A selective serotonin reuptake inhibitor, citalopram, modulates purinergic $P2Y_{12}$ receptor downstream signaling pathways in platelets

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Background: SSRIs have been reported to reduce platelet aggregation induced by ADP. ADP induces platelet aggregation through two purinergic receptor $P2Y_1$ and $P2Y_{12}$.

Objectives: To characterize the inhibitory effects of citalopram on ADP-induced platelet aggregation and to investigate how citalopram affects signaling transductions downstream of $P2Y_1$ and $P2Y_{12}$ receptors.

Methods: Platelet aggregation was triggered by ADP and measured by aggregometry. Signaling pathways of each of receptors were evaluated by Western blotting. Intracellular calcium mobilization was determined by flow cytometry.

Results:

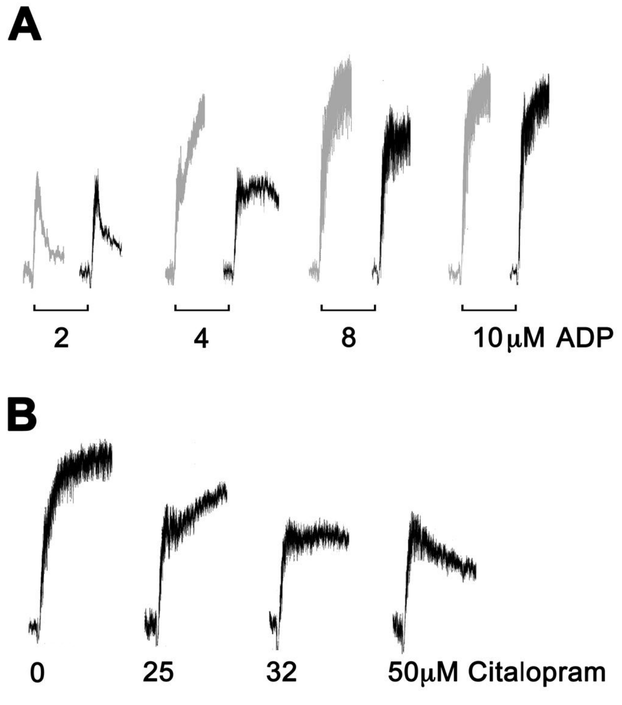

Fig. 1. The primary phase of ADP-induced aggregation was not inhibited by citalopram. Citalopram inhibited the secondary phase of ADP-induced platelet aggregation in a concentration-dependent manner.

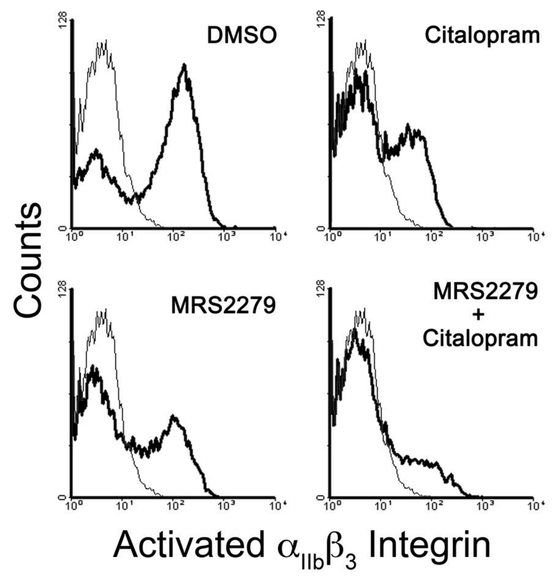

Fig. 2. Under $P2Y_1$ blockade, citalopram inhibited integrin $\alpha_{IIb}\beta_3$ activation in platelets

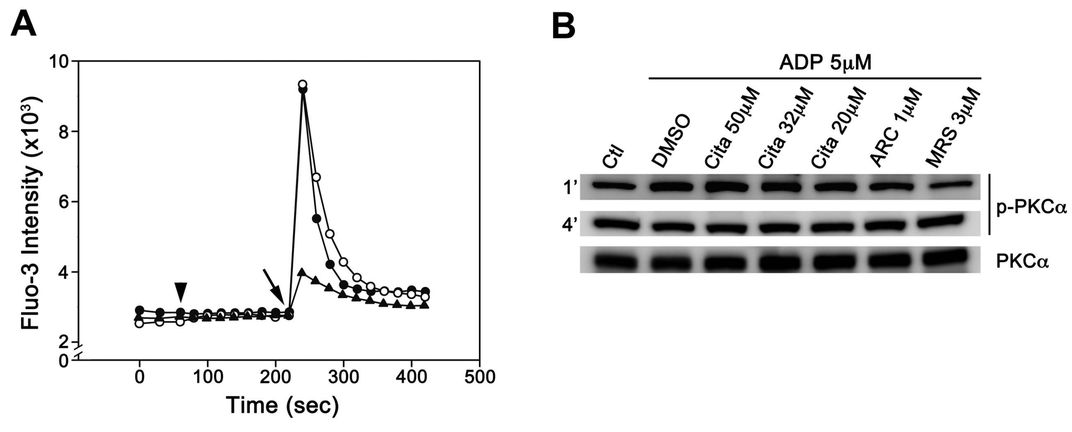

Fig. 3. Citalopram failed to influence ADP-induced intracellular calcium mobilization in platelets and the early phosphorylation of PKC evoked by $P2Y_1$ receptor activation.

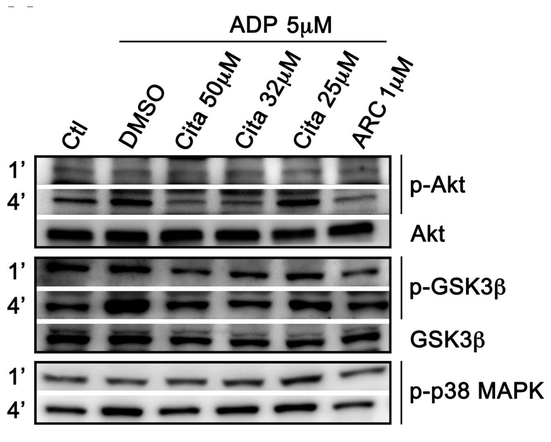

Fig. 4. Citalopram inhibited the phospho-rylation of $P2Y_{12}$ receptor-mediated downstream signaling molecules, including Akt, GSK3β and p38 MAPK induced by ADP.

Conclusions: Through the regulation of $P2Y_{12}$ receptor-mediated singaling pathways involving Akt, GSK3β and P38 MAPK, citalopram inhibits ADP-stimulated sustained aggregation of platelets.