1-Phenyl-3-pyrazolidone: an inhibitor of arachidonate oxidation in lung and platelets

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The oxidation of arachidonic acid in lungs and platelets proceeds by two main pathways: in the first, arachidonate is transformed into prostaglandin (PG) endoperoxides and thence to various other PGs and thromboxanes (TXs) (Hamberg & Samuelsson, 1974a, b; Hamberg, Svensson & Samuelsson, 1975); in the second it is transformed to an unstable hydroperoxide (HPETE) and ultimately to the stable hydroxyacid (HETE) (Hamberg & Samuelsson, 1974a, b; Nugteren, 1975). The former reaction is catalyzed by the membrane-bound cyclo-oxygenase and is inhibited by non-steroidal anti-inflammatory drugs (Vane, 1971). The latter reaction is catalyzed by a cytoplasmic lipoxygenase, and not inhibited by the non-steroidal anti-inflammatory drugs at concentrations which inhibit the cyclo-oxygenase (Hamberg & Samuelsson, 1974a) and as yet only nordihydroguataric acid has been reported to inhibit this enzyme selectively (Hamberg, 1976). Hitherto, inhibition of both enzymes has only been demonstrated by the acetylenic arachidonic acid analogue 5,8,11,14-eicosatetraynoic acid TYA (Hamberg & Samuelsson, 1974a). We now report that 1-phenyl-3-pyrazolidone (phenidone, 1-P-3-P; obtained from Sigma), a commercially available reagent used in the photographic industry, inhibits both the cyclo-oxygenase and lipoxygenase pathways in horse platelets and guinea-pig perfused lungs.

The oxidation of arachidonic acid by lysates of horse platelets was estimated radiochemically. The technique, including details of t.l.c. systems and methods of quantitation, has been previously described (Blackwell, Duncombe, Flower, Parsons & Vane, 1977). Guinea-pig isolated lungs were perfused through the pulmonary artery at 5 ml/min with Krebs' bicarbonate solution at 37°C. Arachidonic acid (10 μg + 0.2 μCi [1-^{14}C]-arachidonic acid) was injected as a bolus into the lungs into which were infused 1-P-3-P (20 μg/ml), or an appropriate control vehicle. The effluent was collected for 5 min, extracted and processed as above.

In platelet lysates the addition of 1-P-3-P resulted in a simultaneous decline in the formation of both lipoxygenase and cyclo-oxygenase products and a concomitant increase in unreacted arachidonate: I_{50} concentrations were calculated at 50 μg/ml (lipoxygenase) and 63 μg/ml (cyclo-oxygenase).

When labelled arachidonate was injected through the lung it was transformed into at least six products, some of which corresponded to known cyclo-oxygenase or lipoxygenase products. In the presence of 1-P-3-P (20 μg/ml), however, only labelled arachidonate was recovered in the lung effluent and the conversion to all other products was blocked.

1-P-3-P may be considered an analogue of phenylbutazone, oxyphenbutazone, antipyrine and dipyrone, but whilst all these drugs were active against the cyclo-oxygenase none of them possessed the ability to block the lipoxygenase pathway as well.

We conclude that phendione could be a useful pharmacological tool to investigate the role of the lipoxygenase pathway in platelets and other cells. The discovery that this type of structure inhibits both enzymes may enable a specific inhibitor of lipoxygenase to be designed or could give information about similarities in the active site of the lipoxygenase and cyclo-oxygenase enzymes.

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