Prostaglandin D(2) and J(2) induce apoptosis in human leukemia cells via activation of the caspase 3 cascade and production of reactive oxygen species.

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Abstract

The presence of prostaglandins (PGs) has been demonstrated in the processes of carcinogenesis and inflammation. In the present study, we found that 12-o-tetradecanoylphorbol 13-acetate (TPA) induced cyclooxygenase 2 (COX-2), but not COX-1, protein expression in HL-60 cells, and the addition of arachidonic acid (AA) in the presence or absence of TPA significantly reduced the viability of HL-60 cells, an effect that was blocked by adding the COX inhibitors, NS398 and aspirin. The AA metabolites, PGD(2) and PGJ(2), but not PGE(2) or PGF(2alpha), reduced the viability of the human HL60 and Jurkat leukemia cells according to the MTT assay and LDH release assay. Apoptotic characteristics including DNA fragmentation, apoptotic bodies, and hypodiploid cells were observed in PGD(2)- and PGJ(2)-treated leukemia cells. A dose- and time-dependent induction of caspase 3 protein procession, and PARP and D4-GDI protein cleavage with activation of caspase 3, but not caspase 1, enzyme activity was detected in HL-60 cells treated with PGD(2) or PGJ(2). Additionally, DNA ladders induced by PGD(2) and PGJ(2) were significantly inhibited by the caspase 3 peptidyl inhibitor, Ac-DEVD-FMK, but not by the caspase 1 peptidyl inhibitor, Ac-YVAD-FMK, in accordance with the blocking of caspase 3, PARP, and D4-GDI protein procession. An increase in intracellular peroxide levels by PGD(2) and PGJ(2) was identified by the DCHF-DA assay, and anti-oxidant N-acetyl cysteine (NAC), mannitol (MAN), and tiron significantly inhibited cell death induced by PGD(2) and PGJ(2) by reducing reactive oxygen species (ROS) production. The PGJ(2) metabolites, 15-deoxy-Delta(12,14)-PGJ(2) and Delta(12)-PGJ(2), exhibited effective apoptosis-inducing activity in HL-60 cells through ROS production via activation of the caspase 3 cascade. The proliferator-activated receptor-gamma (PPAR-gamma) agonists, rosiglitazone (RO), troglitazone (TR), and ciglitazone (CI), induced apoptosis in cells which was blocked by the addition of the PPAR-gamma antagonists, GW9662 and BADGE, via blocking of caspase 3 and PARP cleavage. However, neither GW9662 nor BADGE showed any protective effect on PGD(2)- and PGJ(2)-induced apoptosis. A differential apoptotic effect of PGs through ROS

production, followed by activation of the caspase 3 cascade, was demonstrated.