determining the taurine conjugation of carboxylic acids, and this is the first report of this reaction occurring with an aryloxyacetic acid in mammalian species. It must be mentioned that the taurine conjugation of arylacetic acids in general occurs at random with certain combinations of acid and species, although it is especially evident in carnivores.

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References

CALDWELL, J. & EMUDIANUGHE, T.S. (1979) The structure of the glucuronic acid conjugate of clofibric acid. *Biochem. Soc. Trans.* in press.

CAYEN, M.N., FERNANDINI, E.S., GRESELIN, E., ROBINSON, W.T. & DVORNIK, D. (1977). Clofibrate and clofibric acid: comparison of the metabolic disposition in rats and dogs. *J. Pharmac. exp. Ther.* **200**, 33–43.

HOUIN, G. & TILLEMENT, J-P. (1978). Clofibrate and enzymatic induction in man. *Int. J. Clin. Pharmac.* **16**, 150–154.

Differences in toxicity due to species variation in the metabolism of an oral anti-allergy agent

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During the toxicological evaluation of an oral anti-allergy compound FPL 57787 (6,7,8,9-tetrahydro-5-hydroxy-4-oxo-10-propyl-4H-naptho (2,3-b) pyran-2-carboxylic acid) (Augstein *et al.*, 1977) a marked difference was noted in the oral toxicity when the compound was administered to rat and dog. The compound proved severely hepatotoxic to some dogs during 90 days administration at 60 mg kg^{-1} day^{-1}. No toxicity was seen in the rat after 180 days administration at dose levels up to 125 mg kg^{-1} day^{-1} even though absorption was similar (>50%).

The species difference in toxicity corresponded to a variation in the rate of metabolism. The only metabolites of the compound in rat, dog, hamster, rabbit, monkey and man were produced by hydroxylation of the alicyclic ring. The rate of hydroxylation as judged by *in vivo* and *in vitro* evidence was much slower in dog than in other species examined. Microsomes prepared from dog liver metabolised the compound at a rate $<6 \times 10^{-12}$ moles metabolites formed min^{-1} mg $protein^{-1}$. In contrast rat liver microsomal fraction metabolised the compound at a rate of 38×10^{-12} moles min^{-1} mg^{-1}. Analysis for FPL 57787 and its metabolites in the urine, faeces and plasma after administration of FPL 57787 substantiated the *in vitro* data. After oral doses the hydroxylated metabolites were present in the plasmas of man and rat whilst only unchanged compound was present in plasma samples obtained from the dog. Similarly the dog excreted most of the administered dose (either i.v. or oral) as unchanged compound in the faeces, whilst the other species excreted substantial proportions of metabolites in the urine.

Since unchanged FPL 57787 was not cleared renally by any species the slower rate of metabolism of the dog resulted in a dependence on biliary excretion for the elimination of the compound. Transport maximum values for the biliary excretion of FPL 57787 in the dog obtained from animals after biliary cannulation ranged from 0.09–1.25 mg kg^{-1} $hour^{-1}$. The dose levels that produced toxicity in the dog were sufficient to saturate the biliary excretion of the compound and resulted in a very high area under the plasma curve (AUC) (4600 h μg/ml at 60 mg/kg). The species capable of clearance by metabolism had a much lower plasma AUC (e.g. rat – 300 h μg/ml at 80 mg/kg) at corresponding doses.

The dog is widely used as a species for toxicological evaluation. The reported work indicates the value of studying metabolism both from a quantitative as well as the normal qualitative view point when interpreting toxicological data. The inability of the dog to readily hydroxylate alicyclic carbon in a compound extensively metabolised by rat and man may be viewed as unusual. It has, however, been noted in previous publications. (Dayton, Cunningham, Israili & Weiner, 1973; Gros, Dari, Chasseaud & Hawkins, 1974; & Zacchei, Wishousky & Watson, 1978).

References

AUGSTEIN, J., CAIRNS, H., HUNTER, D., LEE, T.B., SUSCHITZKY, J., ALTOUNVAN, R.E.C., JACKSON, D.M., MANN, J., ORR, T.S.C. & SHEARD P. (1977). New orally effective chromone derivatives for the treatment of asthma. *Agents and Actions*, **7**, 443–445.

DAYTON, P.G., CUNNINGHAM, R.F., ISRAILI, Z.H. & WEINER I.M. (1973). Studies of the fate of metabolites and analogs of probenecid. *Drug Metab. Disp.*, **1**, 742–751.

GROS, P.M., DARI, H.J., CHASSEAUD, L.F. & HAWKINS,

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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