Nicotine Dependence Associated with Functional Variation in FMO3

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A common haplotype of the flavin-containing monooxygenase gene FMO3 is associated with aberrant mRNA splicing, a two-fold reduction in in vivo nicotine N-oxidation and reduced nicotine dependence. We determined the effects of common variants in FMO3 on plasma levels of nicotine-N-oxide in 170 European Americans administered deuterated nicotine. The polymorphism rs2266780 (E308G) was associated with N-oxidation of both orally administered and ad libitum smoked nicotine. In vitro, the FMO3 G308 variant was not associated with reduced activity, but rs2266780 was strongly associated with aberrant FMO3 mRNA splicing in both liver and brain. Surprisingly, in treatment-seeking European American smokers (n=1558) this allele was associated with reduced nicotine dependence, specifically with a longer time to first cigarette, but not with reduced cigarette consumption. Since N-oxidation accounts for only a small percentage of hepatic nicotine metabolism we hypothesized that FMO3 genotype affects nicotine metabolism in the brain or that nicotine-N-oxide itself has pharmacological activity. We demonstrated nicotine N-oxidation in human brain, mediated by FMO3 and FMO1, and show that nicotine-N-oxide modulates human α4β2 nicotinic receptor activity in vitro. These results indicate possible mechanisms for associations between FMO3 genotype and smoking behaviors, and suggest nicotine N-oxidation as a novel target to enhance smoking cessation.