

# The unique role of nitric oxide as a signaling molecule in the cardiovascular system

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The field of nitric oxide (NO) research has developed in explosive proportions since the discovery of endogenous NO in 1986. The biological importance of NO was first suggested by the observations that nitroglycerin and related nitrovasodilators elicit vascular smooth muscle relaxation by liberating NO in the smooth muscle. NO was shown to be a potent smooth muscle relaxant that worked by activating cytosolic guanylate cyclase and elevating smooth muscle levels of cyclic GMP. These observations were quickly followed by those demonstrating that nitro compounds and NO inhibit platelet aggregation by mechanisms also involving cyclic GMP. In view of the findings that NO elicits two important biological actions via cyclic GMP, studies were initiated to ascertain the mechanism by which NO activates guanylate cyclase. The enzyme was found to contain heme as a prosthetic group, which functioned to bind NO and alter the configuration of the active site to increase access to the substrate, MgGTP. Activation of guanylate cyclase by NO results in a 200- to 400-fold increase in  $V_{max}$  and a 3-fold decrease in  $K_m$  for MgGTP. This property makes guanylate cyclase activatable only by NO, and thereby confers great selectivity of the cyclic GMP system such that only NO can stimulate significant cyclic GMP production in tissues. The cyclic GMP system represents the principal signal transduction mechanism by which NO elicits many of its physiological effects in the mammalian species. More recently, however, cyclic GMP-independent pathways have been discovered which can account for cer-

tain biological actions of NO. The most important is S-nitrosylation of proteins and consequent modification of protein function. This mechanism may be important in both physiological and pathophysiological actions of NO. For example, NO appears to inhibit vascular and tumor cell proliferation by inhibiting ornithine decarboxylase via S-nitrosylation of active site cysteine residues. By similar mechanisms, NO appears to inhibit certain caspase enzymes and thereby prevent apoptosis. NO plays an important regulatory role not only in blood vessels *per se* but also in the peripheral nervous system, where NO is the principal neurotransmitter of the nonadrenergic-noncholinergic neurons that innervate various tissues including the erectile tissue. The neurotransmitter NO directly relaxes vascular and nonvascular smooth muscle to cause the erectile response. NO may function in a similar way also in the gastrointestinal tract, in the genitourinary tract, and in the airways.

Based on these properties of NO, new drugs can be developed such as vasodilators and antiplatelet agents and antiproliferative agents for the treatment of hypertension, atherosclerosis, stroke, angina pectoris, heart failure, vascular complications of diabetes, gastrointestinal ulcers, impotency and other vascular disorders. An excellent example of the application of basic information learned about NO has been the development of sildenafil or Viagra<sup>®</sup>, which has revolutionized the treatment of impotency, the most prevalent disorder in the United States. Other novel therapeutic benefits of NO will

include the prevention and treatment of gastrointestinal ulcers, inflammatory bowel disease, and related gastrointestinal disorders as well as urinary incontinence.

NO elicits many other actions in mammalian systems including inhibition of cell proliferation, airway bronchodilation, antimicrobial effects, other host defense

effects, and also modulates learning and memory as well as other central functions. There are undoubtedly many as yet unknown functions of NO. This allows for an extensive opportunity to develop novel drugs for the diagnosis, prevention and treatment of a multitude of cardiovascular disorders.