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Comparison of Psilocin with Psilocybin, Mescaline and LSD-25

By

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In the course of isolation of psilocybin (4-4-Phosphoryl-N:N-dimethyltryptamine) from the mushroom, *psilocybe Mexicana*, Hofmann *et al.*, (1958) noticed trace amounts of another substance, which they termed psilocin. Later Hofmann and Troxler (1959) identified psilocin as 4-Hydroxy-N:N-dimethyltryptamine, or dephosphorylated psilocybin. These investigators mentioned that Kielholz and Gnirss of the University Psychiatric Clinic in Basel had administered psilocin to humans and found that its action was similar quantitatively and qualitatively to that of psilocybin. More recently Horita and Weber (1961) found that psilocybin was rapidly dephosphorylated to psilocin by alkaline phosphatase in diverse tissues of various mammals. Horita and Weber speculated on the possibility that psilocin was the active substance in psilocybin.

The purpose of the present communication is to show that the objective and subjective effects of psilocin in man are similar to those of psilocybin, mescaline, and LSD-25, and further to report that psilocin and psilocybin are equipotent on a molecular basis.

Methods

Experiments. Two experiments were performed. In the first experiment 10 subjects received in randomized order 0.75 mcg/kg and 1.5 mcg/kg of LSD; 2.5 mg/kg and 5.0 mg/kg of mescaline; and 37.5 mcg/kg, 75 mcg/kg and 150 mcg/kg of psilocybin. The data on LSD and mescaline are also being reported separately in a paper dealing with cross tolerance between mescaline and LSD (Wolbach *et al.*, in press). In the second experiment, 5 different subjects received in randomized order 37.5 and 75.0 mcg/kg of psilocin and 75 and 150 mcg/kg of psilocybin.

Subjects. All subjects were former morphine addicts serving sentences for violations of the U.S. national narcotic laws. All were in good physical condition, and none presented any evidence of the major psychoses at the time the experiments were begun. Their ages varied between 25 to 33 years.

General Conditions. The experiments were conducted in a special ward devoted to clinical research. The patients entered the ward on the night before experiments were conducted and remained until the morning after receiving the drug. They were awakened at 6:30 a.m. and were free to mix and mingle with other patients in a common dayroom or to remain in their own rooms, as they preferred. Observations were made by specially trained attendants with many years of experience in observing patients that receive various drugs. The patients were not told what drugs they were to receive or the purposes of the experiment.

Drugs. All drugs were given intramuscularly at 8 a.m. Mescaline hydrochloride[1], and diethylamide of lysergic acid monotartrate[2], were dissolved in distilled water in appropriate concentration and autoclaved for 10 minutes at 15-lbs pressure. Psilocin[2], and psilocybin[2] bases were dissolved in a solution containing 10 mg/cc of cevitamic acid (Vitamin C) and autoclaved for 10 minutes at 15-lbs pressure. The addition of Vitamin C effectively prevented the alteration of psilocin to a compound with a deep-violet hue. The patients were not aware of the identity of the drugs, the doses used, or reasons for the experiments. The observers however did know these facts.

Observations. The following observations were made at hourly intervals from 7 a.m. to 4 p.m. after the patients had rested quietly for 10 minutes in bed: rectal temperature, pulse rate, respiratory rate, systolic blood pressure, diameter of the pupils, and thresholds for eliciting the kneejerk. The methods for making these measurements were those previously described (ISBELL *et al.*, 1956; ISBELL 1959). At hourly intervals from 7:30 a.m. to 3:30 p.m. patients completed a questionnaire, with the help of an aide, modified from that of ABRAMSON *et al.* (1955). A short mental status examination was made by one of the attending physicians at the height of the mental reaction and on the morning following the administration of the drugs. A grade of the intensity of the reaction was assigned, according to the system used in rating intensity of the LSD reaction (ISBELL *et al.* 1956).

Analysis of Data. The data were analyzed by methods identical with those previously reported (ISBELL 1959). Relative potency calculations were made according to the method of GADDUM (1953) for four-point assays, using the data obtained with the 37.5 and 75.5 mcg/kg dose of psilocin in all instances. The measurements obtained with 150 mcg/kg of psilocin were not used for relative potency calculations since responses with this dose were far above the range obtained with the highest doses of LSD or mescaline. Since the time courses of mes-

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[2] Psilocin and psilocybin were supplied through the courtesy of Dr. R. BIRCHER, Sandoz Pharmaceuticals, Hanover, N. J.

caline and LSD differed significantly from those of psilocin, relative potency calculations utilized the peak rather than the area (total course) values. In calculating the relative potencies of psilocin and psilocybin, both peak and area values were utilized.

Results

Experiment 1. The mean values on the area figures for the various parameters after the different doses of psilocin are shown in the Table.

Table. *Total course of the psilocin reaction*

Measure	Treatment			
	Placebo[1]	Psilocin (mcg/kg)		
		37.5	75	150
Temperature[2] . .	+ 2.7 ± 0.3	+ 4.0 ± 0.4	+ 4.3 ± 0.4	+ 5.2 ± 0.25
Pulse rate[2] . . .	+37.8 ± 14.5	+37.2 ± 10.6	+16.6 ± 12.4	+41.1 ± 12.3
Systolic blood pressure[2] . . .	+15.6 ± 13.5	+33.4 ± 14.9	+41.8 ± 10.5	+57.8 ± 10.4
Pupillary diameter[2]. . .	+ 0.2 ± 1.4	+ 6.5 ± 1.2	+ 8.7 ± 0.8	+14.6 ± 1.6
Kneejerk[2] . . .	−20.7 ± 11.1	−47.4 ± 15.7	−38.6 ± 9.2	−67.9 ± 17.1
No. positive answers[3] . . .	0.1 ± 0.3	19.1 ± 4.7	49.0 ± 7.8	94.1 ± 6.4
Clinical grade[4] .	0 ± 0	1.6 ± 0.2	2.6 ± 0.2	3.3 ± 0.2

[1] Data from ISBELL (1959) on 9 subjects.

[2] Figures are the means (10 subjects) ± standard errors of areas under time-action curves ("degree-hours", "beat-hours", etc.). The signs indicate increases (+) or decreases (—) in the measures after drugs as compared with pre-drug controls.

[3] Means ± standard errors of numbers of questions scored positively in the $7\frac{1}{2}$ hours after the drugs, which were not scored positively before drugs were given.

[4] Means ± standard errors on a scale of 0—4.

For comparison, values obtained after administration of a placebo taken from another experiment (ISBELL 1959) are included in this table. Data on LSD and mescaline can be found in the paper of WOLBACH *et al.* (1962), Like LSD and mescaline, psilocin caused significant increases in body temperature, systolic blood pressure, pupillary diameter and decreased the threshold for kneejerk.

Subjectively all three drugs caused anxiety, elation, euphoria or dysphoria, difficulty in thinking and concentration, marked alterations in sensory perception (especially visual perception), alterations in body image, kaleidoscopic visual "pseudo hallucinations", true hallucinations, and occasionally loss of insight (failure to realize that the effects experienced were due to the drug).

Psilocin appeared to differ from LSD and mescaline only in potency and time course. Symptoms after psilocin appeared within a few minutes, were nearly at peak within 30 minutes, and had largely sub-

sided in less than 4 hours. Peak effects of LSD occurred in 1—$^1/_2$ hours, and were largely dissipated within 5 to 6 hours. The peak effects after mescaline occurred at 2 to $2^1/_2$ hours and persisted longer than the effects of either LSD or psilocin. Using the peak values for pupillary dilatation, 1 mcg/kg of LSD tartrate was calculated to be equal to 45 mcg/kg of psilocin (95 percent confidence limits, 28.2 to 71.9 mcg/kg); and 1 mcg/kg of psilocin was calculated to be equivalent to 66 mcg/kg of mescaline (95 percent confidence limits, 44.4 to 82.5 mcg/kg). Relative potencies, calculated from the number of positive responses on the questionnaire at peak and from the clinical grade, agreed well with the estimates derived from the pupillary figures.

Experiment 2. Reactions after psilocin and psilocybin were very similar qualitatively, quantitatively, and in time course. Using the values of total effect on pupillary diameter (area figure), it was calculated that 1 mcg/kg of psilocin base was equivalent to 1.48 mcg/kg of psilocybin base (95 percent confidence limits, 1.08 to 2.05 mcg/kg). Nearly identical values were obtained using the data for peak pupillary response, total or peak number of answers on the questionnaire, and clinical grade.

Discussion

The data show that the spectrum of subjective and objective effects induced by LSD, mescaline, psilocin and psilocybin are quite similar with the drugs differing chiefly in potency and in time course.

The results confirm the conclusion of HOFMANN *et al.*, that the phosphoryl group is not essential for the psychotropic action of psilocybin. It is interesting that the relative potency of psilocin to psilocybin (1.48) is almost identical to the ratio of the molecular weight of the two drugs (1.4). Since HORITA and WEBER (1961) have shown that psilocybin is readily dephosphorylated by alkaline phosphatase this result supports, but does not prove, the hypothesis that psilocybin is dephosphorylated to psilocin before exerting its action.

Summary

1. Reactions induced by LSD, mescaline, psilocin, and psilocybin are qualitatively similar.

2. The time course of the psilocin and psilocybin reactions are shorter than those of LSD or mescaline reactions.

3. 1 mcg/kg of LSD tartrate is approximately equivalent to 45 mcg/kg of psilocin; 1 mcg of psilocin is approximately equivalent to 66 mcg/kg of mescaline.

4. Psilocin is approximately 1.4 times as potent as psilocybin. This ratio is the same as that of the molecular weights of the two drugs.

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