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Review

Activation of intracellular matrix metalloproteinase-2 by reactive oxygen–nitrogen species: Consequences and therapeutic strategies in the heart

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ABSTRACT

Reactive oxygen–nitrogen species play important roles in physiological and pathological processes in the heart. This review will focus on the activation of matrix metalloproteinases (MMPs) as a result of oxidative stress, and the consequences of this on heart function. Although the MMPs are considered to be secreted proteases acting on the extracellular matrix to effect tissue remodeling, it is now recognized that MMPs also rapidly act on intracellular protein targets to cause intracellular protein remodeling. Of the 23 known human MMPs, MMP-2 is widely expressed in almost all cell types, is one of the most abundant MMPs in cardiac tissue, and recent evidence has revealed mechanisms by which it is a bona fide intracellular protein. This review will discuss the intracellular localization and novel substrates of MMP-2 within the heart, how intracellular protein proteolysis leads to cardiac dysfunction, as well as the potential of MMPs inhibitors as therapy for cardiovascular diseases caused by enhanced reactive oxygen–nitrogen species.

Introduction

Oxidative stress, which is the temporal accumulation of reactive oxygen–nitrogen species (RONS)[1] in cells and tissues due to an imbalance between oxidant stress and antioxidants, plays an important role in the pathogenesis of many types of heart disease, including cardiac hypertrophy, ischemia/reperfusion injury and heart failure [1]. RONS are products of normal cellular metabolism, and are well recognized for playing a dual role as both beneficial and deleterious species, since they are involved in both physiological and pathological conditions [2]. Beneficial effects of RONS occur at low/moderate concentrations and invoke physiological functions via a number of cellular signaling systems, while harmful effects occur at higher concentrations when there is an overproduction of RONS and/or deficiency of antioxidants [2]. Excessive RONS cause cellular dysfunction, protein and lipid peroxidation, DNA damage, impairment of contractile function by modifying proteins central to excitation–contraction coupling, induction of cell death [3], and activation of metalloproteinases (MMPs) [4].

MMPs are zinc-dependent proteases, synthesized by a variety of cells in a zymogen form, and can be activated by either proteolytic cleavage [5] or oxidative stress [6]. They are best known to be involved in the proteolysis of extracellular matrix proteins, and contribute to long-term remodeling processes such as embryogenesis, tumor cell invasion, and wound healing [7]. However, it has been shown that MMPs (in particular MMP-2) can have rapid effects in regulating diverse cellular functions, independent of actions on the extracellular matrix, including effects on platelet aggregation [8], vascular tone [9,10], and the acute mechanical dysfunction of the heart immediately following ischemia/reperfusion injury [11]. In this review we will focus on the intracellular localization and activation of MMP-2 by oxidative stress, and its newly emerging roles in targeting specific intracellular proteins in the heart. We will also discuss the potential of MMPs inhibition as therapy for cardiac dysfunction resulting from oxidative stress.

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[1] *Abbreviations used:* RONS, reactive oxygen–nitrogen species; MMPs, matrix mettaloproteinases; ROS, reactive oxygen species; NO, nitric oxide; RNS, reactive nitrogen species; O_2^{-}, superoxide; SOD, superoxide dismutase; H_2O_2, hydrogen peroxide; NOS, nitric oxide synthase; $ONOO^{-}$, peroxynitrite; ONOOH, peroxynitrous acid; $ONOOCO_2^{-}$, nitrosoperoxycarbonate; CO_3^{*-}, carbonate radical; $^{*}NO_2$, nitrogen dioxide radical; $^{*}OH$, hydroxyl radical; NO_2^{-}, nitrite ion; SERCA, sarcoplasmic reticulum Ca^{2+} ATPase; GSH, glutathione; GSSG, oxidized glutathione; PARP, poly(ADP-ribose) polymerase; TIMPs, tissue inhibitors of metalloproteinases; APMA, 4-aminophenylmercuric acetate; PMA, phorbol 12-myristate 13-acetate; L-NAME, L-NG-nitroarginine methyl ester.

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Reactive oxygen–nitrogen species (RONS)

Free radicals are chemical species with one unpaired electron. Molecules including free radicals derived from molecular oxygen are termed reactive oxygen species (ROS) and some of them can be powerful oxidants [12]. The oxidants derived from nitric oxide (NO) have been called reactive nitrogen species (RNS) [12]. In this review we will use the collective term "RONS" to refer to biologically relevant oxidants, as peroxynitrite is a key component and mediator of oxidative stress (Fig. 1) [13].

Synthesis

The addition of one electron to oxygen yields superoxide (O_2^{-}), the precursor of most RONS [12,14]. Enzymatic sources of O_2^{-} include NADPH oxidases and cytochrome p450-dependent oxygenases whereas the proteolytic conversion of xanthine dehydrogenase to xanthine oxidase is another source of O_2^{-} [12]. Low levels of O_2^{-} (1–2% of oxygen consumed by the cell [15]) are generated by electron leakage within the mitochondrial electron transport chain under physiological conditions [16].

Hydrogen peroxide biosynthesis is attributed to the dismutation of O_2^{-} by superoxide dismutase (SOD) [17]. Hydrogen peroxide can also be produced inside peroxisomes [18], subcellular organelles with an essentially oxidative type of metabolism and probably the major site source of intracellular hydrogen peroxide (H_2O_2) [18]. It was thought that the main function of peroxisomes was the removal by catalase of hydrogen peroxide generated in the peroxisomal respiratory pathway by different oxidases [18]. However, peroxisomes are also involved in a range of important cellular functions in almost all eukaryotic cells, including beta-oxidation of fatty acids [18]. Catalases prevent cell oxidative damage by degrading H_2O_2 to water and oxygen with high efficiency [19].

Hydroxyl radical is an extraordinarily powerful oxidant, which attacks most organic compounds at diffusion-limited rates [20,21], and avidly reacts with double bonds that become reduced to single bonds [21,22]. Hydroxyl radicals are generated in the presence of hydrogen peroxide and Fe^{2+} in the Haber–Weiss reaction [22].

NO is produced during the oxygen dependent conversion of L-arginine to L-citruline, catalyzed by nitric oxide synthase (NOS) [23] of which there are three isoforms: neuronal NOS (nNOS or NOS1), endothelial NOS (eNOS or NOS3), and inducible NOS (iNOS or NOS2) [24], all three are present in the heart. NOS1 and NOS3 are constitutively present enzymes and their activity is Ca^{2+}-dependent whereas the expression of NOS2 is induced by inflammation, mediated through cytokine-inducible transcription factors that bind to elements within the NOS2 promoter [25]. Ca^{2+}-dependent NOS activity was first described in normal cardiac myocytes and cardiac tissue [26]. They also found that endotoxemia *in vivo* or pro-inflammatory cytokines *in vitro* induced the expression of Ca^{2+}-dependent NOS activity in heart tissue and cardiac myocytes, respectively [26]. Endocardial and coronary endothelial cells are other important sources of NO in the heart [27].

Peroxynitrite ($ONOO^{-}$) is a short-lived oxidant species that is produced by the reaction of NO and O_2^{-} at a diffusion-limited rate [28]. The oxidant reactivity of $ONOO^{-}$ is highly pH-dependent with the anion being stable at pH 8 and above. At physiological pH and below $ONOO^{-}$ is protonated to form peroxynitrous acid (ONOOH) which is highly unstable and participates directly in one- and two-electron oxidation reactions with biomolecules [28].

A fundamental reaction of $ONOO^{-}$ in biological systems is its fast reaction with carbon dioxide to form $ONOOCO_2^{-}$ (nitrosoperoxycarbonate), which following protonation leads to the formation of carbonate (CO_3^{*-}) and nitrogen dioxide ($^{*}NO_2$) radicals, which are one-electron oxidants [28]. Alternatively, ONOOH can undergo homolytic fission to generate one-electron oxidants, hydroxyl ($^{*}OH$) and $^{*}NO_2$ radicals [28]. Direct two-electron oxidation reactions of thiols caused by ONOOH results in the formation of nitrite (NO_2^{-}) and sulphenic acid derivatives that can be stabilized or more frequently converted to disulphides such as cysteinyl or glutathionyl disulphides [28]. Many biomolecules are oxidized by $ONOO^{-}$-derived radicals, including tyrosine residues, thiols, DNA, unsaturated fatty acids and fatty acid containing phospholipids [28]. Biological reactions of $ONOO^{-}$ include inhibition, inactivation

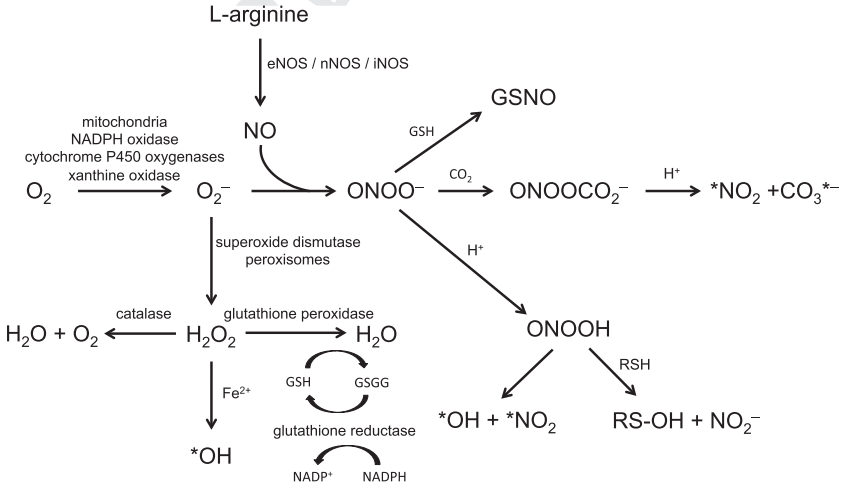

Fig. 1. Sources of RONS and some detoxification pathways. Superoxide (O_2^{-}) is formed by the addition of one electron to oxygen (O_2) by a variety of mechanisms, including enzymatic sources and within the mitochondrial electron transport chain. The dismutation of O_2^{-} by superoxide dismutase, or inside peroxisomes, generates hydrogen peroxide (H_2O_2). H_2O_2 can be degraded by catalase to water and oxygen, or reduced to water by glutathione peroxidase. Hydroxyl radicals ($^{*}OH$) are generated in the presence of H_2O_2 and Fe^{2+} in the Haber–Weiss reaction. Nitric oxide (NO) is produced during the oxygen dependent conversion of L-arginine to L-citruline, catalyzed by nitric oxide synthase (NOS), and can react with O_2^{-} to form peroxynitrite ($ONOO^{-}$). $ONOO^{-}$ is pH sensitive, and at physiological pH and below it is protonated to form peroxynitrous acid (ONOOH), which can undergo homolytic fission to generate hydroxyl ($^{*}OH$) and nitrogen dioxide ($^{*}NO_2$) radicals. Direct two-electron oxidation reactions of thiols caused by ONOOH results in the formation of NO_2^{-} and sulphenic acid derivatives (RS–OH). $ONOO^{-}$ reacts with carbon dioxide (CO_2) to form nitrosoperoxycarbonate ($ONOOCO_2^{-}$), which following protonation leads to the formation of carbonate (CO_3^{*-}) and $^{*}NO_2$ radicals. Glutathione (GSH), a key cellular antioxidant, is capable of reacting with RONS to form nitrosoglutathione (GSNO) and oxidized glutathione (GSSG).

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