Response

Inhibition of platelet activation by NO involves both cGMP-dependent and -independent mechanisms

We are grateful for the opportunity to reply to the letter from Tsikas et al in regard to our recent publication in Blood. Tsikas et al write that “Zhang and colleagues stated in their recent article that it was unknown until their study whether NO donors inhibit platelet function by cGMP-dependent and cGMP-independent mechanisms.” The truth is that we discussed previous function by both cGMP-dependent (references 11, 12, and 16 in Zhang et al) and -independent mechanisms (references 38, 39, 40, 43, and 45 in Zhang et al). Although previous reports suggested cGMP-independent mechanisms involved in NO-mediated platelet inhibition, this conclusion was recently disputed by the Friebe group, which reported that inhibition of platelets by NO donors is solely dependent on soluble guanylyl cyclase (sGC) using sGC whole-body knockout mice. Therefore, whether cGMP-independent mechanisms are involved in NO-mediated inhibition of platelets is unclear. I agree that it would be more accurate to say “whether the inhibitory effect of NO on platelet activation involves these sGC/cGMP-independent mechanisms is unclear,” instead of saying “whether the inhibitory effect of NO on platelet activation involves these sGC/cGMP-independent mechanisms is not known.”

Our results show that NO donors at high concentrations inhibited platelet function from sGC conditional knockout mice, which support the conclusion that cGMP-independent mechanisms are involved in NO-mediated platelet inhibition and are also consistent with the previous reports from the authors of this letter.

The data in the letter that showed NO/NO donors can both decrease and increase COX-1 activity in platelets are not contradictory to our results but support our findings that NO/cGMP plays a biphasic role in platelet activation.

Tsikas et al show in their letter that they failed to detect NOS activity in platelets using a sophisticated gas chromatography–mass spectrometry method. In our paper we reported that sGC is a required agonist-induced platelet activation and that exogenous NO donors inhibit platelet aggregation and secretion through sGC-dependent and -independent mechanisms. Thus our study does not involve whether or not platelets express NOS. However, data shown in the letter are contradictory not only to many previous reports from different groups but also to a report from the authors of the letter that L-arginine inhibits platelet aggregation and thromboxane A2 formation through NOS dependent mechanisms (reference 2 in Tsikas et al).

References


Response: inhibition of platelet activation by NO involves both cGMP-dependent and -independent mechanisms

Zhenyu Li