

P029 IGF-1 potentiates platelet aggregation via the IRS-1/PI3 kinase/PKB pathway

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Insulin-like growth factor-1 (IGF-1) is secreted by many cell types and is an important mediator of cell growth and differentiation. IGF-1 is also present in the α -granules of platelets and is released during the secretion process. As IGF-1 has been reported to potentiate platelet aggregation, it may be an important contributor to the amplification process of platelet responses and pathogenesis of cardiovascular disease. The signalling pathways that are involved in this priming effect of IGF-1 however are presently unknown. Here I report that IGF-1 stimulation of platelets results in dose-dependent phosphorylation of the IGF receptor in the range of 1-100 nM. Phosphorylation of the IGF receptor is rapid and sustained, with maximal phosphorylation reached within 1-2 min. Furthermore, IGF-1 stimulates tyrosine phosphorylation of IRS-1 and its association with the p85 subunit of PI3 kinase. The association between p85 and IRS-1 is rapid and reaches a plateau (1-30 min). In contrast, IGF-1-stimulated tyrosine phosphorylation of IRS-1 is transient and correlates to phosphorylation of PKB on Ser473. The PI3 kinase inhibitors wortmannin and LY294002 completely block IGF-1-stimulated PKB phosphorylation and prevent potentiation of PAR-1-mediated platelet aggregation by IGF-1. Together, these results demonstrate that IGF-1 activates the IGF receptor/PI3 kinase/PKB pathway and that this pathway is essential for the priming effect of IGF-1 on PAR-1-mediated platelet responses.