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Review

Reductive potential — A savior turns stressor in protein aggregation cardiomyopathy

Madhusudhanan Narasimhan [d], Namakkal S. Rajasekaran [a,b,c,*]

[a] Cardiac Aging & Redox Signaling Laboratory, Division of Molecular & Cellular Pathology, Department of Pathology, The University of Alabama at Birmingham, Birmingham, AL 35294-2180, United States
[b] Center for Free Radical Biology, The University of Alabama at Birmingham, Birmingham, AL 35294-2180, United States
[c] Division of Cardiovascular Medicine, Department of Medicine, University of Utah School of Medicine, Salt Lake City, UT 84132, United States
[d] Department of Pharmacology and Neuroscience, Texas Tech University Health Sciences Center, 3601 4th Street, Lubbock, TX 79430, United States

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ABSTRACT

Redox homeostasis is essential for basal signaling of several physiological processes, but a unilateral shift towards an 'oxidative' or 'reductive' trait will alter intracellular redox milieu. Typically, such an event influences the structure and the native function of a cell or an organelle. Numerous experimental research and clinical trials over the last 6 decades have demonstrated that enhanced oxygen-derived free radicals constitute a major stimulus to trigger damage in several human diseases, including cardiovascular complications supporting the theory of oxidative stress (OS). However, until our key discovery, the dynamic interrelationship between "Reductive Stress (RS)" and cardiac health has been obscured by overwhelming OS studies (Rajasekaran et al., 2007). Notably, this seminal finding spurred considerable interest in investigations of other mechanistic insights, and thus far the results indicate a similar or stronger role for RS, as that of OS. In addition, from our own findings we strongly believe that constitutive activation of pathways that enable sustained generation of reducing equivalents of glutathione (GSH), reduced nicotinamide adenine dinucleotide phosphate (NADPH) will cause RS and impair the basal cellular signaling mechanisms operating through harmless pro-oxidative events, in turn, disrupting single and/or a combination of key cellular processes such as growth, maturation, differentiation, survival, death etc., that govern healthy cell physiology. Here, we have discussed the role of RS as a causal or contributing factor in relevant pathophysiology of a major cardiac disease of human origin.

1. Redox homeostasis vs. redox stress

Intracellular stress is known as an abnormal state or a stimulus that challenges physiological function of an organelle, cell, organ or organism as a whole. Based on the source and nature, stress exerts physiological or pathological consequences. Profound changes in the intracellular redox milieu are broadly termed as redox stress. Under basal state of redox milieu known as "redox homeostasis (RH)", a biological pas de deux involving oxidants and reductants is essential to regulate many fundamental biological processes including, but not limited to, cellular signaling pathways, chromatin remodeling, transcriptional and post-transcriptional activities, protein folding/conformation, mitochondrial biogenesis and membrane permeability [1–4]. Thus, interference in the balance of reactive oxygen species (ROS; oxidants) and reductants (antioxidants) can dis-equilibrate RH and derange normal cellular life processes. Though ROS and reactive nitrogen species (RNS) candidates, such as superoxide, hydroxyl radicals, hydrogen peroxide, nitric oxide and peroxynitrite, are indispensable to support cellular vitality, when in excess can accumulate oxidative stress (OS), causing oxidation of lipids, proteins, and DNA, leading to a multitude of pathological conditions including myocardial infarction, vascular abnormality, neurodegenerative diseases and accelerated aging [5–9]. Depending on the chemistry and concentration of molecules that preserve intracellular RH, cellular stress can be classified as (a) oxidative, (b) reductive and (c) nitrosative. Usually, OS is defined as the shift of balance between cellular oxidative and reductive potential towards oxidative one that are caused both by excessive generation of highly reactive free radicals from the mitochondria or other ROS generating sources and an impairment of cytoprotective defense mechanisms that scavenge ROS generation during normal physiological and/or pathological processes. In contrast, an increase in reducing equivalents including, but not restricted to, GSH, NADH, NADPH, and cysteine etc. in conjunction with immense activation of antioxidant system and suppressed oxidative activity is referred to as reductive stress (RS). In other words, the imbalance between oxidants and antioxidants in favor of the latter forms the core of the definition for "reductive stress". Typically, RS is

* Corresponding author at: Cardiac Aging & Redox Signaling Laboratory, Division of Molecular & Cellular Pathology, Department of Pathology, UAB, The University of Alabama at Birmingham, BMR2 Room 533, 901 19th Street South, Birmingham, AL 35294-2180, United States. Tel.: +1 205 996 9839; fax: +1 205 934 7447.
E-mail address: rajnsr@uab.edu (N.S. Rajasekaran).

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likely to be elicited from the intrinsic signals that enable cellular defense through a pro-oxidative or optimal-oxidative setting (i.e.) the body's cytoprotective defense system turning against itself. Since the body's own defense system itself attacks the system which it is supposed to shield, we feel that RS could be a potent threat and thus, in a given context, RS could be as deleterious as and/or more deleterious than the OS. To better understand this concept, an analogy could be drawn as to what would happen to civilians (cellular system) if the law maker (reductive potential, the cop) turns to a law breaker (stressor). The redox regulation of cellular response to acute versus chronic stress is illustrated in Fig. 1.

Over 6 decades of research strongly support that a shift in the redox state towards OS as one of the leading causes for various pathological processes and diseases in humans [5,7,8,10–13]. Specifically, studies using animals have demonstrated that either activation of enzymes that generate ROS, such as NADPH oxidases and xanthine oxidase, or inhibition of enzymatic pathways counterbalancing ROS production [such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), and the thioredoxin/thioredoxin-reductase (Trx/TrxR system)] foster pathological cardiac remodeling and end-stage heart failure [14]. Nevertheless, the cause and consequences of RS have neither thoroughly been studied using appropriate in vitro and/or in vivo models, nor reviewed in the context of human health. Here, we intend to describe the role of RS in cardio-pathophysiology through analyzing the available reports since our first discovery of reductive stress in a major human cardiac disease.

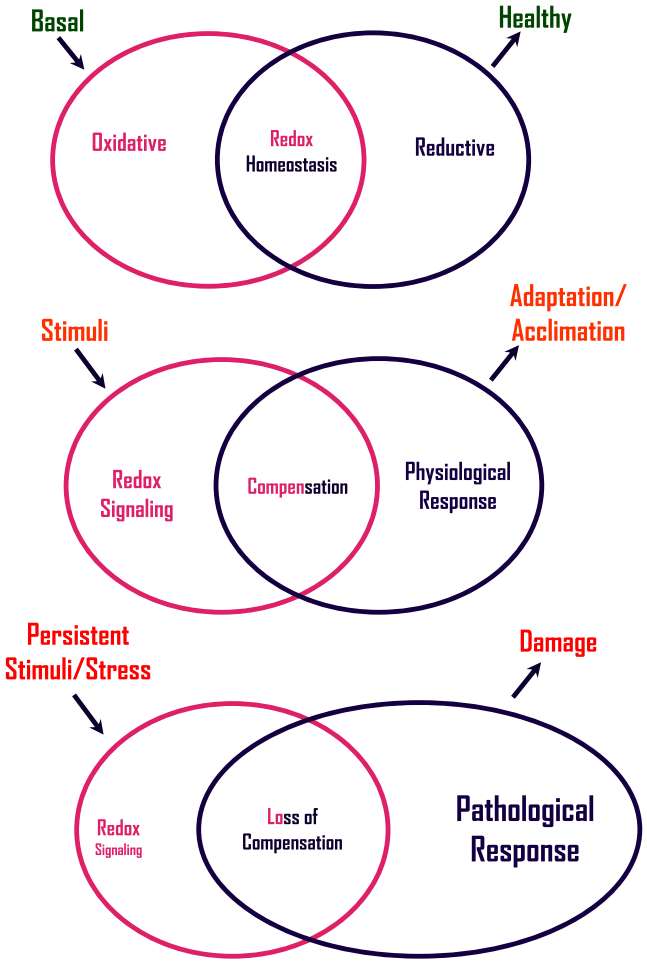

Fig. 1. Cellular fitness associated with redox state. (A) Basal state: Under normal physiology, an equilibrium is maintained between the generation of reactive oxygen/nitrogen species (ROS/RNS) (oxidative species) and counteracting reductant molecules that quench free radical/oxidant species which are broadly termed as "redox homeostasis (RH)". (B) Defensive state: An acute stress stimulus induces intracellular redox signals evoking compensatory responses which moderately adjusts the concentrations of oxidants and reductants and helps maintaining a normal physiology. This is a state of adaptation or acclimation. (C) Stress: When the stress signal is sustained, the redox signaling might go awry and abnormal reflecting in loss of compensatory responsiveness leading to pathological consequences.

2. Reductive stress

RS was first introduced by Albert Wendel, to denote the excessive accumulation of reduced cofactor, NADH that can facilitate reduction of chelated ferric iron [15–17]. Later, Ghyczy and Boros suggested that RS could be defined as an abnormal increase in pathological processes — associated electron pressure or reducing power or high energy reducing electrons (NADH) accompanied by failure of mechanisms to quench the rise in electron pressure [16]. Alternatively, the simplest definition for RS could be that a shift of RH with excessive levels of reducing bioequivalents. Our laboratory reported a breakthrough finding that RS (in the form of increased GSH and NADPH production) coupled with increased antioxidative pathway enzymes and decreased oxidative stress biomarkers could be genetically and causally linked to cardiac hypertrophy and mutant protein aggregation cardiomyopathy [18]. Subsequently, overabundance of reducing power in various experimental models and humans is increasingly linked with several complications, such as lipid membrane damages [19], triacyl glycerol deposition and mitochondrial stress [20], mitochondrial dysfunction and cytotoxicity [21], cardiac ischemic injury [22], risk of Alzheimer's disease [23] and several others.

3. Reductive stress induces protein aggregation cardiomyopathy

It is well known that the equilibrium between molecular duos, such as the oxidation–reduction ratio of glutathione (GSH/GSSG), nicotinamide adenine dinucleotide phosphate (NADPH/NADP) or that of cysteine to its oxidized form cystine (disulfide), tend to regulate various signaling processes including a number of transcription factors responsible for controlling redox genes and thereby maintaining intracellular homeostasis [1,24–26]. However, reductant/antioxidative stress remains to be an under-represented phenomenon in the fields of biochemistry and medicine since the cause (for RS) and consequences (of RS) are not familiar. In the recent past, we have found a transcriptional link that likely provokes or contributes to RS in vivo and in vitro [18,27]. In a mouse model of human heart disease named mutant protein aggregation cardiomyopathy (MPAC), we demonstrated that increased activity of glutathione-6-phosphate dehydrogenase (G6PD) enhanced the levels of NADPH, a major cofactor/substrate for multiple enzymes such as glutathione reductase (GSR), NADPH oxidases and nitric oxide synthase (NOS), and GSH, a ubiquitously present intracellular redox controller. In addition, the exemplified production of two most abundant antioxidants is linked with activation of antioxidative pathway enzymes such as G6PD, GSR, GPx and catalase further bolstering the reductive environment. This oxido-redox shift towards "reductive side" facilitated a diminution of oxidative stress modifications of lipids and proteins and all of which were strictly correlated to protein aggregation related pathophysiology and heart failure [18]. Notably, this clue of toxic gain-of-function mutation causing excessive reducing equivalents and pathological remodeling of heart may also reconcile conflicting data and unanticipated outcomes from clinical trials assessing antioxidant therapies in patients with different cardiovascular diseases including heart failure. While some of the beneficial effects of drugs antagonizing the beta-adrenergic and the angiotensin II systems have been recognized for their ability to partially quench ROS [2,14], the direct suppression of ROS-generating enzymes (i.e. superoxide dismutase, xanthine oxidase etc.) has produced rather debilitating consequences [28]. This raises an important question as to whether dysregulation of redox homeostasis towards any extreme (either reductive or oxidative) condition in a living cell is a biochemical