α-Naphthoflavone, a Potent Antiplatelet Flavonoid, Is Mediated through Inhibition of Phospholipase C Activity and Stimulation of Cyclic GMP Formation

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摘要

Abstract

The aim of this study was to systematically examine the inhibitory mechanisms of the flavonoid α-naphthoflavone (α-NF) in platelet activation. In this study, α-NF concentration dependently (5-20 μM) inhibited platelet aggregation stimulated by agonists. α-NF (5 and 10 μM) inhibited intracellular Ca2+ mobilization, phosphoinositide breakdown, and thromboxane A2 formation stimulated by collagen (1 μg/mL) in human platelets. In addition, α-NF (5 and 10 μM) markedly increased levels of cyclic GMP and cyclic GMP-induced vasodilator-stimulated phosphoprotein (VASP) Ser157 phosphorylation. Rapid phosphorylation of a platelet protein of Mr 47 000 (P47), a marker of protein kinase C activation, was triggered by phorbol-12,13-dibutyrate (60 nM). This phosphorylation was markedly inhibited by α-NF (5 and 10 μM). However, α-NF (5 and 10 μM) did not reduce the electron spin resonance (ESR) signal intensity of hydroxyl radicals in collagen (1 μg/mL)-activated platelets. These results indicate that the antiplatelet activity of α-NF may be involved in the following pathways. (1) α-NF may inhibit the activation of phospholipase C, followed by inhibition of phosphoinositide breakdown, protein kinase C activation, and thromboxane A2 formation, thereby leading to inhibition of intracellular Ca2+ mobilization. (2) α-NF also activated the formation of cyclic GMP, resulting in inhibition of platelet aggregation. These results strongly indicate that α-NF appears to represent a novel and potent antiplatelet agent for treatment of arterial thromboembolism.