Characterization of a novel and potent collagen antagonist, caffeic acid phenethyl ester, in vitro and in vivo studies

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摘要

Abstract

Objective Caffeic acid phenethyl ester (CAPE), which is derived from the propolis of honeybee hives, has been demonstrated to possess multiple pharmacological activities. In the present study, CAPE (6−25 μM) specifically inhibited collagen-induced platelet aggregation and the ATP release reaction in platelet suspensions.

Methods Platelet aggregation, flow cytometric analysis, immunoblotting, and electron spin resonance (ESR) were used to assess the anti-platelet activity of CAPE. Fluorescein sodium-induced platelet thrombi in mesenteric microvessels of mice were used for an in vivo study.

Results CAPE (15−100 μM) produced a concentration-related rightward displacement of the collagen concentration−response curve, and the Schild plot gave pA2 and pA10 values of 4.28±0.07 and 3.14±0.73, respectively, with a slope of −0.83±0.16, indicating specific antagonism. CAPE (25 μM) also inhibited platelet aggregation stimulated by the glycoprotein VI agonist, convulxin, and the α2β1 integrin agonist, aggretin. CAPE (25 μM) also markedly interfered with FITC-collagen binding to platelet membranes. CAPE (15 and 25 μM) concentration-dependently inhibited collagen-induced platelet activation accompanied by [Ca+2]i mobilization, phosphoinositide breakdown, activation of protein kinase C and mitogen-activated protein kinases (i.e., ERK2, JNK, and p38 MAPK), Akt phosphorylation, and thromboxane A2 formation. In the ESR study, CAPE (15 and 25 μM) markedly reduced hydroxyl radical (OH·) formation in collagen-activated platelets. In an in vivo study, CAPE (5 mg/kg) significantly prolonged the latency in inducing platelet plug formation in mesenteric venules of mice.

Conclusions The most important findings of this study suggest that CAPE specifically inhibits collagen-induced platelet activation. Thus, CAPE treatment may represent a novel

approach to lowering the risk of or improving function in thromboembolism-related disorders.