Lysophospholipid-enriched HDL suppresses platelet activation
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Background: Secretory phospholipases A2 (sPLA2) are enzymes that hydrolyze the sn-2 ester bond in phospholipids generating nonesterified free fatty acids and lysophospholipids. sPLA2 levels are highly increased under inflammatory conditions, and epidemiologic studies showed strong associations between elevated sPLA2 levels and several inflammatory diseases. sPLA2 is mainly associated with high-density lipoproteins (HDL), which are the principal plasma carriers of phospholipids and major substrates for sPLA2. Surprisingly, clinical trials testing sPLA2 inhibitors failed and sPLA2 inhibition was associated with an unexpected 60% increased risk of myocardial infarction and stroke. Platelets are best known as main mediators of hemostasis and thrombosis. However, they are also potent immune modulators and can promote inflammation, which can be detrimental. HDL directly interacts with platelets and regulates their function. However, very little is known about the effects of inflammation-induced changes in HDL composition (especially enrichment with lysophospholipids) on HDL–platelet crosstalk and fundamental platelet responses and immune interactions. Therefore, we investigated the effects of sPLA2-mediated modification of HDL on platelet function, a critical player in atherosclerosis and inflammation.

Methods: Platelets were isolated from peripheral blood from healthy human volunteers. Platelet aggregation was measured by light transmission aggregometry. P-selectin expression, GPIIb/IIIa activation, and Ca2+ flux were measured by flow cytometry. Kinase phosphorylation was assessed by western blot.

Results: Treatment of HDL with sPLA2 (sPLA2-HDL) resulted in the formation of palmitoyl-lysophosphatidylcholine (LPC 16:0) and stearoyl-lysophosphatidylcholine (LPC 18:0) as the most prominent LPC species. sPLA2-HDL rapidly inhibited platelet aggregation, P-selectin expression and GPIIb/IIIa activation. Moreover, sPLA2 treatment of HDL inhibited Ca2+ flux as well as ERK and Akt phosphorylation. Enrichment of native HDL with LPC 16:0 and LPC 18:0 mimicked sPLA2-HDL effects.

Discussion: Overall, our studies suggest that the suppression of rise in intracellular Ca2+ levels and inhibition of kinase phosphorylation are likely mechanisms that counteract agonist-induced activation of platelets. Our results raise the possibility that sPLA2-induced modification of HDL composition and function modulates platelet function during inflammation.

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