Mechansims involved in the antiplatelet activity of midazolam in human platelets

許準榕
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Abstract

Background: Midazolam is widely used as a sedative and anesthetic induction agent. The aim of this study was to systematically examine the inhibitory mechanisms of midazolam in platelet aggregation. Methods: The inhibitory mechanisms of midazolam in platelet aggregation were explored by means of analysis of the platelet glycoprotein IIb-IIIa complex, phosphoinositide breakdown, intracellular Ca+2 mobilization, measurement of membrane fluidity, thromboxane B2 formation, and protein kinase C activity. Results: In this study, midazolam dose-dependently (6-26 μM) inhibited platelet aggregation in human platelets stimulated by agonists. Midazolam also dose-dependently inhibited phosphoinositide breakdown and intracellular Ca+2 mobilization in human platelets stimulated by collagen. Midazolam (6-26 μM) significantly inhibited thromboxane A2 formation stimulated by collagen in human platelets. Moreover, midazolam (15 and 26 μM) dose-dependently decreased the fluorescence of platelet membranes tagged with diphenylhexatriene. Rapid phosphorylation of a platelet protein of Mr 47,000 (P47), a marker of protein kinase C activation, was triggered by collagen (2 μg/ml). This phosphorylation was markedly inhibited by midazolam (26 μM). Conclusions: These results indicate that the antiplatelet activity of midazolam may be involved in the following pathways: the effects of midazolam may initially be caused by induction of conformational changes in platelet membrane, leading to a change in the activity of phospholipase C, and subsequent inhibition of phosphoinositide breakdown and thromboxane A2 formation, thereby leading to inhibition of both intracellular Ca+2 mobilization and phosphorylation of P47 protein.