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Review

Biological signaling by small inorganic molecules

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ABSTRACT

Small redox active molecules such as reactive nitrogen and oxygen species and hydrogen sulfide have emerged as important biological mediators that are involved in various physiological and pathophysiological processes. Advancement in understanding of cellular mechanisms that tightly regulate both generation and reactivity of these molecules is central to improved management of various disease states including cancer and cardiovascular dysfunction. Imbalance in the production of redox active molecules

Abbreviations: ALDH, aldehyde dehydrogenase; CGRP, calcitonin gene-related peptide; CO, carbon monoxide; COX, cyclooxygenase; CBS, cystathionine β-synthase; CSE, cystathionine γ-lyase; P450, cytochrome P450; N_2O_3, dinitrogen trioxide; N_2O_4, dinitrogen tetraoxide; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; H_2O_2, hydrogen peroxide; H_2S, hydrogen sulfide; •OH, hydroxyl radical; IPA/NO, isopropylamine diazeniumdiolate; LPS, lipopolysaccharide; LOX, lipoxygenase; MST, 3-mercaptopyruvate-S-transferase; NOHA, N^{ω}-hydroxy-L-arginine; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; NOS, nitric oxide synthase; NO_2, nitrogen dioxide; HNO, nitroxyl; PARP, poly(ADP-ribose) polymerase; RNS, reactive nitrogen species; ROS, reactive oxygen species; STP, standard temperature and pressure; O_2^-, superoxide; SOD, superoxide dismutase; HSNO, thionitrous acid.

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can lead to damage of critical cellular components such as cell membranes, proteins and DNA and thus may trigger the onset of disease. These small inorganic molecules react independently as well as in a concerted manner to mediate physiological responses. This review provides a general overview of the redox biology of these key molecules, their diverse chemistry relevant to physiological processes and their interrelated nature in cellular signaling.

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1. Introduction

Investigation of the biological effects of nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H_2S) initially concentrated on their context in environmental toxicology. For example NO and other nitrogen oxide species (often grouped as NO_x) are major components of air pollution [1], carcinogenic nitrosamines are found in food [2,3] and H_2S and CO are industrial poisons [4,5]. Given this history, the discovery of endogenous production of NO and related nitrogen oxides for eradication of pathogens including bacteria, parasites and viruses by the immune system and for regulation of physiological functions in the circulatory and nervous system was quite surprising [6–10]. The significance of the discovery of NO biosynthesis and its role in regulation of blood pressure was recognized by award of the 1998 Nobel Prize in Physiology or Medicine to Murad, Ignarro and Furchgott [11]. More recently, other small inorganic molecules, including CO, H_2S and even H_2, have also been identified as essential mediators of physiological processes. Their disequilibrium has been associated with disease onset and progression in cancer, immune response and cardiovascular function among others [12–14]. In addition, the diverse pharmacology of nitroxyl (HNO), for example in treatment of heart failure, alcoholism and cancer [15–19], strongly suggests that HNO is likely biosynthesized.

These signaling molecules are increasingly been referred to as endogenous gasotransmitters since they are all gases in pure form at STP. As gases, these molecules share important physical characteristics such as low molecular weight and neutral charge, which when coupled with lipophilicity, are important to their function as diffusible signaling agents. In the diverse environments of biological systems, the term gasotransmitter is a misnomer for these solute molecules. In addition, this term overlooks the fact that signaling is often indirect, for example after conversion of NO or H_2S into redox-related derivatives. Furthermore, the importance of O_2 is neglected because its production is not regulated, unlike NO, CO and H_2S.

Although redox activity is a major component of the signaling processes mediated by NO and H_2S, other reaction types, for example association of NO with heme systems, are also essential. Moreover, CO is not redox active. Here, we collectively consider the impact of small inorganic molecules on signaling from the perspective of the direct and indirect effects of the neutral species: O_2, NO, HNO, CO, H_2S and H_2. A heavy emphasis is placed on the involvement of these and related species in redox signaling.

Redox active molecules play diverse and critical roles in all aspects of cell biology and physiology including metabolism, cellular signaling and host defense. Redox homeostasis is maintained by regulated production of redox active molecules, redox buffering and a diverse antioxidant system. Homeostatic regulation allows for initiation of signaling processes upon the interaction of reactive redox active species with specific targets. Under stress conditions, such as those often considered in chemical toxicology, overproduction of these species can induce damage to macromolecules including proteins, lipids and DNA. Antioxidants and other repair systems can promote survival under conditions of environmental stress; however, chemically induced stress can overwhelm such protective mechanisms creating an imbalance and leading to deterioration of cellular function. Since the boundary between normal and stress conditions is not precise, pathways exist to resolve the stressful incident and restore homeostasis or to induce cell death. Induction and control of stress-induced signaling by reactive redox active species is therefore important in both normal physiology and disease processes.

While the deleterious roles of small inorganic species, particularly reactive oxygen species (ROS), have been studied extensively, including impacts on pathological conditions such as aging and neurodegenerative diseases [20], analysis of their functions as signaling molecules is relatively new [21,22]. Understanding of the fundamental chemistry of these species as well as the kinetic factors that control their generation and consumption is critical in order to build a realistic model for their participation in biological signaling mechanisms and physiological outcome.

Redox biology includes reactions of these chemical species with molecular targets, which have significant biological implications, especially in the context of cellular signaling. Often, cellular signaling pathways involve receptor–ligand interactions that rely on a structure–function relationship. In contrast, signaling by small inorganic messenger molecules typically involves covalent or coordinate covalent bond formation. Specificity occurs through spatial-, temporal-, and concentration-dependent constraints, typically *via* regulation of their biosynthesis pathway. The sources of these endogenous species are often metalloenzymes, and their targets can be considered to be primarily, although not exclusively, metal complexes and thiols [23–26]. While the reaction sites of these species overlap, their chemical and biological signatures are distinct, due to induction of different chemical modifications. In this review we discuss and highlight their biosynthesis, chemistry, and the interplay in and between subclasses of small inorganic signaling molecules.

2. Oxygen and reactive oxygen species

Molecular oxygen serves as the ultimate electron acceptor during oxidative phosphorylation. Incomplete reduction of O_2 in the mitochondrial electron transport chain can lead to accumulation of ROS including superoxide (O_2^{-}), hydroxyl radical ($^{\bullet}OH$) and hydrogen peroxide (H_2O_2), which as highly reactive species can be damaging to cellular macromolecules including lipids, proteins and DNA when produced in an unconstrained fashion [27,28]. A variety of antioxidants including glutathione, flavonoids and vitamins A, C and E protect against ROS toxicity. Cellular levels of ROS are also tightly regulated enzymatically (Fig. 1) [29–31]. Despite the known implications of ROS imbalance in the initiation of oxidative stress and disease, ROS regulate various biological and physiological processes. Understanding of the signaling cascades mediated by these species is therefore important [32].

One-electron reduction of O_2 is thermodynamically unfavorable (−0.33 V *vs.* NHE), which prevents indiscriminate oxidation. Direct reaction of O_2 with organic substrates is also kinetically inhibited due to ground state differences (*i.e.*, spin restrictions). These kinetic barriers can be overcome by a variety of metalloenzymes, such that activation of O_2 is coupled to diverse metabolic transformations. Hydroxylation reactions, for example during purine catabolism by