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Anti-fibrotic effects of soluble guanylate cyclase stimulators and activators: A review of the preclinical evidence

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ABSTRACT

It is now well established that the NO-sGC-cGMP signal transduction system mediates many different physiological functions in almost every conceivable organ system; this has been best characterized in the cardiovascular system where NO-driven cGMP production exerts a plethora of cytoprotective and anti-atherogenic effects, including dilatation, inhibition of vascular smooth muscle proliferation, blockade of leukocyte recruitment, and anti-platelet activity. Accordingly, dysfunctional NO-sGC-cGMP mediated signaling is perceived as the underlying pathophysiological cause of many cardiovascular and non-cardiovascular diseases. Due to the fundamental role of sGC in the signaling pathways triggered by NO, novel sGC 'modulators' have been identified that directly stimulate both heme-containing as well as heme-free sGC, the so-called 'sGC activators' and 'sGC stimulators', respectively. The beneficial effects of this new family of sGC 'modulators' extend beyond vasodilation, and their potential in other cardiovascular diseases aside from pulmonary arterial hypertension is promising. In animal models of hypertension and heart failure, reno-protective effects, attenuated cardiac fibrosis, and attenuated hypertrophy independent of hemodynamic effects have been shown. During recent years it has become obvious that cGMP increase by sGC modulators exerts direct antifibrotic efficacy in various organs as well as the skin. This review will provide an overview of the preclinical in vitro and in vivo studies for different fibrotic disorders including chronic renal, cardiac, liver, and lung fibrosis, as well as sclerosis and wound healing. Moreover, this review provides evidence for a new mode of action of sGC 'modulators' and its implication for clinical investigations in the treatment of fibrotic disorders such as pulmonary fibrosis and skin fibrosis.

1. Signal transduction and pharmacotherapy

1.1. The NO-sGC-cGMP pathway

The nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) pathway, an important therapeutic target for cardiopulmonary disease [1], was first elucidated in 1980 [2]. This pathway is also an important target for cardiopulmonary disease [2]. Key to understanding this pathway was the discovery of NO as the "endothelium-derived relaxing factor" that is released from the endothelium, which increases levels of cGMP through the activation of sGC and induces vascular smooth muscle relaxation [3–6]. The implications for this pivotal research in cardiovascular signaling led to Furchgott, Ignarro, and Murad receiving the Nobel Prize for Physiology or Medicine in 1998.

Binding of NO to its receptor, sGC, stimulates the synthesis of cGMP from guanosine triphosphate, which substantially regulates vascular tone. In addition, effects on proliferation, fibrosis, and inflammation in the cardiopulmonary system and beyond are described [5,7–9]. The effects of cGMP are mediated by several downstream targets, most importantly the cGMP regulated protein kinase (PKG), which phosphorylates key components of different downstream pathways and mediates the cGMP signal [10,11]. cGMP-regulated phosphodiesterases (PDEs) and cGMP-regulated ion-channels (CNGCs) also contribute to these effects [12,13]. Thus, PKG, PDEs, and CNGCs translate the cGMP signal at the molecular level on different intracellular targets and ultimately trigger

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cellular response. Given the broad influence of cGMP elevation on various intracellular targets and distinct cellular functions, several pharmacologic approaches were developed and are still in development to fully exploit the therapeutic potential of this common pathway [14]. In this review we will discuss the components of the NO-sGC-cGMP pathway, cellular pathways that trigger fibrosis, and the current state of cGMP elevators in the treatment of fibrosis in multiple etiologies.

1.2. Organic nitrates

Organic nitrates serve as NO donors to activate the NO-sGC-cGMP pathway by bioconversion. These NO donors have been used as vasodilators to treat vascular dysfunction [1]. NO is synthesized by conversion of L-arginine via the enzyme nitric oxide synthase (NOS) (Fig. 1). This process can be inhibited using asymmetric dimethyl-arginine (ADMA) and NG-methyl-L-arginine (L-NMMA) [15]. Disruption of NO synthesis, which leads to interruption of NO-sGC-cGMP signaling, has been shown to be largely responsible for vasoconstriction of coronary vessels. This results in reduced conduit vessel diameter and coronary blood flow as well as an increase in coronary vascular resistance [16]. This is clinically associated with angina pectoris and pulmonary hypertension (PH), which is characterized by endothelial dysfunction, altered smooth muscle cell growth, and impaired production of vasoactive mediators) [1,17–21]. Organic nitrates such as nitroglycerin were the earliest pharmacotherapies to target NO-sGC-cGMP signaling and have been used for over a century to treat cardiovascular disease [1,7,22,23].

1.3. PDE5 inhibitors

Phosphodiesterase-5 (PDE5) inhibitors entered into clinical practice for treatment of erectile dysfunction in 1999 and for the treatment of PAH in 2005 [2]. PDE5 inhibitors block the downstream degradation of cGMP to GMP, increasing intracellular cGMP levels. However, the efficacy of PDE5 inhibitors is dependent on the presence of sufficient amounts of endogenous NO to activate sGC and generate cGMP [2]. Thus, low endogenous NO/cGMP production significantly limits or impairs the effects of PDE5 inhibitors.

1.4. sGC modulators

The more recently developed sGC modulators, which stimulate and activate sGC in an NO-independent manner, have been shown to have broad treatment potential. The sGC modulators as a class comprise sGC stimulators and sGC activators. The sGC stimulators bind to the heme-containing sGC and act heme dependently, while the sGC activators preferentially bind to oxidized sGC and act heme-independently [7,24,25]. The sGC stimulators, such as BAY 41-2272, BAY 41-8543, BAY 60-4552, riociguat (BAY 63-2521), or vericiguat (BAY 102-1189) have a dual mode of action: they act in synergy with NO to restore the NO-sGC-cGMP pathway by sensitizing sGC in low-NO environments and directly stimulate sGC to synthesize cGMP independent of NO [26–29]. Both mechanisms of sGC stimulation lead to substantial elevation of cGMP in low-endogenous NO and low-cGMP environments.

Riociguat (BAY 63-2521) is the first sGC stimulator that has made a successful transition from animal experiments to controlled clinical studies in human patients with PH. In 2013, riociguat (Adempas®) was approved by the Food and Drug Administration and European Medicines Agency for the treatment of these two forms of PH: inoperable recurrent or persistent chronic thromboembolic pulmonary hypertension and pulmonary artery hypertension (PAH) [28]. Because cGMP elevation has been associated with anti-fibrotic, anti-proliferative, and anti-inflammatory effects, sGC modulators may possess treatment potential beyond vasorelaxation in fibrotic disorders. This review will describe the anti-

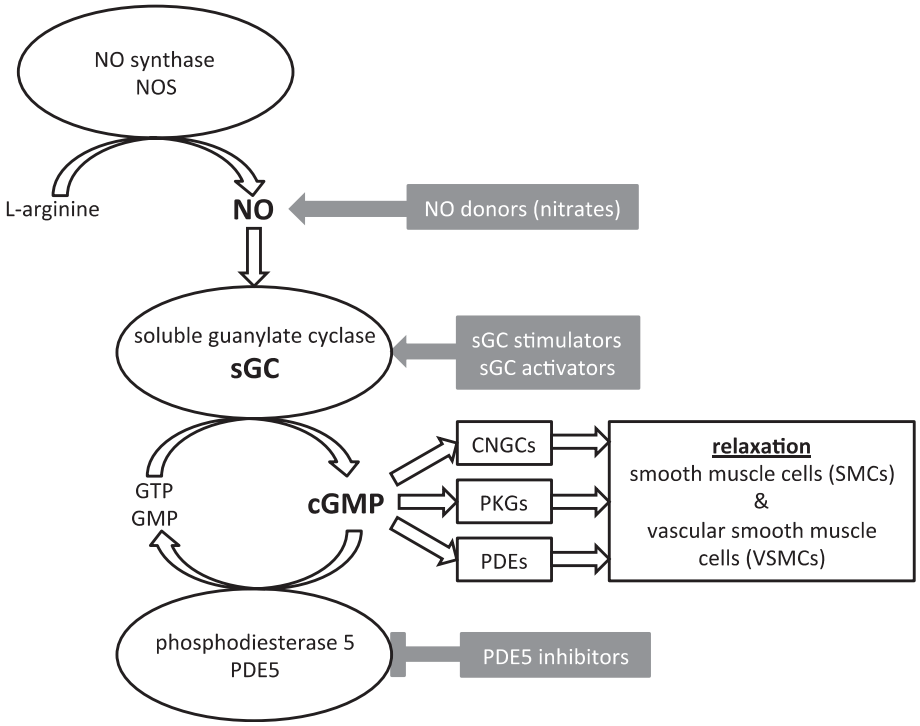

Fig. 1. NO-sGC-cGMP Pathway. Abbreviations: cGMP, cyclic guanosine monophosphate; CNGC, cyclic nucleoside-gated ion channels; GMP, guanosine monophosphate; GTP, guanosine triphosphate; NO, nitric oxide; PKG, protein kinase G.