plays a critical role in the maintenance of vasculature in a state of vasodilation. The overall effect of inadequate amount of NO would be impaired endothelium-dependent vasorelaxation, blood pressure regulation and acceleration of atherogenesis with an onset of acute atherothrombotic events. Arterial smooth muscle proliferation has also been reported to be a complication of decreased activity of NOS secondary to increased iron status (Sengoelge et al., 2005). So whatever is capable of causing increases in iron and nitric oxide levels may abate the homeostatic balance between the iron and nitric oxide. This could have devastating effects on the cellular system as both iron and nitric oxide are capable of promoting the generation of free radical species which may lead to cell oxidative stress.

(3) Another possibility is that, if a factor raises the iron status, this may positively affects the activity of myeloperoxidase (MPO) and phagocyte associated NADPH oxidoreductase in the neutrophil and hence potentiate the formation, instability and rupture of plaque (Ikura et al., 2002; Tavora et al., 2009). Report by Vita et al. (2004) revealed that high cellular iron correlated with increased circulating MPO which plays a vital in neutrophilic inflammation. MPO which has emerged as a potential promoter of atherosclerosis (Hazen, 2004; Nichols and Hazen, 2005) is stored and secreted from activated neutrophils and monocytes.This as an important component in degranulation material of leukocytes, a critical process in human innate host defenses (Sugiyama et al., 2001; Naruko et al., 2002). The role of MPO in the initiation and propagation of atherosclerosis may not be unconnected with its potential to initiate lipid peroxidation as well as promote post-translational modification of target proteins (Podrez et al., 2000; Zhang et al., 2002). Recent studies have found that MPO is capable of promoting oxidation of lipoproteins which could lead to increase in cholesterol deposit and formation of foam cells in fatty streaks (Podrez et al., 2000; Roman et al., 2008). MPO was observed to be increased in human atheromas (Daugherty et al., 1994) and it has also been demonstrated in a variety of inflammatory conditions (Zhang et al., 2002) which could potentiate the development of cardiovascular disease. The emergence of myeloperoxidase as an important coronary risk factor underscores the links among iron, oxidative stress, and inflammation in cardiovascular

disorders. Myeloperoxidase contains iron, and its level could be increased in high iron status (Vita et al., 2004). In a separate report, Sullivan, (1989) proposed that decreased activity of potentially injurious iron-dependent enzymes could be one of the mechanisms by which iron depletion protects against ischemic heart disease. Moreso, diminished inflammatory injury in association with reduction in myeloperoxidase activity by induction of iron deficiency had been demonstrated by Baldus et al. (2003). Myeloperoxidase may thus be a potentially modifiable coronary risk factor whose level may be decreased by iron removal and vice versa (Figure 1).

HYPOTHESIS

Our hypothesis is that exposure capable of sustaining increases in iron levels and subsequently nitric oxide could predispose to or potentiate the development of cardiovascular disorders.This is based on the catalytic role of iron in the generation of free radical species which, if aided by sustained production of nitric oxide, may lead to cell oxidative damage or stress.

Testing the hypothesis

Our approach to testing the hypothesis would be experimental with subjects randomised to receive different concentrations of iron salts, nitric oxide donor or placebo. Increased tissue or serum iron and nitric oxide concentrations that correlate with sustained oxidative stress and cardiac damage biomarkers would be confirmatory.

CONCLUSION

We are of the view that a disruption of the delicate homeostatic balance existing between iron and nitric oxide could lead to potentiation of heart disease. Moreso all the evidences outlined further put together appear to support a potential association between iron and development of cardiovascular disorders viz-a-viz sustained increases in the generation of free radicals. Thus it is plausible to hypothesise that chronic exposure leading to sustained increases in the labile iron pool as well as nitric oxide could predispose to myocardial infarction and/or affects the fatality of existing heart disease. It may be necessary to consider the significance and potential effects on public health owing to the fact that coronary heart disease (CHD) which is one of the leading causes of death in most industrialized countries of the world is now also considered a prominent health problem in developing nations (WHO, 1981).
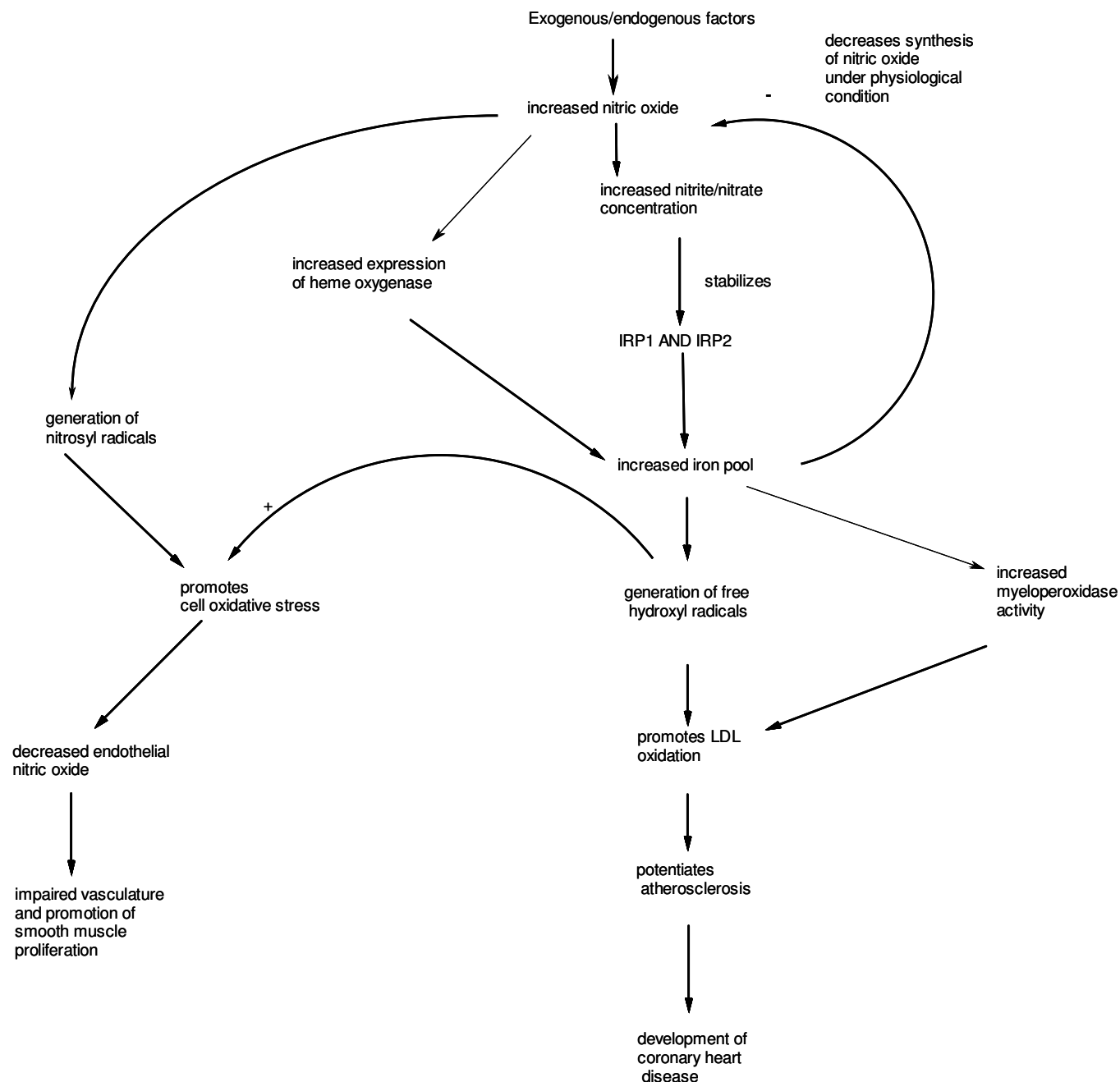
Figure 1. Proposed mechanistic interactions between iron and nitric oxide in living cells (IRP1 and IRP2: Iron regulatory protein 1 and 2).

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