Expression of amyloid beta peptide in human platelets: Pivotal role of phospholipase Cgamma2-protein kinase C pathway in platelet activation

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摘要

Abstract

The amyloid beta peptide (Abeta), a mediator of neuronal and vascular degeneration in the pathogenesis of Alzheimer's disease and cerebral amyloid angiopathy may have peripheral actions. Platelets are enriched with Abeta and have been shown to enhance platelet actions. However, the detailed signaling pathways through which Abeta activates platelets have not been previously explored. In this study, we examined the intra-platelet Abeta distribution using a gold labeling technique and noted that Abeta was predominantly localized in the cytoplasm of resting platelets. A marked increase in Abeta-gold labeling in an open canalicular system was observed in collagen-activated platelets. Exogenous Abeta (2-10 microM) stimulated platelet aggregation accompanied by phospholipase Cgamma2 (PLCgamma2) phosphorylation, phosphoinositide breakdown, and [Ca(2+)]i mobilization as well as protein kinase C (PKC) activation. Ro318220, an inhibitor of PKC, suppressed Abeta-induced platelet aggregation, PKC activation, and [Ca(2+)]i mobilization in platelets, suggesting that the PLCgamma2-PKC pathway is involved in Abeta-induced platelet aggregation. In the electron spin resonance study, Abeta (2 and 10 microM) markedly triggered hydroxyl radical formation in platelets. In an in vivo study, Abeta (2mg/kg) significantly shortened the latency for inducing platelet plug formation in the mesenteric venules of mice. In conclusion, we are the first to demonstrate (1) the distribution of Abeta in human platelets; and that (2) Abeta activation of platelets is mediated, at least partially, by the PLCgamma2-PKC pathway; and (3) Abeta triggers thrombus formation in vivo.