Activating Effects of GPIIb/IIIa Blockers: An Intrinsic Consequence of Ligand-Mimetic Properties

To the Editor:

An intrinsic activating property of GPIIb/IIIa blockers as first described by us in 1998 is widely discussed as one potential contributing factor for the disappointing outcome of trials with oral GPIIb/IIIa blockers. In a recent article in Circulation, Frelinger et al question the existence of an activating property of GPIIb/IIIa blockers. However, several research groups were able to extend our knowledge about the activating effects of GPIIb/IIIa blockers, a fact that was not discussed by Frelinger et al. In addition, the authors’ own data provide evidence for the existence of an intrinsic activating property of GPIIb/IIIa blockers. In Figure 3, fibrinogen binding is induced by abciximab with a dose dependency typical for the intrinsic activating property of GPIIb/IIIa blockers, revealing maximal induction of fibrinogen binding at low concentrations of abciximab.

The intrinsic activating effect of GPIIb/IIIa blockers may be more prominent if platelets are preactivated, as for example, by thrombin. Indeed, preactivation by low concentrations of ADP has been shown to reveal the platelet-activating effect of GPIIb/IIIa blockers. During the use of oral GPIIb/IIIa blockers, antithrombins are generally not given and thus platelet activation by GPIIb/IIIa blockers may be unmasked. Indeed, platelet activation has been reported in patients receiving oral GPIIb/IIIa blockers.

As in other integrins, outside-in signaling by binding of ligands or ligand-mimetics to GPIIb/IIIa is expected and has indeed been described. Activation of the GPIIb/IIIa integrin by ligand binding, including ligand-mimetic agents, is well in line with established integrin-signaling mechanisms.

Our finding of a conformational change of the GPIIb/IIIa molecule transforming it to a receptor competent for fibrinogen binding, after association and dissociation of GPIIb/IIIa blockers, was confirmed by Frelinger et al (Figure 5) for 2 of the 3 commercially available agents. The most important question that has to be addressed now is whether there is a reverse conformational change of GPIIb/IIIa to a receptor not competent to bind fibrinogen. This reversibility may be dependent on temperature, ion concentrations (prone to experimental differences based on the variance of anticoagulants used), comedications, and platelet activation status. These issues have to be addressed before a conclusion on the potential role of the intrinsic activating effect of GPIIb/IIIa blockers for the clinical situation can be drawn.

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Response

In our recent article, we concluded that “under physiological conditions, the intravenous GPIIb/IIIa antagonists currently in use, as well as the oral GPIIb/IIIa antagonist xemilofiban, do not have an intrinsic activating property that results in platelet aggregation or stable fibrinogen binding to GPIIb/IIIa.” We do not question the ability of GPIIb/IIIa blockers to induce a fibrinogen-binding competent conformation of GPIIb/IIIa that can be preserved by (nonphysiological) chemical fixation, as first described in 1991 by Du et al, and confirmed and extended in 1998 by Peter et al, and more recently us (Figure 5). However, this conformational change is readily reversible in intact (nonfixed) platelets (see Discussion in Frelinger et al). Thus, as Peter et al point out in their letter, the important question to be addressed is whether, under physiological conditions, GPIIb/IIIa reverts to a resting state or binds fibrinogen and mediates platelet aggregation. We addressed this question by incubating intact platelets with a wide range of GPIIb/IIIa antagonist concentrations (without chemical fixation) under conditions in which the antagonists bind reversibly and found no evidence of platelet aggregation, increased fibrinogen binding, or P-selectin expression (Figures 1, 2, and 3 open bars, and Figure 4).

The studies cited in Peter et al’s letter also demonstrated no direct activating effect of GPIIb/IIIa antagonists: (1) exposure of platelets to abciximab or orbofiban did not increase binding of the activation-dependent antibody PAC1 to GPIIb/IIIa; (2) neither abciximab nor orbofiban by themselves induced thromboxane generation; (3) none of the GPIIb/IIIa antagonists tested, including tirofiban, increased intracellular Ca2+ concentrations in nonactivated platelets.

We strongly disagree with Peter et al’s interpretation of results shown in our Figure 3. The increased fibrinogen binding shown was blocked by addition of hirudin, indicating that thrombin, not abciximab, was responsible for platelet activation.

Neither our study, nor that of Peter et al, addressed the separate, but very important, question of whether the GPIIb/IIIa antagonists enhance platelet activation stimulated by traditional platelet agonists. While results from various studies are consistent with this hypothesis, they may only apply to selected GPIIb/IIIa antagonists. For example, although orbofiban enhanced thromboxane production stimulated by CD41-induced clustering of GPIIb/IIIa receptors, abciximab did not.

Therefore, we agree with Peter et al that additional studies specifically addressing this potential effect are needed.

In summary, as we previously concluded, based on our results and those of others, the evidence is that, under physiological conditions, currently approved GPIIb/IIIa antagonists do not directly stimulate platelet aggregation or stable fibrinogen binding.

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