THE IN VITRO METABOLISM OF S-(-)-NICOTINE BY LIVER PREPARATION FROM FEMALE RATS PRETREATED WITH ORAL CONTRACEPTIVE STEROIDS

M.W. Davies and G. Keysell, Pharmacology Section, School of Pharmacy, Portsmouth Polytechnic, King Henry I Street, Portsmouth, PO1 2DZ, U.K.

Many factors can affect the extent and type of drug metabolism in man and animals. Generally, pregnancy causes a decrease in drug metabolism due to the endogenous steroids (Guarina, 1969). Oral contraceptive steroids (OCS) also alter drug metabolism in women and rats (Carter et al, 1973), but not all routes are equally affected because the pretreatment of rats with OCS led to an increase in the hydroxylation of aniline and a decrease in the hydroxylation of hexobarbitone (Jori et al, 1969).

S-(-)-Nicotine, the major alkaloid found in tobacco smoke was metabolised in vitro by liver preparations obtained from female rats that had been pretreated with either, OCS (human dose level, mg/Kg for 6 weeks), phenobarbitone (P), or 3-methylcholanthrene (3MC). Untreated sister rats were used as controls. The two major metabolites, cotinine and nicotine-N-oxide, were extracted from incubation mixtures and estimated by gas-liquid chromatography.

The results (Table 1) indicate that the formation of cotinine and nicotine-N-oxide are not affected to the same extent, presumably because cotinine involves the haem protein, the cytochrome P450 and the N-oxide the flavoprotein, the mixed function amine oxidase. Pretreatment with the progestogenic steroid, ethinodioldiacetate (ED), produced an increase in cotinine and decrease in N-oxide formation thus increasing the cotinine/N-oxide ratio, which has been associated with bladder cancer in smokers (Gorrod et al, 1974). The steroids, ethinyloestradiol (EE2) and norgesterol (N), reduced both nicotine metabolites. The observed reductions may be due to steroid remaining in the liver preparations, since OCS inhibit drug metabolism in vitro (Carter, 1973). Therefore, the increase in cotinine formation produced by ED suggests that induction of the P450 type of haem protein, may have occurred. The classic enzyme inducers, phenobarbitone (P) and 3-methylcholanthrene (3MC) show that P450 induction, produced by P, does increase cotinine formation whereas P448 induction, produced by 3MC, does not.

Table 1. Nicotine metabolism expressed as a % of controls

PRETREATMENT OF RATS BY	COTININE (A)	NICOTINE 1'N OXIDE (B)	TOTAL (A+B) METABOLISM	RATIO A/B
EE2	58.8 ± 8.2%**	94.3 ± 8.9%	79.3 ± 5.1%*	78.2 ± 13.5%
ED	135.1 ± 10.1%**	77.5 ± 7.6%	106.5 ± 6.3%	149.5 ± 13.5%*
N	84.7 ± 9.5%	83.6 ± 9.3%	83.0 ± 8.6%	86.2 ± 7.6%
EE2 + ED	79.5 ± 9.6%	110.0 ± 8.1%	100.6 ± 4.5%	91.1 ± 22.3%
P	228.3 ± 20.3%**	54.8 ± 14.0%*	126.7 ± 16.5%	555.0 ± 111.0%**
3MC	93.1 ± 9.8%	80.0 ± 3.4%	85.6 ± 6.6%	88.0 ± 6.5%

* = $p < 0.05$ ** = $p < 0.01$ SISTER CONTROLS = 100%

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