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Review article

Monoamine oxidases as sources of oxidants in the heart

Nina Kaludercic [a], Jeanne Mialet-Perez [b,c], Nazareno Paolocci [d], Angelo Parini [b,c], Fabio Di Lisa [a,e,*]

[a] Neuroscience Institute, National Research Council of Italy (CNR), Padua, Italy
[b] INSERM UMR 1048, Institute of Metabolic and Cardiovascular Diseases, Toulouse, France
[c] Paul Sabatier University, Toulouse, France
[d] Johns Hopkins Medical Institutions, Baltimore, MD, USA
[e] Department of Biomedical Sciences, University of Padua, Italy

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ABSTRACT

Oxidative stress can be generated at several sites within the mitochondria. Among these, monoamine oxidase (MAO) has been described as a prominent source. MAOs are mitochondrial flavoenzymes responsible for the oxidative deamination of catecholamines, serotonin and biogenic amines, and during this process they generate H_2O_2 and aldehyde intermediates. The role of MAO in cardiovascular pathophysiology has only recently gathered some attention since it has been demonstrated that both H_2O_2 and aldehydes may target mitochondrial function and consequently affect function and viability of the myocardium. In the present review, we will discuss the role of MAO in catecholamine and serotonin clearance and cycling in relation to cardiac structure and function. The relevant contribution of each MAO isoform (MAO-A or -B) will be discussed in relation to mitochondrial dysfunction and myocardial injury. Finally, we will examine both beneficial effects of their pharmacological or genetic inhibition along with potential adverse effects observed at baseline in MAO knockout mice, as well as the deleterious effects following their over-expression specifically at cardiomyocyte level. This article is part of a Special Issue entitled Redox Signalling in Heart.

Contents

Abbreviations: 5-HT, serotonin; β-AR, β-adrenergic receptor; ALDH, aldehyde dehydrogenase; ATP, adenosine triphosphate; CHF, congestive heart failure; COMT, catechol-O-methyl-transferase; EMT, extraneuronal monoamine transporter; ERK1/2, extracellular signal-regulated kinases; FAD, flavin adenine dinucleotide; H_2O_2, hydrogen peroxide; I/R, ischemia/reperfusion; LV, left ventricle; MAO, monoamine oxidase; NET, norepinephrine transporter; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; Nox, NADPH (nicotinamide adenine dinucleotide phosphate) oxidase; ROS, reactive oxygen species; SOD, superoxide dismutase; TAC, transverse aortic constriction; WT, wild type.

* Corresponding author at: Department of Biomedical Sciences, University of Padua, Viale G. Colombo 3, 35131 Padua, Italy. Tel.: +39 0498276132; fax: +39 0498276040.
E-mail address: dilisa@bio.unipd.it (F. Di Lisa).

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1. Introduction

Although it is generally accepted that mitochondria are the major source of reactive oxygen species (ROS) in cardiac myocytes [1–4], relevant issues, such as sites at which ROS formation occurs, control mechanisms, relationships between formation and removal reactions and the relative contribution of the various processes to the total accumulation of ROS are far from being elucidated conclusively. Mitochondria contain several enzymes that catalyze ROS formation either as the obligatory product or as the result of an occasional, possibly undesired, reaction.

1.1. Occasional ROS formation within the mitochondria

This latter possibility is exemplified by the mitochondrial respiratory chain. A minor fraction of the electrons (about 0.1%) flowing through the transport chain is diverted causing the partial reduction of O_2 into superoxide [3]. This process occurs at the level of the first three complexes where flavins or quinones are able to act as single electron donors. In isolated mitochondria the relative contribution of sites I_F, I_Q, II_F and III_{Qo} (the roman number indicates the complex and the letter specifies the involvement of flavin or quinone moieties) appears to depend on the substrate utilized [5]. The electron detour at these upstream sites is favored when flow is hampered downstream as a result of either protein alterations in respiratory complexes or inhibitory effects of toxicants.

Superoxide that does not cross the inner mitochondrial membrane is rapidly dismutated into the freely permeable H_2O_2 by Mn-superoxide dismutase (Mn-SOD). The finding that Mn-SOD deficient mice develop ROS toxicity and dilated cardiomyopathy [6], underlines the importance of ROS in this pathology and mitochondria as their source and target. This concept is further supported by the beneficial effects afforded by targeting catalase expression in the mitochondria [7–10].

Besides superoxide generation by respiratory chain complexes, several other mitochondrial enzymes have been described as potential ROS producers. These include (but are not limited to) the flavin containing glycerol-3-phosphate-, proline- and dihydroorotate-dehydrogenase at the outer leaflet of the inner mitochondrial membrane, the electron transfer flavoprotein–ubiquinone (ETF:Q) oxidoreductase system of fatty acid β-oxidation within the inner mitochondrial membrane, and pyruvate- and 2-oxoglutarate dehydrogenase within the mitochondrial matrix [5]. All these enzymes and respiratory complexes normally catalyze reactions other than ROS formation, that are required for energy metabolism, cell function and viability maintenance. Their characterization as ROS forming enzymes has been carried out in the isolated mitochondria by means of inhibitors or non-physiological procedures, such as glutathione depletion. Obviously, these approaches can hardly be adopted in living cells or tissues without jeopardizing a wide array of vital functions. This is a major caveat that eventually does not allow obtaining definite evidence that these potential ROS sources contribute to oxidative stress *in vivo*. If these processes were the only ones responsible for mitochondrial ROS formation, it would be actually impossible to demonstrate that these organelles are primarily involved in oxidative stress in living organs. In fact, oxidative changes within the mitochondria could be just the result of alterations caused by ROS formed at other cellular sites. However, this is not the case because the mitochondria contain other enzymes that generate hydrogen peroxide (H_2O_2) as a direct and obligatory product. Inhibition of these enzymes does not affect other energy-linked functions and it provides convincing evidence of mitochondrial ROS formation *in vivo* and its role in pathophysiology of many organs including the cardiovascular system.

1.2. Obligatory ROS formation within the mitochondria

$p66^{Shc}$ is a cytosolic adaptor protein that upon stress translocates to mitochondria where it catalyzes electron transfer from cytochrome c to oxygen [11], a process that can result in the formation of ROS. Indeed, ROS generation is reduced in cells lacking $p66^{Shc}$ and in $p66^{Shc-/-}$ mice, whose lifespan is increased by 30% [11–14] in a protected environment [15]. Furthermore, genetic deletion of $p66^{Shc}$ protects against ischemia/reperfusion (I/R) injury in mice hearts [16] and brain [17] and diabetic complications such as cardiomyopathy, nephropathy, delayed wound healing, and endothelial dysfunction [18–21]. Nicotinamide adenine dinucleotide phosphate oxidase 4 (Nox4) is another ROS generating enzyme that localizes not only in the plasma membrane but also intracellularly, in the mitochondria, focal adhesions, nucleus, endoplasmic reticulum. Nox4 associates with $p22^{phox}$ for its activation, and, unlike other Noxs, generates H_2O_2 in preference to superoxide [22]. Nox4/$p22^{phox}$ appears to be constitutively active [23], although several studies have shown that Nox4 activity can be modulated by different stimuli [24–27]. Mice in which Nox4 is targeted in a cardiac-specific manner demonstrate that Nox4 is both protective and injurious in models of cardiac pressure overload [28,29]. Furthermore, while certain studies reported Nox4 to be deleterious, contributing to mitochondrial dysfunction and several pathologies such as ischemic stroke, diabetic cardiomyopathy, vascular inflammation and remodeling [30–32], others concluded that Nox4 might be vascular-protective rather than vascular-damaging [33]. These controversies may stem from different genetic models in which Nox4 was either silenced or overexpressed, or they may reflect different roles and regulation under pathophysiological conditions. Either way, they warrant further investigation.

Another enzyme localized in the mitochondria is monoamine oxidase (MAO). Activation of this enzyme leads to H_2O_2 formation and has been shown to contribute to a number of neuronal disorders, such as Parkinson's or Alzheimer's disease, most likely due to formation of ROS responsible for oxidative damage to neurons [34]. Although MAO inhibitors are currently used in the clinic for treatment of neurodegenerative diseases, the role of MAO in cardiac pathophysiology has gained attention only recently. However, charting this territory is likely to be of major pathophysiological relevance because oxidative stress impairs functions in viable cardiac myocytes, leading to contractile failure. In this review we are going to focus mostly on their role in the heart and speculate on the potential use of these compounds for treating cardiovascular diseases.

1.3. Interaction among mitochondrial ROS sources

It is likely that an intense cross-talk exists between different ROS sources in the cell. This is supported by the observation that frequently, inhibition of single ROS source is able to completely abolish oxidative stress and the resulting damage. One way to explain this is to envision that there is an “amplification mechanism”, whereby a single ROS source is activated by an initial stress, starts to generate ROS and triggers other sites in the cell to start producing free radicals leading therefore to oxidative stress. On the other hand, it should not be disregarded that there is significant “buffering” due to cellular antioxidant systems and that ROS formation or oxidative stress may become evident only after a certain threshold has been reached [35]. Either way, inhibition of a single ROS source is able to lower overall ROS levels and, in most cases, to prevent cellular structural and functional derangements. In this regard, it is worth mentioning that inhibitors of $p66^{Shc}$ are not yet available, Nox inhibitors are not isoform-specific or approved for clinical use, whereas it is inconceivable to think that electron transport chain inhibitors could be used in patients. On the contrary, MAO inhibitors are available and already used in the clinic for the treatment of mood disorders, Parkinson's and Alzheimer's disease [34,36,37]. Development of a new generation of reversible MAO-A inhibitors, such as moclobemide, makes it worthwhile investigating whether MAO inhibitors could also be used to treat cardiovascular pathologies.

Here, we will discuss the relevant contribution of MAO isoforms to myocardial injury and mitochondrial dysfunction. Next, we will

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