Amyloid beta peptide-activated signal pathways in human platelets

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摘要

Abstract

Amyloid beta peptide (amyloid-β), which accumulates in the cerebral microvessels in an age-dependent manner, plays a key role in the pathogenesis of cerebral amyloid angiopathy. Platelets are an important cellular element in vasculopathy of various causes. Amyloid-β may activate or potentiate platelet aggregation. The present study explored the signaling events that underlie amyloid-β activation of platelet aggregation. Platelet aggregometry, immunoblotting and assays to detect activated cellular events were applied to examine the signaling processes of amyloid-β activation of platelets. Exogenous amyloid-β (1−2 μM) potentiated platelet aggregation caused by collagen and other agonists. At higher concentrations (5−10 μM), amyloid-β induced platelet aggregation which was accompanied by an increase in thromboxane A2 (TxA2) formation. These amyloid-β actions on platelets were causally related to amyloid-β activation of p38 mitogen-activated protein kinase (MAPK). Inhibitors of p38 MAPK and its upstream signaling pathways including proteinase-activated receptor 1 (PAR1), Ras, phosphoinositide 3-kinase (PI3-kinase), or Akt, but not extracellular signal-regulated kinase 2 (ERK2)/c-Jun N-terminal kinase 1 (JNK1), blocked amyloid-β-induced platelet activation. These findings suggest that the p38 MAPK, but not ERK2 or JNK1 pathway, is specifically activated in amyloid-β-induced platelet aggregation with the following signaling pathway: PAR1 → Ras/Raf → PI3-kinase → Akt → p38 MAPK → cytosolic phospholipase A2 (cPLA2) → TxA2. In conclusion, this study demonstrates amyloid-β activation of a p38 MAPK signaling pathway in platelets leading to aggregation. Further studies are needed to define the specific role of amyloid-β activation of platelets in the pathogenesis of vasculopathy including cerebral amyloid angiopathy.