Implication of endogenous lysophosphatidic acid in intimal thickening in rat injured artery

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[Background] Vascular endothelial injury is followed by platelet adhesion to the vessel wall and thrombus formation. Subsequently vascular smooth muscle cells may proliferate, leading to intimal thickening. Such events can promote restenosis after recanalization treatment. Lysophosphatidic acid (LPA) is a lipid mediator with diverse effects via LPA receptors. LPA has been shown to have mitogenic effect for vascular smooth muscle cells (VSMC). The topical treatment with exogenous LPA has been reported to induce vascular intimal thickening in non-injured artery via PPAR-gamma; not via LPA receptors. However, the implication of endogenous LPA in intimal thickening after vascular injury has never been clarified. We examined the ability of GDPP, a LPA1/3 receptor antagonist, to reduce intimal thickening in endothelial injury model in rat femoral artery.

[Methods] Intimal thickening was measured 28 days after the endothelial injury in rat artery by photochemical reaction. DGPP inhibited rat VSMC proliferation induced by LPA (10 uM) in concentration-dependent manner (0.1-100 uM). The intimal thickening (the ratio of intima/media) was dose-dependently decreased by a 14-day infusion of DGPP (0.1-1mg/kg/day, s.c.) in addition to bolus i.p. injection after the injury. The content of LPA especially composed of arachidonic acid (20:4) was significantly increased in the artery 4h after the injury. LPA(20:4) was released from the rat platelets aggregated by collagen in plasma. LPA increased p-ERK and p-IkB in rat VSMC concentration-dependently, like TNFalpha. In the presence of TNFalpha, LPA increased p-ERK additionally, whereas LPA decreased the p-IkB. The effect of LPA on p-ERK was inhibited by DGPP, but that on p-IkB was not.

[Conclusion] Endogenous LPA(20:4) released from activated platelets may implicate in intimal thickening after vascular endothelial injury via LPA1/3 receptors that induces VSMC proliferation by the activation of ERK-MAPK pathway. On the other hand, LPA have dual opposing actions not via LPA1/3 receptors on NFkB pathway; activation and suppression in the absence and presence of other inflammatory cytokines, respectively, that may regulate the inflammation response after injury.