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ACTIVATION OF NF-κB AND INDUCTION OF CYCLOOXYGENASE-2 BY NITRIC OXIDE IN MOUSE SKIN

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Nitric oxide (NO) has multifaceted roles in carcinogenesis. Besides acting as an initiator, NO may also play a role in the promotional stage of tumorigenesis or neoplastic transformation. In line with this notion, our previous studies have revealed that the tumor promotor phorbol ester induces expression of inducible nitric oxide synthase (iNOS) and NO production in mouse skin. NO has been considered to regulate the expression of cyclooxygenase-2 (COX-2) and subsequent production of prostaglandin E_2. In the present study, we have investigated the possible role of NO in COX-2 induction as well as in mouse skin tumor promotion. Aminoguanidine, a selective iNOS inhibitor, suppressed phorbol ester-induced COX-2 expression in mouse skin. In another experiment, topical application of the NO releasing compound sodium nitroprusside (SNP) at 20 mmole caused induction of epidermal COX-2, but not COX-1, up to 2h, which was further confirmed by immunohistochemical localization of the enzyme. The induction of COX-2 by SNP was accompanied by gradual activation of typical mitogen-activated protein kinases (MAPKs), such as extracellular regulated protein kinases (ERK1/2), c-Jun NH2 protein kinase (JNK) and p38 MAPK. The 5-flanking region of *cox-2* promoter has NF-κB binding sites. While topical application of 2 mmole of SNP induced activation of epidermal NF-κB, larger amounts of the same compound repressed the constitutive NF-κB DNA binding activity. The phorbol ester-induced COX-2 expression in iNOS knockout mice was not significantly different from that of normal mice. Supported by a grant (HMP-00-B-20800-0085) from the Ministry of Health and Welfare, Republic of Korea.