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CELECOXIB INHIBITS PHORBOL ESTER-INDUCED PGE_2 PRODUCTION AND COX-2 EXPRESSION BY TARGETING OF p38 MAP KINASE AND AP-1 IN MOUSE SKIN

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Celecoxib, a selective COX-2 inhibitor, has been reported to prevent experimentally induced colon, breast, bladder, and skin carcinogenesis. Moreover, daily intake of celecoxib resulted in significant reduction of polyps in patients with familial adenomatous polyposis. In the present study, we examined the effect of celecoxib on COX-2 activity/expression in 12-O-tetradecanoylphorbol-13-acetate (TPA)-treated mouse skin. Topical application of 0.1, 1.0, or 10 μmole celecoxib onto shaven backs of female ICR mice (6 wk of age) 30 min prior to 10 nmole TPA inhibited expression of COX-2 protein and subsequent production of prostaglandin E_2 in a dose-related manner. Under the same experimental conditions, the levels of the constitutive enzyme COX-1 remained unchanged. To further elucidate the molecular mechanisms by which celecoxib suppresses COX-2 expression and PGE_2 production, we have investigated its effects on activation of upstream mitogen-activated protein kinases (MAPKs) and transcription factors in mouse skin. Celecoxib dose-dependently inhibited TPA-induced AP-1 activation, which was associated with inhibition of Fos and Jun expression. Furthermore, celecoxib inhibited both activation of p38 MAP kinase and ERK1/2. Pretreatment of mouse skin with the selective inhibitors of MAPKs produced substantial inhibition of TPA-induced AP-1 activation by p38 MAPK inhibitor (SB 203580) while the ultrapotent MEK inhibitor (U0126) failed to block AP-1 DNA binding. The above findings suggest that celecoxib suppresses TPA-induced COX-2 expression in mouse skin by blocking preferentially activation of p38 MAP kinase, which appears to be mediated through inactivation of AP-1. Supported by a grant (02-PJ2-PG3-20802-0003) from the Ministry of Health & Welfare, Republic of Korea.

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