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# Mescaline, Lysergic Acid Diethylamide and Psilocybin: Comparison of Clinical Syndromes, Effects on Color Perception and Biochemical Measures

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MESCALINE, lysergic acid diethylamide (LSD-25) and psilocybin each tend to evoke analogous disturbances of mental functions when administered to normal subjects or psychiatric patients. Although a number of differences between the clinical syndromes produced by mescaline and LSD-25 have been noted (mescaline tending to increase withdrawal or "catatonia", LSD-25 tending to produce giggling, silliness or "hebephrenia"), the similarities are more striking.[1] Seldom have both drugs been given to the same subjects under comparable conditions, making comparisons of clinical syndromes difficult. One direct comparison between LSD-25 (1 to 1.5 mcg/K) and psilocybin (57 to 114 mcg/K) has revealed remarkably similar clinical reactions, that from psilocybin being somewhat shorter.[2] A recent study of each of the three drugs given to 16 normal subjects indicated minor differences between them in the autonomic, neurologic or psychic symptoms evoked, mescaline tending to be more potent than the others in producing psychic effects.[3] Additional controlled observations of the comparative clinical syndromes from these three drugs seemed needed.

Even less data were available for comparing perceptual or biochemical changes from these drugs. Visual effects, particularly hallucinations involving color, have been the most striking perceptual change from all three drugs. We decided to study some aspects of this phenomenon, our hypothesis being that color perception is enhanced by these drugs from the participation of stimuli not ordinarily eliciting color. Selected physiologic and biochemical measurements were also studied. Total circulating eosinophils were measured because of conflicting reports in the literature regarding the effect of LSD-25. Urinary inorganic phosphorus (P) and creatinine were measured because of reports of decreased urinary inorganic P following LSD-25.[4] Determinations of total lipids, cholesterol, and free fatty acids (FFA) were used as possible indicators of fat mobilization. Measurement of blood glucose was done to make certain this moiety was not changed in such a way as to secondarily affect FFA levels. This aspect of action of these drugs had not been previously studied. Serum glutamic oxalacetic transaminase (SGO-T) titer, alkaline phosphatase and pseudocholinesterase activity were measured to determine whether the drugs had any deleterious effect on hepatic functions, a point previously raised.[5] The test for pseudocholinesterase activity was also of interest in that activity of human serum in vitro has been reported to be strongly blocked by LSD-25, but actual measures of changes in serum activity following the drugs had not

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been made before.[6] Copper oxidase activity was also studied for the first time and seemed of possible interest in view of notions relating ceruloplasmin to schizophrenia or to endogenous psychotogens (taraxein).

## Procedures

We systematically compared these three drugs on the basis of the clinical syndromes produced, effects on certain aspects of color perception and selected physiologic and biochemical measurements. Doses of drugs were fixed as follows: Mescaline, 5 mg./K; LSD-25, 1 mcg/K; psilocybin, 150 mcg/K; each was given orally. Volunteer subjects selected on the basis of prior screening to rule out overt psychopathology were tested at weekly intervals. Order of drug administration was randomly assigned to each subject. Although subjects were aware of the nature of the drugs being studied, they were not told the order in which the drugs were administered until all trials were completed. Subjects were intelligent, being able to report experiences well and cooperate fully in the trials. Drugs were administered in a comparatively austere environment, a small room with a chaise longue and the test equipment present. An attendant stood by but subjects remained alone except during periods of testing. Twenty subjects were studied, 18 completing trials with all three drugs.

An assessment of the clinical syndrome produced by the drugs was made immediately after each drug experience had cleared. Subjects were asked to complete a questionnaire of 43 items regarding symptoms and signs experienced. Twenty-five of these were questions most frequently answered positively by subjects in other studies with psychotomimetic drugs, involving chiefly somatic or perceptual effects.[7] The remaining 18 questions were derived from another similar questionnaire, emphasis being laid upon specific psychic symptoms.[8]

Color perception studies were accomplished just prior to drug administration and two hours after. Two types of stimuli were used: those which are ordinarily associated with color phenomena and those which are not. Adequate color stimuli included the Farnsworth-Munsell hue discrimination test, consisting of 85 colored buttons to be arrayed in order of graded hues, and induction of a strong after-image by a light stimulus following which the induced colors were named and matched on a color comparator. Inadequate color stimuli included a black and white disc rotated at four speeds, four pure tones at approximately the same degrees of loudness, and both visual and auditory stimuli presented together. If during these tests the subject perceived colors, these were named and matched on a color comparator.

Before each drug trial, subjects had fasted for from 8 to 12 hours. Urine was collected for determination of inorganic P and creatinine prior to drug administration and for two hours after on 18 subjects. Determinations of total circulating eosinophils, total lipids,[9] inorganic P, creatinine, SGO-T, and copper oxidase[10] were made on blood specimens obtained prior to each drug and two hours later on 18 subjects. Similar determinations of free fatty acids (FFA)[11] and alkaline phosphatase activity were made on 12 subjects, and of cholesterol, glucose and pseudocholinesterase activity[12] on six.

## Results

Clinical syndromes from the three drugs were comparable in kind and degree, considering the possible failure to achieve ideally "equivalent" doses of drugs. The frequency of specific symptoms is summarized in table 1. As a rule, severity of symptoms paralleled frequency. Mescaline proved most active in evoking somatic effects, differences between drugs being less marked with perceptual or psychic symptoms. Psychic symptoms were encountered less frequently than anticipated. This was especially true of symptoms frequently mentioned as psychotomimetic: visual, auditory, or other types of hallucinations, depersonalization, paranoid ideation, or alterations of body image. Most

Table 1.—*Symptoms and Signs Reported by Subjects Receiving Psilocybin (150 mcg./K), Mescaline (5 mg./K) or LSD-25 (1 mcg./K) in Random Order with Blind Control under Like Conditions*

| Symptom/Sign | Psilo N = 19 | Mesc N = 20 | LSD N = 20 | Comments |
|---|---|---|---|---|
| *Somatic* | | | | |
| Dizziness, unsteadiness | 16 | 18 | 17 | |
| Weakness, fatigue | 13 | 14 | 11 | |
| Hot or cold feelings | 11 | 13 | 14 | Both reported |
| Appetite changed | 5 | 15 | 14 | Most decreased |
| Shaking of hands or body | 8 | 14 | 11 | |
| Nausea | 7 | 18 | 6 | |
| Drowsiness | 13 | 9 | 8 | |
| Paresthesias, extremities | 9 | 13 | 8 | |
| Heavy or light extremities | 8 | 11 | 8 | Both equally |
| Ill feeling, malaise | 5 | 15 | 6 | |
| Blurred vision | 11 | 6 | 8 | |
| Change in sweating | 7 | 10 | 5 | |
| Salivation changed | 4 | 11 | 7 | Most decreased |
| *Perceptual* | | | | |
| Altered shapes or colors | 9 | 17 | 9 | |
| Difficulty in focussing | 13 | 11 | 11 | |
| Change in hearing | 9 | 8 | 7 | Sharpened |
| Synesthesias | 2 | 2 | 3 | |
| *Psychic* | | | | |
| Change in mood | 12 | 13 | 14 | Happy, sad, irritable equally |
| Trembling inside | 9 | 16 | 10 | |
| Distorted time sense | 9 | 11 | 11 | |
| Difficulty expressing thoughts | 7 | 11 | 11 | |
| Visual hallucinations | 7 | 9 | 7 | Colored patterns most |
| Depersonalization | 9 | 6 | 8 | |
| Unusual tension, anxiety | 7 | 7 | 7 | |
| Dreamlike feeling | 9 | 8 | 6 | |
| Loss of control of thoughts | 2 | 5 | 7 | Come too fast |
| Altered body image | 1 | 4 | 2 | Distorted acral parts |
| Sexual feelings | 1 | 1 | 5 | |
| Paranoid ideas | 1 | 3 | 2 | |
| Hallucinations of smell, taste | 1 | 3 | 1 | Possibly real stimuli |
| Time disorientation | 2 | 1 | 1 | |
| Space disorientation | 2 | 1 | 1 | |
| Hallucinations of touch | 2 | 0 | 2 | Possibly real stimuli |
| Auditory hallucinations | 0 | 2 | 1 | Possibly real stimuli |

subjects found the mescaline experience to be the most intense and longest, lasting eight to ten hours in a few cases.

Color discrimination, as measured by the Farnsworth-Munsell test, was decreased by all drugs, but only significantly by psilocybin, without significant differences between the drugs. The effects of drugs differed for various hues: LSD-25 increased errors significantly in the red-yellow and yellow-orange areas, mescaline increased errors through a wider range but not significantly in any, and psilocybin did likewise. All drugs tended to increase the duration of after-image, though only psilocybin significantly; the numbers of colors

reported in the after-image were significantly increased by all three drugs. Each of the three drugs increased perception of color evoked by flicker to a highly significant degree. The more error in hue discrimination, the less color was evoked by flicker in the same spectral area. Combined flicker and tone stimuli led to responses beyond those elicited for either alone, but a significant increase occurred only with LSD-25. These studies have been reported in detail elsewhere.[13]

Results of the biochemical and physiologic measurements are summarized for each of the three drugs in table 2. Significant decreases were noted in urinary excretion of inorganic phosphorus relative to creatinine and in total circulating eosinophils in the blood. Free fatty acids were significantly increased. These changes were consistently observed with each of the three drugs and were of comparable magnitude. Only one other significant change was noted, an increase in copper oxidase activity after treatment with psilocybin.

## Discussion

Under the conditions of this study and among the screened subjects used, clinical syndromes from the three drugs were quite comparable. In terms of relative frequency, somatic changes were most common and psychotomimetic ones least. Possibly the latter would have been more pronounced with higher doses of drugs, but it does not seem likely that appreciably different qualitative syndromes would have been produced. One must surmise that in any given subject, the clinical syndrome produced by any of the three drugs could be reproduced by the others under appropriate test conditions and using "equivalent" doses.

The major finding of interest in regard to color perception was the increased role of normally inadequate stimuli for eliciting color perception during treatment with psychotomimetic drugs. This finding held true for each of the inadequate stimuli tested: Colors evoked by flicker, either with or without combined pure tones. Response to an adequate stimulus, the Farnsworth-Munsell color discrimination test, was reduced on the other hand, errors in arraying hues increasing under the drugs. These findings tend to support the hypothesis that heightened and unusual perception of colors following psychotomimetics may result from the action of normally inadequate stimuli. Although slight differences were noted between the drugs, similarities of their effects on color perception were more pronounced.

Reduction in urinary excretion of inorganic P, previously described from LSD-25, has now been found to occur equally with mescaline and psilocybin. The mechanism of this reduction is still not clear. A definite fall in circulating eosinophils was also demonstrated for each of the three drugs, very likely being a nonspecific effect analogous to the fall following epinephrine administration. Mobilization of lipids as manifested by increased FFA has not been previously described from these drugs, but occurred to a comparable degree from all three. Each drug evoked symptoms and signs suggestive of sympathetic stimulation (feelings of anxiety and tension, blurred vision, dilated pupils, tremors, nausea, increased deep tendon reflexes). Possibly fats were mobilized by a

Table 2.—*Changes in Biochemical Measures Two Hours After Treatment with Mescaline (5 mg./K), LSD-25, (1 mcg./K) and Psilocybin (150 mcg./K), Given Orally*

| Determination | Mescaline | | LSD-25 | | Psilocybin | |
|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After |
| *Urine* | | | | | | |
| Inorganic phosphorus (mg./100 mg. creatinine) | 61.3 (51.5) | 35.2 (23.8)°° | 51.1 (18.6) | 37.7 (18.4)°°° | 54.1 (14.7) | 41.6 (23.7)° |
| *Blood* | | | | | | |
| Inorganic phosphorus | 3.5 (.43) | 3.2 (.52) | 3.4 (.42) | 3.2 (.45) | 3.5 (.42) | 3.3 (.84) |
| Creatinine | 1.0 (2.1) | 1.0 (.17) | .97 (.18) | .94 (.19) | 1.04 (.21) | 1.04 (.30) |
| Total lipids | 769 (189) | 819 (253) | 783 (317) | 780 (347) | 763 (242) | 764 (252) |
| Cholesterol | 218 (32) | 224 (31) | 221 (38) | 227 (31) | 218 (42) | 222 (39) |
| FFA (umol/L.) | 391 (242) | 784 (483)°°° | 366 (185) | 666 (240)°°° | 388 (185) | 730 (315)°°° |
| Glucose | 95 (7.2) | 97 (5.7) | 97 (7.0) | 98 (3.9) | 99 (4) | 98 (3) |
| SGO-T (Sigma units) | 15 (4.9) | 14 (4.3) | 13 (3.8) | 14 (3.3) | 14 (4) | 15 (6) |
| Alk. Phos. (Bodansky units) | 2.6 (.98) | 2.3 (.68) | 2.8 (.94) | 2.5 (.69) | 2.57 (.90) | 2.71 (.89) |
| Pseudocholinesterase (umol/ml./hr.) | 230 (29) | 228 (35) | 214 (32) | 214 (32) | 224 (22) | 224 (18) |
| Copper oxidase (O.D.) | .352 (.120) | .361 (.118) | .366 (.134) | .376 (.133) | .379 (.140) | .393 (.150)° |
| Eosinophils (per cu. ml.) | 124 (82) | 94 (91)°° | 134 (89) | 96 (93)°° | 155 (112) | 104 (101)°° |

Figures represent means and (standard deviations).
All values in mg. per 100 ml. unless otherwise specified.
p-values for t-test of correlated measures °$p < .05$, °°$p < .01$, °°°$p < .001$.

direct neurogenic mechanism or secondarily by adrenal release of catecholamines. As might have been expected, serum total lipids and cholesterol were not sensitive enough to measure such acute effects on lipid mobilization.

Some of the remaining findings are of interest. No significant alterations were noted in three fairly sensitive hepatic tests. If any impairment of hepatic function occurs with these drugs, it is more subtle than can be tested by usual laboratory means or follows the peak clinical effects. The significant rise in copper oxidase with psilocybin is difficult to explain, but the actual change in activity was minor, appearing to be of little consequence.

## Summary

Mescaline, lysergic acid diethylamide (LSD-25) and psilocybin were studied in 20 screened subjects, 18 receiving all three drugs. Drugs were administered under similar test conditions, doses were constant between drugs and subjects, assignments to drug followed a latin-square sequence, and subjects were unaware of the drug given on each trial. Clinical syndromes were assessed by a questionnaire completed by the subjects following each drug trial. Color perception was studied by means of both adequate and inadequate stimuli for eliciting color phenomena, measurements being taken before and two hours after drug was administered. A number of selected biochemical and physiologic measurements were also made at similar times.

Clinical syndromes were comparable in kind and degree from all three drugs, that from mescaline being most pronounced. Somatic manifestations predominated, psychotomimetic symptoms (other than visual hallucinations) being relatively uncommon. Color perception was not much altered when adequate stimuli were used, but color phenomena were appreciably enhanced from inadequate stimuli. Minor differences in color perceptual effects were noted between the three drugs, but similarities were greater. Each of the three drugs significantly decreased urinary excretion of inorganic phosphorus, increased plasma free fatty acids and decreased total circulating eosinophils. Of the other biochemical measurements made, only one other significant change was noted; an increase in copper oxidase activity after psilocybin.

The three psychotomimetic drugs were quite comparable in the areas studied. One might assume that they have many common mechanisms of action despite their chemical differences.

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