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EFFECTS OF LYSOPHOSPHATIDIC ACID ON VASCULAR TONE

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Our aim was to investigate the vasoactive effect(s) of lysophosphatidic acid (LPA) in order to better understand its role in cardiovascular physiology. Thoracic (TA) and abdominal aorta (AA) segments were isolated from adult male wild type (WT) and knock out (KO) mice deficient in LPA1 or LPA2 receptors, endothelial NO synthase (eNOS), cyclooxygenase-1 (COX1) or thromboxane receptors (TP). Wire myography was used to measure the isometric tension changes of the vessels. The endothelium was mechanically removed in some segments. Expression of LPA receptors in freshly isolated mouse aortic endothelial cells (MAEC) and the vascular smooth muscle (VSM) were analyzed by quantitative real-time PCR.

The integrity of the endothelium determined the vasoactive effects of LPA: it induced relaxation in intact vessels (both TAs and AAs), whereas in the absence of endothelium or eNOS vasoconstriction developed which was stronger in the AA. PCR experiments demonstrated the presence of mRNA encoding the 1, 2, 4, and 5 subtypes of LPA receptors in MAEC. In VSM LPA1 was predominantly expressed whereas LPA3 and LPA4 were expressed at lower levels. The LPA1–3 agonist VPC31143 mimicked the effects of LPA, while the LPA1,3 antagonist Ki16425 inhibited it. Likewise, LPA-induced vasorelaxation was missing in case of the genetic deletion of LPA1 but not that of LPA2. Inhibition of the protein kinase B/Akt pathway by wortmannin and MK-2206 had no effect on LPA-mediated vasorelaxation, while inhibition of phospholipase C gamma; by U73122 or edelfosine eliminated it. Surprisingly, inhibition of COX by indomethacin and genetic deletion of either COX1 or TP abolished LPA- and VPC31143-evoked vasoconstriction in endothelium denuded AA segments.

Our results indicate that in intact vessels LPA induces LPA1- and PLC gamma;-dependent activation of eNOS and consequent relaxation of the VSM. In contrast, in the absence of endothelium or eNOS LPA induces vasoconstriction by activating VSM COX1 and autocrine/paracrine release of a prostanoid, most likely thromboxane A2. This latter effect of LPA may contribute to the altered vascular reactivity in pathophysiological states associated with endothelial dysfunction.