HUMAN BLOOD PLATELET AGGREGATION BY ESTERS OF 12-DEOXYPHORBOL

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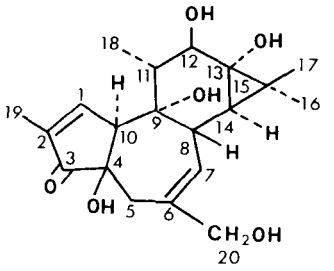

Figure 1. Phorbol

Esters of phorbol (Figure 1), are potent tumour promoters and inflammatory agents (Evans and Soper 1978). Platelet aggregation is a simple model which can be used to study the release of inflammatory mediators. Since 12-O-tetra decanoyl-phorbol-13-acetate (TPA) has been shown to induce platelet aggregation (Zucker et al 1974) we have investigated the platelet aggregating properties of a series of closely related compounds. Blood from male donors was collected into sodium citrate and platelet-rich plasma (PRP) produced by centrifugation. Ten esters, dissolved in acetone to give a final acetone concentration of less than 0.5%, were added to citrated PRP and platelet aggregation monitored as described by Westwick and Webb (1978). The compounds were examined in a concentration range of 0.05 to 10 µmoles. 0.5% acetone solution did not produce platelet aggregation. TPA induced 50% maximum aggregation at a concentration of 0.13 µmolar, while phorbol, the parent alcohol, was inactive at 6 µmolar. Four C-13 monoesters of 12-deoxyphorbol produced 50% aggregation in concentrations of 1.19 to 6 µmolar, but a further four diesters in which the C-20 primary hydroxy group was acetylated had no effects at a similar concentration range. Two closely related compounds, resiniferatoxin and tinyatoxin, which have aromatic ester groups at C-20, also failed to produce aggregation of platelets. From comparison of the aggregating effects of TPA and 12-deoxyphorbol esters it can be seen that the removal of an acyl group at C-12 of the nucleus reduces the potency of the compound in the platelet aggregation test. Furthermore a free primary hydroxy group at C-20 and an ester function at C-13 are necessary for induction of human platelet aggregation.

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