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Review Article

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Reciprocal regulation of cellular nitric oxide formation by nitric oxide synthase and nitrite reductases

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Summary

Our mini-review focuses on dual regulation of cellular nitric oxide (NO) signaling pathways by traditionally characterized enzymatic formation from L-arginine via the actions of NO synthases (NOS) and by enzymatic reduction of available cellular nitrite pools by a diverse class of cytosolic and mitochondrial nitrite reductases. Nitrite is a major metabolic product of NO and is found in all cell and tissue types that utilize NO signaling processes. Xanthine oxidoreductase (XOR) has been previously characterized as a housekeeping enzyme responsible for cellular uric acid formation via enzymatic conversion of hypoxanthine and xanthine. It has become apparent that XOR possesses multi-functional enzymatic activities outside the realm of xanthine metabolism and a small but significant literature also established a compelling functional association between administered sodium nitrite, XOR activation, and pharmacologically characterized NO transductive effects in positive cardiovascular function enhanced pulmonary perfusion, and protection against ischemia/reperfusion injury and hypoxic damage and oxidative stress. Similar positive vascular and cellular effects were observed to be functionally associated with mitochondrial aldehyde dehydrogenase and cytochrome c/cytochrome c oxidase. The profound implications of a reciprocal regulatory mechanism responsible for cytosolic and mitochondrial NO production are discussed below.

key words: **nitric oxide • nitrite • nitric oxide synthase • nitrite reductases • vascular • immune • mitochondria • xanthine**

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Nitric Oxide Synthases and Nitrite Reductases

Over the last two decades, the biological preeminence of cellular nitric oxide (NO) signaling pathways has been intimately linked to many processes and to its regulated enzymatic formation from L-arginine via the actions of NO synthases (NOS) and to secondary activation of soluble guanylate cyclase as a major physiological target/effector system [1–20]. Evolutionary pressure has established a functional diversity in cellular expression of NOS isoenzymes derived from three distinct genes and designated as endothelial (e), neuronal (n) and inducible (i) NOS. E- and n-NOS are constitutively expressed, display Ca^{2+} dependent activation, and rapidly produce and release NO within spatially defined cellular domains. In contrast, iNOS expression is intimately linked to proinflammatory processes, displays a significant latency period due to transcriptional and translational processing, and effects unregulated Ca^{2+}– independent release of NO for extended periods of time [7,21–28]. Interestingly, a significant body of literature supports the contention that constitutively released NO can attenuate the expression of iNOS in vascular smooth muscle, neutrophils, microglia, astrocytes and hepatocytes [29–35]. Work from our laboratory has demonstrated significant feedback inhibition of NO on constitutively derived NO release [12,14–16,36–41] as well as iNOS derived NO release [27].

Within the past decade, an important body of work has challenged the primacy of NOS/L-arginine derived NO in cellular signaling processes and involves the existence of chemically stable nitrite and nitrite reductase activities in these same cell/tissue types [42–56]. Nitrite is a major metabolic product of NO and is found in all cell and tissue types that utilize NO signaling processes [42–46,52,53,55–67]. Accordingly, the establishment of a parallel and complementary NO signaling pathway utilizing recycled nitrite chemical equivalents, independently expressed from well established NOS/L-arginine signaling pathway, requires the identification and biochemical characterization of key candidate enzymes displaying significant nitrite reductase activities within meaningful biological contexts. Until now, accumulated NO/nitrite reductase literature has focused on xanthine oxidoreductase (XOR) as the major candidate nitrite reductase enzyme linked to cellular NO signaling events [49,51,52,54–58,60–64,68–76]. Other candidate nitrite reductases displaying potentially important biological roles as accessory players in NO signaling events include the mitochondrial enzymes aldehyde dehydrogenase [42,44,50,57], cytochrome c/cytochrome c oxidase [45,47,77], deoxymyoglobin [48,53] and deoxyhemoglobin [57,78].

Potent Vascular and Anti-inflammatory Effects of Sodium Nitrite: Functional Involvement of Xanthine Oxidoreductase and Accessory Nitrite Reductases

Xanthine oxidoreductase has been previously characterized as a housekeeping enzyme responsible for cellular uric acid formation via enzymatic conversion of hypoxanthine and xanthine [55,56,70,79]. Based on its intrinsic state-dependent biochemical properties to exist as both a dehydrogenase and an oxidase, it became apparent to several investigators that XOR possessed multi-functional enzymatic activities outside the realm of xanthine metabolism [54–56,70,79]. Hallmark positive vascular effects were well established to be mediated by cellular NOS/L-arginine NO signaling pathways [7–11]. A small but significant literature has also established a compelling functional association between administered sodium nitrite, XOR activation, and pharmacologically characterized NO transductive effects in positive cardiovascular function [62,63,75,80–82], enhanced pulmonary perfusion [60,80], and protection against ischemia/reperfusion injury [64,72–75] and hypoxic damage [56,58,83-85] and oxidative stress [63,76]. Similar positive vascular and cellular effects were observed to be functionally associated with mitochondrial aldehyde dehydrogenase [42,44,50,57], cytochrome c/cytochrome c oxidase [45,47,77].

Nitric oxide derived from NOS/L-arginine systems functions not only as a vasodilator but as a general antibacterial and antiviral agent and, counter-intuitively, it can down-regulate proinflammatory events [27,86–92]. Accordingly, significant anti-inflammatory properties of administered sodium nitrite have been attributed to XOR activation via pharmacologically characterized NO transductive effects [58,68].

Microenvironmental Modulation of NO Production: A Putative Role for Xanthine Oxidoreductase and Accessory Nitrite Reductases

Work from our laboratory supports the contention that constitutively derived NO provides a basal or 'tonal' level of chemical mediator keeps particular types of cells in a state of inhibition [93]. We have hypothesized that certain classes of cells are always 'on', i.e., respond to environmental changes, and that this low basal level of NO [94] provides an organism with a major pathway that functions to dampen microenvironmental "noise" which would otherwise nonspecifically and inappropriately activate them [93]. NO may control the threshold for activation of these cells. This kind of activation really represents a disinhibition process, i.e., an overcoming of the inhibitory influence of NO by changing the balance between basal NO and the levels of excitatory signals.

In support of the hypothesis stated above, there is considerable evidence that constitutively derived NO down-regulates the immunocyte-endothelial interaction [86,93,94]. NO has been shown to inhibit platelet and neutrophil aggregation [90]. *In vitro,* NO inhibits monocyte adhesion to porcine aortic endothelial cells [95]. In human vessels, the adherence of monocytes and granulocytes is reduced following the stimulation of cNOS [86,94,96] and, in the presence of NO, monocytes, granulocytes and endothelial cells become round and inactive [25,97]. These findings strongly indicate that NO can diminish the adherence and level of activation of leukocytes and endothelial cells. It also suggests these are phenomena that occur within a microenvironment given NO short-half life and the strength of the effect produced by many of these cells via autocrine and/paracrine signaling. It is now possible to add a functionally reinforcing mechanism whereby basal levels of cellular nitrite are recycled to active NO equivalents via the actions of XOR and accessory nitrite reductases upon physiological demand (Figure 1) [58,68].

Nitric Oxide Regulation of Mitochondrial Respiration and Intermediary Energy Metabolism: Functional Involvement of Xanthine Oxidoreductase and Accessory Nitrite Reductases

It has been well established that mitochondrial respiration linked to homeostasis of intermediary energy metabolism

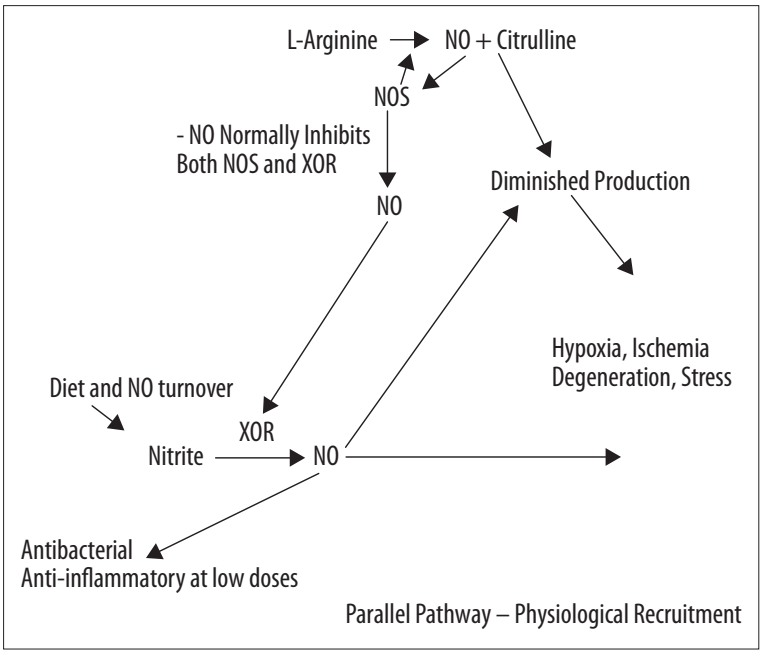

Figure 1. Nitric oxide synthase (NOS) and nitrite reductases, e.g., xanthine oxidoreductase (XOR) physiological recruitment pathways. Nitric oxide synthase and nitrite reductases all can produce constitutive nitric oxide (NO) either alone or in synchrony to meet physiological demands in the modulation of tissue health. Their diminished reduction in NO production and ability to modulate their respective enzymes mediating their synthesis may contribute to pathophysiological sequelae. Given the presence of these parallel systems for NO production highlights the significance of baseline NO presence in "normal" health [93].

is regulated by NO signaling systems [12,98–104]. For example, pharmacological inhibition of constitutively derived NO has been shown to increase oxygen consumption in many animal species [105–109]. Furthermore, a novel NOS isoform, mtNOS, is present in mitochondria [12,99,110] and appears to modulate local circuit regulatory functions within electron transport complexes. Interestingly, nitrite-derived NO has been shown to potently regulate respiration, reactive oxygen species, and energy metabolism in plant mitochondria [83,111–113]. The apparent redundancy of plant mitochondrial NOS/L-arginine- and nitrite-derived NO signaling systems [83,111–113] provides a compelling platform for further investigation into reciprocal regulatory effects of mtNOS and concerted nitrate reductase actions in mammalian mitochondria (Figure 1) [42–46,53,85,114].

A recent important publication has described local circuit nitrite/NO cycling to produce biologically active NO within liver mitochondria [47]. The investigators have demonstrated that nitrite mediates cellular signaling through its reduction to NO via reactions with the mitochondrial electron carrier cytochrome c. Cytochrome c-mediated nitrite reductase activity is dependent on pentacoordination of the heme iron in the protein and occurs under anoxic and in the presence of nitrite, pentacoordinate cytochrome c generates bioavailable NO that is able to inhibit mitochondrial respiration. An elegant complementary study has demonstrated in yeast that state-dependent hypoxia recruits cytochrome c oxidase as a functionally competent nitrite reductase [77]. The investigators have also evaluated nitrite-dependent NO production by specific isoforms of cytochrome c oxidase in support of a functional role of the enzyme in hypoxic signaling events. Additionally, the study findings suggest a positive feedback mechanism for nitrite-derived mitochondrial NO on selective gene expression of a cytochrome c oxidase subunit that is functionally associated with enhanced production of NO in hypoxic/anoxic cells.

Further Investigation Into the Dual Regulation of Nitric Oxide Production by Nitric Oxide Synthases and Nitrite Reductases

On a functional basis it has become clear that the basal level of NO derived from cNOS in concert with cellular nitrite reduction by XOR within a diverse class of nitrite reductases may serve as a key regulatory mechanism underlying complex, cascading, physiological processes associated with maintaining cellular and organ viability. Further studies are required to probe selective regulatory effects of NOS-derived and nitrite-derived NO on gene expression of their cognate synthetic enzymes. Similar compelling studies are needed to elucidate biologically meaningful cellular coupling of cytosolic XOR and mitochondrial nitrite reductases in normal and pathophysiological states (Figure 1) [68–70,80,115–117]. Finally, holistic pre-clinical and studies to evaluate conversion of dietary nitrate to recycling active cellular nitrite pools hold great promise for improving quality of life in human and animal populations [52,81,118,119].

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