Nitric Oxide: A Regulator of Inflammatory Balance

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The many physiological roles of nitric oxide (NO) have been the focus of intensive research. This simple gas molecule has demonstrated very complex and diverse actions that powerfully control our inclination to health or disease. NO has been best studied in the blood vessels where it regulates vasodilation and inhibits platelet aggregation, blood cell adhesion to the endothelium, and vascular smooth muscle proliferation—factors that increase vascular inflammation and lead to atherosclerosis. These actions represent but a few of the numerous areas of NO modulation of inflammatory mechanisms.

Dual role of NO in inflammatory balance

NO plays a significant role in oxidative stress and the inflammatory response. In this regard, the Nitric Oxide Synthase (NOS) enzymes which produce NO create a difference in the concentration of NO and thus modify its function. It is important to recognize that **there are 3 distinct isoforms of NOS** which differ both in structure and specific function. For example, endothelial NOS (eNOS) and neuronal NOS (nNOS) are called ***constitutive* NOS** enzymes. They constantly generate “basal” levels of NO that are necessary for regulating normal physiology, such as controlling blood pressure, vascular integrity, and neurotransmission. It is **constitutive NO production that is subject to age-related declines** due to factors that result in loss of NOS enzyme function. As constitutive NO decreases, endothelial dysfunction increases.

In contrast, when higher sustained levels of NO are necessary for host defense, as in antimicrobial cytotoxic activity or a pro-inflammatory response, the iNOS isoform called ***inducible* NOS** emerges. This isoform is responsible for NO production in immune cells, such as macrophages and neutrophils, as part of the immune response. There is evidence that constitutive NO helps regulate the production of NO from iNOS. And so, while a high concentration of NO is cytotoxic (inducible), a relatively low concentration of NO (constitutive) promotes cytoprotection and cell survival, demonstrating an important role for NO in immunological balance.

Mode-of-action

The scope of NO involvement in inflammatory balance is wide, but a few examples of its diversity may help support understanding. For instance, the action of NO on vascular function is predominantly anti-inflammatory, partly because **NO reduces endothelial permeability to inflammatory mediators** which include white blood cells and platelets. The effect of NO may involve the inhibition of NF-κβ, an important nuclear transcription factor that activates the inflammatory response. Physiological production of NO has the ability to down-regulate an inflammatory event by inhibiting NF-κβ activation of pro-inflammatory cytokines in a variety of cells, including endothelial cells, glia, and monocytes.
Another transcription factor called Nrf2 (NF-E2-related factor 2) serves as a regulator of our cellular defense system against oxidative stress by promoting the expression of a wide array of antioxidant and detoxification genes. NO has been shown to activate Nrf2 by at least 2 pathways (S-nitrosylation of Keap1 and phosphorylation of Nrf2).

NO and nitrite have also been shown to inhibit NADPH oxidase and mitochondrial production of the superoxide radical ($O_{2\cdot}$), which will decrease the toxic damaging effects of inflammation and oxidative stress. **Not only can NO inhibit superoxide production, but it can also act as a free radical scavenger**, and the ability of NO to scavenge superoxide has been well documented. The reaction of superoxide with NO, however, can potentially lead to the formation of peroxynitrite ($ONOO^-$). Peroxynitrite typically will simply rearrange to form inorganic nitrate ($NO3^-$). Notice the exact molecular formula for both nitrate and peroxynitrite. In some cases peroxynitrite can nitrate specific tyrosine residues in protein and lead to irreversible damage. Having sufficient antioxidant capacity in that local environment can mitigate peroxynitrite reactivity and protect the cells from nitrative stress.

Additionally, NO can prevent the oxidative modification of low-density lipoprotein (LDL) cholesterol and regulate mast cell reactivity (i.e. degranulation) in inflammatory processes. **NO plays a protective role in autoimmune diseases and infections**, demonstrating many effects in the innate and adaptive immune systems.

Maintaining NO bioavailability

The capability of the human body to control its NO production is the premise for health. A healthy body is amazingly adept at responding to a changing internal and external environment, particularly through its ability to modulate the amount of NO produced. It is becoming increasingly clear that **the loss of the ability to produce and control NO is the earliest sign of disease**.

A revolutionary therapeutic strategy to address declines in constitutive NO production would be to provide an alternative source of NO (from that produced from NOS) which can compensate for NO insufficiency and rescue individuals with endothelial dysfunction, for example. Also, this strategy should not only be able to exogenously supplement NO deficiency, but also enhance the body's own endogenous production. Likewise, an understanding of the reaction mechanism of peroxynitrite formation and reactivity would allow for specific stoichiometric addition of certain antioxidants to prevent the toxic effects of peroxynitrite.

The current need for such a strategy has been met in Neo40®. Created at the University of Texas Therapeutic Institute, **Neo40 provides a 2-phase NO restoration system**. In the first phase, the unique oral lozenge generates therapeutic NO gas as it dissolves. While NO permeates the system, supporting nutrients work to ultimately **restore the body's own NO production**. This Neo40 system is clinically proven in effectiveness and verified by several landmark clinical trials. Moreover, the unique formulation of Neo40 contains the appropriate stoichiometric addition of specific antioxidants that **prevent peroxynitrite formation and its potentially damaging effects**. The patented Neo40 technology dictates and controls the metabolic fate of NO, allowing for all the benefits of NO without the potential for toxic reactive oxygen or nitrogen species formation. Clearly, Neo40® is set apart as the safest and most sophisticated NO restoration system for medical professionals and their patients.