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Poster 23

SIGNALING PATHWAYS OF LYSOPHOSPHATIDIC ACID ELICITED VASOCONSTRICTION

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Lysophosphatidic acid (LPA) is a bioactive lysophospholipid with numerous biological actions. However, its definitive effect on the vascular tone has remained yet elusive. We have reported that LPA induces endothelium-dependent vasorelaxation via LPA1 receptors, phospholipase C, and nitric oxide (1). Removal of the endothelium abolished this effect and converted it to vasoconstriction. Here we describe the signaling pathways mediating this constrictor effect.

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 receptor (TP). Vessels of mice subjected to smooth muscle specific deletion of Galphaq/11 or Galpha12/13 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.

LPA1, LPA2, LPA4 and LPA6 transcripts were abundantly detectable in VSM. LPA elicited dose-dependent vasoconstriction in endothelium-denuded vessels. The LPA1-3 agonist VPC31143 mimicked, whereas the LPA1-3 antagonist Ki16425 inhibited the contraction. Lack of LPA1 but not that of LPA2 abolished VPC31143-induced vasoconstriction. Genetic deletion of Galphaq/11 or Galpha12/13 as well as inhibition of Galphai/o by pertussis toxin (PTX) attenuated the vasoconstriction. Galphai/o signaling 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.

The direct effect of LPA on VSM is vasoconstriction, which opposes the endothelium-dependent vasodilation. Interestingly, both effects are mediated by LPA1, which, in VSM via Gi/o, facilitates COX1-mediated autocrine/paracrine TXA₂ release. Subsequent activation of VSM TP causes vasoconstriction involving Galphaq/11 and Galpha12/13 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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References

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