Letter to the Editor

Does Sildenafil Indirectly Inhibit Phosphodiesterase 3 in Vascular Smooth Muscle?
To the Editor:
I read with great interest the recent report by Schalcher et al., entitled “Interaction of Sildenafil With cAMP-Mediated Vasodilation In Vivo.”1 The data presented deals with a potentially important issue and, given the increasing interest in using phosphodiesterase 5 (PDE5) inhibitors for various conditions, in addition to erectile dysfunction, are also timely. As a researcher studying the role of cyclic nucleotide phosphodiesterases (PDEs) in cardiovascular tissues, I would like to take this opportunity to comment on some of the statements made in the discussion of these data. First, since a considerable literature describing the importance of interactions between cGMP and cAMP hydrolyzing PDEs has accumulated in recent years, the finding that sildenafil and cAMP-dependent vasodilators interacted to regulate forearm blood flow (FBF) in this study should, perhaps, not have been described as “unexpected.”2 In earlier work, Dr Richard Haslam and I reported that cGMP elevating agents (for example nitroprusside) increased cAMP through a cGMP-dependent inhibition of the cAMP-hydrolyzing phosphodiesterase 3 (PDE3) in blood platelets and arterial smooth muscle.3–5 This effect of cGMP on cAMP hydrolysis in these cells allowed a marked synergistic increase in platelet or smooth muscle cAMP when activators of adenyl cyclase and guanylyl cyclase were used together, as well as a CAMP-dependent synergistic inhibition of blood platelet aggregation and arterial smooth muscle contraction. More recently, similar reports have described this effect in cardiac myocytes and mesangial cells.6–7 Perhaps indicating that interactions between cGMP and cAMP are important in several cell types and challenging the concept that the CAMP and cGMP signaling cascades operate as parallel and independent systems. Second, although the interaction between sildenafil and isoprenaline, an activator of adenyl cyclase, described by Schalcher and colleagues is consistent with a role for PDE3 in mediating the interaction between the compounds on forearm blood flow (FBF), the documented interaction with milrinone, a PDE3 inhibitor, is not. Indeed, if sildenafil and milrinone ultimately each had their effects by inhibiting PDE3, their combination would have been sub-additive, not additive, as reported in Figure 2. In contrast, presentation of this same data after controlling for the basal effect of sildenafil on flow, as depicted in Figure 3, is consistent with an effect of a sildenafil-mediated, cGMP-dependent inhibition of PDE3. Perhaps an inhibitor of adenylyl cyclase activity would be helpful in clarifying the issue of mechanism. Third, while Schalcher and colleagues correctly state that PDE5 is not expressed in cardiac myocytes, they suggest that sildenafil could potentially inhibit cardiac PDE3 indirectly by increasing plasma cGMP levels. Since plasma cGMP accumulates as a result of its extrusion from cells and would not be taken up from the circulation by cardiac myocytes, or any other cell, this possible indirect effect of sildenafil on cardiac PDE3 is highly unlikely to occur.

Donald H. Maurice
Career Investigator
Heart and Stroke Foundation of Ontario
Associate Professor of Pharmacology and Toxicology
Queen’s University
Kingston, Ontario, Canada
E-mail mauriced@post.queensu.ca

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Donald H. Maurice

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