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Research review paper

State of the art, challenges and perspectives in the design of nitric oxide-releasing polymeric nanomaterials for biomedical applications

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ABSTRACT

Recently, an increasing number of publications have demonstrated the importance of the small molecule nitric oxide (NO) in several physiological and pathophysiological processes. NO acts as a key modulator in cardiovascular, immunological, neurological, and respiratory systems, and deficiencies in the production of NO or its inactivation has been associated with several pathologic conditions, ranging from hypertension to sexual dysfunction. Although the clinical administration of NO is still a challenge owing to its transient chemical nature, the combination of NO and nanocarriers based on biocompatible polymeric scaffolds has emerged as an efficient approach to overcome the difficulties associated with the biomedical administration of NO. Indeed, significant progress has been achieved by designing NO-releasing polymeric nanomaterials able to promote the spatiotemporal generation of physiologically relevant amounts of NO in diverse pharmacological applications. In this review, we summarize the recent advances in the preparation of versatile NO-releasing nanocarriers based on polymeric nanoparticles, dendrimers and micelles. Despite the significant innovative progress achieved using nanomaterials to tailor NO release, certain drawbacks still need to be overcome to successfully translate these research innovations into clinical applications. In this regard, this review discusses the state of the art regarding the preparation of innovative NO-releasing polymeric nanomaterials, their impact in the biological field and the challenges that need to be overcome. We hope to inspire new research in this exciting area based on NO and nanotechnology.

Contents

1. Introduction

Nitric oxide (NO) is an endogenously synthesized small molecule that regulates multiple functions in physiological processes, such as the control of vascular tonus, immune responses, the inhibition of platelet and leukocyte adhesion and aggregation, angiogenesis, apoptosis, wound healing, tissue repair, neurotransmission and inflammation (Fig. 1) (Howard et al., 2014 Ignarro, 2000; Kim et al., 2014; Seabra, 2011). Accumulating experimental evidence supports multiple roles for NO, such as an anticancer (Choudharil et al., 2013; Muntané et al., 2013; Seabra et al., 2014) and antibacterial agent (Cardozo et al., 2014; Schairer et al., 2013; Seabra et al., 2010), an efficient inhibitor of restenosis (Naghavi et al., 2013), and a key molecule involved in the

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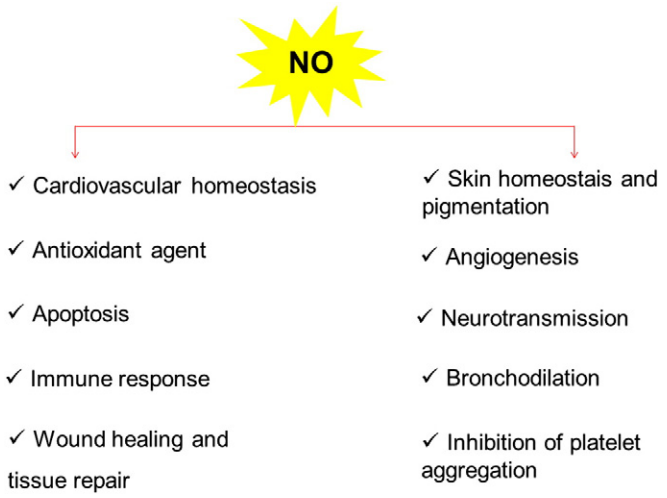

Fig. 1. Some of the physiological roles mediated by NO are endogenously produced.

promotion and acceleration of wound repair (Amadeu et al., 2008; Georgii et al., 2011; Nichols et al., 2012; Seabra, 2011).

In vivo, NO is catalytically produced by the action of three NO synthase (NOS) isoforms: endothelial (eNOS), neuronal (nNOS) and inducible (iNOS) (Gaucher et al., 2013; Moncada et al., 1989,1991; Palmer et al., 1988). The constitutive eNOS enzyme, which is expressed by endothelial cells, catalyzes the oxidation of L-arginine to L-citrulline upon receptor stimulation, such as via acetylcholine or sheer stress, leading to the formation of NO (Duran et al., 2010; Ignarro, 1999; Ignarro et al., 1987; Moncada et al., 1989; Stasio et al., 2009). As NO is a small uncharged gaseous molecule, it readily diffuses from endothelial cells to smooth muscle cells, where it nitrosylates soluble guanylate cyclase (sGC), converting guanosine-5′-triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) and initiating the vasodilation signal pathway (Fig. 2) (Gaucher et al., 2013; Ignarro, 1999). Homeostasis is maintained by intact endothelial cells lining the blood vessels, which release vessel constrictors and vessel dilators (Forstermann and Sessa, 2012). NO produced by endothelial cells plays a key role in the cardiovascular system by controlling blood flow and blood pressure and inhibiting thrombus formation (Toda and Toda, 2011). eNOS produces pico- to nanomolar concentrations of NO for short periods of time to promote vasodilation, thereby increasing blood flow (Naghavi et al., 2013). Similarly, nNOS produces low nanomolar NO concentrations for neurotransmission, whereas iNOS produces high concentrations of NO (micromolar range) for longer periods of time (hours to days) in immunological responses (Griffith and Stuehr, 1995). The NO produced by iNOS is a potent antibacterial and antiviral agent (Pautz et al., 2010). Recent studies have described the antimicrobial effects of NO against a wide range of organisms, including anti-biofilm actions, indicating the promising strategy of administering exogenous NO donors as bactericidal agents (Cabrales, 2011; Cardozo et al., 2014; Hetrick et al., 2009; Jardeleza et al., 2014; Seabra et al., 2010). Moreover, important evidence has demonstrated the efficiency of NO in reducing the proliferation of different cancer cell lines (Kielbik et al., 2013; Seabra et al., 2014). NO can have pro- or anti-proliferative activity, depending on its concentration, half-life and microenvironment (Burke et al., 2013; Choudharil et al., 2013), and the combination of NO with traditional chemotherapy drugs (e.g., doxorubicin and cisplatin) optimizes their cytotoxicity toward cancer cells (de Luca et al., 2011; Deng et al., 2013). Thus, NO has emerged as a potent anti-cancer agent that might be able to overcome drug resistance in cancer treatment (Reynolds et al., 2013). NO is also a critical mediator in skin physiology and plays a key role in the wound healing process, accelerating wound re-epithelialization and promoting granular tissue organization (Amadeu et al., 2008; Georgii et al., 2011; Seabra, 2011; Weller, 2003).

As NO is an important signaling molecule associated with several physiological processes, deficiencies in NO production or a reduction in its bioavailability has been associated with several pathological conditions, such as cardiovascular complications (including hypertension, endothelial dysfunction and atherosclerosis), cancers, diabetes, obesity and neurodegenerative processes (Gaucher et al., 2013; Ignarro, 2000). Within this context, the development of strategies for carrying and delivering exogenous NO is considered a promising approach in a number of biomedical applications (Carpenter and Schoenfisch, 2012; Riccio and Schoenfisch, 2012).

1.1. Nitric oxide donors

In vivo, NO has a short half-life (1–5 s), and it is readily inactivated by reacting with oxygen or hemoglobin (Nichols et al., 2012). Due to the reactive chemical nature of NO, several strategies have been developed for NO storage, thus allowing its manipulation and biomedical applications. Due to the difficulties in delivering NO gas directly, low molecular weight (LMW) NO donors, generally called NO pro-drugs, are frequently administered in pharmacological applications (Gaucher et al., 2013; Jo et al., 2009; Seabra et al., 2007). Typical NO donors are sodium nitroprusside (SNP), nitroglycerin, NO-aspirin, S-nitrosothiols (RSNOs), organic nitrates, ruthenium nitrosyl complexes and 1-substituted diazen-1-ium-1,2-diolates (NONOates) (Keefer, 2011; Kim et al., 2014; Seabra et al., 2004, 2007; Serafim et al., 2012), with nitroglycerin being largely used in the clinical set (Yasuda et al., 2006a,b).

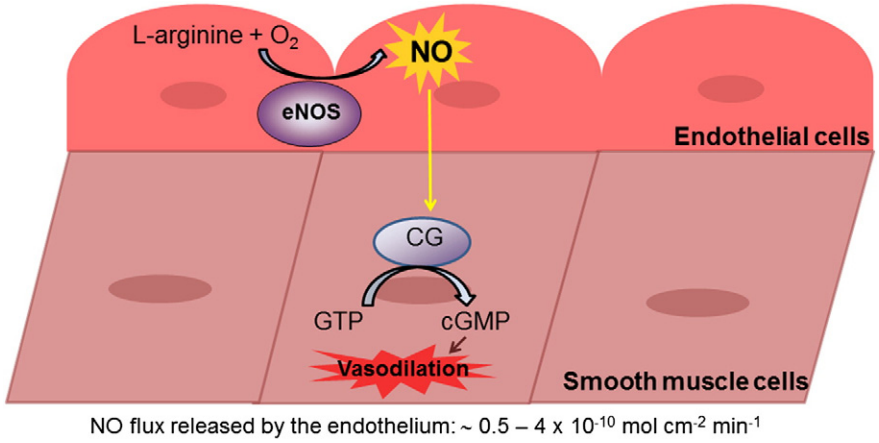

Fig. 2. Schematic representation of vasodilation produced by endogenous NO. The constitutive eNOS is expressed in endothelial cells and catalyzes the oxidation of L-arginine to L-citrulline, leading to the formation of NO. NO readily diffuses from endothelial cells to smooth muscle cells, where it nitrosylates soluble guanylate cyclase (sGC), converting guanosine-5′-triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), initiating the vasodilation signaling pathway.