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(I) The Metabolism of Mescalin in the Human
(II) Delayed Clinical Reactions to Mescalin

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(I)

The metabolism of mescalin in the human is of interest for two reasons. The first is that the more we know of the metabolism of the known hallucinogens the easier will become the search for the unknown hallucinogens thought to be responsible for schizophrenia. The second is that the action of mescalin presents several interesting features suggesting that it is not the active hallucinogenic agent itself. These features are as follows: (1) the effective dose – 400 milligrams – is considerably larger than that of other hallucinogens; (2) the effects typically take from 1–2 hours to develop and 5–6 hours to reach a maximum, which suggests the action of a derivative; (3) Block has shown that in the mouse, mescalin rapidly becomes fixed to liver protein and during the phase of active central nervous system effects, scarcely any is to be found in the brain. These facts suggest either (a) that some breakdown product of mescalin is the active agent or (b) that mescalin blocks the detoxication in the liver of some bodily metabolite, which is a potential hallucinogen.

We therefore studied the excretion of mescalin and its metabolites in the urine of 6 subjects. These received 400 milligrams of mescalin at 10 a.m. and the urine was collected for the next 24 hours. After

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concentration, paper chromatography was carried out and comparison made with a control specimen from the same subject. A spot was consistently found after mescalin administration, which was absent from the controls. The material was eluted from the paper and obtained in crystalline form. On acid hydrolysis, it gave glutamine, glutamic acid, ammonia and 3 : 4-dihydroxy-5-methoxyphenylacetic acid (I), which was identified by comparison with a synthetic sample. The material was therefore the glutamine conjugate of (I): it may be noted in this connection that phenyl acetic acid itself is excreted as the glutamine conjugate in man.

The average figure for the six subjects of recovered mescalin in the 24 hour specimens was 35 % $\pm$ 5 % and the metabolite only accounted for about 1–2 % of the dose. No 3 : 4 : 5-trimethoxyphenylacetic acid (the metabolite found in rabbit urine) could be detected; thus some 65 % of the dose remains unaccounted for. As it is possible that the excretion of some of the mescalin may be subjected to delay (e.g., if it is bound into liver protein), measurements of the excretion of mescalin were made for one week following a single dose. However all the mescalin excreted as such was excreted during the first 24 hours apart from a trace found in the second 24 hours.

The course of the metabolism of mescalin in the human disclosed by our isolation of the above metabolite is of interest. It may firstly be noted that *Axelrod* (Biochem. J. *63:* 634, 1956) has shown that mescalin is demethylated by a rabbit liver preparation, though the product was not identified. On the other hand, suggestions made earlier by one of us (J. H.-M.) in *Osmond* and *Smythies* (J. Ment. Sci. *98:* 309, 1952) that in schizophrenia O-methylation of adrenalin and nor-adrenalin might give rise to methoxy-amines with mescalin-like properties, has recently found support from the findings of *Axelrod* (Science *126:*400, 1957) that adrenalin is indeed O-methylated in a rat liver preparation. Another interesting possibility is that if in the formation of our metabolite, demethylation precedes deamination, ring-closure to a dihydroxyindole might occur. However, the very small amount of metabolite isolated may indicate that this represents only a minor and unimportant pathway of detoxication.

(II)

We should like to describe three cases of delayed reactions to mescalin. The first, who had no previous history of psychosis or

neurosis had a mild reaction to 400 milligrams and then two weeks later, after a period of lack of sleep and fatigue, he became ill and described his symptoms as follows: "At 11 p.m. I suddenly felt exceedingly tired and going to bed I had a horrible night between waking and sleeping. I should describe my experience as being a continuous experience of hallucinations seen as through a glass darkly – that is to say there was no question of the bright clear experience of the drug but an uneasy, not to say gloomy experience of muddy green patterns, slowly moving all night long. The next morning I felt dead to the world and in a state of extreme exhaustion. This lasted for 4–5 days. There was also a very marked diminution of urinary flow, loss of appetite and above all a sense of complete physical and mental exhaustion. I have never had any of these symptoms normally. I noticed on the first morning that a suit of mine was in the wrong colours. All colours were very dull in contradistinction to those at the time I took the drug. Most of them were olive greens and muddy browns. For several days I was almost obsessed by hypnagogic hallucinations whenever I closed my eyes."

The second case had a severe panic reaction to mescalin and this led to distressful panic attacks lasting some hours on two subsequent occasions in situations of fatigue and stress some months after taking the mescalin. The subject had had no similar symptoms before or since.

In the third case a major effect of mescalin was to produce apparent movement. This effect recurred quite frequently for months – the subject found that statues in churches and museums would move in a life-like way, such experiences being quite foreign to him. Similar cases have been encountered by *Hoffer* and others.

These cases, together with the well-known occurrence of hallucinations and psychotic symptoms in cases of severe fatigue and sleep deprivation, suggest that these latter effects may be produced by a metabolic upset akin to that of schizophrenia and that a dose of mescalin renders one particularly sensitive to this uspset for some time. It is just possible that this may, in some cases, be brought about by a direct chemical action of mescalin or mescalin breakdown products retained in the body fixed, e.g. to liver protein. But it seems more likely that the mescalin widens some functional change in metabolism. Certainly metabolic studies of adrenolutin, leucoadrenochrome, ceruloplasmin, and taraxein in cases of severe fatigue and sleep deprivation would be of great interest to link the bio-

chemistry of stress, fatigue and psychosis on a possible common basis of adrenalin breakdown products.

Discussion

Zeller: As mescalin is a good substrate for amine oxidase it is probable that the side chain is oxidized before the ring changes, and so the indolic compound could not be formed.

H. Waelsch: I should like to report briefly on some recent findings made in our laboratory which may be of significance for the metabolism of biogenetic amines. There exists an enzymatic system in mammalian organs which incorporates very efficiently a large number of amines from methylamine to serotonin (*Sarkar* et al.: Biochim. Biophys. Acta *25:* 451, 1957). Whether these amines are incorporated by exchange of the amide group of protein bound glutamine or asparagine or by exchange with amino acids or peptides cannot be stated definitely today. It is of particular interest that the incorporation of some amines is inhibited by small amounts of lysergic acid and larger concentrations of mescaline. Although the biological significance of the amine incorporating system is not obvious at the present time it is of interest to speculate whether or not the activities of protein bound amines may be changed. By this enzymatic reaction, modified proteins are formed and the question arises whether such proteins would have antigenic properties or would interfere with enzymatic reactions.

Jatzkewitz: Ist die Hemmung des Einbaues biogener Amine in Proteine durch LSD besonders stark und spezifisch?

H. Waelsch: Darüber läßt sich im jetzigen Stadium der Versuche nichts sagen.

G. A. Buscaino: (1) I would like to know whether you tested the elimination of mescaline in the urine for only 24 hours or for many consecutive days. Perhaps this substance could be eliminated in a slow and continuous manner. I would also like to know whether mescaline could be eliminated through the bile and also through the faeces.

(2) It is well known that during the prolonged stress there occurs an accentuation of the protein metabolism, so that theoretically it is possible that aminic substances or other toxic substances able to engender psychic modifications and even hallucinations could be produced. But these modifications being of provisional character, the organism is able through enzymatic mechanisms to neutralize such substances. The authors think that the toxic action of mescaline is brought about by the substance itself or by some metabolic product of this substance; indeed researches of *de Jong* have proved that in dogs the exclusion of the liver through a fistula of Eck is able to produce the toxic symptomatology which we obtain if we administer only 9 mg. of mescaline. This proves beyond doubt that the liver brings about a protective actions against mescaline intoxication.