FUNCTIONAL MODULATION OF THE ANTIOXIDANT ENZYME SYSTEM UNDER OXIDATIVE STRESS CONDITIONS

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Abstract

Oxidative stress is a redox imbalance in which the generation of reactive oxygen species (ROS) exceeds the capacity of cellular antioxidant defenses. Enzymatic antioxidants, particularly superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR), constitute a coordinated first-line defense against excessive ROS accumulation. During mild or moderate oxidative challenge, the activity and/or expression of these enzymes may increase as part of an adaptive response mediated in part by the KEAP1–NRF2 signaling pathway. In contrast, prolonged or severe oxidative stress can promote oxidative modification of enzyme proteins, depletion of glutathione and reducing equivalents, mitochondrial dysfunction, and a subsequent decline in antioxidant capacity. This thesis reviews the functional modulation of major antioxidant enzymes under oxidative stress, emphasizes their interdependence within the cellular redox network, and discusses the value of integrated assessment of enzymatic activity together with markers of oxidative damage.

Keywords: oxidative stress, reactive oxygen species, superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, NRF2, antioxidant defense, lipid peroxidation.

Oxidative stress has been widely investigated as a common molecular component of both physiological adaptation and pathological processes. ROS are continuously generated by mitochondrial electron transport, NADPH oxidases, peroxisomal reactions, and several other enzymatic systems. At controlled concentrations, ROS participate in redox signaling; however, when ROS production exceeds antioxidant capacity, oxidative modification of lipids, proteins, and nucleic acids becomes more pronounced [1,2].

The enzymatic antioxidant system is organized as an interconnected network. SOD catalyzes the dismutation of superoxide anion into hydrogen peroxide (H_2O_2), whereas CAT and GPx remove H_2O_2 through different but complementary mechanisms. GPx also reduces lipid hydroperoxides and therefore contributes directly to the protection of cellular membranes from peroxidative injury [2,3]. The efficiency of GPx depends on reduced glutathione (GSH), while GR regenerates GSH from oxidized glutathione (GSSG) using NADPH, linking antioxidant defense to cellular metabolic status.

The KEAP1–NRF2 pathway is a major transcriptional regulator of the adaptive antioxidant response. Under oxidative or electrophilic challenge, NRF2 accumulates and induces the transcription of genes involved in antioxidant defense, glutathione metabolism, detoxification, and redox maintenance [4,5]. Consequently, mild or moderate oxidative stress may initially increase the capacity of the antioxidant system. Nevertheless, persistent or high-intensity stress can overwhelm these compensatory mechanisms and lead to loss of enzyme activity and progressive oxidative damage.

Current methodological recommendations emphasize that oxidative stress should not be characterized by a single ROS-related parameter. A more reliable approach combines measurements of antioxidant enzyme activity with markers of glutathione redox status, lipid peroxidation, protein oxidation, and, where appropriate, direct or indirect ROS indicators [6]. This integrated strategy provides a more physiologically meaningful interpretation of redox imbalance.

Table 1. Major antioxidant enzymes and their functional roles during oxidative stress

Enzyme	Primary	Biological role	Expected response to oxidative

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	substrate		stress
SOD	$O_2^{\bullet-}$	Converts superoxide to H_2O_2 and O_2	May increase during mild/moderate stress; activity may decline during severe or prolonged stress
CAT	H_2O_2	Rapidly decomposes H_2O_2 to H_2O and O_2	Often induced by increased H_2O_2; sustained stress may cause oxidative inactivation
GPx	H_2O_2 and lipid hydroperoxides	Reduces peroxides using GSH and protects membranes	Depends on GSH availability and selenium status; may decline when reducing capacity is depleted
GR	GSSG	Regenerates GSH using NADPH	Supports the glutathione cycle and depends on cellular NADPH supply

The data summarized in Table 1 demonstrate that antioxidant enzymes function as a coordinated sequence rather than as independent protective factors. H_2O_2 generated by SOD becomes a substrate for CAT and GPx, whereas GPx activity is sustained by the glutathione cycle and cellular NADPH. Therefore, impairment of one component may alter the effectiveness of the entire antioxidant defense network.

Oxidative stress may be intensified by heat exposure, hypoxia, xenobiotics, inflammation, excessive physical load, nutritional imbalance, and other endogenous or environmental factors. Although ROS generation is a normal component of cellular physiology, excessive ROS accumulation promotes oxidative damage to membranes, proteins, enzymes, and genetic material. The antioxidant enzyme system is therefore essential for maintaining redox homeostasis and limiting irreversible cellular injury.

Unlike many low-molecular-weight antioxidants, antioxidant enzymes catalytically eliminate specific reactive species and can provide rapid protection when substrate levels increase. Understanding how SOD, CAT, GPx, and related enzymes respond to different degrees and durations of oxidative stress is relevant to physiology, biochemistry, toxicology, and experimental medicine.

To analyze, on the basis of contemporary scientific literature, the patterns of change in the activity of major antioxidant enzymes—superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase—under oxidative stress conditions, and to evaluate their functional interrelationship and contribution to adaptive cellular protection.

Superoxide dismutase acts at an early stage of enzymatic antioxidant defense. Manganese-dependent SOD (SOD2) is located mainly in mitochondria, whereas copper/zinc-dependent SOD (SOD1) predominates in the cytosol. By converting superoxide into H_2O_2, SOD reduces the direct reactivity of superoxide but simultaneously increases the requirement for efficient peroxide removal. During short-term or moderate oxidative stress, SOD expression and activity may increase as an adaptive response. Under excessive oxidative load, however, oxidative modification of enzyme proteins, disturbed metal cofactor homeostasis, and mitochondrial damage may contribute to reduced SOD activity [2,3].

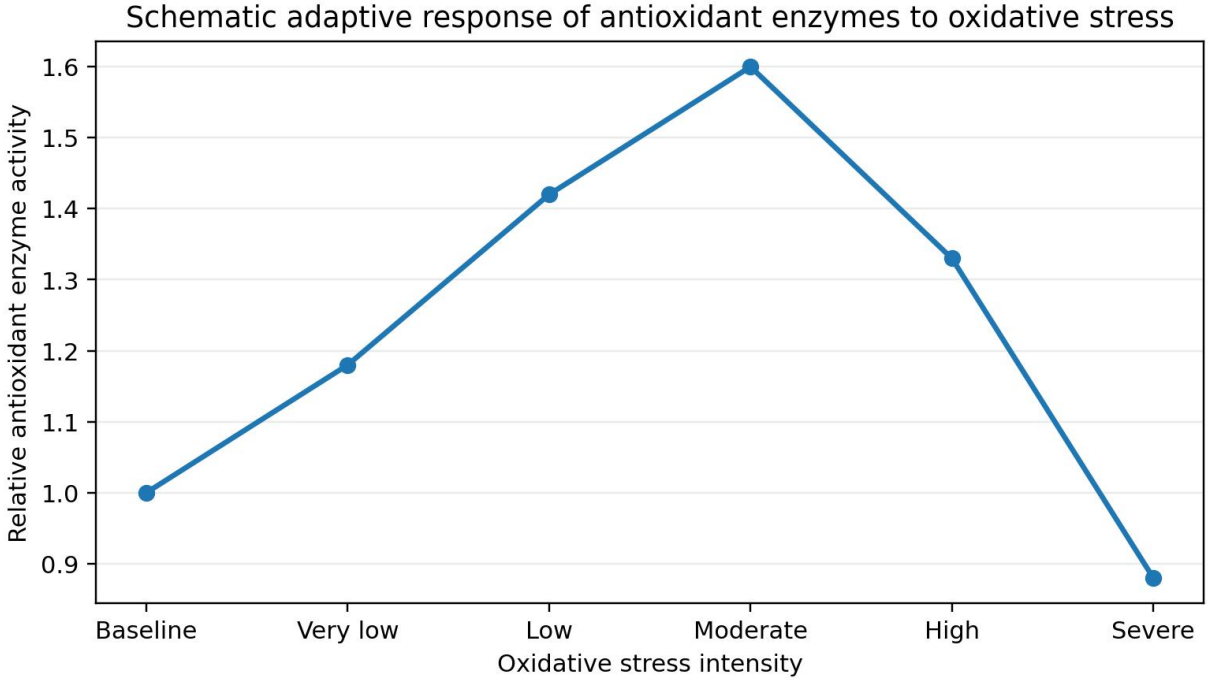
Catalase is concentrated mainly in peroxisomes and efficiently decomposes relatively high concentrations of H_2O_2. Coordinated activity of CAT and GPx is particularly important when SOD-mediated dismutation increases H_2O_2 formation. If H_2O_2 is not removed effectively, redox-active metal ions can facilitate the generation of highly reactive hydroxyl radicals, thereby amplifying oxidative injury.

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Glutathione peroxidases reduce both H_2O_2 and, depending on the isoform, organic and lipid hydroperoxides. GPx4 is of particular interest because of its role in limiting phospholipid peroxidation and its close relationship to ferroptotic cell death pathways. GPx activity requires GSH, which is oxidized to GSSG and subsequently regenerated by GR using NADPH. Thus, the GPx–GR system links peroxide detoxification directly to glutathione metabolism and cellular reducing power [3].

At the early stage of oxidative stress, activation of NRF2-dependent transcription can increase the expression of antioxidant and cytoprotective genes. This adaptive phase may enhance resistance to oxidative challenge. With prolonged or severe stress, however, antioxidant reserves can become insufficient. Depletion of GSH, disruption of NADPH supply, oxidative modification of proteins, and mitochondrial dysfunction may reduce enzyme efficiency and promote accumulation of lipid peroxidation products and protein carbonyls. Accordingly, the antioxidant response is often non-linear: compensatory activation may be followed by functional exhaustion when oxidative load exceeds cellular capacity.

Figure 1. Schematic model of antioxidant enzyme activity across increasing oxidative stress intensity



Note: The figure is a conceptual model derived from trends described in the literature and does not represent a specific experimental dataset. Mild to moderate oxidative stress may induce compensatory antioxidant enzyme activation, whereas severe or persistent stress may result in functional decline because of enzyme damage, glutathione depletion, impaired cofactor availability, and mitochondrial dysfunction [2–5].

Interpretation of antioxidant enzyme activity should therefore be integrated. High SOD activity in the presence of insufficient CAT or GPx activity may favor H_2O_2 accumulation. Conversely, depletion of GSH can limit GPx-dependent peroxide removal even when enzyme protein is present. For this reason, simultaneous evaluation of SOD, CAT, GPx, GR, the GSH/GSSG ratio, malondialdehyde or other lipid

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peroxidation indices, and protein oxidation markers provides a more informative assessment of redox status [6].

The NRF2/KEAP1 system remains a major mechanistic target in contemporary redox biology. NRF2 activation can strengthen cellular defenses by increasing the transcription of multiple cytoprotective genes; however, persistent activation is not universally beneficial and may support maladaptive stress tolerance in certain pathological contexts. The central biological principle is therefore maintenance of redox balance rather than maximal antioxidant activation [4,5].

Under oxidative stress conditions, the antioxidant enzyme system represents one of the principal endogenous mechanisms protecting cells from excessive ROS. SOD converts superoxide into H_2O_2, while CAT and GPx remove H_2O_2 and other peroxides. During mild or moderate oxidative stress, enzyme activity may increase adaptively, whereas severe or prolonged oxidative exposure may reduce antioxidant efficiency through oxidative enzyme damage, depletion of glutathione and reducing equivalents, and mitochondrial dysfunction.

A comprehensive assessment of antioxidant enzyme activity is important for characterizing oxidative stress intensity, estimating adaptive capacity, and clarifying mechanisms of redox imbalance. Future research should combine measurements of SOD, CAT, GPx, and GR with NRF2/KEAP1 signaling, glutathione redox status, and validated markers of oxidative damage. Such an integrated approach is more consistent with current methodological recommendations and can improve the biological interpretation of antioxidant responses.

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