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Inhibitory Effects of PPARγ Ligand, KR-62980, on Collagen-Stimulated Platelet Activation

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Abstract : The peroxisome proliferator-activated receptors (PPARs) are member of nuclear receptor superfamily that act as a ligand-activated transcription factors. Although platelets lack a nucleus, previous studies have shown that PPARγ agonists, rosiglitazone, inhibited platelet activation induced by collagen. In this study, we investigated the inhibitory effects of KR-62980, a newly synthesized PPARγ agonist, on collagen receptor-stimulated platelet activation. The specific tyrosine phosphorylations of key components (Syk, Vav1, Btk and PLCγ2) for collagen receptor signaling pathways were suppressed by KR-62980. KR-62980 also attenuated downstream responses including cytosolic calcium elevation, P-selectin surface exposure, and integrin αIIbβ3 activation. PPARγ was found to associate with multiple proteins within the LAT signaling complex in collagen-stimulated platelets. This association was prevented by KR-62980, indicating a potential mechanism for PPARγ function in collagen-stimulated platelet activation. Furthermore, KR-62980 inhibited platelet aggregation and adhesion in response to collagen in vitro and prolonged in vivo thrombotic response in carotid arteries of mice. Collectively, these data suggest that KR-62980 inhibits collagen-stimulated platelet activation and thrombus formation through modulating the collagen receptor signaling pathways.

Keywords : KR-62980, PPARγ, antiplatelet, thrombosis
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