AN IMPORTANT STIMULATORY ROLE FOR THE cGMP-DEPENDENT PROTEIN KINASE II IN PLATELET ACTIVATION, IN VIVO THROMBOSIS AND HAEMOSTASIS

Zhenyu Li[1], Ying Liang[2], can wang[2], Guoying Zhang[1], Jens Schlossmann[3], Melanie Baron[4], Matthias Schiemann[4], Sven Fraterman[5], Matthias Wilm[6], Franz Hofmann[4], Robert Feil[7], and Xiaoping Du[2]

[1]University of Kentucky
[2]University of Illinois at Chicago
[3]University of Regensburg Institute of Pharmacy
[4]Technische Universität München
[5]European Molecular Biology Laboratory
[6]University College Dublin
[7]University of Tübingen

December 15, 2020

Abstract

Background and Purpose: The intracellular second messenger cGMP mediates signals by activating two types of cGMP-dependent protein kinases (PKG), PKG I and PKG II, differentially expressed in different cells. In platelets, cGMP mediates biphasic signals that stimulate and inhibit platelet activation, and the downstream signaling of cGMP is mediated by PKG I, the only PKG known to be expressed in platelets. However, functional defects of PKG I knockout platelets did not fully explain the roles of cGMP and the effect of PKG inhibitors on platelet activation. Experimental Approach: To determine if PKG II is present in platelets and plays a role in platelet activation, we performed RT-PCR and isolation of PKG II protein using cGMP-conjugated beads. We further determined platelet aggregation and ATP release in vitro, and FeCl3-injured carotid artery thrombosis as well as tail bleeding time in vivo. Key Results: PKG II is expressed in platelets and plays an important role in selectively stimulating platelet activation but not in the negative regulatory role of cGMP. Collagen-induced platelet aggregation and ATP secretion were reduced in PKG II-deficient mice but not PKG I-deficient mice. In contrast, low-dose thrombin-induced platelet activation depended on PKG I but not PKG II. Tail bleeding time and FeCl3-induced artery thrombus formation were significantly prolonged in PKG II knockout mice. Conclusion and Implication: PKG II-mediated cGMP signals are important in platelet activation, thrombosis and haemostasis in vitro and in vivo.

Hosted file

`Li et al PKG II Paper 20201210.pdf` available at https://authorea.com/users/382979/articles/498845-an-important-stimulatory-role-for-the-cgmp-dependent-protein-kinase-ii-in-platelet-activation-in-vivo-thrombosis-and-haemostasis