A stimulatory role for cGMP-dependent protein kinase in platelet activation.

It is currently accepted that cGMP-dependent protein kinase (PKG) inhibits platelet activation. Here, we show that PKG plays an important stimulatory role in platelet activation. Expression of recombinant PKG in a reconstituted cell model enhanced von Willebrand factor (vWF)-induced activation of the platelet integrin alpha(IIb)beta(3). PKG knockout mice showed impaired platelet responses to vWF or low doses of thrombin and prolonged bleeding time. Human platelet aggregation induced by vWF or low-dose thrombin was inhibited by PKG inhibitors but enhanced by cGMP. Furthermore, a cGMP-enhancing agent, sildenafil, promoted vWF- or thrombin-induced platelet aggregation. The cGMP-stimulated platelet responses are biphasic, consisting of an initial transient stimulatory response that promotes platelet aggregation and a subsequent inhibitory response that limits the size of thrombi.