Discussion of the Fate and Metabolism of Some Hallucinogenic Indolealkylamines

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Ever since Woolley and Shaw suggested that 5-HT had some function in mental processes on the basis of an *in vitro* interaction between 5-HT and the hallucinogenic indole derivative lysergic acid diethylamide (LSD) in 1954 (*Science*, **119**, 587), there has been considerable interest in exploring this hypothesis in two major directions. The interest in the role of 5-HT in neural processes is clearly demonstrated by the excellent papers on the subject presented by the distinguished international panel on this symposium.

The other direction—the one Woolley and Shaw's hypothesis has led to—was the exploration of the mechanism of action of hallucinogenic indolealkylamines, the study of their metabolism and their interaction with 5-HT metabolism. Drs. Holmstedt, Ahlborg, and Lingren have presented convincing evidence that the main acidic metabolite of a probably hallucinogenic compound, 5-methoxy-*N*-dimethyltryptamine (5-MeO-DMT) is the corresponding acid. It is unfortunate that they did not study the bases excreted in the urine. In cur experience DMT and diethyltryptamine (DET) are metabolized to the 6 OH-dialkyl derivatives and excreted as glucuronides of the same.

We ourselves have been engaged in similar studies ever since we have shown that simple *N*-alkylated derivatives of tryptamine (DMT, DET and dipropyltryptamine (DPT) are hallucinogenic in man. We have shown that these compounds are metabolized through 6-hydroxylation, dealkylation, and deamination to form the corresponding intermediates.

In rodents 6-hydroxylation is a major pathway, but in man it is a minor one (between 5–20% of the administered drug was found in the urine as 6-hydroxy metabolites). We have suggested that 6-hydroxylation might be a pathway to form psychotropically active metabolites, but 6-OHDMT—one of the metabolites of DMT—was shown to be practically inactive in man. It is of interest, however, that, if 6-hydroxylation is prevented by substituting a fluoro atom in the 6-position of the indole ring, the resulting compound (6-FDET) is not hallucinogenic when compared with the parent compound DET in the same dose, in the same subjects.

This finding, together with earlier findings that the individual rate of 6-hydroxylation correlated fairly well with the individual intensity of hallucinogenic reaction, suggests that 6-hydroxylation might be necessary but not sufficient to account for the psychotropic action. Accordingly, last year we proposed that besides 6-hydroxylation another pathway, *N*-dealkylation, might also be important in producing the active metabolite. This proposal was based on the finding that 6-OHDMT is a poor substrate for the dealkylating microsomal enzyme but DMT was about 6 times as good a substrate for the same enzyme. It is interesting that psilocin, the 4-OHDMT, is also a better (2–3 times as good) substrate for the dealkylating enzyme than 6-OHDMT.

So the search for the active metabolite goes on, and Dr. Holmstedt and his collabora-

tors' paper reveals that in the case of 5-MeO-DMT the behavioral action is more likely due to the unchanged drug rather than to a metabolite.

But this compound is distinctly different from the other hallucinogenic indolealkylamines since it seems to produce tremors at a much smaller dose level than DMT does.

I would like to see, however, psychological and metabolic studies in man with 5-MeO-DMT before final conclusions can be drawn concerning this question.

The search for active metabolites is greatly hampered by the lack of an easy and reliable test for hallucinogenic activity. The behavioral tests in animals are not specific. Woolley and Shaw's hypothesis may be useful in developing a biochemical test, but to look for a metabolic effect in the whole brain is probably misleading and this meeting is a living testimony to the sharp regional differences within small areas of the brain.

Perhaps a more selective, quantitative, regional method which could measure drug effects *in vivo* would be more helpful in finding a specific metabolic test for hallucinogenic activity.

Recent work in our laboratory by D. Morton, A. Aikens, and myself indicates that such a test might not be far away.