Nitric Oxide: Biological Relevance

S. Moncada
The Wolfson Institute for Biomedical Research, University College London, Gower Street, London WC1E 6BT.

The discovery in 1987 that endothelial cells release nitric oxide (NO) and the subsequent identification of its generation from the amino acid L-arginine revealed the existence of a ubiquitous biochemical pathway. NO is formed by a family of enzymes, the NO synthases, and is involved in many physiological functions. Its formation in vascular endothelial cells maintains a vasodilator tone that is essential for the regulation of blood flow and pressure. NO produced by the endothelium and/or platelets also inhibits platelet aggregation and adhesion, inhibits leukocyte adhesion and modulates smooth muscle cell proliferation. Thus NO acts as a homeostatic regulator of vessel wall functions and a decrease in its synthesis or actions contributes to the development of some vascular pathologies. Impaired production of NO has been implicated in several cardiovascular disorders, including hypertension and atherosclerosis. Agents that modulate the L-arginine: NO pathway such as NO donors and L-arginine, are beneficial in these conditions. NO is also synthesized in neurones of the central nervous system, where it acts as a neuromediator with several physiological functions, including the formation of memory, coordination between neuronal activity and blood flow, and modulation of pain. In the peripheral nervous system, NO is now known to be the mediator released by a widespread network of nerves, previously recognized as nonadrenergic and noncholinergic. These nerves mediate some forms of neurogenic vasodilation and regulate certain gastrointestinal, respiratory and genitourinary functions. All these physiological actions of NO are mediated by activation of the soluble guanylate cyclase in target cells.

In addition, NO is generated in large quantities during host defence and immunological reactions. Such generation of NO was first observed in activated macrophages, where it contributes to their cytotoxicity against tumour cells and invading microorganisms. When NO is released in this way it contributes to the development of certain pathologies, including septic shock, the hyperdynamic state of cirrhosis and some forms of inflammation. Thus NO is a physiological mediator which, when released in large quantities for long periods, acts as a defence mechanism and may be involved in pathophysiology including tissue damage.

One of the ways in which NO may be transformed from a physiological mediator to a pathophysiological entity may be through its actions on mitochondrial function. It has been established recently that at low physiological concentrations NO inhibits cytochrome c oxidase in a reversible manner which is competitive with oxygen. At higher concentrations it irreversibly inhibits other enzymes in the respiratory cycle, either directly or through interaction with superoxide anion leading to the generation of peroxynitrite.