NICOTINE METABOLISM IN THE HUMAN BODY

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Introduction. An understanding of the pharmacology of nicotine and how nicotine produces addiction and influences smoking behavior provides a necessary basis for therapeutic advances in smoking cessation interventions. This chapter provides a review of several aspects of the human pharmacology of nicotine. These include the presence and levels of nicotine and related alkaloids in tobacco products, the absorption of nicotine from tobacco products and nicotine medications, the distribution of nicotine in body tissues, the metabolism and renal excretion of nicotine, nicotine and cotinine blood levels during tobacco use or nicotine replacement therapy, and biomarkers of nicotine exposure [1].

Materials and methods. Analysis of experimental data from practical medicine, US Public Health Service grants and from the National Institute on Drug Abuse, National Institutes of Health, and carried out at the General Clinical Research Center at San Francisco General Hospital Medical Center with support of the Division of Research Resources, National Institutes of Health.

Results and discussion. Nicotine is extensively metabolized to a number of metabolites by the liver. Six primary metabolites of nicotine have been identified. Quantitatively, the most important metabolite of nicotine in most mammalian species is the lactam derivative, cotinine. In humans, about 70–80% of nicotine is converted to cotinine. This transformation involves two steps. The first is mediated primarily by CYP2A6 to produce nicotine-Δ1′ (5′)-iminium ion, which is in equilibrium with 5′-hydroxynicotine. The second step is catalyzed by a cytoplasmic aldehyde oxidase. Nicotine iminium ion has received considerable interest since it is an alkylating agent and, as such, could play a role in the pharmacology of nicotine [2]. In addition to oxidation of the pyrrolidine ring, nicotine is metabolized by two nonoxidative pathways, methylation of the pyridine nitrogen giving nicotine isomethonium ion and glucuronidation. Nicotine glucuronidation results in an N-quaternary glucuronide in humans. This reaction is catalyzed by uridine diphosphate-glucuronosyltransferase enzymes producing (S)-nicotine-N-β-glucuronide. About 3–5% of nicotine is converted to nicotine glucuronide and excreted in urine in humans.

Oxidative N-demethylation is frequently an important pathway in the metabolism of xenobiotics, but this route is, in most species, a minor pathway in the metabolism of nicotine. Conversion of nicotine to nornicotine in humans has been demonstrated. We found that small amounts of deuterium-labeled nornicotine are excreted in the urine of smokers administered deuterium-labeled nicotine. Metabolic formation of nornicotine from nicotine has also been reported. Nornicotine is a constituent of tobacco leaves. However, most urine nornicotine is derived from metabolism of nicotine with less than 40% coming directly from tobacco, as estimated from the difference in nornicotine excretion in smokers during smoking and transdermal nicotine treatment (0.65 and 0.41%, respectively) [3]. 2′-Hydroxylation of nicotine was shown to produce 4-(methylamino)-1-(3-pyridyl)-1-butanone with 2′-hydroxynicotine as an intermediate. 2′-Hydroxynicotine also yields

nicotine-Δ1′(2′)-iminium ion. 4-(methylamino)-1-(3-pyridyl)-1-butanone is further metabolized to 4-oxo-4-(3-pyridyl)butanoic acid and 4-hydroxy-4-(3-pyridyl)butanoic acid. The new pathway is potentially significant since 4-(methylamino)-1-(3-pyridyl)-1-butanone can be converted to carcinogenic NNK. However, endogenous production of NNK from nicotine has not been detected in humans or rats.

Although on average about 70–80% of nicotine is metabolized via the cotinine pathway in humans, only 10–15% of nicotine absorbed by smokers appears in the urine as unchanged cotinine. Six primary metabolites of cotinine have been reported in humans: 3′-hydroxycotinine, 5′-hydroxycotinine (also called allohydroxycotinine), which exists in tautomeric equilibrium with the open chain derivative 4-oxo-4-(3-pyridyl)-N-methylbutanamide, cotinine N-oxide, cotinine methonium ion, cotinine glucuronide, and norcotinine (also called demethylcotinine).

3′-Hydroxycotinine is the main nicotine metabolite detected in smokers' urine. It is also excreted as a glucuronide conjugate. 3′-Hydroxycotinine and its glucuronide conjugate account for 40–60% of the nicotine dose in urine. The conversion of cotinine to 3′-hydroxycotinine in humans is highly stereoselective for the trans-isomer, as less than 5% is detected as cis-3′-hydroxycotinine in urine. While nicotine and cotinine conjugates are N -glucuronides, the only 3′-hydroxycotinine conjugate detected in urine is O-glucuronide [4].

Quantitative aspects of the pattern of nicotine metabolism have been elucidated fairly well in people (Fig. 1). Approximately 90% of a systemic dose of nicotine can be accounted for as nicotine and metabolites in urine. Based on studies with simultaneous infusion of labeled nicotine and cotinine, it has been determined that 70–80% of nicotine is converted to cotinine. About 4–7% of nicotine is excreted as nicotine N′–oxide and 3–5% as nicotine glucuronide. Cotinine is excreted unchanged in urine to a small degree (10–15% of the nicotine and metabolites in urine). The remainder is converted to metabolites, primarily trans–3′–hydroxycotinine (33–40%), cotinine glucuronide (12–17%), and trans–3′–hydroxycotinine glucuronide (7–9%).

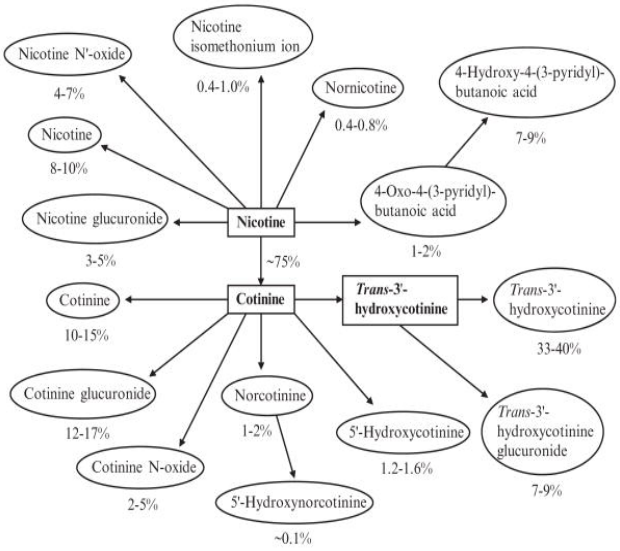

Fig. 1. Quantitative scheme of nicotine metabolism, based on estimates of average excretion of metabolites as percent of total urinary nicotine.

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ELDERBERRY AS A DIETARY SUPPLEMENT FOR IMMUNE HEALTH

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Introduction. *Sambucus nigra* L., also called elderberry is a traditional herbal medicine. Studies have shown that elderberry extracts contain a lot of active compounds and have been used since ancient times. These days elderberry is included in dietary supplements as an extract and are used to support immune health because of their antiviral, antibacterial effect [1]. Elderberry supplements are produced in a variety of formulations. Syrups is one of the forms which are widely used not just for children but also in adults. It is a pharmaceutical form that is easy to dose and has high bioavailability.

Aim. To analyze *Sambucus nigra* dried and frozen fruits extracts with the aim of identifying the extract with the highest amount of bioactive compounds for the use in the formulation of syrup.

Materials and methods. Dried and frozen fruits of elderberries were extracted with 50 % v/v ethanol using ultrasound assisted extraction. Quality parameters were determined using UV spectrophotometer. Total phenolic content was measured by Folin-Ciocalteu method, the amount of phenolics was expressed in gallic acid equivalents (mg/g GAE). Antioxidant activity was measured using 2,2-diphenyl-1-picrylhydrazyl free radical, results expressed in inactivation %. Anthocyanins were determined by the pH-differential method and results were expressed in mg/g.

Results. The highest yields of phenolic compounds were obtained by using dried elderberries which contained 53.93 mg/g GAE. Extract with frozen fruits contained 6.46 mg/g GAE. The DPPH method also showed higher results for dried elderberries. Extracts with dried fruits have a high antioxidant activity, inactivation of DPPH was 74.82 % while frozen berries inactivation of DPPH was 56.61 %. Comparing results between dried fruits and frozen, the amount of anthocyanins is higher in dried fruits extract 12.20 mg/g while frozen fruits extract was 1.98 mg/g.

Conclusions. The highest amount of bioactive compounds was determined in liquid extract made from dried *Sambucus nigra* fruits. The high antioxidant activity of elderberry fruit is associated with the amount of active compounds. These results showed that dried berries are more suitable for syrup production.

References:

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