

PERSPECTIVE

## Cyclic GMP and Phosphodiesterase 5 Inhibitor Therapies: What's on the Horizon?

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A little more than 6 years ago, the first therapeutic agent targeting cyclic nucleotide phosphodiesterases (PDEs) for the treatment of erectile dysfunction (ED) was introduced into clinical medicine (Boolell et al., 1996). The PDE5 inhibitor sildenafil (Viagra) was the first orally active, effective therapy for the treatment of ED by virtue of its capacity to inhibit cyclic GMP hydrolysis in penile cavernosal and arterial smooth muscle. This *Perspective* will focus on a “bench-to-bedside” view of PDE5 inhibitors, including comments relating to the emergence of newer PDE5 inhibitor drugs, and the extraordinary explosion of research into novel therapeutic uses of PDE5 inhibitors.

Figure 1 reviews the role of PDE5 in the metabolism of cyclic GMP and how PDE5 inhibition alters the activity of cellular pathways regulated by cyclic GMP. Cyclic GMP is synthesized in cells by guanylyl cyclases. There are two types of guanylyl cyclase: a membrane-bound, particulate form that is activated by circulating natriuretic peptides and guanylin and a soluble, cytosolic form that is activated by nitric oxide (NO). NO diffuses from cells that express NO synthases, such as neurons and endothelial cells, into target cells, such as smooth muscle cells, to activate soluble guanylyl cyclase. Cyclic GMP interacts with cellular receptors, which, in smooth muscle, include the serine/threonine kinase cyclic GMP-dependent protein kinase (PKG) and the cyclic AMP specific phosphodiesterase 3 (PDE3). The binding of cyclic GMP activates PKG but inhibits PDE3 activity. In cavernosal tissue in particular, but also in most vascular and nonvascular smooth muscle, PDE5 represents a major cyclic GMP-hydrolyzing activity. PDE5 itself is activated by phosphorylation catalyzed by PKG. Phosphorylation increases cyclic GMP binding to noncatalytic cyclic GMP binding GAF domains; this results in the activation of cyclic GMP hydro-

lysis at distinct catalytic sites. The interactions between PKG and PDE5 insure that cyclic GMP levels do not accumulate too rapidly in the cell. The catalytic cyclic GMP binding sites on PDE5, but not the GAF sites, bind PDE5 inhibitors with high affinity to block cyclic GMP hydrolysis. Therefore, a greater degree of activation of PKG occurs in the cell, and in smooth muscle, enhanced PKG-dependent phosphorylation of a variety of protein substrates inhibits contraction.

In this issue of *Molecular Pharmacology*, Blount et al. (2004) assess the binding properties of the newer PDE5 inhibitors, vardenafil (Levitra) and tadalafil (Cialis), and compare the properties of these compounds with those of sildenafil. The order of potency for inhibition of PDE5 correlates closely with the binding affinity of the drugs for the catalytic sites. Because each of these inhibitors competes with the other inhibitors for access to PDE5, each must bind in the same manner to PDE5. Of particular interest regarding the potent biological effects of these compounds is that cyclic GMP addition increased the binding affinity (inhibitory activity) of the newer inhibitors vardenafil and tadalafil. These results imply that PDE5 inhibitors potentiate their own inhibitory activity by merely elevating cyclic GMP in the cell via PDE5 inhibition. Herein lies the secret to the potent biological effects of these drugs. The kinetic findings in this study also indicate that the three therapeutically available PDE5 inhibitors have the same inhibitory activity toward cyclic GMP hydrolysis. The difference in potency of inhibition, however, indicates that vardenafil and tadalafil may produce biological effects at lower concentrations and perhaps for longer durations. The therapeutic activity of tadalafil, for example, is of longer duration than sildenafil; this may be caused in part by its higher affinity for PDE5. Other factors such as metabolic degradation may affect the duration of action.

The availability of different PDE5 inhibitors with different

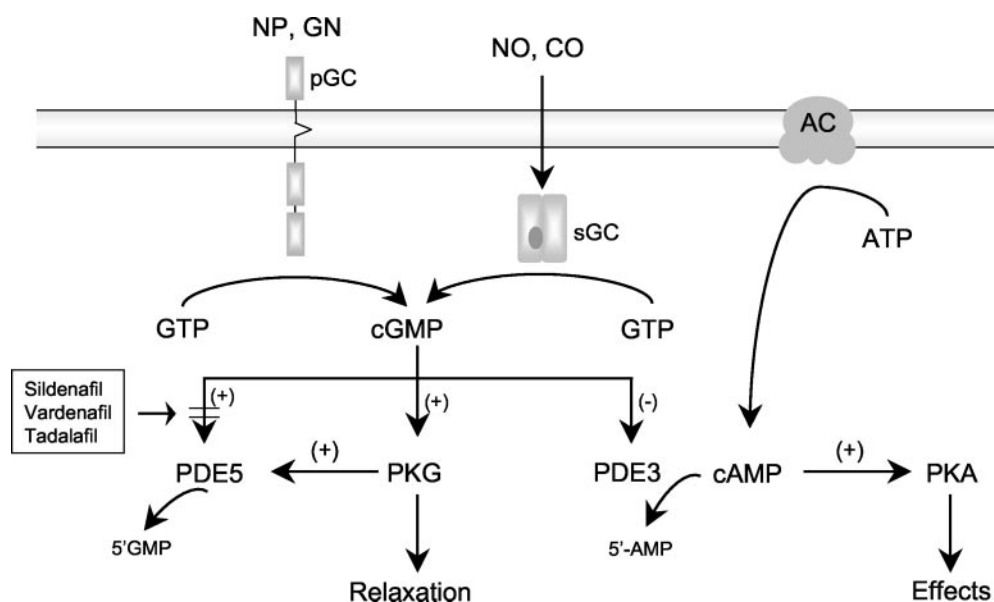
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affinity and dissociation kinetics means that the physician now has available not only several drugs having some unique properties with respect to the inhibition of PDE5, but drugs that may be more aptly suited for the treatment of specific disorders in patient populations. For example, one side effect of sildenafil in certain individuals is a blurring or blue “tinting” of vision caused by the inhibitory effects of sildenafil on retinal PDE6 (Gresser and Gleiter, 2002). Vardenafil, on the other hand, has greater specificity toward PDE5 than PDE6, perhaps making vardenafil the drug of choice for persons who develop this sildenafil side effect. Nevertheless, the PDE5 inhibitors are remarkably similar with respect to efficacy and side effects in all the clinical trials conducted to date. Notably, none of the PDE5 inhibitors leads to untoward cardiac episodes in patients; the only exception is that all PDE5 inhibitors are contraindicated in patients taking oral nitrate drugs.

When one delves into the history of the development of cyclic GMP PDE inhibitor drugs, it becomes clear that the notion for using these drugs to treat ED was in part an accidental finding. In the early 1980s, investigations into the role of cyclic GMP in smooth muscle relaxation began in earnest. Elevation of cyclic GMP by PDE inhibition seemed a logical approach for treating disorders from hypertension to vascular spasms. Yet, sildenafil, the first drug synthesized that possessed the two important properties of specificity and potency for PDE5 inhibition, did not seem promising for treating angina in early clinical trials. Its now famous side effect, reported by a large number of volunteers that participated in these trials, led to the major focus of later studies. Likewise, there was much discussion at meetings on the biological role of NO in the early 1990s, spurred on by the landmark paper from Ignarro et al. (1990) demonstrating a critical role for NO/cyclic GMP in penile erection, leading to the proposed use of PDE inhibitors for treating ED.

Even so, there is a large growing literature on other potential clinical uses for PDE inhibitors. Perhaps the most promising therapeutic potential for PDE5 inhibition is in the treatment of pulmonary hypertension (Humbert and Simonneau, 2004). Increased pulmonary arterial pressure may arise from endothelial cell dysfunction where excessive endothelial vasoconstrictors or impaired production of endothelial cell vasodilators occurs. Pulmonary hypertension may be a primary (idiopathic) or secondary to procedures such as heart-lung transplantation. Pulmonary vascular inflammation, remodeling, and fibrosis often have serious and devastating consequences, and there have been relatively few effective therapeutic approaches. Early studies demonstrated that inhaled NO, especially in neonatal pulmonary hypertension, was a potentially effective approach for the management of the disease, but rebound hypertension and difficulties in therapeutic protocols suggested that alternate targets of the NO/cyclic GMP pathway should be pursued. Sildenafil decreases pulmonary vascular resistance in adult and neonatal patients with positive effects on cardiac indices. Predictably, inhaled NO and sildenafil together were more effective than either alone. Likewise, sildenafil in combination with the prostaglandin receptor agonist iloprost produced prominent reductions in pulmonary arterial pressure and favorable cardiac indices. Perhaps one of the more exciting developments is the potential use for PDE5 inhibitors to treat pulmonary hypertension in fibrotic lung disease, a condition that has been all but untreatable in the past. It must be pointed out that many of these studies have been performed on small populations of patients with pulmonary hypertension of various causes. Furthermore, although use of PDE5 inhibitors to treat animal models of pulmonary hypertension has been encouraging, many of these animal models do not precisely replicate the human disease. Consequently, several clinical trials are currently under way to examine the



**Fig. 1.** The metabolism of cyclic GMP and the effects of PDE5 inhibitors on cell function. Natriuretic peptides (NP) and guanylin (GN) bind to particulate surface guanylyl receptors (pGC) whereas nitric oxide (NO) and carbon monoxide (CO) bind to cytosolic soluble guanylyl cyclases (sGC). Cyclic GMP (cGMP) activates cGMP-dependent protein kinase (PKG) which catalyzes the phosphorylation of substrates leading to smooth muscle relaxation, and also catalyzes the phosphorylation of PDE5. The phosphorylated PDE5 binds cGMP and is activated to hydrolyze cGMP to inactive 5'-GMP. Cyclic GMP also binds to cyclic AMP phosphodiesterase 3 (PDE3) to inhibit its activity to hydrolyze cAMP. Cyclic AMP produced by the activation of adenylyl cyclase (AC), activates cAMP-dependent protein kinase (PKA) to produce additional effects, including smooth muscle relaxation. The PDE5 inhibitors, sildenafil, vardenafil and tadalafil, are selectively potent for the inhibition of PDE5.

use of PDE5 inhibitors to assess the efficacy of these agents in the human disease.

The use of PDE5 inhibitors for managing the systemic circulation remains a topic of interest. The original disappointing outcomes from clinical trials for treatment of coronary angina with sildenafil notwithstanding, it has been demonstrated in several human and animal models that sildenafil, vardenafil, and tadalafil modestly reduce arterial pressure (Brindis and Kloner, 2003). There is currently considerable interest in the potential use of PDE5 inhibitors in combination therapy for systemic hypertension. In addition, the use of the B-type natriuretic peptide nesiritide (Natrecor) in patients with congestive heart failure (Zinch et al., 2003) may represent another potential combination therapy with PDE5 inhibitors. More recently, sildenafil has been shown to increase retinal blood flow without increasing intraocular pressure, suggesting that PDE5 inhibitors may be useful for retinal ischemic diseases (Polak et al., 2003). In circulatory disturbances in which endothelial dysfunction is regarded as a primary cause (peripheral arterial occlusive disease, diabetes), PDE5 inhibitors may be of use alone or in combination with other therapeutic agents. For example, Raynaud's phenomenon, a peripheral vasospastic disorder for which there have been few effective treatments, may be a prime candidate for PDE5 inhibition and preliminary clinical trials are encouraging (Rosenkranz et al., 2003). The examination of the use of PDE5 inhibitors as specific therapeutic agents to increase blood flow in various systemic beds may just only be beginning (Refflemann and Kloner, 2003).

Because cyclic GMP is the major intracellular signaling messenger for most smooth muscle relaxation pathways, PDE5 inhibition may prove of use in treatment of asthma or gastrointestinal disturbances. Preliminary reports demonstrate potential beneficial effects of sildenafil for esophageal motor activity in patients with achalasia or other motility disorders and in animal studies for gastrointestinal transit (Lee et al., 2003). One of the major phenotypic disorders described in the PKG-deficient mouse produced by targeted gene ablation is gastrointestinal obstruction. Decreased peristaltic activity and increased tone of gastrointestinal sphincters was directly related to the disruption of the cyclic GMP pathway, leading to smooth muscle relaxation. Thus, in human patients demonstrating varying

abnormalities in gastrointestinal function, PDE5 inhibitors provide a novel therapy.

In summary, the availability of multiple drugs that selectively inhibit PDE5 could be important for the targeting of PDE5 in specific tissues or cells. As demonstrated by Blount et al. (2004) in this issue, the differences in potency and therefore duration of action of these drugs may be advantageous for treating the variety of disorders currently under investigation. The unique capacity for PDE5 inhibitors to elevate cellular cyclic GMP levels and to further increase inhibitor affinity for the catalytic site on the enzyme is a novel mechanism for the sustained generation of cyclic GMP. The therapeutic potency coupled with the low incidence of side effects of this class of drugs will probably be explored in a wide range of human conditions.

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