D.R. (1974). Metabolic and pharmacokinetic study of bucloxic acid. *Arzneim-Forsch.*, (*Drug. Res.*), **24**, 1385–1389.

ZACCHEI, A.G., WISHOUSKY, T.I. & WATSON L.S. (1978). The physiological disposition of (2-cyclopentyl-6,7-dichloro-2-methyl-1-oxo-5-indanyloxy) acetic acid in the rat, dog, rhesus monkey and baboon. *Drug Metab. Disp.*, **6**, 313–320.

Induction by phenobarbitone or 3-methylcholanthrene of the hepatic microsomal metabolism of harmine

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Harmine is a monoamine oxidase inhibitor, which undergoes extensive metabolism, through O-demethylation to harmol (Slotkin & Distefano, 1970; Burke & Upshall, 1976). We have investigated the metabolism of harmine by hepatic microsomal suspensions *in vitro*, as part of a study of the metabolism of tricyclic drugs by different forms of cytochrome P-450. Apparently different forms of hepatic microsomal cytochrome P-450, showing different substrate specificities, are induced by pretreatment of animals with either phenobarbitone (PB) or 3-methylcholanthrene (MC) *in vivo* (Lu, Levin, West, Jacobson, Ryan, Kuntzman & Conney, 1973; Burke & Mayer, 1975).

Adult (20–25 g), male C57/BL strain mice were used, either untreated (control group) or pretreated with PB or MC. Liver microsome suspensions were prepared and incubated with harmine, under conditions suitable for cytochrome P-450-mediated mixed function oxidation. A differential extraction assay was developed for the separation of harmine and harmol and their subsequent fluorimetric measurement. The rates listed below are mean initial reaction rates for 5 mice.

The rate of total metabolism of harmine (100 μM) was faster with liver microsomes of MC-treated mice (18 nmol min^{-1} mg $protein^{-1}$) than with liver microsomes of either control or PB-treated mice (4 and 8 nmol min^{-1} mg $protein^{-1}$ respectively). Harmol was the major metabolite with liver microsomes of control mice and seemingly the sole metabolite with PB-treated mice, but it was only a minor metabolite with MC-treated mice. (The rates of harmol production were approximately 50%, 100% and 10% of the rates of harmine degradation with control, PB-treated and MC-treated mice respectively. This could be partly due to extensive further microsomal metabolism of harmol itself, which occurred with MC-treated mice (6 nmol min^{-1} mg $protein^{-1}$ at 25 μM harmol) but not with control or PB-treated mice (0.3 and 1.0 nmol min^{-1} mg $protein^{-1}$ respectively). It could also be partly due to the apparent induction by MC of an alternative pathway for microsomal metabolism of harmine. A yellow product, which was not a further metabolite of harmol, was formed by the metabolism of harmine with liver microsomes of MC-treated mice, but it was not detected with microsomes of control mice and only barely detectable with microsomes of PB-treated mice.

References

BURKE, M.D. & MAYER, R.T. (1975). Inherent specificities of purified cytochromes P-450 and P-448 toward biphenyl hydroxylation and ethoxyresorufin deethylation. *Drug Metab. Disposition*, **3**, 245–253.

BURKE, M.D. & UPSHALL, D.G. (1976). Species and phenobarbitone-induced differences in the kinetic constants of liver microsomal harmine O-demethylation. *Xenobiotica*, **6**, 321–328.

LU, A.Y.H., LEVIN, W., WEST, S.B., JACOBSON, M., RYAN, D., KUNTZMAN, R. & CONNEY, A.H. (1973). Reconstituted liver microsomal enzyme system that hydroxylates drugs, other foreign compounds and endogenous substrates. *J. Biol. Chem.*, **248**, 456–460.

SLOTKIN, T. & DISTEFANO, V. (1970). A model of harmine metabolism in the rat. *J. Pharmac. exp. Ther.*, **174**, 456–462.

The relative inducing potency of antiepileptic drugs in mice

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