

Reconciliation of the vasodilator and vasoconstrictor actions of lysophosphatidic acid in the mouse aorta

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Introduction. Lysophosphatidic acid (LPA) is a bioactive lysophospholipid with numerous biological actions in the immune-, nervous-, and cardiovascular systems. The vasodilator and vasoconstrictor effects of LPA have long been known yet no explanation has been provided for these opposite effects. We have reported recently that LPA induces endothelium-dependent vasorelaxation mediated by LPA₁ receptors, phospholipase C, and nitric oxide (1). However, removal of the endothelium not only abolished this effect but converted it to vasoconstriction. Here we describe a novel paracrine/autocrine lipid mediator cascade mediating the vasoconstrictor action of LPA.

Materials and methods. Aortic segments were isolated from wild type (WT) and knockout (KO) mice deficient in LPA₁ or LPA₂ receptors, cyclooxygenase-1 (COX1) or the thromboxane prostanoid receptors (TP). Vessels of mice subjected to smooth muscle specific deletion of Gα_{q/11} or Gα_{12/13} were also tested. Isometric tension of endothelium-denuded vascular segments was measured via myography. Expression of LPA receptors in aortic vascular smooth muscle (VSM) was analyzed by qPCR. Thromboxane A₂ (TXA₂) release from aortae was measured by TXB₂ ELISA.

Results. LPA₁, LPA₂, LPA₄ and LPA₆ transcripts were abundantly detectable in VSM. LPA elicited dose-dependent vasoconstriction in endothelium-denuded abdominal WT segments. The LPA₁₋₃ agonist VPC31143 mimicked, whereas the LPA_{1&3} antagonist Ki16425 inhibited the contractile effect. Lack of LPA₁ but not that of LPA₂ abolished VPC31143-induced vasoconstriction. Genetic deletion of Gα_{q/11} or Gα_{12/13} as well as inhibition of Gα_{i/o} by pertussis toxin (PTX) also attenuated the vasoconstriction. Gα_{i/o} signaling is can be coupled to phospholipase A₂ and COX1 activation, thus the potential involvement of autocrine/paracrine TXA₂ release in the LPA₁-mediated vasoconstriction was tested. Vessels deficient in COX1 or TP showed diminished vasoconstrictor responses to VPC31143. Furthermore, VPC31143 increased TXA₂ production in WT and TP KO but not in LPA₁ KO, COX1 KO or PTX-treated WT vessels.

Discussion. The direct effect of LPA on VSMC is vasoconstriction, which is in contrast to the endothelium-dependent vasodilation. Interestingly, both effects are also mediated by LPA₁ receptors, which, in VSMC via G_i, facilitates COX1-mediated autocrine/paracrine release of TXA₂. Subsequent activation of VSMC TP causes vasoconstriction involving Gα_{q/11} and Gα_{12/13} proteins. We propose that in case of endothelial damage the interaction between the LPA/LPA₁ and TXA₂/TP pathways may represent a vicious circle between platelet activation and vasoconstriction.

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1. Ruisanchez, Dancs, Kerék, et al. FASEB Journal 28: 880-890, 2014.