Cocaethylene
What Is It?

In this issue of the Journal, Thompson and Dasgupta describe the use of microwave irradiation to drive the derivatization of cocaine, its ethyl homologue and the major cocaine metabolites, benzoylecgonine and ecgonine methyl ester. Although more needs to be done to characterize the reaction, this interesting approach may have broad applications to the analysis of drug metabolites and other biologic compounds with appropriate functional groups. Also in this issue, Bailey has described the binding of cocaine and its ethyl homologue to serum proteins. While its binding to alpha-1-acid glycoprotein and albumin, respectively, appears to be qualitatively similar to other basic drugs, cocaine appears to be less highly bound. Knowledge of binding to plasma proteins is fundamental to the understanding of the clinical pharmacology of any drug. What then do these two articles unexpectedly have in common? The authors of each saw fit to incorporate cocaethylene into their respective studies, and to cite it in the title. Because this compound is of relatively recent interest and may be unfamiliar to many readers of the two articles, a brief discussion of its neuropharmacologic properties and possible clinical significance may be helpful.

Most cocaine users concurrently ingest ethanol. Indeed, the comorbidity for alcoholism among cocaine abusers is reported to be twice that for heroin users. Street users indicate that ethanol ingestion improves the cocaine experience in various ways. It turns out that when cocaine and ethanol are used together, cocaine is transesterified in the liver to form its ethyl homologue, cocaethylene, actually the ethyl ester of benzoylecgonine. The hepatic enzyme that catalyzes this pathway is reported to be the same as that responsible for the hydrolysis of cocaine to benzoylecgonine. Although concentrations of cocaethylene are relatively modest following administration of single doses of cocaine and ethanol to human subjects, concentration in forensic and emergency room specimens can exceed those of cocaine.

This active metabolite shares many neurochemical and behavioral properties with cocaine. It has an equal affinity for the dopamine transporter, blocks uptake of dopamine into presynaptic neurons, and increases concentrations of dopamine at the synaptic cleft, all properties that are thought to play a role in drug reinforcement. Like cocaine, cocaethylene increases locomotor activity in rodents and is self-administered by nonhuman primates. Some studies suggest that cocaethylene may even be more lethal than the parent compound. Interestingly, cocaethylene is much less potent than cocaine at the serotonin uptake site, and thus is a more selective indirect dopamine agonist.

Administration of cocaine and ethanol to human volunteers produces an enhancement of the cocaine high that cannot be explained by the additive effects of the two substances. When administered directly to human by the intranasal route, cocaethylene, like cocaine, increases heart rate, and evokes a euphoria that subjects cannot distinguish from that produced by cocaine. Cocaethylene appears to be eliminated more slowly than cocaine, and thus might be expected to accumulate during a binge, which is consistent with analyses of forensic and clinical samples.

Is cocaethylene clinically important and does it contribute to the consequences of combined cocaine, ethanol abuse? Based on current experimental and clinical data, one can reasonably speculate that it may. Moreover, cocaethylene’s similarities and dissimilarities to cocaine may provide some additional insights into the neurochemical basis for cocaine’s actions. Regardless, cocaethylene is a cocaine-like pharmacologically potent metabolite that is found at significant concentrations in the blood of many cocaine abusers. Thus, it seems plausible to consider it in the design of studies of the type reported in this issue.

PETER JATLOW, MD
Department of Laboratory Medicine
Yale University School of Medicine
New Haven, Connecticut

REFERENCES

Cocaethylene: What Is It?


