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Nitric oxide based strategies for applications of biomedical devices

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Abstract

Since the first report describing nitric oxide (NO) in the mid-1980s, research efforts have been devoted to elucidating the pathway of NO generation and the mechanism of NO function *in vivo*. The worldwide expansion of NO investigations have helped advance progress in biomedical device applications of NO-based strategies for cardiovascular devices, wound healing and antimicrobial agents, including recent *in vivo* investigations. Here we describe the general concepts of NO discovery, mechanisms of NO synthesis *in vivo* and NO producing materials. Both design strategies and results are discussed and compared in release kinetics, NO dose and biological effects, with the aim of providing foundations for the development of new NO-based therapeutics.

Keywords: Nitric oxide; Biomedical devices; Vascular devices; Antimicrobial; Wound healing

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1. Introduction

Prior to 1987, NO was generally regarded as a pollutant in the environment produced from factory fumes, exhaust emissions and electrical storms. The sensational discovery by Robert Furchgott, Louis Ignarro and Ferid Murad that the endothelium-derived relaxing factor (EDRF) was in fact NO marked the beginning of a major worldwide expansion in NO investigation not only in the basic sciences but also in applied sciences [1]. Meanwhile, research efforts have been devoted to elucidating the pathway of NO generation and the mechanism of NO function *in vivo*. Thereafter NO is known as a diatomic free radial endogenously synthesized in the body, and is generated when L-arginine is converted to L-citrulline by nitric oxide synthases (NOS) [2,3].

With research ongoing and knowledge increasing, NO has been found to present manifold physiological and pathophysiological functions associated with cardiovascular homestasis, immune response to infection, wound repair, tumor biology and pathology [4–7]. It was declared as the "molecule of the year" by the journal *Science* in 1992. NO-based strategies hold promise for a number of biomedical applications including cardiovascular regulation, antimicrobial action and wound healing. In terms of the cardiovascular system, NO is naturally produced by endothelial cells (ECs) to maintain a healthy microenvironment surrounding blood vessels by supporting the smooth flow of blood to all parts of the human body. NO influences the cellular behavior of circulating platelets and monocytes. The activation of them could lead to further aggregation and ultimately initiation of thrombosis, as well as acceleration of atherosclerotic process and unexpected immune system response [8–12]. Simultaneously, NO is involved in tumor biology as an intricate balance where both NO concentration and lifetime affect whether it acts as a tumor progressor or suppressor [13]. NO-based therapeutic presents excellent antibacterial candidates as it is at the crux of the innate immune system of higher organisms [14]. Finally, NO-based strategies can promote good wound healing. The scientific community has gradually developed an understanding of the many functions of NO and the underlying principle involved [15].

In addition to NO's numerous physiological functions, the effects of NO are often localized due to its short half-life, rapid diffusion and high reactivity [2]. Many studies of NO's importance to physiology have focused on exposing biological targets to different concentrations of NO and exploring changes to cellular activity [16]. Taking these factors into account, NO dose and release kinetics properties should be considered in developing NO-based therapeutics. Generally, current NO-based therapies can be classified into two categories: materials that directly release active NO or act as NO redox catalysts, and drugs that regulate the enzymatic production of NO from the body. In addition, several promising strategies are based on altering NOS activity to regulate endogenous NO concentrations [17–21]. Many studies have focused on constructing NO-releasing and NO-generating materials. NO gas loading as well as synthesis, incorporation and covalent attachment of NO donor compounds are the major methods of NO delivery [22]. However, challenges such as the short half-life of most NO donors and lack of targeted NO delivery are the still restrictions in the commercialization of NO-releasing materials. NO-generating materials mainly mimic the capability of the selenium-contacting enzyme, glutathione peroxidase (GPx) that exists in blood, by catalytically decomposing RSNO into NO with the presence of glutathione (GSH) as the reducing substrate [23]. The potential advantage of NO-generating materials is that a sustained NO flow can be achieved through the constant level of endogenous RSNO in circulating blood [24]. Endogenous RSNOs could be decomposed to release NO in the presence of catalysts such as thiol-containing agents like L-cysteine, organoselenium, transition metal-ions derived from Cu^{2+}, Hg^{2+}, Fe^{2+}, Ag^{+} or tellurium [12]. These catalysts are highly selective for reduction of *S*-nitrosothiol.

This review will cover the biomedical applications associated with NO-based strategies for cardiovascular devices, wound healing and antimicrobial agents, with emphasis on recent *in vivo* investigations. Of these, primary attentions will be paid to NO-based modifications of extracorporeal circuits, vascular stents and bypass grafts of cardiovascular devices. Both the design strategies and results are discussed and compared in release kinetics, NO dose and biological effects, with the aim of providing a foundation for developing new NO-based therapeutics. General concepts behind the discovery of the NO signaling pathway and the main types of NO donors as well as NO-releasing and NO-generating materials are also discussed.

2. Production of nitric oxide

As a gas and diatomic free radical with an unshared electron, NO regulates an ever-growing list of biological processes. NO can function as an intracellular messenger, an autacoid, a paracrine substance, a neurotransmitter, or a hormone that can be carried to distant sites for diverse effects that are either cyclic guanosine monophosphate (cGMP) dependent or independent, altering and regulating important biochemical and physiological events in cell regulation and function. Thus it is a unique simple molecule with an array of signaling functions [1]. However, the discovery and identification of NO has taken a long time, with twists and turns.

2.1. Discovery of nitric oxide

Early in 1980, Furchgott and Zawadzki first described the phenomenon of endothelium-dependent relaxation, whereby acetylcholine relaxes isolated preparations of blood vessels with an intact vascular endothelium lining the vessels. Subsequently it was demonstrated that various arteries from different species of animals exhibited relaxation in response to acetylcholine only in the presence of ECs. Acetylcholine-induced relaxation of transverse strips revealed that acetylcholine stimulated the produce of a diffusible relaxing substance by ECs, which was later referred as EDRF [25,26]. Within a few