Ticagrelor increases its own affinity to P2Y12 receptor by directly changing the plasma membrane lipid order in platelets

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Abstract

Background and Purpose: Although the amphiphilic nature of the widely used antithrombotic drug Ticagrelor is well known, it was never considered as a membranotropic agent, which is able to interact with lipid bilayer in a receptor-independent way. In this work we investigate the influence of Ticagrelor on plasma membrane lipid order in platelets and whether this could modulate affinity of P2Y12 receptor to Ticagrelor. Experimental Approach: Here, we combined fluorescent in situ, in vitro and in silico approaches to probe the interactions between the plasma membrane of platelets and Ticagrelor. The influence of Ticagrelor on the lipid order of the platelets' plasma membrane and large unilamellar vesicles was studied using advanced fluorescent probe NR12S. Further, the properties of the model lipid bilayers in presence of Ticagrelor were characterized by molecular dynamics simulations. Finally, the influence of an increased lipid order on the dose response of platelets to Ticagrelor was studied. Key Results: Ticagrelor incorporates spontaneously into lipid bilayers and affects the lipid order of the membranes of model vesicles and isolated platelets in non-trivial composition and concentration-dependent manner. We showed that higher plasma membrane lipid order in platelets leads to the lower IC50 for Ticagrelor. It is shown that membrane incorporation of Ticagrelor increases the affinity of the drug to its own therapeutic target, the P2Y12 receptor, by means of increasing the order of the platelet's plasma membrane. Conclusion and Implications: A novel dual mechanism of Ticagrelor action is suggested that combines direct binding to P2Y12 receptor with simultaneous modulation of receptor's lipid microenvironment.

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