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NO/cGMP/PKG pathway in platelets: inhibitory but not stimulatory

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Platelets are specialized anucleate cells that play a key role in hemostasis through their ability to rapidly adhere to subendothelial matrix proteins and endothelial cells (platelet adhesion) and to other activated platelets (platelet aggregation). The importance of cyclic nucleotides and especially the NO-cGMP-PKG pathway as potent inhibitors of platelet activation has been well established by many investigators in human and animal platelets. However, recently a new mechanism of platelet activation by vWF, mediated by PKG (that sequentially activates p38 and ERK MAP kinases), was proposed [1,2]. Here we present data that activation of PKG by cGMP analogs or NO donors does not stimulate, but rather inhibits, p38 and ERK MAP kinases [3]. However, some PKG stimulators and inhibitors do affect platelets independently of PKG activity [4]. Our data also show that human and mouse platelets do not express functionally active eNOS. However, activation of the vWF receptor in human and mouse platelets stimulates basal guanylyl cyclase activity independently of NOS activation. Furthermore, a PDE5 inhibitor (sildenafil) increases cGMP content in both eNOS KO and WT mouse platelets, whereas in mouse aorta (in which sGC activity is strongly eNOS-dependent), sildenafil increased cGMP only in WT but not eNOS KO mice. In summary, our data do not provide any evidence for a "stimulatory role" of PKG in platelets. Our data suggest that vWF-induced increase in platelet cGMP is independent of platelet eNOS activity and may involve regulation of basal sGC activity by tyrosine phosphorylation.

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