THE METABOLISM OF MESCALINE WITH A NOTE ON CORRELATIONS BETWEEN METABOLISM AND PSYCHOLOGICAL EFFECTS[1]

L. C. MOKRASCH, PH.D.[2] AND IAN STEVENSON, M.D.[3]

INTRODUCTION

The hypothesis that a biochemical mechanism underlies the symptoms of schizophrenia has received increasing attention in recent years. Osmond and Smythies proposed that some substance related to epinephrine and mescaline might play a part in the mechanism of schizophrenia (12). Mescaline and other chemically related compounds have been shown capable of depressing the oxidation of nervous tissue (14) and also of acting as synaptic inhibitors in the brain (10). Mescaline thus qualifies as capable of producing the cerebral changes which can in turn underlie important psychological disorders. Although mescaline is not a naturally occurring substance of the human body, its chemical kinship with such substances and its known chemical and psychological effects make its further study valuable.

Epinephrine is rather rapidly oxidized in the human body but some of the related amines such as amphetamine, ephedrine and mescaline are not. The effects of these latter compounds may last for twenty-four hours or more. These differences may depend on different speeds of oxidation of the compounds (15). Alternatively, compounds such as mescaline may be converted into or activate the production of other compounds which are the active psychotogenic substances. The work of Block in animal experiments (5) has yielded some evidence of the conversion of mescaline into some other possibly active substance.

Although the administration of mescaline is accompanied by a pattern of well-studied psychological changes (7, 21) the symptoms vary widely between different subjects receiving comparable doses. The same is true of the psychological changes accompanying the administration of lysergic acid diethylamide (1). Few studies have been made on the metabolism of mescaline in human subjects (6, 8, 11, 15, 17) most of them before the development of modern analytical methods.

The foregoing data and speculations made worthwhile a study of the metabolism of mescaline in human subjects together with an attempt to correlate metabolic and psychological changes.

METHODS

The subjects were eleven young men and women between the ages of twenty and forty drawn through volunteering from the students and staff of the Louisiana State University School of Medicine. We are aware that this method of selection is far from random and can attract persons who are not average and possibly quite abnormal (9). However, the subjects were ostensibly in good physical and mental health at the time of the experiments. The subjects knew they were to receive mescaline during the experiment and at the time of invitation to participate were told briefly about the usual effects of the drug. Subsequently most of them learned more about the action of the drug either during a preliminary interview with one of us or from reading.

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[2] Medical Center, University of Kansas, Kansas City, Kansas.

[3] Department of Neurology and Psychiatry, School of Medicine, University of Virginia, Charlottesville, Virginia.

The experiments were conducted in the fasting state beginning between 7 and 9 A.M. On most experimental days experiments were conducted simultaneously on two subjects. The subjects were in the same room usually lying on beds, although occasionally walking around. The subjects sometimes interacted with each other, but much more often became involved in their own subjective experiences and paid little attention to the other subject in the room. After initial samples of blood and urine had been taken, and an initial psychological evaluation made, mescaline sulfate (Hoffman-LaRoche) was administered intravenously in doses of 5 mgm. per Kgm. This meant that most of the subjects received between 350 and 400 mgm. of mescaline. The drug had been dissolved in distilled water at a concentration of 40 mgm. per ml. and subsequently sterilized before injection. Studies of the actual concentration of the drug injected showed that some variations in concentration had occurred during the preparation of the solution. These variations were considered small enough to be disregarded.

After the administration of the mescaline, psychological evaluations were continued throughout the period of the drug's effects. Detailed notes were made of the subject's verbalizations and other behavior. At frequent (usually hourly) intervals a complete mental status examination was made. For these evaluations a rating sheet was devised consisting of some forty items grouped under the headings of perception (*e.g.*, illusions, after-images, synesthesiae), mental processes (*e.g.*, ability to calculate, capacity for abstract thinking) and emotion and behavior (*e.g.*, anxiety, elation). In every experiment two or more observers studied the psychological state of the subject. The data of the rating scale were used to evaluate the total psychological changes in the subjects. For this purpose ten major parameters of change (*e.g.*, alterations of mood, alterations of perception of the environment, interference with mental processes) were used and two observers independently scored the subjects with regard to such changes. From these scores estimates were derived of the degree of psychological changes in each subject. Throughout the period of observation samples of blood and urine were drawn. Between six and eight specimens of blood and urine were obtained from each subject. The subjects were kept under close observation until they were judged to have nearly or completely recovered from the effects of mescaline when they were taken home. The duration of close observation thus extended over eight to ten hours. Over the next day or several, subsequent contacts with the subjects permitted study of residual effects which occasionally occurred.

Some of the subjects received sodium succinate whose antidotal action was studied and reported elsewhere (20). Most of the subjects received mescaline on two occasions, once with and once without the administration of succinate. Twenty experiments were conducted altogether.

ANALYTICAL PROCEDURES

BLOOD ANALYSIS

Methoxylated acids. Duplicate 5 ml. samples of whole blood, (preserved immediately on drawing by NaF to a concentration of 0.01 M and by refrigeration) were mixed with 25 ml. 0.59 M trichloroacetic acid and allowed to stand at room temperature for one hour with occasional stirring. The suspensions were then centrifuged 15 minutes at 1800 g. 25.0 ml. of the supernates were transferred to beakers containing 1.0 ml. 0.5 N metaphosphoric acid and were evaporated to about 1 ml. by the application of heat. The concentrated solutions were transferred quantitatively with distilled water washes to centrifuge tubes and diluted to 4 ml. The acid solutions were extracted twice with 5.0 ml. toluene (redistilled). The toluene phases were separated quantitatively from the aqueous phases which were saved for the procedure described in the next section.

The combined toluene extracts were treated with 1.0 ml. 0.5 M $NaHCO_3$ followed by 2 × 1 ml. of distilled water. The combined $NaHCO_3$ extracts were evaporated to dryness in a Zeissel flask and the usual Zeissel technic (24) was then applied to determine the methoxylated acids.

Since the extracted material was free of interfering substances and since no additional methoxyl compounds could be recovered from the acid blood extract, no additional extractions for the acid products were performed.

Methoxylated amines. The aqueous phases remaining from the first toluene extraction (preceding section) were made strongly alkaline by 1.2 to 1.5 ml. 10 M NaOH. These were then extracted with 2 × 5 ml. toluene, following which the aqueous phases were discarded. The combined toluene extracts were treated serially with 1.0 ml. 0.1 M HCl and 2 × 1 ml. distilled water. The combined HCl extracts were evaporated to dryness in the Zeissel flasks and the usual Zeissel technic applied.

Additional extractions recovered no more methoxyl compounds and no interfering materials were present; therefore the procedure is satisfactory in its simple form.

URINE ANALYSIS

Methoxylated acids. Duplicate 3.0 ml. samples of urine (preserved by the addition of 0.1 mg. $ml.^{-1}$ HgI_2 and by refrigeration immediately after collection) were mixed with 0.25 ml. 12 M HCl and heated 15 minutes at 100° in stoppered tubes. The cooled solutions were extracted with 3 × 5 ml. toluene and the aqueous phases were saved for the procedure described in the next section. The combined toluene extracts were treated with 1.0 ml. 0.5 M $NaHCO_3$ and 2 × 1 ml. water. The $NaHCO_3$ extracts and water washes were combined and evaporated to dryness in the Zeissel flask.

Methoxylated amines. The aqueous phases remaining from the first toluene extraction (preceding section) were made strongly alkaline with 10 M NaOH and extracted with toluene as before. The toluene phases were treated with 0.1 M HCl as described for blood analysis at the same stage. Exactly 0.10 of the HCl solutions were taken for Zeissel determinations.

Alternatively the total toluene-soluble amines in the urine was determined by a method similar to that of Woods *et al.* (23).

The results of the colorimetric determination on urine amines and of the Zeissel determination on urine amines are consistent with the assumption that mescaline or a closely related trimethoxyamine was the amine solely elevated in concentration in the urine of intoxicated subjects. The colorimetric method was not suitable for measuring blood mescaline owing to the presence of interfering substances giving high blank values.

Rigorous characterization of the mescaline metabolites was not attempted; however, blood and urine extracts separated on paper chromatograms disclosed the presence of an amine associated with three alkoxyl groups and an acid associated with three alkoxyl groups, as the main alkoxyl-bearing compounds (about 80 per cent of the total). The acid had a pKa of about 5, consistent with the notion that it is a carboxylic acid. A third methoxyl component migrated between the main two but was not characterized.

RESULTS

Blood levels and rates of excretion of mescaline and trimethoxyphenylacetic acid. The blood levels and rates of excretion of mescaline in the urine are illustrated in Figures 1 and 2. Figure 1 also includes a line indicating the severity of symptoms. The curves of blood level and rates of excretion of mescaline did not fall asymptotically, but instead showed a definite flattening and in most instances an elevation between the third and sixth hour after administration of the drug. The curves of blood level and rates of excretion of trimethoxyphenylacetic

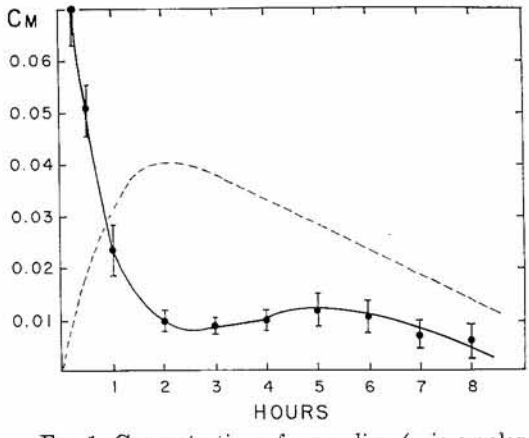

FIG. 1. Concentration of mescaline (micromoles per cc.) in blood after intravenous administration (solid curve). Means and mean deviations are indicated. Broken curve indicates usual severity of symptoms after administration of mescaline.

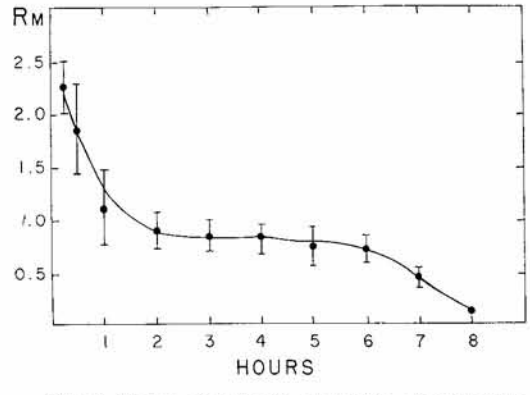

FIG. 2. Rates of urinary excretion of mescaline after intravenous administration. Rates expressed as micromoles per hour per kilogram of body weight. Means and mean deviations are indicated.

acid (Figures 3 and 4) showed this second rise to an even greater degree.

The amount of mescaline which was recovered in the urine within the first six hours ranged between 11.8 per cent and 66.7 per cent of the drug administered. The mean recovery during this period was 31 per cent. In fourteen experiments the excretion of trimethoxyphenylacetic acid was measured and it was found that an average of 7.4 per cent of the ingested drug was recovered in this form. Rather wide variations were found in the curves of blood levels and rates of excretion of mescaline of the same subject on different experimental days.

Correlations between blood levels, rates of excretion of mescaline and psychological changes. With the intravenous administration of mescaline we found that the height of psychological effects usually occurred between 1½ hours and 2 hours after the injection of the drug. Thereafter the effects wore off and had usually disappeared to the extent of about 80 per cent recovery by the end of nine hours. Most of the subjects declared

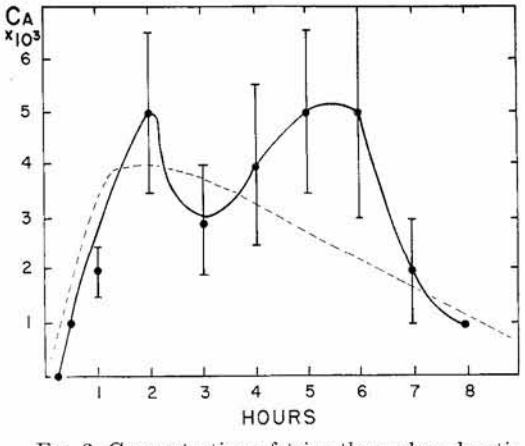

FIG. 3. Concentration of trimethoxyphenylacetic acid (micromoles per cc. times 10^3) in blood after intravenous administration of mescaline (solid curve). Means and mean deviations are indicated. Broken curve indicates usual severity of symptoms after administration of mescaline.

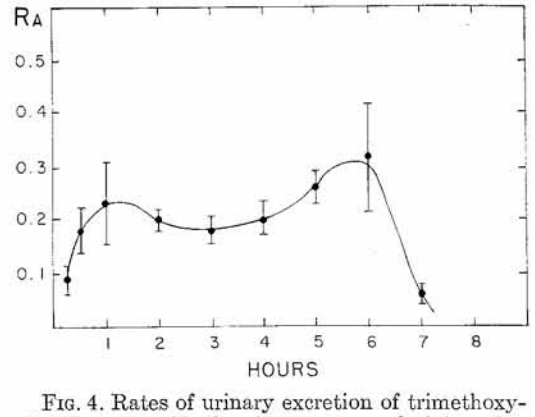

FIG. 4. Rates of urinary excretion of trimethoxyphenylacetic acid after intravenous administration of mescaline. Rates expressed as micromoles per hour per kilogram of body weight. Means and mean deviations are indicated.

themselves entirely free of symptoms by the next morning (24 hours after the injection). Two of our subjects had residual symptoms lasting several days.

In general the height of psychological effects followed the period of maximal blood levels and rates of excretion of mescaline by an hour or two (see Figures 1 and 2). On the other hand, the period of maximal psychological effects did coincide rather closely with the first peaks in the blood levels and rates of excretion of trimethoxyphenylacetic acid (Figures 3 and 4).

The psychological effects in our subjects resembled those described by previous authors (7, 12, 21). These effects were far from uniform, however, since wide variations in psychological responses to these drugs occur (1, 13, 19). Variations occurred both in degree of response and in the mental functions most affected. Thus some subjects experienced marked changes in visual perception with little change in mood. Others showed marked elevation of mood with little or no change in perception and an impoverished thought content. Others showed great enrichment of thought content with little change in perception. We were unable to correlate these variations of severity and quality with any of the following: a) blood levels of mescaline at the height of psychological effects; b) rate of excretion of mescaline at the height of psychological effects; c) amount of mescaline (per cent of drug administered) excreted within six hours; d) differences in the ratio of mescaline and trimethoxyphenylacetic acid excreted. The latter ratio presumably reflects somewhat the breakdown of mescaline. We also found no correlations between the severity of symptoms judged by our criteria and either the rapidity with which the height of psychological effects was reached or the total duration of these effects.

DISCUSSION

The observation of a delayed decline and even increase in the blood level and urinary excretion of mescaline and trimethoxyphenylacetic acid several hours after the injection of mescaline supports the hypothesis that some of the mescaline is deposited in the tissues from which portions of it not otherwise metabolized are subsequently released and excreted as mescaline or, after deamination, as trimethoxyphenylacetic acid. In experiments with mice using mescaline containing radioactive carbon, Block *et al.* found evidence that mescaline is incorporated in the tissue proteins from which it is subsequently released with excretion in the urine and feces. Moreover, he traced rather little of the mescaline to the brain compared to the liver and other organs (5). Vogt (22) and Cochin *et al.* (6) also found significantly smaller amounts of mescaline in blood and brain (of dogs) compared to the amounts found in liver and kidney.

Slotta and Mueller (17) identified and measured the excretion of trimethoxyphenylacetic acid in rabbits and dogs, but were unable to recover any of this substance in the urines of humans after the ingestion of mescaline. Cochin *et al.* (6) also found some trimethoxyphenylacetic acid in the urine of dogs given mescaline. Harley-Mason *et al.* (8), using a paper chromatographic technique, also failed to find any trimethoxyphenylacetic acid in the urines of six subjects given doses of mescaline comparable to our doses. They also reported finding small amounts (1–2 per cent of the dose) of the glutamine conjugate of 3:4-dihydroxy-5-methoxyphenylacetic acid.

Some variations have occurred in the recoveries of mescaline in the urines of experimental animals and humans. Working with dogs, Cochin *et al.* (6) recovered between 28 and 46 per cent of the administered dose within 24 hours. Richter (15) in one human subject recovered 58 per cent of the administered drug after 24 hours. These investigators measured amino groups. Harley-Mason *et al.* using a paper chromatographic method recovered from six human subjects an average of 35 per cent of the adminis-

tered drug within 24 hours. Salomon *et al.* (16) recovered an average of 30 per cent of the administered drug in six human subjects within eight hours, measuring methoxy groups by the Zeissel method. Our own recovery with the same method was somewhat larger than this and averaged in our eleven subjects 31 per cent of the administered drug within six hours.

A number of investigators have studied the breakdown of mescaline *in vitro*. Bernheim and Bernheim (3) derived evidence that a rabbit liver preparation, presumably through the activity of amine oxidase, oxidized mescaline to trimethoxyphenylacetic acid which they isolated. Preparations of rat, guinea pig, cat and dog liver had little or no capacity to oxidize mescaline. Blaschko (4) and Steensholt (18), on the basis of other experiments, doubted that amine oxidase takes part in the oxidation of mescaline. Axelrod (2) has shown that a rabbit liver preparation demethylates mescaline. Recently Zeller has studied the oxidation of mescaline by tissue preparations from a number of species. The enzyme studied by Zeller (most active in rabbit preparations) oxidized the mescaline presumably to trimethoxyphenylacetic acid and had inhibitor characteristics of a diamine oxidase. Our own observations show that in humans at least some mescaline is deaminated before demethoxylation occurs or is completed.

Our failure to find correlations between the levels of mescaline in the blood and urine and the psychological effects of this drug may derive from the difficulties in evaluating the psychological changes. The occurrence simultaneously of several different psychological changes and the diversity of these changes in different subjects makes difficult an estimation of severity of changes for the comparison of one subject with another. Moreover, the communication of their experiences by the subjects to the observers can become seriously limited by alterations in communication as a result of elation and garrulity, withdrawal into reveries, or fears of revealing psychopathological changes to the observers.

Alternatively, the different responses may derive from other factors in the study of which our biochemical techniques are still inadequate. The study of the blood and urine alone permits few inferences of what may occur in the tissues. However, the observations of Vogt, Cochin *et al.* and Block *et al.* show that some mescaline is incorporated in the tissues of animals for a time. Our observations similarly suggest a temporary storage in humans. The usual gap of about one or two hours between the time of maximal psychological effects and the time of greatest blood levels and urinary excretions of mescaline suggest that the action of the drug may depend upon its conversion to another substance or to its slowly inducing a metabolic dysfunction which outlasts the presence of the drug itself in the brain or other tissues affected. The other substances produced from mescaline may then be directly responsible for the effects on the central nervous system.

SUMMARY

Eleven volunteer subjects were given mescaline intravenously in twenty experiments. For the period of intoxication blood levels and rates of urinary excretion of mescaline and trimethoxyphenylacetic acid were measured and observations made of the subjects' behavioral responses.

The behavioral responses of the subjects varied widely in severity of symptoms and in the pattern of disturbance of mental function.

An average of 31 per cent of the drug administered was recovered in the urine within the first six hours after the administration of the drug. An additional 7.4 per cent (average) of the administered drug was recovered as trimethoxyphenylacetic acid.

The blood levels and rates of excretion of mescaline did not fall off asymptotically, but formed a flattening curve and often one

with some elevation between the third and sixth hour after administration of the drug. The blood levels and rates of excretion of trimethoxyphenylacetic acid showed such secondary peaks to an even greater extent.

The period of maximal behavioral changes followed the period of maximal blood level and excretion by one to two hours.

No correlations were observed between degree or type of behavioral responses and blood levels or rates of excretion of mescaline.

The curves of blood levels and rates of excretion of mescaline and trimethoxyphenylacetic acid and the delay in occurrence of maximal behavioral change suggest that mescaline may be converted into some other substance which is directly responsible for the effects on the central nervous system.

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