Effects of Ethanol on Cocaine Metabolism and Disposition in the Rat

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COABUSE OF COCAINE AND ALCOHOL

Abuse of cocaine in combination with other drugs is a widespread practice (Washton and Gold 1987) and the coabuse of alcohol is particularly common, with 99 percent of cocaine addicts reporting excessive use of ethanol in one study (Newcombe and Bentler 1987). Simultaneous ingestion of ethanol also is common, as reported by 77 percent of cocaine users (Grant and Harford 1990). Thirty percent of cocaine users ingest alcohol during almost every episode of cocaine use (Jones 1987).

Why these two drugs are so frequently coadministered is not clearly understood. Potentiation of cocaine-related euphoria by alcohol ingestion may be the basis for this behavior and is consistent with increased plasma ethanol concentrations observed when cocaine is administered after alcohol ingestion (Farré et al. 1993; Perez-Reyes and Jeffcoat 1992). Alcohol ingestion also is reported to diminish undesirable side effects, such as cocaine-induced migraine-like headaches (Weiss et al. 1988). Additionally, coadministration may be influenced by the settings in which cocaine and alcohol are abused. Regardless of the motive for combined use of cocaine and ethanol, this practice is of clinical concern, as it increases the risk of cocaine-related morbidity (Adams et al. 1987; Kreek 1987; Kreek and Stimmel 1984) and mortality (Kreek 1987; Rose et al. 1990). Epidemiological data indicate that simultaneous alcohol ingestion may increase the risk of cocaine-related sudden death by eighteenfold (Rose et al. 1990).

COCAINE METHYL ESTERASE AND ETHYL TRANSFERASE

The rapid clearance of cocaine is in large part mediated by hydrolysis of the methyl ester group. This reaction produces benzoylecgonine (figure 1), a metabolite devoid of cocaine-like psychomotor activity

(Misra et al. 1975; Spealman et al. 1989). While hydrolysis of cocaine to benzoylecgonine occurs spontaneously (Stewart et al. 1979), the slow rate of this reaction at physiological pH (Taylor et al. 1976) does not account for the relatively large percentage of cocaine recovered from urine as benzoylecgonine (Cook et al. 1985). A nonspecific carboxylesterase with cocaine methyl esterase activity was identified in human liver (Dean et al. 1991) and was subsequently purified and characterized (Bosron, this volume; Brzezinski et al. 1994). Under in vitro conditions using purified human liver carboxylesterase, ethanol was found to inhibit cocaine methyl esterase activity, decreasing hydrolysis to benzoylecgonine (Brzezinski et al. 1994; Dean et al. 1991). In the presence of ethanol, this same carboxylesterase catalyzed the ethyl transesterification of cocaine to cocaethylene (benzoylecgonine ethyl ester) (figure 1) (Bosron, this volume; Brzezinski et al. 1994; Dean et al. 1991).

EFFECTS OF ETHANOL ON THE DISTRIBUTION OF COCAINE AND METABOLITES

Cocaine metabolism and disposition following acute ethanol administration were studied in the rat to determine if the in vitro effects of ethanol on cocaine methyl esterase and ethyl transferase activities had significance in vivo (Zachman et al. 1993). The rat was used as it possesses both ethyl transferase and methyl esterase activities, is frequently employed for behavioral and toxicity studies of cocaine, and the size provides sufficient tissue for analytical work. This study was designed to address three questions. First, do significant concentrations of cocaethylene form and accumulate in tissues with controlled coadministrations of cocaine and alcohol? Second, does ethanol administration significantly diminish the hydrolysis of cocaine to benzoylecgonine and methanol, as occurs in vitro when cocaine and ethanol are coincubated with purified human liver carboxylesterase (Brzezinski et al. 1994; Dean et al. 1991)? Third, does ethanol inhibition of cocaine methyl ester hydrolysis increase the N-oxidative metabolism of cocaine, as noted when rodents are pretreated with nonspecific esterase inhibitors (Thompson et al. 1979)?

Male Wistar rats were pretreated with 2.5 grams (g) ethanol per kilogram (kg) bodyweight in water or an equal volume of water via an indwelling intragastric catheter. Sixty minutes after pretreatment, 10 milligrams (mg)/kg cocaine was infused through an indwelling intravenous (IV)

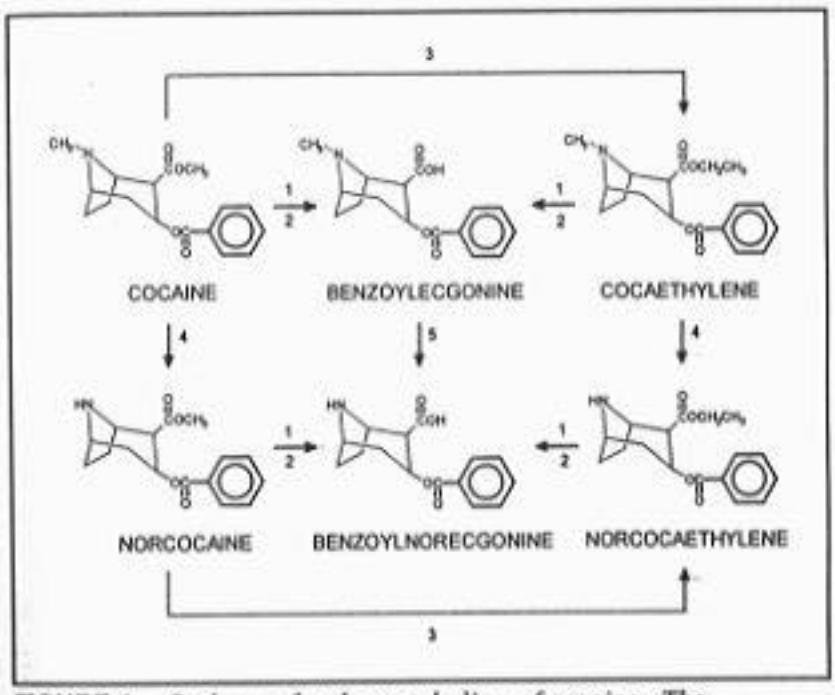

FIGURE 1. *Pathways for the metabolism of cocaine. The metabolism of cocaine and its metabolites involves at least three different classes of reactions: hyhrolysis, transesterification, and N-demethylation. The rapid enzymatic hydrolysis of cocaine and cocaethylene to benzoylecgonine (Dean et al. 1991) and norcocaine and norcocaethylene to benzoylnorecgonine (Dean, unpublished observations) are catalyzed by a carboxylesterase present in human liver (1). Slow, spontaneous hydrolysis of the methyl or ethyl esters of these compounds also occurs (2). Ethanol inhibits the methyl esterase-catalyzed hydrolytic reactions (1) and simultaneously causes the same carboxylesterase to catalyze the ethyl transesterification of cocaine to cocaethylene (Dean et al. 1991) and norcocaine to norcocaethylene (Dean, unpublished observations) (3). N-demethylation of cocaethylene to norcocaethylene occurs in isolated rat liver hepatocytes (Dean, unpublished observations) and rat and human liver microsomes (Dean, unpublished observations)(4).*

catheter. Animals were sacrificed 2.5 to 60 minutes after cocaine administration and serum and solid tissues were harvested for measurement of cocaine, cocaethylene, benzoylecgonine, norcocaine, norcocaethylene, and benzoylnorecgonine.

ALCOHOL-DEPENDENT FORMATION OF COCAETHYLENE

Cocaethylene was detected in all tissues from alcohol-pretreated animals, as previously observed following intraperitoneal (IP) coadministration of cocaine and alcohol (Dean et al. 1992). Based on area under the concentration curves (AUCs) from 2.5 to 60 minutes, the amount of cocaethylene in liver and lung was 14 and 11 percent of the measured cocaine, respectively. Peak cocaethylene concentrations in liver, lung, and kidney were noted within 2.5 minutes after cocaine administration, the earliest time point for specimen collection. These observations answered the first question, demonstrating cocaethylene formation sufficient to contribute to the combined effects of cocaine and ethanol. Cocaethylene AUCs in heart, brain, spleen, and serum were less than 2 to 4 percent of the cocaine AUCs, and peak cocaethylene concentrations in these tissues occurred approximately 10 minutes after cocaine administration.

The relatively high AUCs and rapid peak for cocaethylene in liver, lung, and kidney suggest that cocaethylene formation occurs predominantly in these tissues with subsequent distribution to other tissues. This conclusion was supported by direct measurement of cocaine ethyl transferase activity in tissue homogenate supernatants. Ethyl transferase activity, determined by measuring cocaethylene formation in the presence of saturating levels of cocaine and ethanol, was confirmed in rat liver, lung, heart, and kidney. When normalized for protein content in tissue homogenate supernatants, the relative activity in these tissues decreased in the order listed.

The relative distribution of rat cocaine ethyl transferase activity was consistent with the distribution of immunoreactive protein as determined by gel electrophoresis and Western blot analysis using rabbit anti-human cocaine ethyl transferase antibody. No ethyl transferase activity was identified in brain, spleen, or serum. When rat cocaine ethyl transferase activity was normalized for whole organ volume, liver exhibited activity that was 33-fold greater than that in lung and in excess of 600-fold greater than that in kidney and heart. Formation and accumulation of cocaethylene in liver is of potential concern; this ethylated metabolite undergoes N-demethylation to norcocaethylene and produces cocaine-like cytotoxicity in cultured rat hepatocytes (Boelsterli et al. 1993; Dean et al. 1992) and the intact mouse (Roberts et al. 1992).

Formation and accumulation of cocaethylene is thought to alter the subjective effects and enhance the toxicity of cocaine when used in combination with beverage alcohol. Support for this hypothesis is based on the following evidence. First, cocaethylene has been identified in urine, blood, brain, and liver obtained at autopsy from individuals succumbing after combined exposure to cocaine and ethanol (Hearn et al. 1991*a*; Hime et al. 1991; Jatlow et al. 1991; Rafla and Epstein 1979; Smith 1984). This metabolite was also detected in the blood of emergency room patients seeking treatment after combined use of cocaine and ethanol (Jatlow et al. 1991). Similarly, ethanol-dependent accumulation of cocaethylene in serum and plasma was noted following controlled coadministration of cocaine and ethanol, when the cocaine was known to be free of contaminants, including cocaethylene (de la Torre et al. 1991; Farré et al. 1993; McCance-Katz et al. 1991; Perez-Reyes and Jeffcoat 1992; Perez-Reyes 1994). Second, when administered under controlled conditions, cocaethylene produced similar but milder and more pleasurable subjective effects than cocaine (Peres-Reyes 1993). Comparable affinity of cocaethylene and cocaine for the dopamine transporter in human striatal membranes may explain similarities in the subjective effects of these two drugs (Hearn et al. 1991*a*), while lower cocaethylene affinity for serotonin uptake sites and the norepinephrine transporter might explain differing subjective effects. Third, controlled administration of cocaethylene in humans produced tachycardia comparable to that induced by cocaine (Perez-Reyes 1993). However, cocaethylene is a more potent blocker of cardiac sodium channels in guinea pig ventricular myocytes (Xu et al. 1994) and of muscarinic receptor-stimulated phosphoinositide metabolism in the rat (Tan and Costa 1994), and has a greater negative ionotropic effect in isolated ventricular myocytes from ferret (Qiu and Morgan 1993). If true in humans, cocaethylene may increase the risk of conduction and contractile disturbances in the heart. Finally, the median lethal dose for cocaethylene in the mouse was significantly less than that for cocaine (Hearn et al. 1991*b*; Katz et al. 1992).

ALCOHOL INHIBITION OF BENZOYLECGONINE FORMATION

Ethanol pretreatment of rats dramatically decreased the AUCs for benzoylecgonine in all tissues and serum. This in vivo effect is consistent with in vitro ethanol inhibition of carboxylesterase-catalyzed cocaine hydrolysis to benzoylecgonine and methanol. Although ethanol decreased AUCs for benzoylecgonine in all tissues, the time to peak benzoyl-ecgonine concentrations was variable. In liver, peak concentrations occurred 2.5 minutes after cocaine administration, suggesting high hepatic methyl esterase activity. By contrast, benzoylecgonine levels in serum continued to rise over the entire 60 minutes of the experiment and likely reflect redistribution of this polar metabolite. The distribution of cocaine methyl esterase activity in rat tissues was determined by directly measuring the enzymatic hydrolysis (total minus spontaneous) of cocaine to benzoylecgonine in homogenate supernatants. Methyl esterase activity was identified in kidney, liver, lung, heart, and brain. When normalized for tissue protein, the relative amount of cocaine methyl esterase activity decreased in the order listed. When normalized for whole organ volume, hepatic cocaine methyl esterase activity was 15-fold to 100-fold greater than the activity in other tissues. No such activity was detected in spleen or serum. The presence of cocaine methyl esterase activity and absence of ethyl transferase activity in brain, plus poor correlation between these two activities in other tissues, suggest that more than one enzyme catalyzes these two reactions in the rat. Although a single carboxylesterase is known to catalyze both reactions in humans (Brzezinski et al. 1994; Dean et al. 1991), it is not known if other human enzymes possess cocaine methyl esterase or ethyl transferase activities.

Although lacking psychomotor activity, benzoylecgonine recently was shown to be a more potent vasoconstrictor of cerebral arteries in cat and sheep than cocaine (Covert et al. 1994; Madden and Powers 1990; Schreiber et al. 1994). Similarly, benzoylecgonine increased mean blood pressure with no effect on heart rate or QRS duration in the anesthetized rat (Erzouki et al. 1993). By contrast, cocaine decreased mean blood pressure and heart rate and increased the QRS duration. These different cardiovascular effects of cocaine and benzoylecgonine appear to reflect differing activity within the autonomic nervous system. Unlike cocaine, which produces vasoconstriction by blocking catecholamine reuptake, benzoylecgonine-induced vasoconstriction appears to be mediated predominantly by stimulation of $_1$-adrenergic receptors (Schreiber et al. 1994). Although cause and effect have yet to be established, a temporal relationship exists between recurrent coronary artery

vasoconstriction and increasing blood benzoylecgonine concentrations in humans (Brogan et al. 1992). Similarly, increasing benzoylecgonine concentrations might contribute to the migraine-like vasospastic headaches observed in cocaine users (Satel and Gawin 1989). If so, alcohol ingestion might diminish vasoconstriction of cerebral, coronary, and possibly other vascular beds by inhibiting cocaine methyl esterase activity and benzoylecgonine production. This effect might well contribute to combined use of cocaine and ethanol.

ALCOHOL EFFECT ON N-OXIDATIVE METABOLISM OF COCAINE

In humans, N-demethylation of cocaine to norcocaine is catalyzed by a cytochrome P-450 enzyme either directly or following oxidation of cocaine to cocaine N-oxide by a flavin-adenine dinucleotide (FAD)-containing mono-oxygenase (figure 1, 4) (Kloss et al. 1983). The N-demethylation of benzoylecgonine to benzoylnorecgonine was demonstrated in the rat following administration of radiolabeled benzoylecgonine (figure 1, 5)(Misra et al. 1975).

In animals pretreated with ethanol, metabolism of cocaine to norcocaine and benzoylnorecgonine increased, as reflected by higher tissue AUCs, as compared with those receiving water. Ethanol pretreatment also resulted in measurable levels of norcocaethylene in liver and lung. These observations are consistent with the increased hepatotoxicity (presumably due to enhanced N-oxidative metabolism) observed when mice were exposed to cocaine or cocaethylene and the esterase inhibitor diazinon (Roberts et al. 1992; Thompson et al. 1979). This shift toward N-oxidative metabolism provides a mechanism to explain potentiation of cocaine hepatotoxicity by ethanol (Jover et al. 1991). Detection of norcocaethylene in ethanol- pretreated rats is consistent with norcocaethylene detected in the hair of heavy cocaine users, suggesting common pathways including hydrolysis, transesterification, and N-demethylation (figure 1) (Cone et al. 1991).

ALCOHOL EFFECTS ON COCAINE DISPOSITION

Ethanol pretreatment had variable effects on AUC curves for cocaine from tissue to tissue. Ethanol increased the AUC for cocaine in liver and decreased the AUC for cocaine in serum and the heart. Ethanol pretreatment had little or no effect on the AUCs for cocaine in brain, lung, kidney, and spleen. While lower tissue benzoylecgonine AUCs

support the notion that alcohol inhibits cocaine methyl esterase activity, variable effects of ethanol on cocaine AUCs suggest that the effects of ethanol are not fully explained by inhibition of methyl esterase activity and simultaneous initiation of ethyl transferase activity. The increased AUC for liver and decreased AUC for serum might be explained by increased hepatic extraction of cocaine when coadministered with ethanol. It is not clear how this might occur, but ethanol-mediated vasodilation could increase hepatic blood flow (Orrego et al. 1988; Shaw et al. 1977), which is typically limited by the vasoconstricting effects of cocaine (Garhart et al. 1989). Alternatively, oxidative metabolism of ethanol might decrease the intracellular pH and enhance trapping of cocaine in hepatocytes.

CONCLUSION

It is not known why coabuse of cocaine and ethanol is so common. Similarly, the specific mechanisms by which ethanol potentiates cocaine-related morbidity and mortality are not clearly defined. The studies reviewed in this chapter suggest that multiple effects of ethanol on cocaine metabolism may be contributory. In particular, ethanol inhibition of cocaine methyl esterase may slow normally rapid inactivation of cocaine to benzoylecgonine while simultaneously initiating ethyl transesterification to cocaethylene and increasing N-demethylation to norcocaine. Although acute ethanol exposure did not uniformly increase serum and tissue cocaine AUCs, the collective increase in the levels of the psychoactive compounds cocaine, cocaethylene, norcocaine, and norcocaethylene may enhance or prolong cocaine-related euphoria and toxicity. Additionally, unique and/or relative differences in the activities of these metabolites may contribute to the effects of ethanol on the pharmacokinetics and pharmacodynamics of cocaine. More extensive characterization of the enzymes responsible for cocaine metabolism and the development of pharmacokinetic and pharmacodynamic models for cocaine will facilitate efforts to understand the interactions of this drug with alcohol.

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ACKNOWLEDGMENTS

This chapter was prepared with support from National Institute on Drug Abuse grant DA-08215.

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