

POSTER # 2

Acyl-chain dependent effects of naturally occurring lysophosphatidic acid species on the vascular tone

Zoltán Benyó*, Éva Ruisanchez*, Zsuzsanna Miklós*, Margit Kerék*, Krisztina Eszter Vén*, Dina Wafa*, Jerold Chun† and Gábor Tigyi#

*Institute of Clinical Experimental Research, Semmelweis University, Budapest, Hungary; †Sanford Burnham Prebys Medical Discovery Institute, La Jolla, California, USA; #Department of Physiology, University of Tennessee Health Science Center, Memphis, USA

Lysophosphatidic acid (LPA) has diverse (patho)physiological roles in the cardiovascular system, including angiogenesis, vascular remodeling, atherothrombosis and the regulation of blood pressure. We demonstrated recently that the synthetic LPA analogue VPC31143 via LPA₁ receptor activation can induce either vasorelaxation or constriction, depending on the integrity of the endothelium, and these effects are mediated by nitric oxide and thromboxane A₂, respectively. The commonly used 18:1 LPA however, had slightly smaller vasorelaxant and half the constrictive activity compared to VPC31143. 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. The aim of this study was to determine the effect of LPA with different acyl chains on vascular tone and coronary blood flow.

Vasorelaxing effect of LPA was tested with myography in phenylephrine precontracted isolated murine thoracic aortae with intact endothelium. LPA elicited transient relaxation with highest response to 18:1 LPA that decreased slightly with the number of unsaturated bonds. Saturated, 16:0 LPA elicited smaller relaxation, which decreased even more with the length of the fatty acyl chain. Interestingly, polyunsaturated 18:2 and 18:3 LPA evoked biphasic effect on vascular tone with a transient relaxation and a subsequent constriction. When applied at the resting tone in endothelium denuded aortae, 18:1 LPA elicited only slight constriction. In contrast, polyunsaturated LPA-s evoked strong vasoconstriction whereas, saturated LPAs lacked vasoconstrictive action. Both the relaxant and constrictor responses to the different LPA species were diminished in vessels of LPA1 KO mice.

Atherosclerotic plaques of the coronaries are rich in polyunsaturated fatty acids, the most common of which is 18:2 LPA. Therefore, its effect on coronary flow was also assessed in isolated murine hearts mounted in a Langendorff apparatus and perfused at constant pressure. Administration of 18:2 LPA elicited a rapid drop in coronary flow associated with a significant reduction of the left ventricular developed pressure.

In conclusion, vasoactive effects of LPA in murine aorta are dependent both on acyl chain length and number of unsaturated bonds. Highest vasorelaxant effect is mediated by the mono-unsaturated 18:1 LPA whereas, increase in the number of double bonds results in decreased vasorelaxation and increased vasoconstrictor activity. This is particularly interesting in case of endothelial injury and platelet activation where polyunsaturated LPAs can contribute to the progression of vasospasm. Interestingly, both the vasoconstrictor and vasodilator effects are mediated dominantly by the LPA₁ receptor in the murine aorta. In addition, we demonstrated a strong vasoconstrictor effect of 18:2 LPA in the coronaries. This effect may have utmost relevance in acute coronary events when high amounts of this LPA species are released in the coronary circulation.

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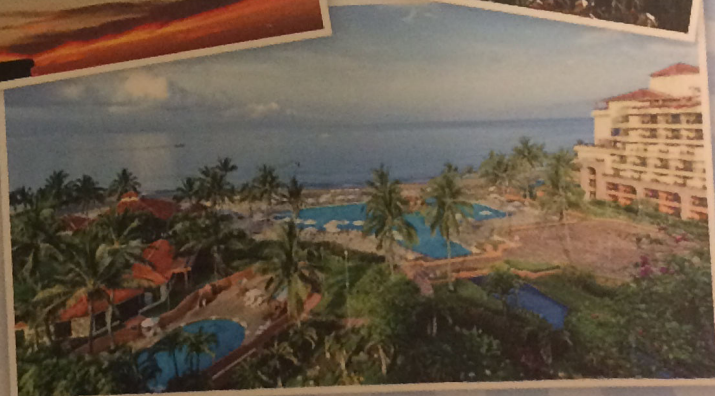


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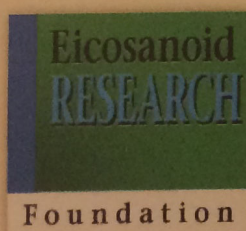
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