A major focus of studies in vascular biology has been the role of the endothelium in modulating tone of vascular smooth muscle by release of nitric oxide (NO), stimulation of soluble guanylate cyclase, and the subsequent increase in intracellular cyclic guanosine monophosphate (cGMP). An alternative second-messenger pathway that plays a key role in eliciting relaxation of vascular muscle involves receptor-mediated activation of adenylylcyclase, formation of cAMP, and activation of protein kinase A and myosin light-chain kinase within smooth muscle cells. In general, cAMP-mediated relaxation of vascular smooth muscle does not involve the endothelium. Although most studies suggest that vasorelaxation to many agents is mediated by release of cGMP or cAMP alone, several studies have suggested that some “typical endothelium-independent” vasodilators may also release NO and activate guanylate cyclase.1–13 Relaxation to some classic endothelium-independent agents, including adenosine, prostacyclin, forskolin, and β-receptor agonists, is reduced by inhibitors of NO synthesis (NOS).1–13 These studies suggest that relaxation of vascular smooth muscle to selected endothelium-independent agents is mediated by an interaction between cGMP and cAMP pathways.

Complex interactions between different vasodilator pathways in vascular smooth muscle have been proposed for cyclooxygenase and NOS. For example, inhibition of either cyclooxygenase or NOS abolished the increase in cerebral blood flow in response to hypercapnia.14,15 Acute or chronic inhibition of NOS enhanced the role of cyclooxygenase in the regulation of vascular resistance in the coronary and renal circulations.16–18 In the coronary circulation of humans with atherosclerosis, inhibitors of both NOS or cyclooxygenase reduced flow-mediated response.19 These studies suggest an interaction between cyclooxygenase and NOS. Mechanisms that may account for this interaction have not been determined but may involve binding of NO to the heme-containing portion of cyclooxygenase to increase its activity.16,20,21 It is possible, however, that the interaction between NOS and cyclooxygenase may be at other downstream signal transduction pathways. Products of cyclooxygenase, including prostacyclin, mediate relaxation through activation of adenylate cyclase and increases in cAMP.22 The complex interaction between NOS and cyclooxygenase may also potentially involve an interaction between NO and cAMP.

Studies of compounds that increase both cAMP and cGMP in vascular tissue may provide insight into the mechanisms of the complex interaction between these 2 supposedly independent pathways. Compounds that increase cGMP and cAMP synergistically inhibit platelet activation by phosphorylation of common proteins and inhibition of cAMP phosphodiesterase by cGMP.23,24 Nitrovasodilators increase the accumulation of cAMP in platelets as a result of the inhibition of cAMP metabolism.25 These studies suggest that cGMP can exert important functional effects by inhibiting cAMP phosphodiesterase and increasing levels of cAMP. cAMP phosphodiesterase is found not only in platelets but also in a variety of cell types, including vascular tissue. Alternatively, agents that increase both cAMP and cGMP attenuate phospholipase C activation and mobilization of Ca²⁺ from intracellular stores.26 Possible interactions may also occur at myosin light-chain kinase or Ca²⁺ adenosinetriphosphatases.26 The mechanism(s) of NO/cGMP-mediated alterations in cAMP-dependent vascular responses is unclear.

The study by Zhang and coworkers27 examined the effects of endothelium-independent agents on NO production in coronary microvessels and the mechanisms involved in cAMP-dependent NO formation. Studies demonstrating that vascular responses to forskolin and isoproterenol are attenuated with inhibitors of NOS suggest that these endothelium-independent agents may also release NO.4,8–13 Zhang and coworkers measured levels of nitrite, a hydration product of NO, released in isolated microvessels in response to forskolin, isoproterenol, and direct activation of protein kinase A by 8-bromo-cAMP. Release of nitrite by forskolin, 8-bromo-cAMP, and isoproterenol was mediated by activation of protein kinase A and phosphatidylinositol 3-kinase, because levels of nitrite were reduced by inhibitors of these pathways. Adrenomedullin and calcitonin, potent endogenous vasodilators, produced similar increases in nitrite mediated by activation of protein kinase A and phosphatidylinositol 3-kinase. This study is the first to directly measure NO production in response to classic cAMP-mediated vasodilators in coronary microvessels. In addition, bradykinin-mediated production of nitrite was potentiated by forskolin or adrenomedullin. Although the role of endothelium in mediating cAMP-dependent production of nitrite was not demonstrated in the microvessel preparation, nitrite production in large arteries was eliminated in the absence of endothelium. Thus, the interaction between cyclic nucleotides and NO production in vascular tissue appears to be localized to the endothelium.

The physiological importance of the interaction between cAMP and NO production in mediating vascular responses is unclear. Although previous studies demonstrated reductions in vascular responses to cAMP-mediated vasodilators after inhibition of NOS, in general inhibition was modest.1–13 Surprisingly, in the present study, production of nitrite by cAMP-mediated vasodilators was similar to levels produced by bradykinin and
acetylcholine, 2 classic endothelium-dependent vasodilators that may function through 2 different mechanisms: release of NO or release of endothelium-derived hyperpolarizing factor. The study by Zhang and coworkers suggests that the cAMP/NO interaction does not involve an increase in levels of message or protein for NO but rather an increase in NOS activity.27 They suggest that CAMP increases NO through activation of protein kinase A and subsequent phosphorylation of endothelial NOS by protein kinase B through a phosphatidylinositol 3-kinase–mediated effect. The various signal-transduction pathways in vascular tissue that modulate vascular reactivity involve complex interactions that need further consideration. It is interesting to speculate about the physiological role of these various redundant and overlapping mechanisms in mediating vascular responses. It is possible that these complex interactions may preserve vascular function in the presence of risk factors for disease or in the early stages of disease. Redundant or overlapping mechanisms may upregulate when normal mechanisms are diminished to maintain function at or near normal. Studies from our laboratory and others have suggested that in the absence of endothelial NOS in mutant mice models, other pathways upregulate to maintain vascular function.28–32 However, these compensatory pathways are dependent on vessel type, because responses to acetylcholine are absent in the aorta and carotid artery,33,34 but relatively normal in cerebral and coronary vascular beds.28–33 These compensatory pathways in the absence of endothelial NOS include upregulation of neuronal NOS, cyclooxygenase, and endothelium-derived hyperpolarizing factor.28–32 The role of a CAMP/NO interaction in mediating vascular responses in normal conditions and in the presence of risk factors and disease should be examined further.

References
Interactions Between NO and cAMP in the Regulation of Vascular Tone
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