Hallucinogenic effects and metabolism of tryptamine derivatives in man

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I BECAME INTERESTED IN THE POSSIBILITY of hallucinogenic action of alkylated tryptamine derivatives in 1955, when I read about the chemical analysis of a snuff powder prepared by Haitian natives from Piptadenia Peregrina seeds which they used in religious ceremonies to produce mystical states of mind which enabled them to communicate with their gods. The chemical analysis by Fish, Horning and Johnson revealed the presence of bufotenin and a small amount of N,N-dimethyltryptamine (DMT) (7).

The hallucinogenic action of bufotenin was reported by Fabing. It was suggested that the psychological action of the snuff powder (called Cohoba) was primarily due to its bufotenin content (6).[1] In 1955, there was no information available whether DMT had similar psychotropic activity.

A relatively simple synthesis, published by Speeter and Anthony, made it possible for us to synthetize DMT and a few higher homologues (14). After toxicity studies in animals, we started to study the psychotropic activity of DMT, first on normal volunteers, and then on patients. The results were reported at the time (4, 9, 13, 15, 16) and were confirmed by other independent investigators (3, 19); therefore, I will restrict myself to mentioning only a few pertinent features.

a) The first and perhaps most striking feature of the effect of DMT is the extremely rapid onset of the symptoms (2–5 min after the intramuscular injection of 1 mg/kg in normal volunteers) and the very short duration of action (40–50 min) in contrast to the 4–10 hr duration of similar symptoms produced by LSD_{25}, or mescaline. This clinical feature pointed to the probability of a very rapid metabolism of the drug and to a more direct action on the CNS.

b) Another important observation was that there was a very striking individual variation in the reaction to the drug, both in the intensity and the symptomatology, after giving it to each subject in the same dose.

The variation in the intensity seems to be very closely related to the individual variation in the metabolism of the drug. This will be discussed later. First, however, I would like to say a few words about the variation in the symptomatology of the drug effect in general.

It is well known that the phenomenology of the psychotropic drug effect, and I am talking here not only about DMT, but DET,[2] mescaline, LSD, and psilocybin as well, depends on many factors.

One group of factors lies in the personality of the subject. These personality variables were comprehensively reviewed recently by Lindemann and Felsinger (10). Different individuals, even with the same mental condition, may react differently to any one of the drugs. These differences not only show themselves in the superficial structure of the changes produced, but reach down deeper into the personality and determine the levels which these effects may reach.

The other group of factors which influence the picture are situational ones. The drug effect is different when it is given in a psychotherapeutic setting (1, 5), in a dark room with maximal sensory deprivation (12), in a pleasant living room without any special "directing" activity (8), or during a religious ceremony.

It is interesting to note that in a psychotherapeutic situation, or sometimes without any structuring of the experiment, these drugs unlock the doors to memory, past experiences—and, it has even been suggested by Abramson (2) to the inborn images of the unconscious. On many occasions, the experience has been described to go even deeper. Defying the conventional categories of space and time, the subjects take long journeys into very vivid, hallucinatory experiences, and become aware of deep philosophical, transcendental, and mystical problems with concomitant deep emotional reactions. Sometimes it seems to me that "mysticomimetic" would be a much more appropriate designation for these compounds than the widely-used, but unjustified, name "psychosomimetic."

But let us return to more earthy realities, to the problem of the relationship between the intensity of the

[1] The hallucinogenic activity of bufotenin, however, has recently been questioned by Turner (19), and independently by H. Isbell (personal communication).

[2] N,N-diethyltryptamine.

drug reaction and the metabolism of the drug, particularly DMT, DET, and α-MT.

In Fig. 1 it can be seen that DMT is metabolized in two main directions. One direction is dealkylation and oxidative deamination, which leads to the formation of indolylacetic acid (3-IAA). The other way is 6-hydroxylation, followed mainly by conjugation and to a slight extent dealkylation and oxidative deamination leading to 6-HIAA. The metabolic route for DET is essentially the same, leading to the excretion of 3-IAA and 6-HDET glucuronide as the end products of the two major pathways.

It is interesting to note that one of these enzymatic steps, namely, the 6-hydroxylation, increases rather than decreases the psychotropic activity of the parent compound. In a series of animal experiments with Dr. Hearst, we have shown that 6-HDET has a significantly lower behavioral threshold in rats, pigeons, and monkeys in a variety of experimental situations using operant conditioning techniques (18). Since this is a unique feature among the various known hallucinogenic drugs, and since it has very interesting implications due to the close similarity in chemical structure to normally occurring compounds like tryptamine and serotonin, we paid extra attention to the enzymatic process of 6-hydroxylation. The results of these enzymatic studies were presented in a separate paper at an intersociety neuropharmacology session of this meeting (17).

In animal experiments we learned that the individual variation in threshold doses of DET is very closely related to the individual variation in the 6-hydroxylation of the drug (18). We suspected that the same metabolic factor, the rate of 6-hydroxylation, is responsible, too, for the individual differences in the intensity of the psychological reactions to DET in man. Therefore, we investigated the correlations between the intensity of the psychological reaction to this drug and the metabolism, especially 6-hydroxylation.

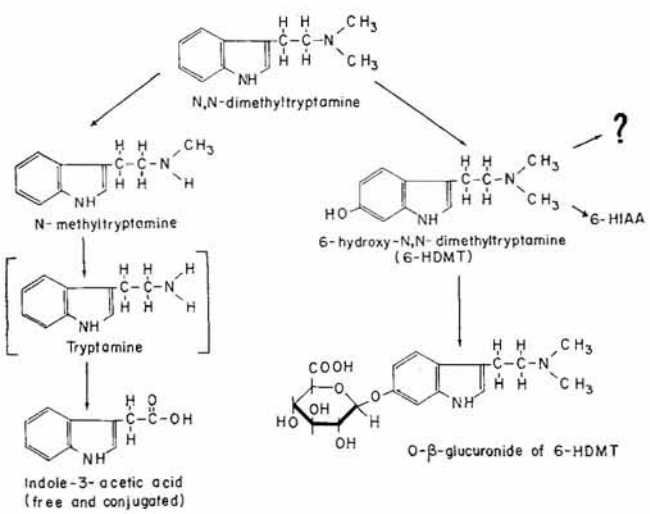

FIG. 1. Metabolic pathways of N,N-dimethyltryptamine in mammals.

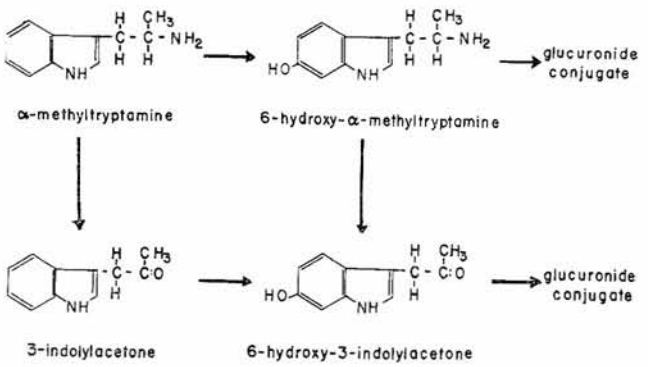

FIG. 2. Metabolic pathways of α-methyltryptamine in rats.

The DET was administered in the same dose (1 mg/kg) to ten normal volunteers, scoring the subjective and objective symptoms, and, at the same time, collecting the urine for quantitative determination of the excreted 6-HDET as a measure of the 6-hydroxylating ability of the individual organism.

The results, which are to be presented at the Third World Congress of Psychiatry in Montreal, confirmed our hypothesis derived from the animal studies, namely that subjects excreting more 6-HDET in the urine showed much more intense reaction to the drug than those excreting less 6-HDET. This result points again to the importance of 6-hydroxylation in producing the psychological effects of a hallucinogenic drug in man and invites speculation on whether or not the same reaction plays a role in producing psychotic 6-hydroxy derivatives from normally occurring indole derivatives, like tryptamine.

One would be tempted to assume that under specific circumstances, as in those experimental situations which are described in this symposium by Dr. Kety, or in the experiments of Drs. Brune and Pscheidt, when an increase in the concentration of tissue tryptamine occurs, there is a chance that a portion of tryptamine could be hydroxylated to form 6-hydroxy-tryptamine (6-HT). But 6-HT, having a lipid solubility similar to 5-HT, probably does not cross the blood-brain barrier readily, and one would not expect that 6-HT could produce CNS symptoms.

The situation, however, is not quite so unpromising. There is another compound which might give us some information in this matter. Another simple tryptamine derivative, α-methyltryptamine (α-MT), produces LSD-like symptoms which develop more slowly and last longer than the symptoms of DMT or DET intoxication and are slightly different as well (11). We found that α-MT is metabolized according to the following scheme (Fig. 2).

As will be seen, α-MT can be hydroxylated to form 6-HO-α-MT, then deaminated to 6-hydroxy-indolylacetone, or deamination occurs first, followed by 6-hydroxylation, to form the same compound. We found that

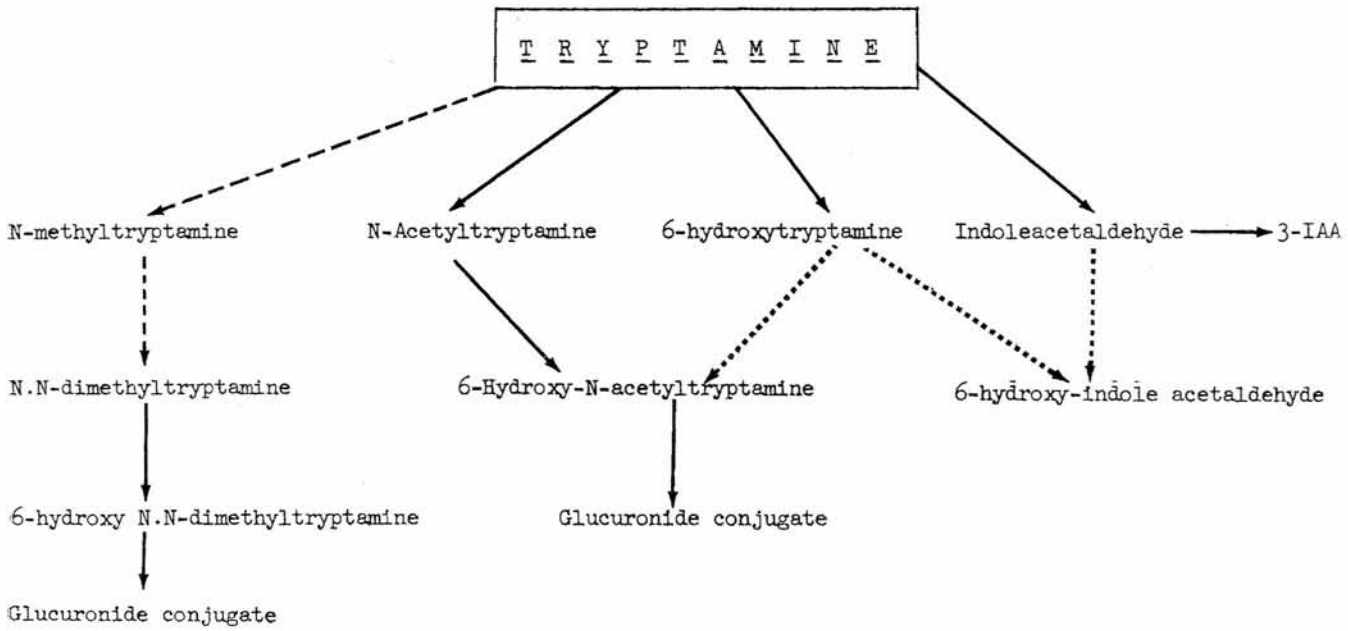

FIG. 3. Possible alternate pathways for tryptamine in mammals. *Solid arrows* represent paths demonstrated both in vitro and in vivo. *Broken arrows* represent paths shown in vitro only. *Dotted arrows* represent hypothetical pathways.

both pathways occur in the rat in vivo, and the hydroxy derivatives are excreted as glucuronides. In man, we found paper chromatographic evidence in the urine of 6-hydroxylation of α-MT. Since indolylacetone is found to be ineffective in producing behavioral changes in animals, we may hypothesize that 6-H-α-MT plays a role in affecting the behavior of animals and producing CNS effects in man. How is this accomplished by a compound which has lipid solubility similar to 5-HT, and therefore, little chance of getting into the brain? We don't know. The permeability of the blood-brain barrier is not uniform through the brain. Perhaps the metabolite affects only those portions which can be easily penetrated; the hypothalamus, and pineal gland area, etc.

Returning to our original problem, tryptamine might also be transformed into other more lipid soluble compounds, which would be more easily 6-hydroxylated and would penetrate the blood-brain barrier.

Three possibilities come readily to mind. One is N-methylation to form N-methyl tryptamine, or even DMT. This possibility seems feasible when we consider the interesting results obtained by Dr. Kety and his group in methionine and tryptophane loading experiments, and Dr. Axelrod's recent findings about the occurrence of an enzyme in mammalian organisms which actually can perform this reaction (J. Axelrod, personal communication). It seems that the whole enzymatic apparatus exists in mammals which can produce tryptamine from tryptophane, DMT from tryptamine, and 6-HDMT from DMT.

The second possibility for transforming tryptamine into a more lipid soluble compound before 6-hydroxylation is acetylation to form acetyl tryptamine (H. Weissbach, and J. Axelrod, personal communication). For the occurrence of this pathway we have preliminary evidence in animals. If we inject tryptamine intraperitoneally into rats or rabbits pretreated with Marsilid, we find 6-HT, 6-HO-acetyltryptamine and their glucuronide in the urine.

The third possibility emerges from studies reported by A. J. Friedhoff and M. Goldstein at the Conference on Some Biological Aspects of Schizophrenic Behavior in New York on April 6, 1961 (organized by the New York Academy of Sciences, and to be published in the Annals of The New York Academy of Sciences). They presented evidence that the intermediate aldehyde formed from mescaline by deamination is a strong candidate for an active metabolite in mescaline action. This finding suggests that we might consider the aldehyde's intermediates in other amines, like tryptamine or 6-HT as psychotropically active metabolites.

Whether these reactions are involved in Dr. Kety's findings with tryptophane and methionine loading experiments, and in the very interesting observations of Drs. Brune and Pscheidt in their reserpine and isocarboxazide combination, which is reported here today, remains to be explored.

REFERENCES

1. ABRAMSON, H. A. *J. Psychol* 42: 51, 1956.
2. ABRAMSON, H. A. (*Ed.*) *The Use of LSD in Psychotherapy*. New York: Macy Foundation, 1960.
3. ARNOLD, O. H., AND G. HOFMANN. *Wien. Z. Nervenheilk* 13: 438, 1957.
4. BOSZORMENYI, Z., AND S. SZARA. *J. Mental Sci.* 104: 445, 1958.

5. CHANDLER, A. *A.M.A. Arch. Neurol. Psychiat.* 2: 286, 1960.
6. FABING, H. D. *Am. J. Psychiat.* 113: 409, 1956.
7. FISH, M. S., N. M. JOHNSON, AND E. C. HORNING. *J. Am. Chem. Soc.* 77: 5892, 1955.
8. HUXLEY, A. *The Doors of Perception.* New York: Harper, 1954.
9. KAJTOR, F., AND S. SZARA. *Confinia. Neurol.* 19: 52, 1959.
10. LINDEMANN, E., AND J. M. FELSINGER. *Psychopharmacologia* 2: 69, 1961.
11. MURPHREE, H. B., JR., E. H. JENNEY, AND C. C. PFEIFFER. *The Pharmacologist* 2: 64, 1960.
12. POLLARD, J. C., C. BAKKER, L. UHR, AND D. F. FEUERFILE. *Compr. Psychiat.* 1: 377, 1960.
13. SAI-HALASZ, A., G. BRUENECKER, AND S. SZARA. *Psychiat. et Neurol.* 135: 285, 1958.
14. SPEETER, M. E., AND W. C. ANTHONY. *J. Am. Chem. Soc.* 76: 6209, 1954.
15. SZARA, S. *Experientia* 12: 441, 1956.
16. SZARA, S. In: *Psychotropic Drugs,* edited by Garattini and Ghetti. Amsterdam: Elsevier, 1957, pp. 460–467.
17. SZARA, S., AND F. PUTNEY. *Federation Proc.* 20: 172, 1961.
18. SZARA, S., AND E. HEARST. *Ann. N. Y. Acad. Sci.* In press.
19. TURNER, W. J., AND S. MERLIS. *A.M.A. Arch. Neurol. Psychiat.* 81: 121, 1959.