A PROSTAGLANDIN, NOT NITRIC OXIDE, IS THE ENDOTHELIUM-DERIVED RELAXING FACTOR IN THE SHARK (SQUALUS ACANTHIAS) VENTRAL AORTA

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In mammals, the vascular endothelium produces an endothelium-derived relaxing factor (EDRF) when it is stimulated by a variety of mediators, including acetylcholine (ACh) and endothelin (ET). It is now generally accepted that the EDRF is the gas, nitric oxide (NO; e.g., (Vane, Philos Trans R Soc Lond [Biol] 343: 225-246, 1994)). Our finding that both ACh (unpublished results) and endothelin (Evans and Gunderson, J Comp Physiol, in press: 1996) produce contraction in aortic vascular smooth muscle (VSM) rings from the spiny dogfish shark, Squalus acanthias, in the presence of an intact endothelium, suggests that this system may be missing in fish VSM. The fact that neither L-arginine nor sodium nitroprusside (NO precursors) stimulate dilation in shark VSM rings (Evans and Gunderson, Bull. MDIBL 34: 109, 1995) supports this hypothesis. In mammals, the vascular endothelium also produces prostaglandins (PGs), such as prostacyclin (PGI_2) and PGE_1, which are dilatory (Vane, Op. Cit.). PGs, however, are not considered to be major EDRFs in mammals (e.g., (Inagami et al., Annu Rev Physiol 57: 171-189, 1995), largely because the original description of the EDRF showed that its production was not altered by inhibition of prostaglandin synthesis (Furchgott and Zawadzki, Nature 288: 373-376, 1980). Nevertheless, it is possible that PGs, rather than NO, may be the dominant EDRF in fishes, and this has been suggested by Miller and Vanhoutte (in Endothelial Regulation of Vascular Tone, Ryan and Rubanyi, eds, pg. 3-20, 1992), based upon work on the ventral aorta of the rainbow trout, Oncorhynchus mykiss.

To test this hypothesis further, we examined the ability of a known NO synthesis inhibitor, L-NAME, and a known prostaglandin synthesis inhibitor, indomethacin, to inhibit the dilation produced by the Ca^{2+} ionophore A23187 in shark VSM rings with an intact endothelium (Evans and Cegelis, Bull. MDIBL 33: 113, 1994). In addition, we examined the ability of NO, PGI_2, and PGE_1 (agonist of PGE_2) to dilate rings after the endothelium had been removed. Rings were prepared and mounted as described previously (e.g., Evans, J Comp Physiol 162: 179-183, 1992), except that tension was monitored using a 4-channel, Biopac A/D recording system connected to a Macintosh 140 Powerbook. In the first series of experiments, endothelium-intact rings were incubated in either 10^{-4} M L-NAME or 10^{-5} M indomethacin (paired with distilled water controls) for 30 minutes before adding 10^{-5}M A23187. In the second series of experiments, endothelium-free rings were exposed to 10^{-6} M of either PGI_2 or PGE_1, or NO (calculated to be $\approx 3 \times 10^{-5}$ M), after an initial equilibration period.

L-NAME did not inhibit the A23187-induced dilation in intact aortic VSM rings from the dogfish shark (N = 6), but indomethacin did, actually reversing the 198 ± 45 mg dilation to an 145 ± 52 mg contraction in paired rings (initial tension = 500 mg; N = 6; $p < 0.01$). Nitric oxide did not produce any dilation in this preparation, although the same NO solution dilated rat thoracic aortae in our control experiments. On the other hand, PGI_2 dilated endothelium-free rings by 95 ± 48 mg (SE; N = 8) and PGE_1 by 389 ± 121 mg (N = 8), showing that PGs are potent EDRFs in this system. Thus, we conclude that, as hypothesized by Miller and Vanhoutte (Op. Cit.) for a single species of teleost fish, the aortic vascular endothelium of the spiny dogfish produces an EDRF that is a prostaglandin, not nitric oxide. (Supported by NSF IBN-9306997 and a Grant in Aid from the Maine Affiliate of the American Heart Association to DHE, a fellowship from the AHA to MG, and EHS-P30-ESO3828 to the Center for Membrane Toxicity Studies).