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Introduction: molecular and functional modifications by nitric oxide and its derivatives

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A decade after the astonishing discovery that nitric oxide (NO) is enzymatically generated from L-arginine by rabbit endothelial cells [1] and murine macrophages [2, 3], the field of research dealing with NO has expanded enormously. Moreover, the 1998 Nobel Prize in Physiology or Medicine was awarded to three pioneers[1] for early findings which established the foundations of this new era in biology. These years were marked by feverish activity, numerous innovations, and major discoveries. Yet NO research remains an area of great promise. The purpose of this timely multi-author review is to provide insights into the molecular basis of NO-dependent modifications of biomolecules and the resulting functional consequences. To this end, several specialists have been invited to cover selected areas ranging from biochemistry to medicine.

In the opening contribution, Henry and Guissani provide relevant insights into the chemistry determining the interaction of NO with hemoproteins, drawing our attention to the differences between hemoglobin and soluble guanylate cyclase. Moreover, they give some useful pointers regarding the somewhat controversial reports dealing with the effect of NO and related species on the heme and nonheme iron proteins of the mitochondrial electron chain. Needless to say, particular attention is devoted to the complex enzymatic system which generates NO from L-arginine in animals. Knowledge of the biochemistry of NO synthesis and of the mechanisms that govern NO synthase activity increases steadily, and Boucher et al. present recent developments concerning these unique enzymes and their inhibitors. They also point to the crosstalk between NO synthase and arginase pathways. With regard to the deleterious consequences of excessive NO synthesis, they describe the specificity of NO synthase inhibitors for the different enzymatic forms. Chabrier et al. discuss the potential therapeutic value in brain diseases of inhibiting the inducible, that is high-output, NO synthase. Schematically, NO-dependent molecular and functional modifications can be categorized into three types: the cGMP-dependent reactions which result from the activation of soluble guanylate cyclase, the nitrosylation of redox-sensitive sites on proteins, i.e., sulfhydryl groups or transition metals (essentially iron), and coupling with other radicals. Broillet describes several examples of S-nitrosation reactions, in particular those associated with olfactory channel activity. Along the same lines, Bouton highlights the functional versatility of two redox-active proteins which ensure post-transcriptional regulation of iron metabolism in response to reactive oxygen- and nitrogen-derived species. NO also reacts with tyrosyl radical-containing proteins at an almost diffusion-limited rate. Ribonucleotide reductase and prostaglandin H synthase are the first well-documented examples of such enzymes in mammals. In plants, a comparable process can occur in photosystem II. Guittet et al. review the available data on regulation by NO of these particular radical-containing proteins.

Beyond the regulatory functions expressed through interactions of NO with thiols, metals, and tyrosyl radicals, it is widely acknowledged that most of the pathological situations resulting from NO synthase activity are the consequence of the fast combination of NO and O_2^- to yield peroxynitrite. Formation of peroxynitrite and its reaction with biomolecules are consequences of a complex chemistry whose fundamentals have recently been established and are reviewed here by Ducrocq et al.

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[1] Robert F. Furchgott, Louis J. Ignarro, and Ferid Murad, 1998 Nobel Prize in Physiology or Medicine for their discoveries concerning 'nitric oxide as a signalling molecule in the cardiovascular system.'

The last part of this review considers the role of NO in the muscular, cardiovascular, and respiratory systems. Relaxation of smooth muscles via NO activation of guanylate cyclase has long been documented. An interesting development regarding vasoregulation has recently emerged from the study of mechanical forces (shear stress and stretch) applied to the endothelium. It transpires that the constitutive endothelial NO synthase can be activated by shear stress via a mechanism involving its redistribution within the signal-transducing membrane domain termed caveolae. Arnal et al. address this issue in their review. NO-related modulation of the contractility force in skeletal muscle has also recently aroused growing interest and is covered by Maréchal and Gailly. Finally, it is worth recalling that one of the most interesting developments of NO therapeutics has been its use as an inhalant. The effect of NO gas in neonatal and adult respiratory syndrome is reviewed in the last paper by Thébaud et al., who also consider the question of the internal source of NO in the respiratory tract. The role and origin of this exhaled NO can now be explored, throwing some light on the cause and evolution of inflammatory diseases of the upper and lower airways.

1 Palmer R. M., Ashton D. S. and Moncada S. (1988) Vascular endothelial cells synthesize nitric oxide from L-arginine. Nature **333:** 664–666

2 Marletta M. A., Yoon P. S., Iyengar R., Leaf C. D. and Wishnok J. S. (1988) Macrophage oxidation of L-arginine to nitrite and nitrate: nitric oxide is an intermediate. Biochemistry **27:** 8706–8711

3 Hibbs J. B. Jr., Taintor R. R., Vavrin Z. and Rachlin E. M. (1988) Nitric oxide: a cytotoxic activated macrophage effector molecule. Biochem. Biophys. Res. Commun. **157:** 87–94