CORRESPONDENCE

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In Reply:—We appreciate the comments by Dr. Sheng-Nan Wu. He raises three important points; (1) the ability of isoproterenol to induce Ca^{2+} influx into endothelium, (2) inhibitory effect of halothane on Ca^{2+} ionophore (A23187)-induced endothelium dependent relaxation, and (3) the possibility of modification of the relaxation response to isoproterenol by Ca^{2+} channel blocking action of halothane. We discuss these points, respectively.

From our findings and other reports (please see the article), it is likely that isoproterenol can not initiate nitric oxide (NO) production by vascular endothelium of other species except for rat and that adenylyl cyclase-mediated signal transduction within endothelium of other species differs from that of rat. From experiments using various inhibitors, we propose that cAMP-PKA play an important role in the activation of Ca^{2+}/calmodulin dependent NO synthase (cNOS) elicited by isoproterenol. The calcium ionophore, A23187, can increase intracellular Ca^{2+} in the endothelium not only via Ca^{2+} influx but also via release from intracellular store. The latter mechanism has been demonstrated to be essential for A23187-induced NO production by endothelium.[1,2] Thus, it is likely that halothane exerts the inhibitory action on NO-cGMP relaxation mechanism only when cNOS is activated by Ca^{2+} releasing mechanism.

Halothane has been shown to modulate Ca^{2+} dynamics in vascular smooth muscle cells including the inhibition of Ca^{2+} influx and the facilitation of Ca^{2+} releasing from sarcoplasmic reticulum (caffeine-like action).[3] These dual actions of halothane on Ca^{2+} dynamics are likely to induce the net effects on vascular tone within a few minutes. Our experimental protocols basically comprised an initial equilibration period followed by elevation of vascular tone with noradrenaline and subsequent test of relaxation response of rings with sustained tone to isoproterenol in the absence or presence of various inhibitors or halothane. Aortic rings were exposed to halothane for more that 40 min, during which the modulation of halothane to Ca^{2+} dynamics might reach plateau. Therefore, isoproterenol was applied to the rings with sustained tone and Ca^{2+} dynamics in the presence of halothane. Further, our study demonstrated that isoproterenol produced endothelium-dependent and NO-mediated relaxation accompanying with the increases in cGMP contents of rat aortic rings and that halothane failed to affect not only the relaxation response but also the cGMP increase elicited by isoproterenol. It has been known that the post-cGMP cascade mediating relaxation of vascular smooth muscle cells includes the modulations of contractile proteins and of various ion currents (Na^+, K^+, Cl^- and Ca^{2+}), however, the contribution of L-type Ca^{2+} inward current to it has not been well known. Even if halothane has an ability to inhibit the L-type of Ca^{2+} inward current through the membrane of vascular smooth muscle cells as shown in the short report by Dr. Wu *et al.*,[4] in our opinion, it seems unlikely that this inhibitory action accounts for the failure of halothane to inhibit the isoproterenol-induced relaxation.

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