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Tonal nitric oxide and health – a free radical and a scavenger of free radicals

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Summary:

Basal/tonal nitric oxide (NO) production helps maintain particular microenvironments, i.e., vascular. Besides NO's function in controlling the activation state of various tissues such as immune cells, its presence appears to modulate other free radical levels, i.e., H_2O_2, in these same tissues and indeed these processes may be one and the same. Thus, by being a free radical, along with the ability to scavenge other free radicals, NO is placed in a pivotal regulatory position. We surmise that in the absence of adequate NO release other free radicals may go 'unchecked' and, therefore, initiate tissue damage. Furthermore, under these circumstances, proinflammatory events will occur due to heightened cell sensitivity and a diminished control of NF-κB. In an excess situation, and one without an appropriate circumstance, i.e., microbial action, NO may become the harmful agent. Hence, balancing basal NO production in body compartments may represent a fundamental process in maintaining general, long-term health.

key words: **nitric oxide • free radical • NF-kB • basal nitric oxide • tonal nitric oxide • antioxidant • immunocytes • vascular endothelial cells**

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NITRIC OXIDE

Nitric oxide (NO) signaling occurs in diverse systems including the immune, cardiovascular and nervous [1–6]. It also occurs in evolutionarily diverse organisms [7,8]. NO is produced from L-arginine by the enzyme NO synthase (NOS) [4,9], which occurs in three forms: endothelial (e), neuronal (n) and inducible (i) NOS.

NO derived from e- or n- (constitutively [c] expressed forms) cNOS may occur in two functional forms: the first is always present at low 'tonal' or 'basal' levels which can be increased slightly for a short time in response to various biological signals [5] such as acetylcholine (ACH). This brief enhanced release of cNOS derived NO can have profound physiological actions that are evident long after NO levels have returned to the basal level of production [10]. In this regard, immune and vascular endothelial cells can be down regulated by NO, see [7]. We have hypothesized that certain classes of cells are always activated and thus can respond to immediate microenvironmental changes [7]. We further speculate that basal or tonal NO levels may provide a major pathway to dampen these cells sensitivity to microenvironmental 'noise' that would otherwise nonspecifically and inappropriately lead to increased activation [7]. In this regard, NO may modulate the threshold required for activation of these cells [7] and the magnitude of the subsequent response [11]. Diminished NO levels would then represent a disinhibition process that results in an overcoming of the inhibitory influence by changing the level of NO production and the corresponding levels of excitatory signals required for cellular activation (see [7]).

NO AND NF-kB

As an example of tonal NO's significance, the transcription factor NF-kB plays a pivotal role in regulation of gene expression induced by inflammatory mediators such as cytokines and adhesion molecules [12]. NO has been associated with NF-kB inactivation [13-17]. Our previous reports document the effect of NO on NF-kB [7,18–20]. NF-kB mediated transcriptional activation of many proinflammatory signal molecules/genes is inhibited by NO in a variety of cells including monocytes [7,18–23]. Thus, NO, aside from its cGMP influences, profoundly impacts DNA events leading to proinflammatory events.

NO AS AN ANTIOXIDANT FREE RADICAL

The intensity and diversity of current research regarding NO demonstrate the complexity of the interactions of this simple molecule. NO, a free radical, has actually been shown to be a beneficial antioxidant against reactive oxygen species (ROS), such as H_2O_2 and O_2^-, [24,25]. When L-arginine, a precursor of NO, was administered to rats in which experimental allergic encephalitis (EAE) was induced, increased levels of NO were shown to be correlated to a decrease in superoxide and hydrogen peroxide levels, demonstrating a role as a protective molecule [26]. There is also evidence of a role in the production of ROS. Varying rates of endogenous NO production resulted in a reciprocal correlation of released H_2O_2 in rat liver mitochondria. This seems to be due to a regulation of O_2 consumption at the level of the cytochrome oxidase [27]. It has been found that the antioxidant properties of NO can be greatly increased by the activation of specific pathways leading to increased endogenous antioxidant production or down regulated pro-inflammatory responses [28].

Much research has also been done to examine NO's role in decreasing lipid peroxidation [24,29–31], but this process appears to be determined by the relative concentration of NO as compared to the reactive oxidant species. When it is in excess of the ROS, then lipid oxidation is decreased; but when NO levels drop below that of the ROS, lipid oxidation reactions propagate [32]. Nitric oxide has also been demonstrated to protect cells from tert-butyl hydroperoxide (tBOOH), a compound of lipid peroxidation. The generation of tBOOH-derived free radicals and tBOOH-induced cytotoxicity were both attenuated by endogenously produced or exogenously added NO [33-35]. In human erythroleukemia cells, t-BuOOH-induced oxoferryl and t-BuO alkoxyl radicals were chemically reduced by NO [34].

From the earlier discussion it becomes clear that the basal level of NO, derived from cNOS, may serve as the key modulator regulating a complex cascading process associated with maintaining cell health [7,36]. It becomes important to determine how a particular microenvironment may alter basal NO levels because, in turn, we learn how NO functions, varied by circumstance. NO has the potential to interact with oxygen, metals and other free radicals [37]. NO can also form peroxynitrite ($ONOO^-$) and dinitrogen trioxide (N_2O_3), following an interaction with the superoxide radical (O_2^-) and oxygen, respectively [38]. In this regard, NO's direct effect is felt when its level is low and of short duration, such as that occurring under physiological conditions, including the right pH [38]. For example, NO interaction with the heme proteins represents the activation of soluble guanylyl cyclase (sGC) and/or cyclooxygenase (COX) [39-41]. This last interaction is important in the regulation of a proinflammatory process [41]. At low concentrations (e.g., when it is scavenged), NO modulates the redox form of COX, converting the ferrous iron to the ferric active form, acting also as a scavenger of superoxide [38]. In addition, NO has the ability to inhibit lipoxygenase, as noted earlier [42]. It can reversibly inhibit the heme moiety of cytochrome P-450, preventing the binding of oxygen to the catalytic sites [43,44].

Interestingly, at low NO levels, H_2O_2 can be consumed to yield HNO_2 [38,45], suggesting that H_2O_2 might serve to control NO levels [38]. Indeed, the activation of monocytes, with interferon γ for 24hr, results in the appearance of activated ameboid monocytes as opposed to inactive cells despite the production of high levels of NO. Cell activation is abrogated in the presence of catalase or superoxide dismutase, suggesting that H_2O_2

inhibition of NO suppression represents an important regulator of cellular activation [46]. Thus, in the absence of H_2O_2, NO activity may be unregulated whereas in the absence of NO, H_2O_2 may generate tissue damage and disruption in energy metabolism as evident in Alzheimer's Disease [7,36]. In any case, the basal/tonal level of NO may represent a specific signal to maintaining 'cell' health.

Mitochondria represent a NO target due to the fact that NO is an inhibitor of cytochrome oxidase of the electron transport process [47-52], which suggests a NO role in modulating oxygen utilization [47]. The inhibition of cNOS-derived NO increases oxygen consumption in many animal species [53-57]. This last fact is critical to our NO hypothesis concerning alterations in basal NO levels since its regulatory process may be stopped (see earlier discussion). Furthermore, a NOS isoform, mtNOS, is present in mitochondria [48,58], suggesting an important modulatory function as well.

Heme proteins (e.g, hemoglobin, cytochromes, etc.) reacting with H_2O_2 results in ferryl cation ($Fe^{4+}+O$), a toxic substance [59]. However, once in contact with NO, this compound is reduced ($Fe^{3+}+NO_2^-$) [38], demonstrating again a NO antioxidant action. NO also has the potential to diminish the formation of $OH^{\bullet}$, again, demonstrating an antioxidant action [60]. This scavenging property gives NO a major intracellular and extracellular action against oxidative stress [38,61–67]. Here, we note that in the absence of NO, these reactive chemical species may cause tissue damage associated with a pathological progression.

In summary, it would appear that basal/tonal NO production helps maintain particular microenvironments, i.e., vascular, see [7,36,68]. Besides NO's function in controlling the activation state of various tissues, such as immune cells, its presence may also control free radical levels in these same tissues and indeed these processes may be one. Hence, by being a free radical, along with the ability to scavenge other free radicals, NO is placed in a pivotal regulatory position. We surmise that in the absence of adequate NO release, other free radicals may go 'unchecked' and, therefore, initiate tissue damage, see [36,68]. Furthermore, under these circumstances, proinflammatory events will occur due to heightened cell sensitivity and a diminished control of NF-kB. In an excess situation and one without an appropriate circumstance, i.e., antimicrobial action, NO, by itself, may become the harmful agent (see above). Thus, balancing and maintaining basal NO production, exerting a tonal effect, in microenvironments may represent a fundamental process in maintaining general health over the long term.

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