

Vasoactive actions of lysophosphatidic acid

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Introduction: Lysophosphatidic acid (LPA) is a recently discovered bioactive lipid mediator of high significance in immunobiology and hemostasis. Endothelium and activated platelets serve as the main source of LPA, which has diverse but yet elusive impact in the cardiovascular system. We aimed to analyze its potential vasoactive effects.

Materials and methods: Thoracic (TA) and abdominal (AA) aortic segments were isolated from wild type (WT) and knockout (KO) mice deficient in LPA₁ or LPA₂ receptors, endothelial NO synthase (eNOS), cyclooxygenase-1 (COX1) or thromboxane A₂ receptors (TP). In some experiments the endothelium was mechanically removed. Isometric tension changes of the vessels were tested via myography. Expression of LPA receptors in freshly isolated mouse aortic endothelial cells (MAEC) and vascular smooth muscle (VSM) were analyzed by quantitative real-time PCR.

Results: The vasoactive effects of LPA depended on the integrity of the endothelium: it induced relaxation in intact vessels (both TAs and AAs), while in the absence of endothelium or eNOS LPA provoked vasoconstriction, which was more prominent in the AA. PCR analysis revealed the presence of mRNA encoding the 1, 2, 4, and 5 subtypes of LPA receptors in MAEC while in VSM LPA₁ was predominantly whereas LPA₃ and LPA₄ moderately expressed. The LPA₁₋₃ receptor agonist VPC31143 mimicked, whereas the LPA_{1/3} receptor antagonist Ki16425 inhibited all vasoactive effects of LPA. Genetic deletion of LPA₁ but not that of LPA₂ abolished LPA-induced relaxation. Blockade of the protein kinase B/Akt pathway by wortmannin or MK-2206 failed to influence, whereas inhibition of phospholipase C β by U73122 or edelfosine abolished LPA-induced relaxation. Surprisingly, inhibition of COX by indomethacin and absence of either COX1 or TP abolished LPA- and VPC31143-evoked contraction in endothelium denuded AA segments.

Conclusions: Our results indicate that in intact vessels LPA induces LPA₁- and PLC β -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, presumably thromboxane A₂. This latter effect of LPA may contribute to the altered vascular reactivity in pathophysiological states associated with endothelial dysfunction.

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