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Increased aggregation of platelets lacking cGKI/PKG

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Atherosclerotic vascular lesions are considered to be the predominant cause of morbidity and mortality in industrialized nations. Rupture of atherosclerotic plaques initiates platelet activation/aggregation with subsequent arterial thrombosis triggering myocardial infarction and stroke. Nitric oxide (NO) and its second messenger cyclic GMP (cGMP) comprise the central regulatory pathway that prevents platelet activation/aggregation under physiological conditions is. A major downstream target of NO is cyclic guanosine 3',5'-monophosphate kinase I (cGKI). In previous work, we have tested the intravascular significance of the NO/cGKI signalling pathway in vivo using cGKI-deficient (cGKI-/-) mice. We show that platelet cGKI but not endothelial or smooth muscle cGKI is essential to prevent intravascular adhesion and aggregation of platelets after ischemia. Correspondingly, loss of cGKI in platelets was associated with an increase in platelet accumulation in the postischemic kidney and with a significant enhancement of both platelet adhesion and aggregation in the postischemic intestinal microvasculature. The defect in platelet cGKI is not compensated by the cAMP/cAMP kinase pathway supporting the essential role of cGKI in prevention of ischemia-induced platelet adhesion and aggregation. Next, we addressed the regulatory cascade downstream of cGKI. We found that the inositol-1,4,5-trisphosphate receptor-associated cGMP kinase substrate (IRAG) is abundantly expressed in platelets and assembled in a macrocomplex together with cGKI and the inositol-1,4,5-trisphosphate receptor type I (InsP3RI). cGKI phosphorylates IRAG at Ser664 and Ser677 in intact platelets. Targeted deletion of the IRAG-InsP3RI interaction in IRAGDelta12/Delta12 mutant mice leads to a loss of NO/cGMP-dependent inhibition of fibrinogen-receptor activation and platelet aggregation. Intracellular calcium transients were not affected by DEA/NO or cGMP in mutant platelets. Furthermore, intravital microscopy shows that NO fails to prevent arterial thrombosis of the injured carotid artery in IRAGDelta12/Delta12 mutants.

These findings reveal that NO/cGMP-dependent inhibition of platelet aggregation involves both cGKI and the interaction between IRAG and InsP3RI. Modulation of cGKI-dependent signaling might therefore provide a powerful strategy to prevent arterial thrombus formation in patients with advanced atherosclerotic vascular lesions.