A STUDY ON MESCALINE IN HUMAN SUBJECTS[1]

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Mescaline, 3,4,5,trimethoxyphenylethylamine, produces hallucinations in the visual modality. This phenomenon has been extensively investigated from a psychiatric and a psychological point of view, but only very few studies of the chemical fate of mescaline in man are available, while to our knowledge, there are no data concerning the physiology of the visual mechanism in response to mescaline.

The hallucinations produced by this drug are due to a great extent to the presence of methoxyl groups in the mescaline molecule, since beta-phenylethylamine, a homologous substance without methoxyl groups, does not cause hallucinations. However, the methoxyl groups alone are not sufficient to produce hallucinations since Slotta and Müller (1) showed that trimethoxyphenylacetic acid, the *in vitro* oxidation product of mescaline, does not produce hallucinatory phenomena in man. It is evident, therefore, that the amino group in the side chain also plays an essential part.

Slotta and Müller were able to isolate from the urine of mescaline-fed humans a substance which contained one methoxyl group only, thus indicating that some of the mescaline ingested is metabolized. Their experiments revealed also that trimethoxyphenylacetic acid is not a step in the *in vivo* decomposition process. They did not investigate whether or not mescaline was excreted unchanged in the urine. However, Richter (2) showed that after oral ingestion of mescaline hydrochloride (191 mgm. base), 58 per cent was excreted unchanged in the urine about 18 hours after ingestion. This observation is in agreement with the findings of Bernheim and Bernheim (3), and Blaschko (4) that the presence of methoxyl groups renders the mescaline molecule more resistant to oxidation.

In this investigation of mescalinized human subjects, we were concerned primarily with two points: 1. A quantitative estimation of the urinary excretion of the methoxyl groups of mescaline. 2. Color perception before and after medication to determine if changes in this physiological function are correlated with visual hallucinations.

EXPERIMENTAL. Six subjects were used in this investigation. The following doses were given: 200 mgm. mescaline sulfate[3] (137.8 mgm. base) to one schizophrenic female; 300 mgm.

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[3] The mescaline sulfate was generously supplied by the Hoffmann-La Roche Company.

mescaline sulfate (206.7 mgm. base) to one schizophrenic male and one schizophrenic female; 400 mgm. mescaline sulfate (275.6 mgm. base) to two schizophrenic males and one neurotic male. All doses were given orally in the morning while the subjects were in a fasting state. Detailed information concerning the subjects used, the hallucinatory responses, and changes in visual imagery, will be published elsewhere.

1. *Urinary excretion of methoxyl groups.* Urine specimens were collected prior to medication and at stated intervals for 18 hours (2, 4, 6, 10, 14, 18) thereafter. A 40 cc. aliquot from each urine sample was extracted for mescaline by first adjusting the pH to about 9 with KOH and then extracting twice with an equal volume of a 1:1 mixture of toluene and isobutylalcohol. Preliminary experiments had shown that this mixture was superior for the extraction of mescaline. The extract was dried with anhydrous sodium sulfate. An appropriate aliquot of the dried extract was used for the determination of methoxyl groups following a modification of the Zeisel method (5). The validity of the forementioned method was tested for known amounts of mescaline added to urine samples. The error of recovery was plus or minus 4 per cent. Methoxyl groups were never found in urines of nonmedicated subjects.

After the content of methoxyl groups of aliquots of urines was determined, the remainder of all the urine samples of one particular patient was combined and extracted after alkalinization with the toluene-isobutylalcohol mixture. These extracts were used for the identification of mescaline and the investigation of the presence of possible breakdown products. Mescaline was isolated and identified as the picrate by the following method. The solvent (toluene-isobutylalcohol) was evaporated *in vacuo*. The brown residue thus obtained was treated with hot water, and the undissolved material was filtered off. The latter was dried *in vacuo* and then developed a resin-like consistency. From the filtrate, crystalline mescaline picrate was obtained and purified by repeatedly dissolving in acetone and precipitating with petroleum ether. Mescaline picrate thus obtained melted at 217–220° C. uncorrected. The mixed melting point with an authentic sample of synthesized mescaline picrate showed no depression.

A sample of the resin-like material mentioned above was analyzed for the presence of methoxyl groups. The Zeisel test revealed that the material contained methoxyl groups. In addition a qualitative test for methoxyl and other alkoxyl groups devised by Tobie (6) was applied to the resin-like material and gave a positive result. Identification of the methoxyl-containing substance or substances present in the resin-like material was not attempted.

2. *Color perception.* Color perception was tested within two days prior to the administration of the drug and again 30 to 180 minutes after the drug was given.

The apparatus used was devised by H. B. Molholm[4] who will describe it in a forthcoming publication. It is based on the principle that when lights of different intensity are seen in rapid alternation, the effect is one of flicker. When the intensity of the two sources is nearly equivalent, the flicker disappears, and the subject perceives one steady light. In this device a single source was used to produce a white light of constant intensity, and a second beam alternated with it. The second beam was modified by passage through a variable density Eastman film, manipulated by the subject. In addition, the second beam could be presented untinted or could be passed through a color filter. The following filters were used: nile green, sextant green, emerald green, lighthouse red, red-yellow, and blue.

The variable light was always presented in greater intensity than the fixed. The subject was instructed to turn a dial which increased the density of the film. When he signified that the light no longer flickered, he was told to reverse the movement and find the point at which flicker was barely apparent. This was used as the end point. The threshold for each color was determined three to five times at each testing and the mean value was used, numbers being read from a scale fixed to the variable film. The threshold for white was

[4] We wish to thank Dr. Molholm for making this apparatus available to us for this investigation.

determined before and after each battery of color tests. All color determinations were corrected for any shift in the threshold for white, the latter accounting for changes in the illumination, the speed of the motor which alternated lights, and the ability to perceive flicker as distinguished from color sensitivity.

RESULTS AND COMMENTS. 1. *Urinary excretion of methoxyl groups.* The various data obtained in this investigation are shown in table I. The majority of the methoxyl groups determined are considered to be representative of mescaline excreted unchanged in the urine. However, the resin-like material

TABLE I

Urinary excretion of methoxyl-containing compounds

SUBJECT	SEX	WT.	DOSE		VOLUME URINE IN 18 HOURS	TOTAL METHOXYL EXCRETED IN 18 HOURS	METHOXYL EXCRETED TO METHOXYL INGESTED
			Mescaline	Methoxyl			
		kgm.	*mgm.*	*mgm.*	*cc.*	*mgm.*	*per cent*
E†	M	93.6	275.6	118.5	990	43.2	36.4
P*	M	63.0	275.6	118.5	975	31.0	26.1
J*	M	70.5	275.6	118.5	1520	16.3	13.7
C*	M	55.5	206.7	88.9	2195	34.7	38.9
S*	F	43.4	206.7	88.9	690	14.5	16.2
A*	F	63.2	137.8	59.3	665	5.1	8.6

* Schizophrenic.
† Neurotic.

TABLE II

Change in color perception after mescaline ingestion

SUBJECT	DOSE MESCALINE	EMERALD GREEN	NILE GREEN	SEXTANT GREEN	RED-YELLOW	LIGHTHOUSE RED	BLUE
	mgm.						
E	275.6	−4	−1	−10	−2	−5	−15
P	275.6	39	−6	1	0	0	4
J	275.6	−17	−5	0	−14	13	6
C	206.7	−15	−14	−12	−8	−24	−22
S	206.7	−3	−10	−4	−9	−22	−6
A	137.8	−6	−9	−7	−1	−16	−2

which remained after water extraction of the residue of the combination of all the toluene-isobutylalcohol extracts of all the subjects contained less than 10 per cent of the total methoxyl groups extracted. It might be assumed that this resin-like material contained one or a mixture of the breakdown products of mescaline. Therefore, no conclusions may be drawn concerning the type of molecule to which these methoxyl groups in the resin-like material are attached. Essentially this finding is in accordance with that of Slotta and Müller (1) who claimed that not all of the mescaline ingested leaves the body unchanged.

Although only a small percentage of the methoxyl groups excreted belonged to breakdown products of mescaline according to our experiment, we have pre-

ferred to express the excretion of the drug in table I in terms of methoxyl groups. The percentage of total methoxyl groups excreted in 18 hours to total methoxyl groups ingested varied among the subjects between 8.6 and 38.9 per cent. These values are lower than the value reported by Richter of 58 per cent, but while the excretion curve of Richter's subject showed that at 18 hours after medication mescaline excretion had approached the zero line, similar excretion curves of our subjects indicated that the mescaline had not all been excreted in this period of time. In addition, the quantitative difference in these two sets of data might be explained by the fact that we determined methoxyl groups of the urinary extract whereas Richter measured the amino groups present.

The average peak excretion of mescaline of our subjects at six hours post medication is in agreement with the maximum excretion time of Richter's subject. It is worth mentioning at this point that the most intense hallucinatory response of each subject as reported to the observers occurred in each case before the peak urinary excretion of methoxyl groups.

Further experimentation along this line with a series of normal subjects as well as schizophrenic subjects may explain from a metabolic point of view the difference mentioned by Slotta and Müller between the hallucinatory response to mescaline of normal and schizophrenic subjects.

2. *Color perception.* Table II shows the corrected changes in scores for color perception after mescaline ingestion. A negative value indicates a decreased color perception following the drug. The general trend is toward a decrease in perception. One of the schizophrenics showed a marked increase for emerald green, and a slight increase in blue, while another schizophrenic who also received 275.6 mgm. mescaline showed a slight increase in blue. The decreases in perception were greater for those receiving the smaller doses.

All subjects were ranked according to the following variables: dose, vividness of hallucinations, amount of methoxyl groups excreted, average change in color perception, and change of each individual color. Thus the subject having the greatest excretion would receive a rank of 1 for that variable, the subject excreting the next greatest amount a rank of 2, etc. Each of these variables was correlated with each other by means of the rank order method.

The following correlations were found to be significant at the 5 per cent level:

Vividness of hallucinations—Change in color perception	−.94
Vividness of hallucinations—Nile green	−.89
Change in color perception—Nile green	+.94

Sizable, but not statistically significant correlations suggested that the larger doses were associated with more vivid hallucinations, greater absolute and relative excretion of methoxyl groups and, to a lesser degree, with total amount of urine excreted. The initial suppression of urine was compensated for by a greater flow in the latter hours of observation. On the other hand, color perception, particularly for lighthouse red and nile green, was more impaired by small doses than by large ones.

Vividness of hallucinations was definitely not associated with impairment of

color perception as is shown by the large negative correlations with average change in color perception and with nile green.

The correlations involving average color change and the individual colors suggest that the effect is manifested throughout the entire range rather than in any particular range.

SUMMARY

The urinary excretion of methoxyl groups was followed quantitatively over an 18-hour period in 5 schizophrenic subjects and 1 neurotic subject after the ingestion of mescaline sulfate. Mescaline was identified in the urinary extracts, and the majority of methoxyl groups determined may be considered to be present as mescaline. Methoxyl groups belonging to breakdown products of mescaline were found in a resin-like residue of the urinary extract.

Orally administered mescaline sulfate (200–400 mgm.) produced visual hallucinations and impairment of color perception. Large doses were associated with greater excretion and more vivid hallucinations than were small doses. The greatest impairment of color vision was observed in those subjects receiving smaller doses.

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