THE INHIBITION OF RABBIT LIVER ALDEHYDE OXIDASE BY HYDRALAZINE

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Aldehyde oxidase and xanthine oxidase are two closely related molybdenum containing enzymes which are present in the liver cytosol of many species including man. Both enzymes catalyse the in vitro oxidation of 2,3-diazanaphthalene(phthalazine) to the 1-hydroxy derivative (Stubley et al 1979).

The anti-hypertensive drug hydralazine (1-hydrazinophthalazine) is an inhibitor of a number of enzymes (Israili & Dayton 1977) and it has been found in the present study that the drug is also a potent inhibitor of aldehyde oxidase. However, neither substrate nor inhibitory activity was observed towards xanthine oxidase.

Freshly prepared slices of rabbit liver, which is a particularly rich source of aldehyde oxidase, were incubated with phthalazine in the presence of hydralazine. The oxidation of phthalazine was monitored by HPLC over a ninety minute period and was found to be considerably reduced compared to control incubations containing no drug.

In vitro experiments were carried out using a partially purified preparation of rabbit liver aldehyde oxidase and three different substrates, viz. purine, phthalazine and the anti-neoplastic drug methotrexate. The latter compound has been shown to be rapidly oxidised by aldehyde oxidase to the relatively inactive 7-hydroxy metabolite (Johns et al 1965). In all cases the rate of oxidation was rapidly reduced to zero by concentrations of hydralazine as low as 10^{-7} M. The inhibition was not competitive and appeared to be progressive in nature.

Parallel studies were carried out in vivo in which rabbits were treated with hydralazine HCl (5mg/kg daily for 21 days orally in solution). A marked reduction in aldehyde oxidase activity was found in the livers from these animals when compared to control animals, indicating that the inactivation of the enzyme also occurs in vivo.

However, hydralazine is extensively metabolised in vivo and one of the major metabolites, 3-methyl-s- triazolo(3,4-α)phthalazine, a cyclised N-acetyl derivative was therefore synthesised (Lesser et al 1974) but found to have no inhibitory activity towards aldehyde oxidase or xanthine oxidase. This indicates that the reduced aldehyde oxidase activity in hydralazine-treated rabbits is due to hydralazine itself rather than this metabolite.

From the above results it may be concluded that hydralazine has no effect on xanthine oxidase activity but is a potent inhibitor of aldehyde oxidase, both in vitro and in vivo.

In humans, oral administration of hydralazine HCl (50-100mg) leads to circulating free hydralazine levels of approximately 10^{-6} M (Israili & Dayton 1977). As hydralazine appears to be such a potent inhibitor of aldehyde oxidase, it is possible that the metabolic profile of any compound whose biotransformation is mediated by aldehyde oxidase may be altered by the concomitant administration of hydralazine.

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