THE RELATIONSHIP BETWEEN THE METABOLIC FATE AND PHARMACOLOGICAL ACTIONS OF SEROTONIN, BUFOTENINE AND PSILOCYBIN[1]

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The startling hypothesis that the presence of serotonin in brain tissue could be equated with sanity had its basis in the fact that lysergic acid diethylamide (LSD) was potent both as a serotonin antagonist and as a psychotomimetic agent (Woolley and Shaw, 1954; Gaddum, 1954). The chemical structure of LSD shows it to be an indole derivative substituted in the 4-position. Furthermore, it has been known for some time that the N:N dimethyl derivative of serotonin itself, better known as bufotenine, is also somewhat psychotomimetic. Recently another potent psychotomimetic compound has been isolated which has features in common with both LSD and bufotenine, namely psilocybin which is the phosphate ester of the 4-hydroxy analogue of bufotenine.

The metabolic fate of serotonin has been studied in detail by McIsaac and Page (1959). Since bufotenine and psilocybin are similar structurally (see fig. 1), yet possess differing pharmacological actions, relationship between metabolic fate and pharmacological activity was studied.

Bufotenine. Originally isolated from the secretion of the glands found on toads' backs (Wieland *et al.*, 1931), bufotenine did not attract much attention until it was also isolated from the seeds of *Piptadenia peregrina* (Stromberg, 1954) where it was found to be the principal constituent among several indole bases (Fish *et al.*, 1955). These seeds have long been used by the South American Indians in the preparation of a psychotropic snuff called "cahoba."

Administration of bufotenine to human subjects intravenously has shown it to cause both psychotic episodes and cardiovascular effects of short duration, the intensity of these being directly proportional to the dose and the speed of injection (Fabing and Hawkins, 1956; Turner and Merlis, 1959).

Pressor responses were noted in cats by Evarts *et al.* (1955) when bufotenine was injected into the carotid artery. In such circumstances 0.2 mg/kg elevated the blood pressure by 20–40 mm Hg which lasted for 2–4 minutes, while 1 mg/kg elevated the blood pressure by 100–150 mm Hg which lasted for 3–5 minutes. Cardiac arrest in rabbits, 0.5–1.0 second after a 0.3-mg/kg intravenous injection, was observed by Rinaldi (1958). This arrest lasted 1–3 seconds and was probably produced by a vagal reflex as it was prevented by atropine. At the same time Rinaldi observed intense stimulation of the body smooth musculature.

Evarts (1956) gave monkeys 5.0 mg/kg and compared the behavioral changes produced with those resulting from an administration of 1 mg/kg of LSD and found them very similar. The monkeys assumed a prone position, which they attempted to preserve when disturbed. This phase lasted 20 minutes. After this they began moving about their cages, but their movements were ataxic and the monkeys appeared to be blind. Normality returned after 2 hours.

On feeding bufotenine to rats, Erspamer (1955) observed excretion of both unchanged bufotenine and 5-hydroxyindole acetic acid in the urine. Govier *et al.* (1953) have shown that while liver homogenates oxidize serotonin and methyl serotonin readily, as evidenced by oxygen uptake, bufotenine is much less readily oxidized, the rate being ⅓ of that of the aforementioned compounds. Blaschko and Philpot (1953) confirmed this finding.

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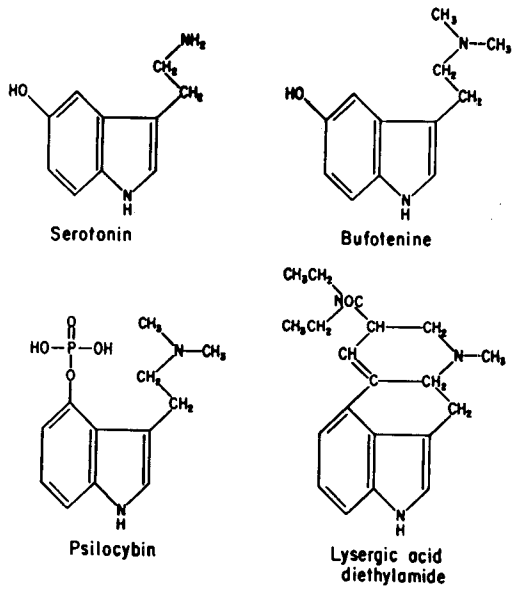

FIG. 1

Psilocybin. The American ethnologist Gordon Wasson and his wife discovered that the ancient religious practices of the Indians in a remote region of Mexico included ingestion of mushrooms. They described the occurrence of hallucinatory experiences during these rituals (Wasson and Wasson, 1957). They were accompanied on a later expedition by Dr. R. Heim, of the Musée Nationale de l'Histoire Naturelle, when it was possible to identify the fungi (Heim, 1956, 1957). Some of these mushrooms (*Psilocybe mexicana Heim*) were successfully cultivated in Paris (Heim and Cailleux, 1957) and the psychotropic principle was isolated in crystalline form from them by Hofmann *et al.* (1958a), who called it psilocybin. The structure of psilocybin was then elucidated and confirmed by synthesis (Hofmann *et al.*, 1958b, 1959) as the phosphoric ester of N,N-dimethyl 4-hydroxytryptamine (see fig. 1).

Some of the pharmacological actions of psilocybin were studied by Weidmann *et al.* (1958), who showed the compound to have no characteristic action on such isolated preparations as the guinea pig intestine and the rat uterus. However, it behaved antagonistically to serotonin in those preparations. Cardiovascular effects were studied in both anesthetized dogs and cats. Although in the former psilocybin proved to be a depressant, in the latter it became so only at higher doses, at low doses being pressor. Unanesthetized rabbits when dosed with psilocybin exhibited mydriasis, tachycardia, tachypnea, hyperthermia, and hyperglycemia. Those authors report a certain amount of sedation in animals dosed with psilocybin, a finding corroborated by Delay *et al.* (1959). Encephalographic studies of the effect of psilocybin on brain electrical activity (Weidmann *et al.*, 1958; Monnier, 1959) show considerable changes implying central action.

Hofmann *et al.* (1959) report that psilocin, the nonphosphorylated analogue of psilocybin, possesses similar pharmacological and psychotic properties to those of psilocybin both qualitatively and quantitatively.

MATERIALS AND METHODS. *Compounds.* Serotonin creatine sulfate, bufotenine bioxalate and psilocybin were used in aqueous solution. In metabolic experiments they were administered by intraperitoneal or subcutaneous injection.

Animals. Virgin female Sprague-Dawley rats, in the weight range 150–250 g, were used. The rats were kept throughout on Purina rat chow.

Chromatography. One-dimensional descending and two-dimensional ascending paper chromatography was used. In both instances Whatman no. 1 paper was employed. The solvents and respective running times were: one-dimensional (a) n-propanol, NH_4OH (4:1), 14 hours; (b) n-butanol –acetic acid–H_2O (4:1:5), 14 hours; two-dimensional: (c) n-propanol, NH_4OH (9:1), 18 hours; (d) 20% aqueous KCl, 2 hours.

The spraying reagents used were as follows: for hydroxyindoles, Ehrlich's Reagent (a 0.5% solution of *p*-dimethylamino-benzaldehyde in 1.5 N HCl) giving blue-violet spots with hydroxyindoles, yellow with urea and brown with indican. For carboxylic acid, either bromocresol green or methyl red. For phosphate groups, the acid molybdate reagent (Hanes and Isherwood, 1949) giving dark blue spots. For glucuronides, 1% naphthoresorcinol in a 10% solution of trichloroacetic acid in n-butanol followed by heating of the chromatogram at 100°C for 10 minutes. This reagent depends for its action on the ability of the trichloroacetic acid to split the glucuronides into the aglycone and glucuronic acid, and as some glucuronides are less readily split than others only positive results are significant.

Assay methods. Glucuronic acid in urine was determined by the method of Paul (1951). 5-Hydroxyindole acetic acid was measured colorimetrically (Udenfriend *et al.*, 1955) and serotonin fluorimetrically (Bogdanski *et al.*, 1956). Some estimations of the excretion of serotonin and its metabolites were made by isotope techniques previously described (McIsaac and Page, 1959).

TABLE 1

Fluorescent spectra of serotonin, psilocybin and bufotenine

	Activation max mμ	Fluorescent max mμ	pH	Sensitivity
Serotonin	310	360	7	1
	295	540	2	0.1
Psilocybin	295	360	7	1
	295	370	2	0.1
Bufotenine	310	360	7	1
	310	360	2	0.38

Attempts were made to develop a colorimetric assay procedure for the estimation of psilocybin using tetra-azotized ortho anisidine, a reagent for hydroxyindoles, but difficulties were encountered due to the instability of the color developed. A fluorimetric method of assay was found to be more practicable. The fluorimetric spectra of psilocybin, bufotenine and serotonin were similar at pH 7, but at pH 2 there were significant differences (table 1). Standard curves were obtained for the estimation of psilocybin and bufotenine at both pH's, and these show that, to obtain the same intensity of fluorescence at pH 2 as is found at pH 7, 2.6 times as much bufotenine and 10 times as much psilocybin is needed.

Bufotenine was recovered from urine at pH 9 by a continuous 3-hour-long n-butanol extraction. Recovery values of 96 ± 4% were obtained, the bufotenine being stable at the temperature of boiling n-butanol. This was shown by the fact that when a solution of bufotenine in n-butanol was boiled under reflux for 2 hours the concentration of bufotenine at the end of the experiment was the same as that at the beginning. Furthermore two-dimensional chromatography of residue left on evaporation of the above boiled solution revealed only one indole spot which corresponded to bufotenine. Psilocybin was found to be unstable in boiling n-butanol and was therefore extracted manually. Urines at pH 9 were extracted 3 times with equal volumes of n-butanol, recoveries of 55 ± 5% being obtained. Since other compounds having a similar fluorescence are normally excreted in the urine, an average normal excretion was determined before the experimental days (this amounted to values equivalent to an average 19.4 ± 6.8 μg bufotenine or 24.0 ± 5.2 μg psilocybin per 24 hours) and the increase above normal on these days was considered to be psilocybin or bufotenine. In the case of bufotenine it was possible to show by two-dimensional chromatography that the butanol extract contained bufotenine and a spot [R_f 0.05 and 0.66 in solvents (a) and (b) respectively] but no 5-hydroxyindole acetic acid. The butanol extract of the psilocybin urine had the same fluorescent spectra as psilocybin.

In vitro procedure. Liver homogenates were made in 0.1 M phosphate buffer, pH 8, so that the resulting homogenate contained 0.5 g wet liver per ml. The homogenates were incubated at 37°C with 0.01 mmol/ml concentrations of substrates. Aliquots of 0.02 ml (containing approximately 60 μg of substrate) were taken out at 10-minute intervals and chromatographed in solvents (a) and (b).

Blood pressure recordings. For blood pressure determinations on rats, the animals were anesthetized with sodium amobarbital (10 mg/100 g intraperitoneally) and pretreated with 5 mg pentolinium tartrate to block the central control of the blood vessels. They also received 0.6 mg atropine and bilateral vagotomy was performed. Blood pressure was recorded from the carotid artery and the compounds to be assayed were injected into a femoral vein.

Determination of sleeping times. Sleeping time determinations were done according to the method of Salmoiraghi *et al.*, (1956b). Sleeping time was measured as the time interval between the loss and the return of the righting reflex following the intraperitoneal injection of hexabarbital sodium (Evipal), 105 mg/kg body weight. The rats used were all of the same colony, virgin females, weighing between 80 and 100 g. The compounds to be tested were injected intraperitoneally 10 minutes before the hypnotic.

Expressions of variability accompanying average values in various portions of the manuscript represent the standard error.

RESULTS. *Toxic effects.* Bufotenine: When administered intraperitoneally to rats a single dose of 125 mg/kg proved fatal in less than 30 minutes, the animal dying in a position similar to that of a decorticate preparation. It was found that fatal effects would be obviated if the same total dose was administered subcutaneously at the rate of 21 mg/kg per hour, six separate injections being made. All the animals exhibited signs of abnormal behavior, by crawling along their cages with their tails held high. On the following day they appeared to be grossly normal and accepted both food and water. Of the five animals treated in this way, four developed prostration on the sixth or seventh day. The syndrome was as follows: considerable flaccidity (the acutely poisoned rat was characterized by its extreme rigidity), dehydration and loss of about ⅓ of the body weight. The vertebral

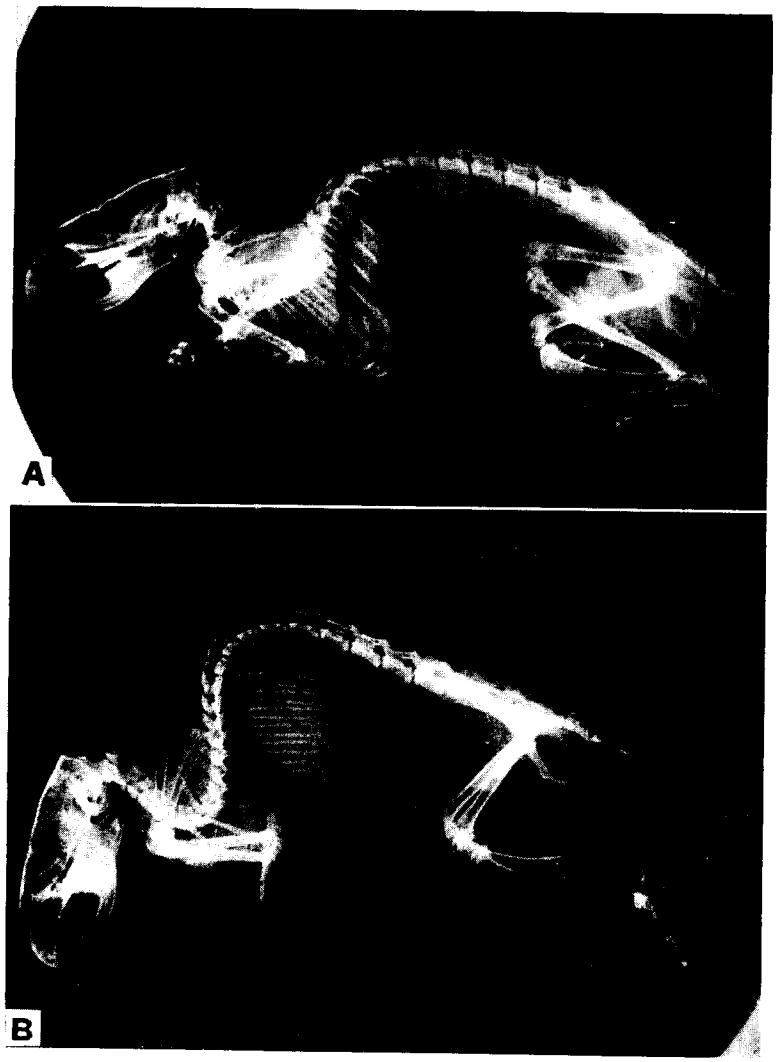

FIG. 2. Post-mortem X-ray photographs: A) bufotenine; B) psilocybin. For explanation, see text.

column was markedly arched between the middle lumbar and the middle thoracic region, and though it could be extended, it returned to the former position on release. The animals were abnormally cold and though the breathing rate was one gasp per 20 seconds the extremities were but slightly cyanosed and the heart rate normal (120/min). Death followed shortly. Autopsy did not reveal any gross abnormalities but X-ray showed the presence of a marked cervical hyperextension as shown in figure 2.

Psilocybin: This compound was found to be much less toxic than bufotenine. Rats given psilocybin intraperitoneally at the dose level of 100 mg/kg exhibited signs of abnormal behavior within 15 minutes which lasted for several hours. During this stage, although the animals were less active than normal, any external stimulus evoked an exaggerated evasive response. Within 24 hours they appeared grossly normal; however, one rat died 10 days later in a manner similar to that caused by bufotenine, there being present the same thoraco-lumbar hyperflexion and cervical hyperextension (see fig. 2).

Metabolic fate. Bufotenine: Rats were given 125 mg/kg of bufotenine subcutaneously in

TABLE 2

Urinary excretion of serotonin, bufotenine, psilocybin and metabolites

Compound	Dose (mg/kg)	Rat No.	Excretion Expressed as Percentage of Dose		
			Unchanged compound	Hydroxyindole acetic acid	Glucuronic acid conjugation
Serotonin*	80	1	5.5	43.5	±
		2	7.3	39.6	
		3	9.4	34.8	
		Avg.	7.1	39.3	
Bufotenine†	125‡	4	29.0	8.7	
		5	14.5	5.7	++
		6	21.5		
		Avg.	21.7	7.2	
Psilocybin*	100	7	10.0	trace	
		8	12.0	trace	+
		Avg.	11.0		

* 24-hour urine collection.

† 48-hour urine collection.

‡ In divided doses over 6-hour period.

divided doses over 6 hours. The 48-hour urines were assayed for unchanged bufotenine, and 5-hydroxyindole acetic acid. The bufotenine excretion was 21.7 ± 3.9% (3 rats) and the 5-HIAA was 7.2 ± 1.5% (2 rats). Glucuronide excretion (3 rats) was measured for 2 days before the experimental day, on the experimental day, and for 2 days following. Increases in glucuronide excretion following administration of bufotenine were equivalent to not more than an average of 25% of the dose. Due to the small amount administered it was impossible to be more exact.

The urine was examined by two-dimensional ascending paper chromatography in solvents (c) and (d). In this way it was possible to confirm the presence in the urine of both unchanged bufotenine (R_f c: 0.76; d: 0.29) and 5-hydroxyindole acetic acid (R_f c: 0.09 d: 0.54). In addition a third spot of roughly the same order of magnitude as the above two appeared at R_f c: 0.25; d: 0.66. This spot when sprayed with bromocresol green gave a yellow color, indicating an acidic compound. When the chromatograms were sprayed with the reagent for glucuronides no glucuronide spot could be detected.

Psilocybin: Two rats (200 g) were each given 20 mg (100 mg/kg) of psilocybin intraperitoneally and the 24-hour urine was examined for metabolites. A strongly positive naphthoresorcinol reaction indicated the presence of increased amounts of glucuronic acid. One-diminensional descending chromatography in solvents (a) and (b) demonstrated the presence of two major metabolites and one minor metabolite. The major spots were a glucuronide which gave a positive reaction when sprayed with the naphthoresorcinol reagent and unchanged psilocybin which gave a blue spot when sprayed with Ehrlich's reagent [R_f 0.04 and 0.63 in solvents (a) and (b) respectively]. Another small indole spot became apparent when Ehrlich's reagent was used; this had similar chromatographic properties to 5-hydroxyindole acetic acid [R_f 0.20 and 0.85; *cf.* 5-hydroxyindole acetic acid 0.20 and 0.84 in solvents (a) and (b) respectively]. The spot also gave positive reactions for a carboxylic acid using bromocresol green and methyl red.

Estimations were made of unchanged psilocybin and glucuronic acid conjugates appearing in the urine. Some 11% of a dose of psilocybin appeared in the urine unchanged. Increases in glucuronide excretion were equivalent to not more than an average of 20% of the dose but the low dose level employed made it difficult to be more exact (see table 2).

In vitro metabolism. A comparison was made of serotonin, bufotenine and psilocybin as substrates for monoamine oxidase activity *in vitro* by the technique described. The chromatograms showed rapid degradation of serotonin to 5-hydroxyindole acetic acid within 10 minutes. However, it was 40 minutes before any trace of 5-hydroxyindole acetic acid could be demonstrated in the bufotenine incubate. Psilocybin seemed to be relatively immune from degradation since only unchanged psilocybin could be found even after 2 hours' incubation. It was concluded that monoamine oxidase could degrade bufotenine with difficulty and psilocybin only with great difficulty, if at all.

Pharmacology. The effect of serotonin on blood pressure in rats is well known, and depends upon the previous treatment of the animal (Salmoraghi *et al.*, 1956a). In normal, anesthetized rats, serotonin is mainly vasodepressor, partly due to the von Bezold-Jarish reflex mechanism, and partly to peripheral vasodilatation. In pithed rats, or rats pretreated with ganglionic blocking agents, serotonin is vasopressor.

Both bufotenine and psilocybin were found to

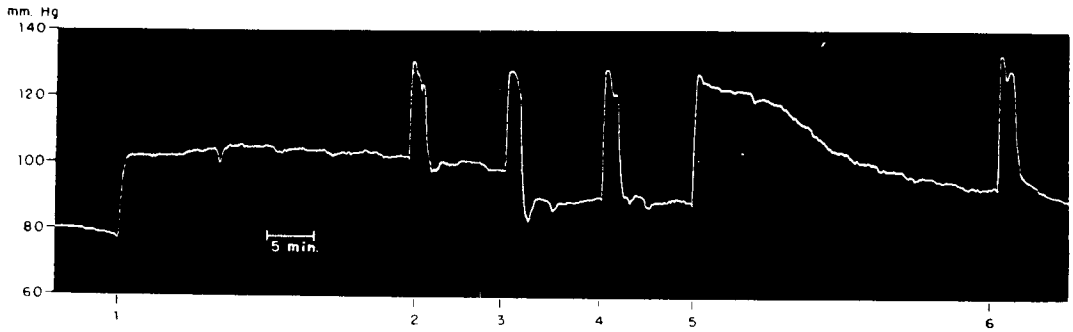

FIG. 3. Effect of various tryptamine derivatives on rat blood pressure. 1) 37.5 μg psilocybin; 2) 0.03 units angiotensin; 3) 20.0 μg serotonin; 4) 20.0 μg serotonin; 5) 20.0 μg bufotenine; 6) 20.0 μg serotonin.

be pressor in blocked and unblocked rats. In blocked animals serotonin creatinine sulfate (20 μg) raised the blood pressure by 30–40 mm of mercury. This effect lasted 2–3 minutes, and then the blood pressure returned to the base line (see fig. 3). Bufotenine (20 μg) raised the blood pressure to the same degree, but the return to the base line took 30 minutes. Psilocybin (37.5 μg) also raised the blood pressure by 30 mm Hg; however, even after 1 hour there was no reversal of the effect, the blood pressure remaining elevated.

Salmoiraghi *et al.* (1957) showed that bromo lysergic acid diethylamide (BOL) would block the vasopressor response to serotonin. It is of interest, therefore, that BOL would reverse the prolonged elevation of blood pressure due to psilocybin, and would block the further pressor effects of both bufotenine and psilocybin (see fig. 4).

In fig. 3 evidence is presented that serotonin can partially reverse the pressor effect of psilocybin. This occurred in 5 out of the 6 experiments performed; on one occasion this did not occur (see fig. 4). Hence while synthetic angiotensin given after psilocybin will only cause a further transient elevation of the blood pressure, 20 μg serotonin as a rule will, after a similar initial elevation, reduce the pressure to the pre-psilocybin level.

Potentiation of sleeping times. The sleeping time of hexobarbital treated rats (150 mg/kg body wt) was increased by pretreatment with the indole derivative at a dosage of 51.5 μmol of compound per kg body weight, this amount being in all cases less than the LD50 value for the indole compounds. The results (see table 3) expressed in percentage increase of sleeping time, show a 58% increase for serotonin, an 81% increase for bufotenine and a 126% increase for psilocybin. Though, as listed above, the doses given were below the LD50 values, nonetheless 52% of the psilocybin-treated animals died during the experiment, by enhancement of the barbiturate effect, all the deaths occurring within 60 min of the administration of the hexobarbital. These animals were excluded from calculations of the potentiation of sleeping time.

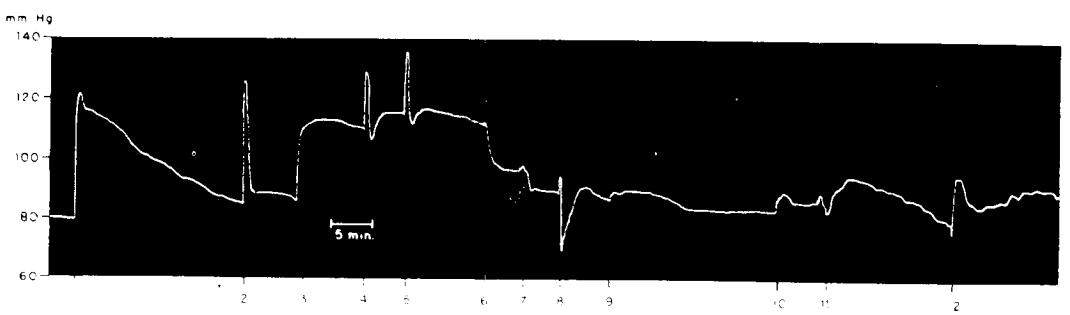

FIG. 4. Effect of various tryptamine derivatives on rat blood pressure. 1) 20.0 μg bufotenine; 2) 20.0 μg serotonin; 3) 37.5 μg psilocybin; 4) 20.0 μg serotonin; 5) 20.0 μg serotonin; 6) 50.0 μg BOL; 7) 50.0 μg BOL; 8) 20.0 μg serotonin; 9) 37.5 μg psilocybin. 10) 20.0 μg serotonin; 11) 75.0 μg psilocybin; 12) 20.0 μg bufotenine.

TABLE 3

Determination of the prolongation of hexobarbital sleeping times by serotonin, bufotenine and psilocybin

Compound Injected	No. of Rats	No. Dead	Avg. Sleeping Time (min)	Prolongation	% Prolongation
Hexobarbital	18	—	99 ± 14	—	—
+ serotonin	10	—	156 ± 18	58	58
+ bufotenine	9	1	179 ± 13	80	81
+ psilocybin	21	11	224 ± 26	125	126

DISCUSSION. One of the more striking differences found between the compounds studied was the duration of their pressor action in rats. Thus, while serotonin has a transient effect on blood pressure, bufotenine possesses an activity which gradually decreases over a period of 30 minutes and psilocybin possesses a prolonged activity (over 1 hour).

A similar gradation was observed in the results of both *in vivo* and *in vitro* metabolic experiments and in the potentiation of sleeping times. *In vitro* studies using the three compounds as substrates indicate that, whereas serotonin is rapidly metabolized by monoamine oxidase, bufotenine is only slowly metabolized and psilocybin even after 2 hours appears to remain unattacked. Studies of the metabolic fate of these compounds *in vivo* tend to confirm that both bufotenine and psilocybin are more resistant to monoamine oxidase attack than serotonin. Thus after the administration of serotonin the 24-hour urinary excretion of 5-hydroxyindole acetic acid accounts for 39% of the dose, yet after the administration of bufotenine only 7% of the dose can be thus accounted for and in the case of psilocybin only a trace of an acid with similar properties could be found in the urine.

In the metabolic fate of bufotenine and psilocybin, as would be expected, the excretion of the unchanged compounds and alternative pathways such as conjugation with glucuronic acid become more important. Thus after administration of these compounds the excretion of the unchanged compound was two to three times as great as after serotonin. Again in both cases the excretion of glucuronic acid conjugates was increased to a greater extent than after the administration of serotonin, though due to the toxic nature of these compounds only relatively small amounts could be administered (0.5 mmol/kg). Owing to this fact, the results are indicated in table 2 by means of plus signs.

In considering the structural differences of this series of compounds and the resulting biological properties, it should be noted that bufotenine is more similar structurally to serotonin than psilocybin, even were it admitted that the phosphate group of the latter has no functional necessity. This is reflected in the pharmacological properties of these compounds, for while bufotenine appears in all known instances to act at the serotonin receptor sites in a manner similar to it as is evidenced by its pressor action and oxytocic activity (Barlow and Khan, 1959), psilocybin acts only at some of the serotonin receptor sites, as shown by its pressor action, but not at others, as shown by the absence of oxytocic activity (Weidmann *et al.*, 1958). Further, the differences in structure between serotonin and psilocybin appear to be such that the compounds are mutually antagonistic, psilocybin being antagonistic to the oxytocic activity of serotonin and serotonin reversing the prolonged pressor action of psilocybin.

The potentiation effect these compounds have on hexobarbital sleeping time is of interest. As before, a gradation in the effects is seen, for while serotonin potentiates the sleeping time by 58%, bufotenine does so by 81% and psilocybin by 126%. In the case of the last compound 52% of the experimental animals died during the experiment.

Finally, it has been found that these compounds (namely, bufotenine and psilocybin) possess very unusual toxic effects. As can be seen from figure 2, rats dying, a week after dosage, from the toxic effects of the administered compound presented the same picture of acute thoracic kyphosis accompanied by a cervical hyperextension of the spine. It has been shown before that kyphoscoliosis is a prominent feature of osteolatherism (Selye, 1957) in a study of the production of spinal curvatures in rats by a series of compounds. Dasler and Storer (1959) suggested that a severe atrophy of the muscles and a shortening of the tissue elements surrounding the spine was the cause of spinal deformity similar to that found in the present experiments. Certainly in the present experiments a gross loss of weight and gross evidence of muscle wasting were found to be part of the syndrome.

SUMMARY

Bufotenine and psilocybin both possess vasopressor activity in anesthetized rats which is similar to serotonin and which can be blocked by BOL. The duration of pressor action is, however, greater, namely 30 minutes, with bufotenine and more than 1 hour with psilocybin.

The duration of pressor activity is proportional and probably related to the rate at which these compounds are inactivated by monoamine oxidase in the *in vitro* experiments.

Experiments *in vivo* confirm that bufotenine and psilocybin are much less readily destroyed by monoamine oxidase than is serotonin; and that the alternative pathways of metabolism, namely excretion unchanged, or in conjugation with glucuronic acid are of more importance.

The potentiation of hexobarbital sleeping times indicates that cardiovascular effects are paralleled by a central effect. The potentiation was 58%, 75% and 126% for serotonin, bufotenine and psilocybin, respectively.

Unusual toxic effects characterized by weight loss and spinal kyphosis were found to occur 7 to 10 days after doses of 125 and 100 mg/kg of bufotenine and psilocybin, respectively.

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