INFLUENCE OF ROUTE OF ADMINISTRATION OF β-NAPHTHOFLAVONE ON INDUCTION OF DRUG METABOLISM IN VARIOUS TISSUES OF THE RAT

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Many consequences of extrahepatic metabolism are well known; for example the low bioavailability of certain drugs administered by extravascular routes and specific organ toxicity from local enzymic activation of certain xenobiotics. Extrahepatic induction of drugs is believed to involve primarily a particular form of cytochrome P-450 which is specifically induced by the polycyclic aromatic hydrocarbons (PCAH). The purpose of this investigation was to determine the effect of route of administration and duration of pretreatment with β-naphthoflavone (BNF), one of the PCAH type inducers (Boobis *et al* 1976), on the induction of various tissues.

Male Sprague-Dawley rats (weight 220-280g) in groups of 2-5 were treated for either 1 day by the iv, po or ip routes or for 3 days by the ip or po routes at BNF doses ranging from 1-100mg/kg. Two vehicles were used; corn oil, the standard vehicle for BNF administration, and a mixture of polyethylene glycol 400:propylene glycol (9:1) to allow iv administration. Microsomes from liver, gut, kidney and lung were prepared by standard procedures. 7-Ethoxycoumarin O-deethylase (ECOD) was employed to assess drug metabolising capacity in the various tissues *in vitro* (Prough *et al* 1978). The control ECOD rates for each tissue were similar after pretreatment with either vehicle and independent of route of administration or days pretreatment.

For the liver, kidneys and gut, there was a dose dependent increase in ECOD activity for each of the three routes of administration and days of treatment. The increase for the liver and kidneys appears maximal at 3 days pretreatment over a 30-100mg/kg BNF range. The lungs show a similar dose dependent increase of ECOD activity after 3 x ip pretreatment. The relative induction of kidneys and gut (Fig.1) with respect to liver increased significantly with dose ($P<0.05$); the kidneys showed an increase from 5% in control microsomes to 30% in maximally induced microsomes after either 1 or 3 days pretreatment and each route of administration. The gut shows a more modest increase in relative induction in microsomes from similarly treated rats, from 2% to 10% after 3 x ip. The lungs in contrast, had a high control contribution, 35%, reducing to 7% over a 3-100mg/kg BNF range after 3 x ip or 1 x ip pretreatment.

ECOD activities for the various tissues studied was greater after 3 days pretreatment and in the order ip>iv>po, the approximate ratio being 1.75:1.5:1. These data suggest that the site of administration and absorption rate are more important in defining the induction response of BNF than the total administered dose.

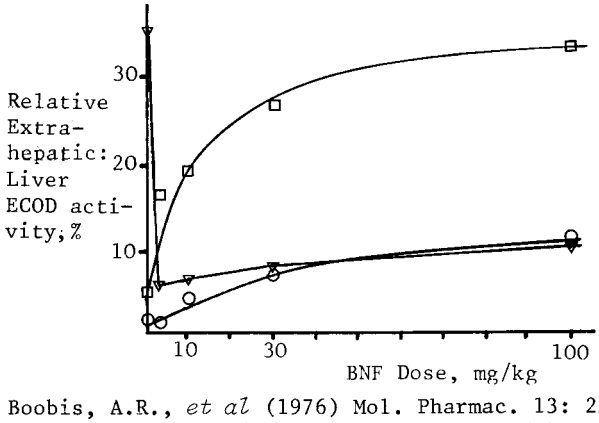

Fig.1. Relative Kidney (□), Gut (○) or Lung (▽) to Liver ECOD activity after induction by 3 x ip BNF at a range of doses.

Boobis, A.R., *et al* (1976) Mol. Pharmac. 13: 259-268
Prough, R.A., *et al* (1973) Meth. Enz. 52(C): 372-377