ROLE OF MICROSOMAL CYTOCHROME P-450-CONTAINING MONOOXYGENASES IN THE METABOLISM AND TOXICITY OF CERTAIN ALKALOIDS

RAMESH R. DALVI and RONALD H. JONES*
Toxicology Program, Tuskegee University, Tuskegee, Alabama 36088, U.S.A.
*Division of Toxicology, Medical Research Institute, Florida Institute of Technology, Melbourne, Florida 32901, U.S.A.

ABSTRACT

The acute or chronic exposure to alkaloids has been shown to cause toxic manifestations ranging from neurotoxicity, hepatotoxicity, carcinogenicity to teratogenicity. Being exogenous substances, most of these compounds are metabolized in body by the hepatic microsomal drug-metabolizing enzyme system. And still, in many cases it remains unknown whether the parent compound or its biologically transformed metabolite is responsible for the major toxic effects of an alkaloid. Only during the past two decades, investigators have really begun to look into this aspect of the toxicology of alkaloids. This short review discusses studies reported on the hepatic microsomal mixed function oxidase catalyzed biotransformation of several alkaloids and its consequences on the ability of liver to metabolize other xenobiotics.

INTRODUCTION

ALKALOIDS are natural substances which are basic or "alkali-like" in reaction and occur in many plants, probably in 5–10% of all plant species. More than 6000 alkaloids have been identified, characterized and given names. They are mostly complex molecules containing nitrogen base, and have bitter taste. Most of them are extremely toxic to man and animals. Nevertheless, many of them possess desirable pharmacological and medicinal properties. In addition to their intentional use as therapeutic drugs, alkaloids may be ingested by man and animals when plant foods, particularly grain and oil seeds, are contaminated by seeds of alkaloid-containing weeds and also through the consumption of herbs as food supplements or in herbal tea[1]. Although their characteristic bitter taste is protective, in many plants they occur largely as N-oxides which are not bitter to the taste. Another important hazard from plant alkaloids to man arises from the widespread use of certain alkaloids as stimulant or narcotic drugs.

The acute or chronic exposure to these natural compounds has been shown to cause various toxic manifestations ranging from neurotoxicity, hepatotoxicity, carcinogenicity to teratogenicity[2–5]. In most cases, it remains unknown whether the parent compound or its biologically transformed metabolite is responsible for the major toxic effects of an alkaloid. Despite the fact that alkaloids being exogenous to the body are expected to be metabolized by the hepatic microsomal monooxygenases, only very few of them such as nicotine, colchicine and reserpine have been studied in detail for their microsomal metabolism[6–11]. It is evident from the literature search that very little is known about the microsomal metabolism of many other common alkaloids. Because of their importance as food and feed contaminants and their usefulness in medicine, metabolic studies of alkaloidal compounds are important, especially to understand the toxicologic implications of their biotransformation. In view of this need, we have examined a number of alkaloids for their metabolism by rat liver microsomes[12–15]. The purpose of this short review is to summarize and present available data on the biotransformation of various alkaloids by hepatic microsomal monooxygenases.

Nicotine

Pharmacological properties of nicotine have been known for many years and it is by far the most extensively studied alkaloid for its metabolism in mammals. Nicotine is a substrate for liver microsomal enzymes and is oxidized mainly to cotinine by liver microsomes[6, 16–17]. Liver preparations from various species have also been shown to catalyze the oxidation of nicotine to nicotine-1′-oxide, an important N-oxide of nicotine, which supposedly plays a key role in

nicotine-induced cancer[6]. Other metabolic products of microsomal metabolism of nicotine include nornicotine and formaldehyde[18]. Formaldehyde as a metabolic product of nicotine is formed during its N-demethylation by liver microsomes[13]. The metabolite nicotine-1′-oxide is further reduced to an amine by microsomal cytochrome P-450-containing monooxygenases[6, 19], which is regarded as an activated metabolite of nicotine since it is involved in tumor formation. While some reports indicate that nicotine is an inducer of microsomal enzymes[12, 16], others[3] show no increase in the activity of microsomal enzymes after nicotine treatment. Like the metabolism of pyrrolizidine alkaloids, a species difference in the microsomal metabolism of nicotine has been observed. For example, nicotine is metabolized by monkeys much faster than dogs probably because the monkey has two-fold more cytochrome P-450 than do dogs[8].

Colchicine

Because of its usefulness as a drug in gout therapy for many centuries, investigators were interested since long in knowing the metabolism and mechanism of action of this highly toxic alkaloid. Axelrod[20] first reported the appearance of small amounts of formaldehyde as a metabolic product of colchicine after incubation with rat liver microsomes, which is confirmed by our findings that colchicine undergoes 0-demethylation by rat liver microsomes[13]. A deacetylation of colchicine in human metabolism was later described by Walaszek *et al*[21]. When incubated with liver microsomes isolated from rat, mouse and hamster, colchicine has been shown to undergo oxidative 0-demethylation at C2, C3 and C10 positions[9]. According to these investigators[9], this microsomal metabolism of colchicine is enhanced after induction of the enzymes by phenobarbital, 20-methylcholanthrene and colchicine itself. However, in our experiments, pretreatment of rats resulted in an increased pentobarbital sleeping time suggesting colchicine may impair metabolism of other drugs given simultaneously with colchicine[12]. Schnell *et al*[22] report that one of the metabolites of colchicine, 0-demethylcolchicine, plays a peculiar role in protecting reduced glutathione and several other sulphydryl enzymes from oxidation.

Pyrrolizidine Alkaloids

Pyrrolizidine alkaloids have been found in as many as 352 plant species, some of which have been traditionally used as food or medicine for man and animals[23]. Many, though not all, of the pyrrolizidine alkaloids are hepatotoxic. Hepatotoxicity of these alkaloids has been attributed to their pyrrol metabolites formed during their liver metabolism[24]. The metabolic products of pyrrolizidine alkaloids have a higher alkylating potential and are necrogenic as compared to the parent alkaloids[25–27]. Involvement of hepatic microsomal monooxygenases in the metabolism and toxicity of a pyrrolizidine alkaloid monocrotaline has been recently shown by Lafranconi and Huxtable[28] who found that liver metabolism of the alkaloid in rats was enhanced by pretreatment with phenobarbital and decreased by the administration of SKF 525-A. Although pyrrolizidine alkaloids are bioactivated by the liver microsomal enzymes, a species difference in the metabolism has been noted by Mori *et al*[29]. For example, phenobarbital induction of microsomal enzymes increases the susceptibility of rats but not of sheep to the alkaloid toxicity. In addition, monocrotalilne is metabolized faster in livers from male rats than female rats suggesting a sex difference in the biotransformation of pyrrolizidine alkaloids.

Caffeine

Caffeine is an alkaloid found in as many as 63 plant species and is probably the most widely used socially acceptable drug ranking next to alcohol and tobacco[30]. It is primarily metabolized in the liver by microsomal enzymes through N-demethylation and oxidation to 1-methyluric acid and 1-methylxanthine[31–32]. A species difference in the metabolism of caffeine has also been noted. While the microsomal metabolism of caffeine is enhanced by phenobarbital pretreatment and smoking, it is decreased during some antibiotic therapy and disease conditions[30].

Reserpine

This alkaloid is used as an antihypertesive drug which is also metabolized by an NADPH, oxygen-dependent mixed function oxidase of the hepatic microsomal drug-metabolizing enzyme system[11]. It can both be metabolized by and serve as a competitive inhibitor for drug-metabolizing enzymes[12, 33]. Reserpine was able to increase microsomal enzyme activity after a single injection to rats and stimulate aniline biotransformation more than that of reserpine[11]. This suggests that this alkaloid has a potential for altering the efficacy and toxicity of other co-administered drugs.

Cocaine

Cocaine, a potent CNS stimulant, is metabolized by liver microsomal enzymes and the work of Evans and Harbison[34] and Thompson *et al*[35] suggests that a metabolite of cocaine, rather than cocaine itself, is responsible for hepatotoxic manifestations in mice. This hepatotoxicity of cocaine is enhanced by phenobarbital pretreatment and decreased by pretreatment of mice with metyrapone[36]. In addition to its N-demethylation by mouse liver microsomes, cocaine is also hydrolyzed by plasma cholinesterase[37]. However, whether the hydrolytic products of cocaine are substrates for the microsomal enzymes is not known. It is pointed out that metabolic biotransformation of cocaine also results in the depression of cytochrome P-450, probably by cocaine or its metabolite/s. According to a recent study by Peterson and Knodell[38], the cocaine-induced toxic liver injury may be prevented by concomitant administration of ascorbic acid.

Morphine

Morphine and its principal derivative heroin are opium alkaloids mostly used as narcotic analgesics. Morphine is metabolized by liver microsomal enzymes to N-demethylated products and repeated administration of morphine to male rats results in marked depression of morphine N-demethylation[39]. Other studies have shown that morphine not only decreased N-demethylation of analogous drugs, but it also decreased N-demethylation of aminopyrine and hydroxylation of hexobarbital[40].

Sanguinarine

Sanguinarine is an alkaloid predominantly found in the seeds of the plant Argemone mexicana, which are common contaminants of grains and mustard seeds in the tropics[1,41]. The alkaloid has been reported to cause numerous outbreaks of human poisoning known as epidemic dropsy. It is a hepatotoxic alkaloid and may be metabolized by microsomal enzymes through N-demethylation and oxidation[13]. It has been reported that it prolongs pentobarbital sleeping time in rats, inhibits microsomal N-demethylase activity, and causes significant loss of hepatic cytochrome P-450[12,14].

Emetine

Emetine is one of the important drugs used in the treatment of intestinal and hepatic amebic infestations[42]. Unlike other alkaloids, emetine does not appear to be metabolically transformed in the body and is slowly excreted unchanged in feces and urine[43]. This observation confirms our findings that emetine is not a substrate for microsomal demethylase enzyme[13]. These data suggest that unlike reserpine, emetine is unlikely to compete with various other substrates for the hepatic drug-metabolizing enzymes for its own metabolism. However, it has been reported to be an inhibitor of protein synthesis and perhaps that is why it inhibits the activity of liver microsomal enzymes when given to experimental animals[12,43].

Other Alkaloids

Several other alkaloids have interactions with the hepatic drug-metabolizing enzyme system and may have direct or indirect impact on the human and animal health. For example, solanine, a potato alkaloid, has been found to be an inhibitor of microsomal enzymes and also to cause hepatotoxicity[15]. Similarly, our studies have shown that while boldine is an inhibitor of the liver microsomal enzymes, brucine, strychnine, and scopolamine are inducers of and metabolized by the liver enzymes[12]. Pilocarpine is an alkaloid of pharmacologic importance and has been found to inhibit markedly the microsomal drug-metabolizing enzyme activities for several compounds[44]. On the other hand, theophylline is metabolized by microsomal enzymes and its metabolism is enhanced in tobacco and marijuana smokers due to the enzyme induction[45].

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