

LYSOPHOSPHOLIPID AND RELATED MEDIATORS - FROM BENCH TO CLINIC

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Lysophosphatidic acid (LPA) has been reported recently to induce endothelium-independent contraction of the murine aorta mediated by LPA₁-coupled release of thromboxane A₂ and activation of thromboxane prostanoid (TP) receptors (FASEB J 31: 1547-1555, 2017). In this study, however, 18:1 LPA had remarkably smaller vasoconstrictive activity compared to the LPA₁₋₃ receptor agonist VPC31143 indicating that it may not be the main endogenous vasoactive LPA species. Platelet activation at sites of vascular injury or plaque rupture yields mostly polyunsaturated LPA species which are reportedly upregulated in the plasma of patients with acute coronary syndrome (Arterioscler Thromb Vasc Biol 35, 463-470, 2015). In the present study we compared the activity of saturated and unsaturated LPA species on the vascular tone and determined their potential effects on the coronary blood flow.

Vasoconstrictor effects of different LPA species were measured with myography in de-endothelialized murine thoracic aortae. When applied at the resting tone, 16:0, 17:0 and 18:0 as well as 18:1 LPA elicited no or moderate changes of the vascular tone. In contrast, the 18:2 and 18:3 LPA-s evoked strong vasoconstriction. All constrictor responses to the different LPA species were diminished in vessels of LPA₁-KO mice.

The effect of LPA species and VPC31143 on coronary flow (CF) were assessed in isolated murine hearts mounted in a Langendorff apparatus and perfused at constant pressure. In contrast to isolated aortae, 18:1 LPA markedly reduced CF even in the presence of intact endothelium, which was accompanied by a reduction of the left ventricular developed pressure (LVDevP) indicating diminished contractile performance. Interestingly, the effect of 18:2 LPA and VPC31143 were not significantly different from those of 18:1 LPA. Finally, 18:1 LPA-induced changes of CF and LVDevP remained unaltered in hearts of LPA₁- and TP-KO mice.

In conclusion, polyunsaturated LPA species appear to have increased vasoconstrictor activity in murine aorta, which is mediated by the LPA₁ receptor. In addition, a strong vasoconstrictor effect of 18:1 and 18:2 LPA as well as the LPA₁₋₃ receptor agonist VPC31143 were demonstrated in the coronary circulation. However, the signaling pathways of the coronary constriction are different from those described in the aorta as do not involve LPA₁ or TP receptors. As atherosclerotic plaques of the coronaries are rich in polyunsaturated fatty acids, this effect may have utmost relevance in acute coronary events associated with plaque rupture.

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