Individual Differences in Nicotine Kinetics and Metabolism in Humans

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INTRODUCTION

Cigarette smoking remains the major preventable cause of premature disability and death in developed countries (Peto et al. 1992). Cigarette smoking is maintained by addiction to nicotine. Nicotine addiction develops in most people before the age of 20 (Department of Health and Human Services 1994). Many youth experiment with cigarettes, but only about 25 percent of high school seniors become addicted smokers (Escobedo et al. 1993). Thus, there appears to be individual variability in susceptibility to nicotine addiction.

In support of the idea of individual variability to nicotine addiction are twin studies showing genetic linkages for never smoking, for quitting (i.e., former smoker status), and even for being a light versus a heavy smoker (Carmelli et al. 1992). The basis for individual differences in susceptibility to addiction is unknown. Possible factors include differences in pharmacokinetics and metabolism of nicotine, pharmaco-dynamic differences, and factors related to personality, including affective disorders and, of course, environmental influences (Benowitz 1992). Of note is an apparent shared inheritance in susceptibility to nicotine addiction and alcohol abuse (Swan et al. 1990).

NICOTINE METABOLISM AND SMOKING BEHAVIOR

This chapter considers individual differences in the pharmacology of nicotine. While there is evidence of genetic difference in pharmacologic response to nicotine in rodents (Marks et al. 1991), there has been very little research into individual differences in pharmacodynamics in humans. Individual differences in pharmacokinetics and metabolism have been much better documented, and are the major focus of this discussion.

Individual differences in nicotine kinetics and metabolism could affect smoking behavior in two ways. First, an individual's rate of nicotine metabolism could affect how much a person smokes. Smokers tend to

adjust their smoking to maintain particular levels of nicotine in the body. A person who metabolizes nicotine quickly may need to smoke more to achieve a particular level of nicotine than does a person who metabolizes nicotine more slowly. The phenomenon of regulation has been demon-strated experimentally in a study in which the rate of nicotine elimination was increased by acidification of the urine (Benowitz and Jacob 1985). In conditions of urinary acidification, smokers consumed 18 percent more nicotine per day from cigarettes, compensating by about 50 percent for the excess loss of nicotine by increased renal clearance.

A second mechanism by which individual differences in metabolism could affect nicotine addiction is through the pattern of metabolites generated. Some nicotine metabolites may be pharmacologically active. These include nicotine iminium ion, -nicotyrine, cotinine, and nornicotine. Nicotine iminium ion is an intermediate in the metabolism of nicotine to cotinine (figure 1). Nicotine iminium ion can covalently bind to macro-molecules (Shigenaga et al. 1988) and may thereby produce tissue injury and/or promote carcinogenesis. -nicotyrine is a minor metabolite of nicotine that has been shown to inhibit nicotine metabolism in vitro (Shigenaga et al. 1989). Cotinine is the major proximate metabolite of nicotine. Cotinine is inactive toward nicotinic cholinergic receptors, but does appear to affect a number of enzyme systems, including those involved in steroid synthesis (Benowitz 1994). Cotinine may also have central nervous system (CNS) activity, reportedly modifying nicotine withdrawal symptoms in abstinent smokers (Keenan et al. 1994). The site or mechanism of CNS action of cotinine is unknown, but if there is CNS activity, cotinine, which is present at 15 times the concentration of nicotine, could contribute significantly to nicotine addiction. Nornicotine is a minor metabolite of nicotine as well as a component of tobacco itself. It is as potent in pharma- cologic activity and toxicity as nicotine (Risner et al. 1988). Thus, considering the activity of various metabolites, individual differences in the amount of various metabolites generated could influence differential susceptibility to nicotine addiction and/or toxic effects of tobacco use.

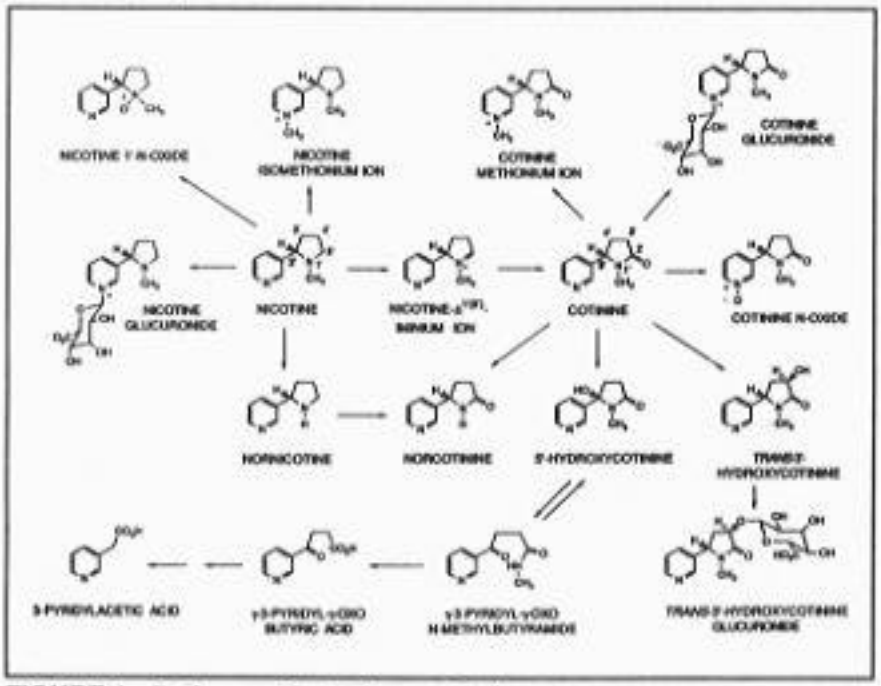

FIGURE 1. *Pathways of nicotine metabolism.*

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INDIVIDUAL VARIABILITY IN NICOTINE METABOLISM

Nicotine is metabolized via cytochrome P450 (CYP 450) to nicotine iminium ion, and then by aldehyde oxidase to cotinine (figure 1). Cotinine is the major proximate metabolite of nicotine, with 70 to 80 percent of nicotine metabolized to cotinine in most smokers (Benowitz and Jacob 1994). Cotinine is, in turn, metabolized to trans-3'-hydroxy-cotine, which is the most abundant nicotine metabolite in the urine of most smokers. Nicotine-N'-oxide is formed via a flavoprotein enzyme and is a minor metabolite, averaging about 4 percent of the systemic nicotine dose (Benowitz et al. 1994). Nicotine, cotinine, and trans-3'-hydroxycotinine are also conjugated (Benowitz et al. 1994; Byrd et al. 1992). Nicotine and cotinine form quaternary N-glucuronides, whereas trans-3'-hydroxycotinine forms an O-glucuronide (figure 1). Figure 2 shows the average pattern of nicotine metabolism and urinary recovery, based on a study in individuals receiving nicotine at steady state via transdermal nicotine patches. While this figure illustrates the average pattern, there is individual variability as shown in figure 3. Thus, for

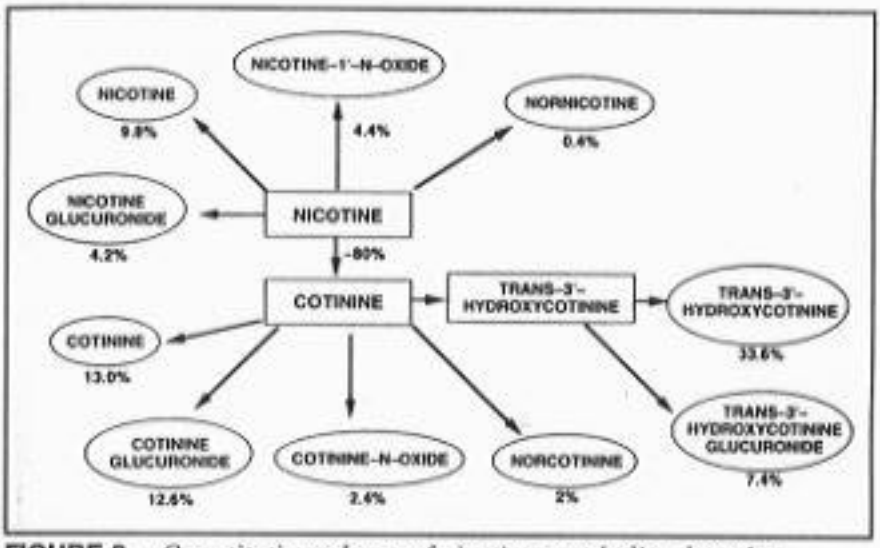

FIGURE 2. *Quantitative scheme of nicotine metabolism based on average excretion of metabolites as percent of systemic dose during transdermal nicotine application. Circled compounds indicate excretion in urine and associated numbers indicate associated percent of systemic dose of nicotine.*

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most individuals, trans-3'-hydroxycotinine is the most abundant metabolite in the urine, but cotinine is more abundant in others.

There is considerable variability in the extent of conjugation. Of note, the extent of conjugation of nicotine and cotinine within subjects is highly correlated, whereas there is no relationship between nicotine or cotinine conjugation and the extent of conjugation of trans-3'-hydroxy-cotinine. These data suggest that nicotine and cotinine are conjugated by the same enzyme, while trans-3'-hydroxycotinine is conjugated by a different enzyme.

These data show that there are considerable individual differences in the metabolism of nicotine. If metabolites contribute to nicotine addiction, individual variability in pattern of metabolism could explain some of the individual variability in susceptibility to nicotine addiction.

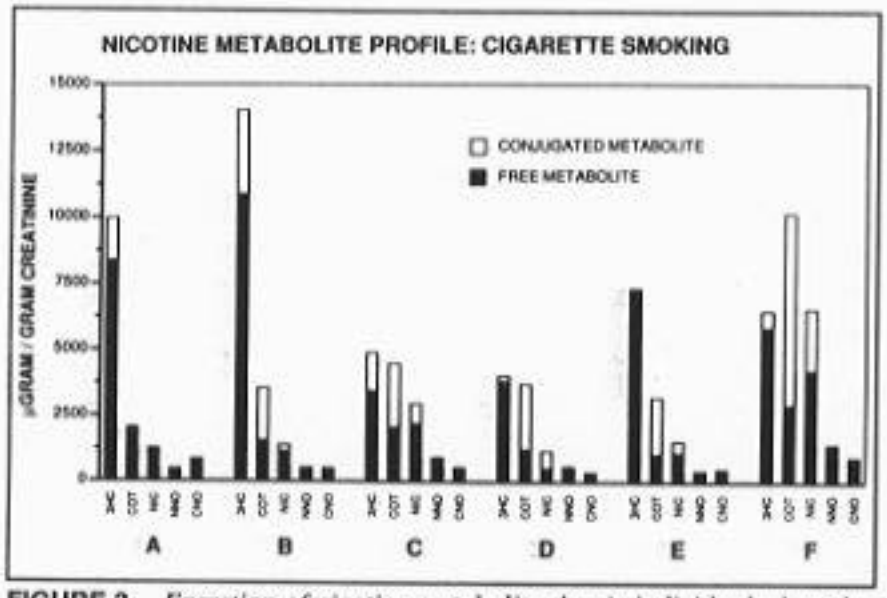

FIGURE 3. *Excretion of nicotine metabolites by six individuals, based on 24-hour urine collection during cigarette smoking.*

KEY: NIC = nicotine; COT = cotinine; 3HC = trans-3'-hydroxycotinine; NNO = nicotine-1'-N-oxide; CNO = cotinine-N-oxide.

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INDIVIDUAL VARIATION IN NICOTINE AND COTININE KINETICS

As expected by analogy to other weak bases that are extensively metabolized, there is considerable individual variability in the clearance of nicotine. Early studies on nicotine kinetics were performed by infusing nicotine in smokers who were abstinent from tobacco (Benowitz et al. 1982; Rosenberg et al. 1980). However, it is most relevant to investigate the disposition kinetics of a drug in the chemical environment where the drug is normally used. Using labeled compounds, one can study the metabolism and kinetics of nicotine in smokers while they are smoking. To do so, deuterium-labeled analogs of nicotine (3',3'-dideuteronicotine, nicotine-d_2) and cotinine (2,4,5,6-tetra-deuterocotinine, cotinine-d_4), both with the natural (S)-configurations, have been synthesized. Concentrations of natural and labeled nicotine and cotinine, as well as their metabolites, are measured by gas chromatography/mass spectrometry (GC/MS). Comparing the pharmacokinetics of labeled and natural compounds, the absence of an isotope effect was demonstrated, validating their use

in studies of nicotine and cotinine metabolic disposition (Benowitz and Jacob 1994; Jacob et al. 1991).

NICOTINE DISPOSITION IN SMOKERS AND NONSMOKERS

Cigarette smoke contains a variety of chemicals, including polycyclic aromatic hydrocarbons, that may affect the metabolism of various other drugs. For example, smokers are well known to have increased metabolic activity of liver CYP 1A2, which results in the accelerated metabolism of caffeine, theophylline, and other drugs (Dawson and Vestal 1982). Earlier research had suggested that smokers metabolize nicotine more rapidly than nonsmokers (Kyerematen et al. 1982, 1990). If true, this might be a significant factor in the natural history of tobacco addiction as a mechanism of metabolic tolerance. That is, the longer a person smoked, the faster nicotine would be metabolized; therefore, one would have to smoke more to maintain a desired nicotine level in the body.

The stable isotope technique described above was used to compare nicotine kinetics in smokers and nonsmokers (Benowitz and Jacob 1993). Labeled (S)-(-)-nicotine was infused intravenously for 30 minutes, and blood and urine samples were collected for 96 hours. Smokers and nonsmokers received the same low dose of nicotine (0.5 micrograms per kilogram per minute (g/kg/min)), and on another day the smokers also received a higher dose of nicotine (2.0 g/kg/min) that resulted in plasma nicotine concentrations similar to those they achieve with smoking. Nonsmokers are unable to tolerate this dose due to toxicity.

As shown in figure 4, nicotine levels were similar in smokers and nonsmokers. Pharmacokinetic analysis revealed that clearance was slightly but significantly greater in nonsmokers than smokers, while the steady-state volume of distribution and half-lives were similar among groups (figure 5). These findings indicate that smokers do not metabolize nicotine more rapidly than nonsmokers. In fact, the reverse appears to be true; cigarette smoking appears to inhibit the metabolism of nicotine. In any case, metabolic tolerance does not appear to be a factor in the natural history of tobacco addiction.

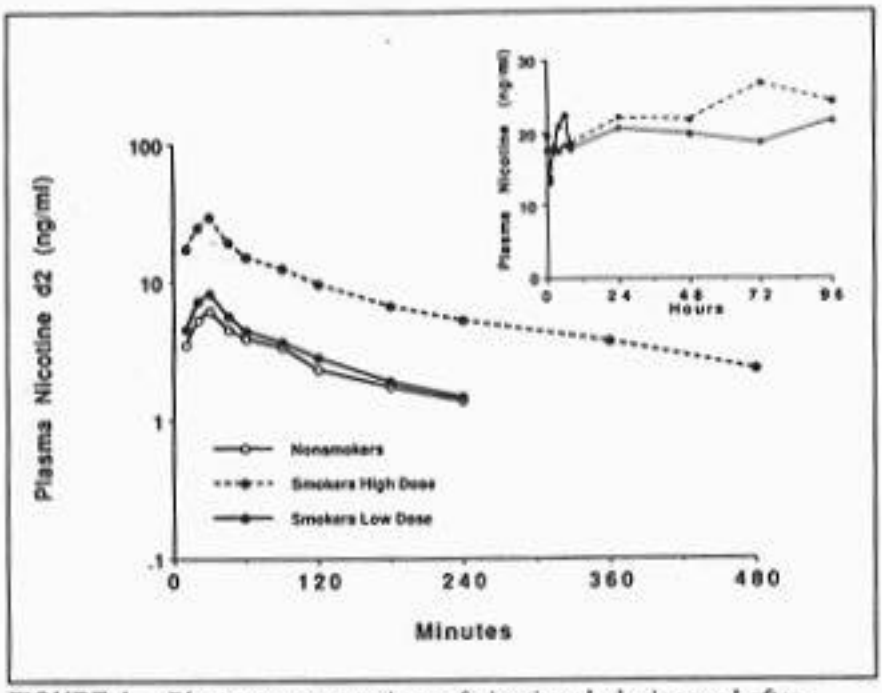

FIGURE 4. *Plasma concentrations of nicotine-d_2 during and after intravenous infusion of 0.5 µg/kg/min for 30 minutes in nonsmokers and smokers (low dose) and 2.0-µg/kg/min for 30 minutes in smokers (high dose). Inset shows plasma concentrations of natural nicotine derived from cigarette smoking during the course of the study. Data represent the mean of 11 subjects.*

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INDIVIDUAL DIFFERENCES IN THE METABOLISM OF NICOTINE TO COTININE

By simultaneously infusing labeled nicotine-d_2 and cotinine-d_4, and by measuring levels of cotinine-d_2 generated from nicotine-d_2, the fractional conversion of nicotine to cotinine can be determined (Benowitz and Jacob 1994). An example of data generated by such a study is shown in figures 6a and 6b. Using this approach in 20 smokers, it was determined that on average 72 percent of nicotine is converted to cotinine (range 55 to 92 percent) (figure 7). No differences in the clearances of nicotine or cotinine or the percentage of nicotine conversion to cotinine were seen

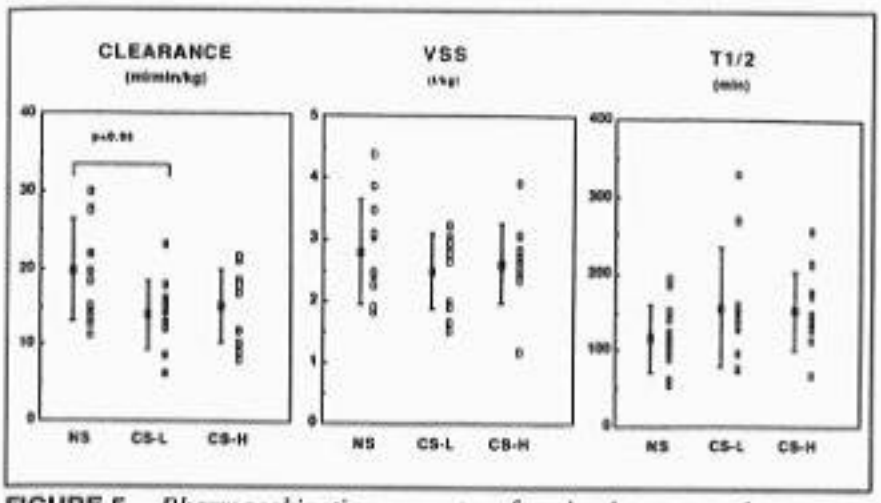

FIGURE 5. *Pharmacokinetic parameters for nicotine comparing nonsmokers, smokers receiving low dose intravenous nicotine, and smokers receiving high dose intravenous nicotine. Mean ± SD indicated next to each data set.*

KEY: Vss = steady state volume of distribution; t½ = half-life; NS = nonsmokers; CS-L = smokers receiving low dose nicotine; CS-H = smokers receiving high dose nicotine.

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when comparing data from men and women. As expected, clearances did vary among individuals, with coefficients of variation of 25 percent and 27 percent for clearances of nicotine and cotinine, respectively. The extent of individual variability and the percentage of nicotine conversion to cotinine was less, with a coefficient of variation of 12 percent.

Data on the fractional conversion of nicotine to cotinine and the clearance of cotinine for an individual can be used to compute a factor (K) that converts the steady-state plasma cotinine concentration to the intake of nicotine from smoking per day. The equation is:

$$D_{nic}\ (mg/24h) = K \times (\text{plasma COT})\ (ng/mL)$$

On average, K = 0.08 with a range of 0.47 to 0.102. The K factor, along with plasma cotinine levels, can be used to estimate daily intake of nicotine from active or passive smoking.

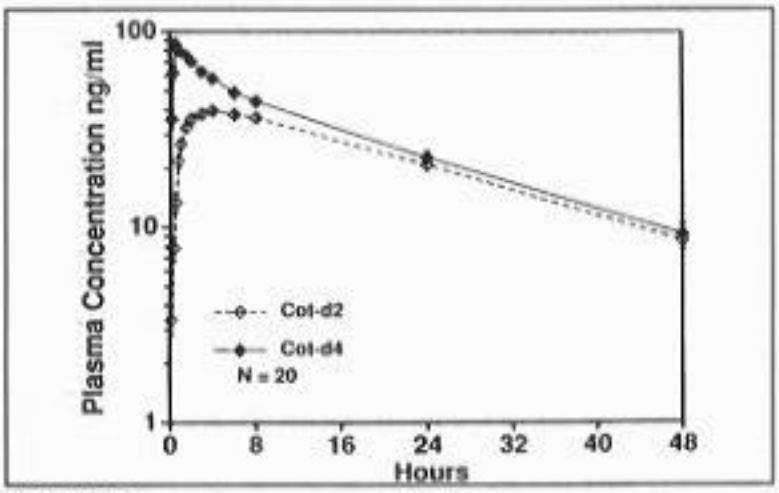

FIGURE 6a.

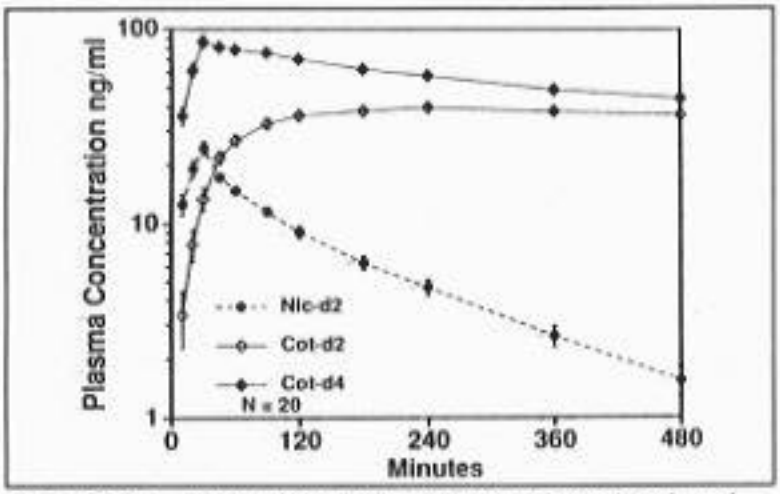

FIGURE 6b. *Mean plasma concentration of nicotine-d_2 and cotinine-d_4 during and after intravenous infusion of a 50:50 mixture of nicotine-d_2 and cotinine-d_4 (2 µg base/kg/min of each for 30 minutes, beginning at time zero). Figure 6a shows values up to 48 hours. Figure 6b shows values up to 480 minutes. Curves represent average values for 20 subjects.*

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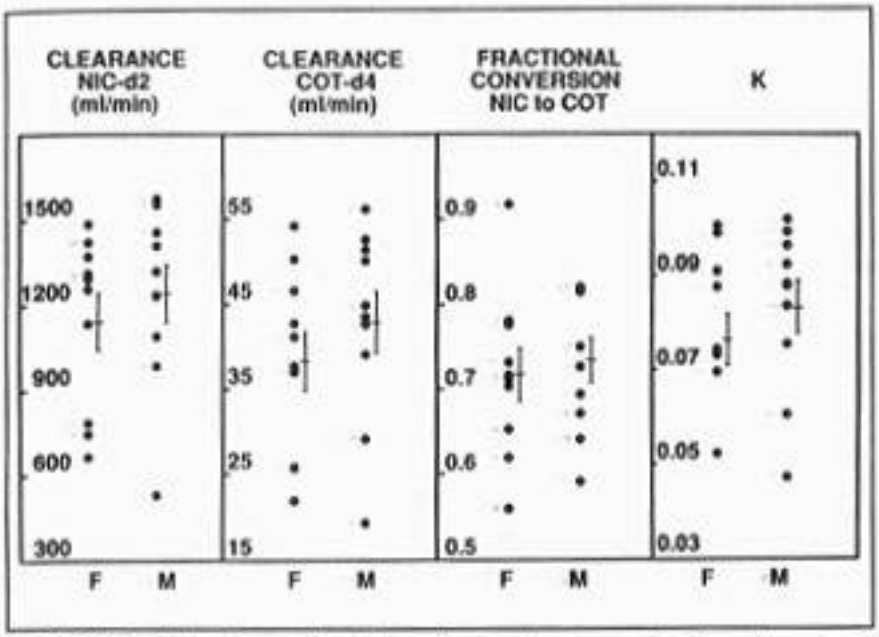

FIGURE 7. *Nicotine and cotinine plasma clearance, fractional conversion of nicotine to cotinine (F), and the factor that converts plasma cotinine concentration to daily intake of nicotine (K). Data are shown for individual subjects by gender. Bars indicate mean ± 95 percent confidence intervals.*

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Of note in the above study was the finding that the clearance of nicotine and the fractional conversion of nicotine to cotinine were significantly correlated (r = 0.59). This correlation suggests that cotinine is the most rapid or rate-limiting pathway for nicotine metabolism. Thus, people who metabolize nicotine via pathways other than those to cotinine are likely to have slower elimination of nicotine in general.

DEFICIENT C-OXIDATION OF NICOTINE

While most people metabolize nicotine extensively into cotinine, a few individuals have been identified who generate very little cotinine. One such person, a 57-year-old woman, was identified in a smoking cessation trial. The subject was found to have unexpectedly low plasma concentrations of cotinine, but normal concentrations of

nicotine (Benowitz et al. 1995*b*), both while smoking and while using nicotine patches. This individual was studied using a dual infusion of labeled nicotine and cotinine. As seen in figures 8a and 8b, little cotinine was generated from nicotine. The subject was found to convert only 9 percent of nicotine to cotinine, in contrast to the average 72 percent seen in the study described previously (Benowitz and Jacob 1994). This individual's clearance of nicotine was unusually low (6.5 mL/min/kg versus 17.2 mL/ min/kg in 20 controls), the half-life was abnormally long (348 versus 138 min), and the formation clearance of cotinine for this individual was exceedingly low (0.4 mL/min/kg) versus that seen in controls (12.1 mL/min/kg). The clearance and half-life of cotinine were, however, normal in this subject.

Thus, an individual with markedly deficient C-oxidation of nicotine has been identified. The liver enzymes responsible for C-oxidation of nicotine have not been fully characterized. In vitro studies suggested a role for CYP 2A6, 2D6, 2E1, and/or 2C9 (Cashman et al. 1992; Flammang et al. 1992; McCracken et al. 1992). Cholerton and colleagues (1994) reported five subjects with unusually high nicotine/cotinine ratios in the urine after oral nicotine who were genotypically homozygous for 2D6 mutations. They suggested that 2D6 is an important enzyme for nicotine metabolism. However, the subject described above was a normal metabolizer of dextromethorphan, and therefore a phenotypically normal metabolizer via CYP 2D6. Studies are ongoing to identify which enzymatic defects are responsible for deficient C-oxidation of nicotine.

The biological significance of deficient C-oxidation of nicotine is unclear, but could be considerable. Slow metabolizers of nicotine such as this subject might be expected to smoke fewer cigarettes and may be at less risk for smoking-related diseases linked to the consumption of cigarette smoke. On the other hand, the long half-life of nicotine may mean that nicotine levels persist at higher levels when the smoker is not smoking, and could lead to more severe physical dependence. In addition, if cotinine has significant biological activity that contributes to the pharmacologic effects of nicotine, people who do not generate cotinine will experience a different profile of pharmacologic effects from nicotine.

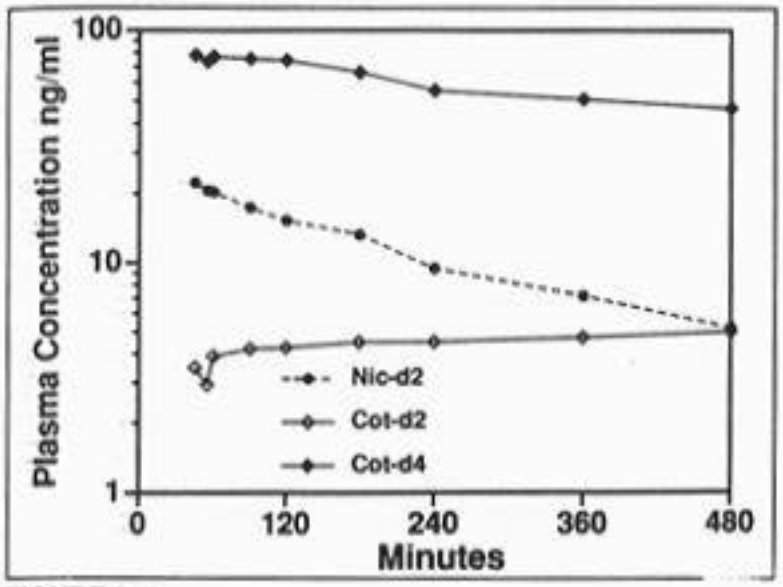

FIGURE 8a.

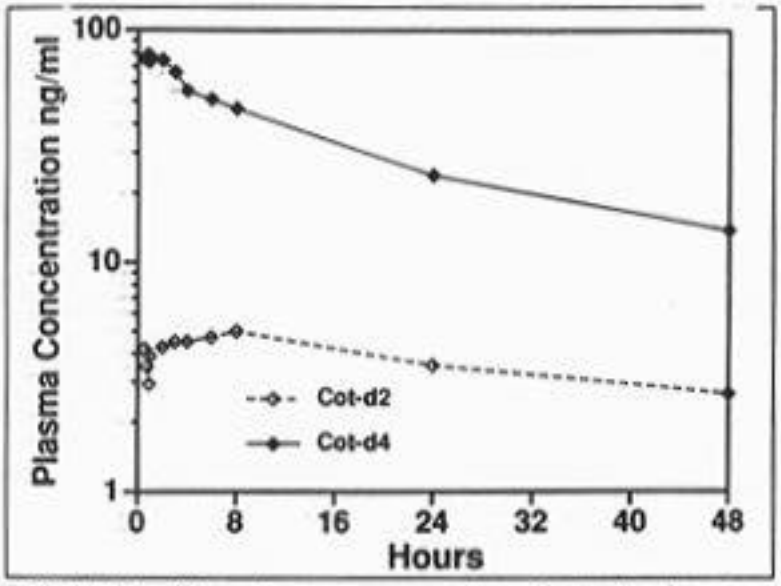

FIGURE 8b. *Mean plasma concentrations of nicotine-d_2, cotinine-d_2, and cotinine-d_4 during and after intravenous infusion of a 50:50 mixture of nicotine-d_2 and cotinine-d_4, as described in figure 6. Figure 8a shows values up to 480 minutes. Figure 8b shows values up to 48 hours.*

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ETHNIC DIFFERENCES IN NICOTINE AND COTININE METABOLISM

Ethnic differences in nicotine metabolism have been hypothesized to contribute to differences in health effects and/or susceptibility to addiction in blacks versus whites (Henningfield et al. 1990). The intriguing observation has been made that cotinine levels per cigarette smoked were significantly higher in blacks versus whites (Wagenknecht et al. 1990). In contrast, plasma levels of thiocyanate, a marker of exposure to cigarette smoke in general, were similar. There is also evidence that blacks have higher rates of lung cancer for any given level of cigarette smoking compared with whites (Satariona and Swanson 1988). Ethnic differences in the metabolism of nicotine or cotinine could help explain these observations.

To examine this issue, dual-labeled nicotine and cotinine infusions were administered to 40 black and 39 white smokers matched for age, gender, and self-reported cigarette consumption (Benowitz et al. 1995*a*). The clearance of nicotine and percentage of nicotine conversion to cotinine were similar for blacks and whites. However, the clearance of cotinine was significantly slower (0.56 versus 0.69 mL/min/kg) and the half-life of cotinine slightly longer (1,064 versus 950 min) in blacks versus whites. These data clarify at least in part the observation of higher cotinine levels when normalized for cigarette consumption in blacks. The implications of differences in cotinine metabolism regarding susceptibility to nicotine addiction or health consequences of smoking are still unclear.

SUMMARY AND CONCLUSION

Individual differences in susceptibility to nicotine addiction, the likelihood of successful smoking cessation, and the development of adverse health effects of smoking are well recognized. The basis for these individual differences is as yet unknown. This chapter examines individual differences in the metabolism and kinetics of nicotine as a possible factor.

Rare individuals appear to be deficient metabolizers of nicotine. Individual differences are described both in the pattern and rates of nicotine metabolism. Ethnic differences in cotinine metabolism have also been observed. However, the enzymes responsible for nicotine metabolism and their genetic regulation have not been fully characterized. Understanding the basis for individual differences in nicotine kinetics and metabolism, and linking these differences to

pharmacodynamic studies, may provide important clues for the prevention and treatment of nicotine and possibly other drug addictions.

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