Nitric Oxide: A Unique Endogenous Signaling Molecule in Vascular Biology

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The properties of nitric oxide as an endogenous cell signaling molecule in vascular biology are described.

KEY WORDS: Cell signaling; nitric oxide; vasculature.

INTRODUCTION

My early research career in graduate school focused on trying to develop a better understanding of catecholamine mechanisms during the embryological development of the sympathetic nervous system. This research required a strong background not only in pharmacology but also in physiology and biochemistry. I recall reading some interesting papers on cyclic AMP, but I never addressed this topic in my early research. At that time, there was no such thing as cyclic GMP, and nitric oxide was considered to be no more than a pollutant in the atmosphere around us. After completing my postdoctoral training at the National Institutes of Health in Bethesda, I accepted an industrial research position to learn more about biochemical aspects of the inflammatory process in order to develop novel antiinflammatory drugs. Although my research did not yet involve cyclic AMP, I continued to read the literature on cyclic AMP and witnessed the discovery of cyclic GMP. I then decided to ascertain whether or not cyclic AMP and cyclic GMP played any modulatory roles in the inflammatory process. We found that cyclic AMP stabilized lysosomal membranes, whereas cyclic GMP promoted instability of lysosomal membranes. Moreover, cyclic AMP production was associated with the inhibition of human neutrophil function such as phagocytosis and lysosomal enzyme secretion, whereas cyclic GMP was associated with increased neutrophil function. In a different research project, it appeared that this new cyclic nucleotide, cyclic GMP, was involved in mediating the negative effects of acetylcholine in the heart, whereas cyclic AMP was already well known to elicit the opposite effects in the heart. A theme was
clearly developing that cyclic AMP and cyclic GMP mediated opposing influences on cell function.

In the midst of our studies on cyclic AMP and cyclic GMP, I recall reading two interesting papers on cyclic GMP that were published by Ferid Murad and colleagues [1, 2]. These studies revealed that nitric oxide and nitro compounds that might release nitric oxide all activated cytosolic guanylate cyclase. Nitroglycerin was one of the nitro compounds studied. Nitric oxide and nitro compounds also stimulated cyclic GMP production in isolated tissues in vitro [3]. These observations suggested that nitroglycerin might activate guanylate cyclase and stimulate cyclic GMP formation by mechanisms involving nitric oxide. Additional studies revealed that nitric oxide might be involved in the nonvascular smooth muscle relaxant effects of nitroglycerin and other nitro compounds [4]. These findings prompted me to conduct some experiments to ascertain whether nitroglycerin and related organic nitrate and nitrite esters could actually release nitric oxide gas in aqueous solution. After observing the generation of nitric oxide from a series of nitro compounds that were known to be smooth muscle relaxants, we thought that nitric oxide might also be responsible for the vasorelaxant effects of nitroglycerin and that cyclic GMP might be the intracellular second messenger mediating this effect of nitric oxide. Accordingly, a series of experiments was conducted to test the hypothesis forwarded by Ferid Murad that nitroglycerin, nitroprusside and nitroso compounds all cause relaxation of smooth muscle, including vascular smooth muscle, by liberating nitric oxide, which elicits its action by stimulating the production of cyclic GMP.

MECHANISM OF RELEASE OF NITRIC OXIDE FROM NITROGLYCERIN AND OTHER NITRO COMPOUNDS

The most important experiment that we conducted to test the hypothesis that nitric oxide is responsible for the vasorelaxant action of nitroglycerin was to determine whether nitric oxide itself causes vascular smooth muscle relaxation. In 1979 [5] we reported that nitric oxide gas is a potent relaxant of bovine coronary artery and activates guanylate cyclase isolated from this tissue (Fig. 1). This observation confirmed what Ferid Murad had found and extended the hypothesis to include vascular smooth muscle. Therefore, nitroprusside, nitroglycerin and related nitro compounds appeared to relax vascular smooth muscle by liberating nitric oxide, which then stimulates cyclic GMP formation and results in vascular smooth muscle relaxation (Fig. 2). The hypothesis that cyclic GMP is involved in smooth muscle relaxation was met with some controversy in the late 1970s because of the prevailing view that cyclic GMP and cyclic AMP mediate opposing biological actions. Cyclic AMP was known to mediate the smooth muscle relaxant effects of certain catecholamines and prostaglandins and cyclic GMP was thought to be involved in mediating smooth muscle contraction. However, the work conducted in several laboratories including those of Ferid Murad and myself indicated that cyclic GMP and cyclic AMP can mediate common biological actions in smooth muscle such as relaxation.

The next step in elucidating the precise mechanism of action of nitroglycerin was to ascertain how nitric oxide was released from the parent molecule in smooth