EUROPEAN JOURNAL OF DRUG METABOLISM AND PHARMACOKINETICS, 1993, Vol. 18, No. 2, pp. 187–197

Metabolism of S-nicotine in noninduced and Aroclor-induced rats

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Received for publication: July 17, 1992

Keywords: Nicotine, urinary metabolites, excretion kinetics, Aroclor induction, sex differences, stereoselectivity

SUMMARY

The urinary excretion of nicotine and its metabolites in noninduced and Aroclor-induced male and female rats has been determined following intravenous administration of 2'-[^{14}C]-labeled S-nicotine at a dose of 4.6 μmol/kg. Complete recovery of the administered radioactivity was achieved: 95% in urine and 4% in feces over 96 h and 1% remaining in the body. More than 40 nicotine metabolites were found by radio-HPLC; 19 were identified including the *cis/trans*-diastereomers of nicotine-N'-oxide and 3'-hydroxycotinine. The urinary metabolite profile and excretion kinetics of nicotine and its metabolites were significantly different between noninduced and Aroclor-induced rats. The major urinary nicotine metabolite in the noninduced rat was *cis*-nicotine-N'-oxide. In the Aroclor-induced rat, cotinine metabolites were the major metabolites found. Sex differences were found for the urinary nicotine metabolite profile, mainly expressed in the excretion of *cis*-nicotine-N'-oxide, 29% in the male and 17% in the female noninduced rat, and the excretion of cotinine, 5% in the male and 12% in the female noninduced rat. High stereoselectivity was found for the formation of the *cis/trans*-diastereomers of nicotine-N'-oxide as well as of 3'-hydroxycotinine, the stereoselectivity being more pronounced in male rats.

INTRODUCTION

Nicotine metabolism has been extensively studied, and more than 20 nicotine metabolites resulting from 5 different metabolic pathways have been described [for review, *see* (1–5)]. The metabolism of the naturally occurring S-enantiomer and of the synthetic R-enantiomer of nicotine were shown to be different in vitro (6) as well as in vivo (7), and one enantiomer was found to interfere with the metabolism of the other (8). In the aforementioned in vivo metabolism study in the rat using enantiomerically pure nicotine tritiated at the methyl group (7), only a limited number of metabolites could be detected. This is because the methyl group is lost at early steps in the metabolic pathways. Therefore, the present study was performed using the enantiomerically pure S-nicotine, [^{14}C]-labeled at the 2'-position in the pyrrolidine ring.

It is known that the metabolism and biokinetics of nicotine are influenced by genetic (e.g. strain, sex) and exogenous factors (e.g. drug treatment, diet) [reviewed in (5)], which can affect the induction status of the metabolizing enzymes. The influence of selective inducers of various cytochrome P-450 isozymes, e.g. phenobarbital, 5,6-benzoflavone, β-naphthoflavone, 3-methylcholanthrene, or ethanol on nicotine metabolism has been shown in vitro on subcellular fractions or isolated organs [e.g. (9–15)]. In vivo, the influence of

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