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Mini Review Open Access

Biochemistry of nicotine metabolism and its significance to lung cancer

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Abstract

Nicotine is the key addictive constituent of tobacco. It is not a carcinogen, but it drives smoking and the continued exposure to the many carcinogens present in tobacco. The investigation into nicotine biotransformation has been ongoing for more than 60 years. The dominant pathway of nicotine metabolism in humans is the formation of cotinine, which occurs in two steps. The first step is cytochrome P450 (P450, CYP) 2A6–catalyzed 5′-oxidation to an iminium ion, and the second step is oxidation of the iminium ion to cotinine. The half-life of nicotine is longer in individuals with low P450 2A6 activity, and smokers with low activity often decrease either the intensity of their smoking or the number of cigarettes they use compared with those with "normal" activity. The effect of P450 2A6 activity on smoking may influence one's tobacco-related disease risk. This review provides an overview of nicotine metabolism and a summary of the use of nicotine metabolite biomarkers to define smoking dose. Some more recent findings, for example, the identification of uridine 5′-diphosphoglucuronosyltransferase 2B10 as the catalyst of nicotine N-glucuronidation, are discussed. We also describe epidemiology studies that establish the contribution of nicotine metabolism and CYP2A6 genotype to lung cancer risk, particularly with respect to specific racial/ethnic groups, such as those with Japanese, African, or European ancestry. We conclude that a model of nicotine metabolism and smoking dose could be combined with other lung cancer risk variables to more accurately identify former smokers at the highest risk of lung cancer and to intervene accordingly.

Keywords: P450lung Ancermetabolismuridine 5′-diphospho-glucuronosyltransferase (UDP-glucurono; syltransferase) Cancer; Nicotine; Cotinine; Smoking

Description

CYP2A6

Nicotine is not a carcinogen but is arguably the compound present in tobacco with the greatest influence on a smoker's cancer risk. Nicotine sustains tobacco addiction and continued smoking Upon inhalation, nicotine enters the circulation by way of the lungs. It then travels to the brain where it readily diffuses into the tissue and stereoselectively binds to nicotinic cholinergic receptors. This results in the release of dopamine, which mediates the pleasurable experience of smoking. The time between inhaling a puff of tobacco smoke and the release of dopamine is a few seconds. Each puff contains more than 70 identified carcinogens, many of which contribute to the risk of a smoker developing lung cancer. Biological effects of the noncarcinogenic toxicants present in tobacco smoke are also involved. These cocarcinogenic and tumor-promoting compounds contribute to the well-established mechanism of tobacco carcinogenesis. However, the entire process is dependent on nicotine. When the nicotine content of a cigarette is reduced below an addictive level, very few individuals continue to smoke these cigarettes [1].

The study of nicotine metabolism began primarily in the purview of chemists, who identified, characterized, and quantified nicotine metabolites in the blood and urine of multiple species. This effort took off in the late 1950s and early 1960s. In 1959, cotinine was identified as the principal nicotine metabolite in the urine of smokers. While a hydroxycotinine metabolite was detected in the early study, it was more than 25 years later that *trans* 3′-hydroxycotinine was characterized and found to be the major urinary nicotine metabolite. About 5 years after that, cotinine glucuronide was identified and determined to be equally or more abundant than cotinine in a smoker's urine. The quantification of cotinine plus these two metabolites led to the realization that cotinine formation by nicotine 5′-oxidation was the critical pathway for the elimination of nicotine in smokers . Prior to this, the *N*-oxidation of nicotine was believed to be as important or possibly more important than 5′-oxidation in the detoxification of nicotine [2].

Overview of nicotine metabolism

Two nicotine metabolism pathways are common to all mammals, 5′-oxidation, and *N*-oxidation. Studies have been carried out in many mammalian systems, from humans to mice and more than 20 nicotine metabolites have been identified. Several comprehensive reviews are available that discuss much of this work.

In humans, nicotine is metabolized by three primary pathways: P450-catalyzed 5′-oxidation, UGT-catalyzed *N*-glucuronidation, and flavin monooxygenase (FMO)–catalyzed *N*′-oxidation. The $^{\Delta 1',5'}$-iminium ion product of nicotine 5′-oxidation is further metabolized to cotinine. The formation of cotinine is quantitatively the most important nicotine metabolism pathway. Three minor pathways: methylation of the pyridine nitrogen to the nicotine isomethonium ion, 2′-oxidation, and oxidative *N*-demethylation also contribute to nicotine metabolism.

Cotinine, like nicotine is metabolized by three major pathways: 3′-oxidation to *trans* 3′-hydroxycotinine, cotinine *N*-glucuronidation, and cotinine *N*-oxidation. In contrast to nicotine, the *N*-oxidation of cotinine occurs on the pyrrolidine nitrogen not the pyridine nitrogen, and the catalyst of this reaction is a P450 enzyme not an FMO. 3′-Hydroxycotinine is further metabolized to its O-glucuronide

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conjugate. Minor metabolites of cotinine include 5′-hydroxycotinine and norcotinine [3].

Nicotine metabolites excreted by smokers

In addition to cotinine, 12 urinary nicotine metabolites have been identified. The pathways that give rise to these metabolites are presented , and the names of the compounds are boxed. A 14th possible urinary metabolite, 5′-hydroxycotinine, is shown; the name is in a dashed box since the concentration of this compound in urine has only been reported in a review article . The estimated percent of each metabolite in the urine of smokers who are not deficient in P450 2A6 or UGT2B10 are presented. These estimates are updated based on more recent data and slightly modified from those presented in the review by Hukkanen. The importance of P450 2A6 and UGT2B10, the predominant catalysts of nicotine and cotinine oxidation and *N*-glucuronidation, to overall nicotine metabolism is discussed later in separate sections [4].

In smokers, eight metabolites (nicotine *N*-oxide, nicotine glucuronide, cotinine, cotinine glucuronide, cotinine *N*-oxide, 3′-hydroxycotinine, 3′-hydroxycotinine glucuronide, and 4-hydroxy-4-(3-pyridyl)butanoic acid (hydroxy acid)) plus unmetabolized nicotine account for >90% of the nicotine dose. The other five nicotine metabolites that have been quantified each account for <1 or 2% of the nicotine metabolites excreted by a smoker. These minor metabolites are discussed briefly here. Nornicotine and norcotinine are both found in the urine of smokers, but norcotinine was not detected in the urine of individuals administered cotinine However, Hukkanen *et al.* reported in unpublished data that smokers administered D_4-cotinine excreted D_4-norcotinine. Also, norcotinine is a major product of P450 2A6–catalyzed cotinine metabolism *in vitro*. Norcotinine is found in the urine of dogs administered nornicotine, and nornicotine is a very minor metabolite of P450 2A6–catalyzed nicotine metabolism. It is unclear from these data if the norcotinine excreted by smokers is a product of cotinine or nornicotine metabolism; both pathways are presented in. Nornicotine is present in tobacco smoke, and a portion of the nornicotine in smokers is from that exposure The urinary concentration of the nicotine isomethonium ion was quantified in smoker's urine but has rarely been measured by others. The most recently identified nicotine metabolite, 3′-hydroxynorcotinine could be a product of norcotinine oxidation or it might form by the demethylation of 3′-hydroxycotinine. It is unknown if one or both pathways occur in smokers [5].

4-Oxo-4-(3-pyridyl)butanoic acid (keto acid), the precursor of hydroxy acid, is a minor urinary nicotine metabolite in smokers, but the sum of these two acids accounts for as much as 15% of the nicotine dose excreted In dogs and rats, keto acid and hydroxy acid are metabolites of cotinine and are proposed to form from 5′-hydroxycotinine or norcotinine but neither norcotinine nor hydroxy acid has been detected in humans administered cotinine Human liver microsomal metabolism of nicotine by 2′-oxidation generates keto acid therefore, this pathway of keto acid and hydroxy acid formation is illustrated in.

In smokers not deficient in P450 2A6 activity, 75% to 80% of the nicotine dose is metabolized to cotinine and its metabolites = However, each smoker's urinary nicotine metabolite profile depends on the relative abundance and activity of the enzymes involved. Significant differences in the relative frequency of genetic variants of P450 2A6 (gene *CYP2A6*) across racial/ethnic groups result in variation in the urinary nicotine metabolite profile *B*) of smokers from these groups Smokers of Japanese ancestry have a high frequency of low or no activity of *CYP2A6* alleles, and this is reflected in the reduced proportion of nicotine metabolized by 5′-oxidation. In individuals who are homozygous for *CYP2A6*∗4, a deletion allele, nicotine 5′-oxidation is a minor pathway, and the percentage of nicotine excreted unchanged increases, as does nicotine metabolism by *N*-glucuronidation and/or **N**-oxidation [6].

Conclusion

This review provides a comprehensive overview of nicotine metabolism; a summary of the use of biomarkers to define smoking dose; and an overview of molecular epidemiology studies of *CYP2A6* genotype, nicotine metabolism, and the risk of lung cancer across different racial/ethnic groups. The discussion of nicotine metabolism is focused on new findings published since 2005 on metabolites and enzyme catalysts, including P450 2A6, UGT2B10, and to a lesser extent FMOs. Nicotine is not a carcinogen, but it is the critical constituent of tobacco that drives continued smoking. The lung cancer studies described are presented to delineate the importance of *CYP2A6* to nicotine and tobacco exposure. Together these very different avenues of research have furthered our understanding of the relative contribution of P450 2A6 activity to an individual smoker's lung cancer risk.

Acknowledgement

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Conflict of Interest

None

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