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Bufotenine: Toward an Understanding of Possible Psychoactive Mechanisms

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Bufotenine: Toward an Understanding of Possible Psychoactive Mechanisms

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Abstract—A review of the neuropharmacology of the alleged hallucinogen bufotenine is presented, including recent experimental results showing activity similar to LSD and other known hallucinogens (psilocin and 5-MeO-DMT) at the purported hallucinogenic serotonin (5-HT) receptors, 5-HT2A and 5-HT2C. In addition, current reports of computer modeling of the receptors and ligand binding sites give evidence of bufotenine's ability to bind and activate these receptors. While binding and activation of the purported hallucinogenic receptors are not the full extent of the hallucinogenic signature, this evidence shows support for the rationale that the reported lack of the drug's classic hallucinogenic response in human experiments is due to poor ability to cross the blood brain barrier (BBB), not lack of activation of the appropriate brain receptors. Further evidence is reviewed that in some physiological states, some drugs with characteristics similar to bufotenine which do not normally cross the BBB, cross it and enter the brain. While direct human experimental evidence of bufotenine's hallucinogenic activity seems lacking, the above combined factors are considered, and possible explanations of bufotenine's reported psychoactivity are suggested. Additionally, updated experimental models testing the possible nature of bufotenine's hallucinogenic potential are proposed.

Keywords—blood brain barrier, *Bufo* toads, bufotenine, hallucinogens, serotonin receptors

In the past century since bufotenine (5-hydroxy-N,N-dimethyltryptamine) was isolated from the toxin of *Bufo sp.* toads and more recently as it has been applied to experimental models of serotonin activity, the debate over its true hallucinogenic nature has been ongoing. While a full review of the history of *Bufo* toads and the purported hallucinogen bufotenine is beyond the scope of this article, an excellent historical perspective of the controversy may be gained through the reviews of Lyttle, Goldstein and Gartz (1996), and Davis and Weil (1992). The consensus of these authors, as well as others (Jacob & Shulgin 1994; McKenna & Towers 1984; Chilton, Bigwood & Jensen 1979), is the rejection of bufotenine as a hallucinogen.

However, numerous anecdotal media reports of psychoactivity through toad licking, toad toxin mixture ingestion and toad skin smoking continue to appear. In particular, the use of *Bufo marinus* is often noted (Lyttle, Goldstein & Gartz 1996; Davis 1985). Additionally, a large body of anthropological and archaeological evidence suggests that toads may have been ritually used as psychoactive agents in ancient Mesoamerican cultures (Furst 1990 & 1981; Reilly 1989; Kennedy 1982; Coe & Deihl 1980).

Early in the application of bufotenine to behavioral studies it was theorized that, while the drug showed significant psychoactive potential due to its structural similarity to known hallucinogens (see Figure 1), its low lipid solubility might prevent it from crossing the blood brain barrier (BBB) to elicit behavioral activity (Migliaccio et al. 1981; Glennon et al. 1979; Vogel & Evans 1977). To circumvent this barrier to central nervous system activity, bufotenine was injected directly into animal brain ventricles (Geyer et al. 1975). By this route, bufotenine was shown to be equiactive with the known hallucinogen 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT). These results were

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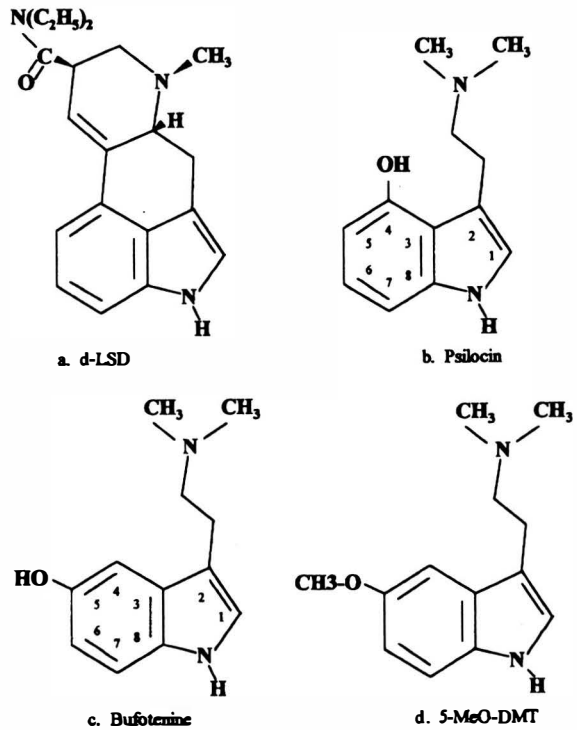
FIGURE 1
Comparative Chemical Structures (Indole Ring Numbering is Shown in Psilocin and Bufotenine)



supported by Vogel and Evans (1977), who measured rat behavior activity versus dosages and brain concentrations of psychoactive drugs. They reported that, although LSD and 5-MeO-DMT were active at relatively low dosage compared to bufotenine (3, 10 and 100 umoles/kg respectively), when measured at brain concentrations LSD was five times more potent than bufotenine, which was almost three times more potent than 5-MeO-DMT (at concentrations of 0.5, 2.5, and 7 umoles/kg respectively). They also suggest that 5-MeO-DMT's high level of activity is due to high BBB penetration, and has "relatively weak" activity at the brain receptors. Gessner and Dankova used a bufotenine ester to penetrate the BBB. This form of bufotenine had greater lipid solubility than its parent compound, and after being hydrolyzed to bufotenine in the brain it elicited behavioral effects (cited in Glennon et al. 1979).

In addition, human experimentation by Fabing and Hawkins (1956) and McLeod and Sitaram (1985) offers some insight into the general physiological effects of the drug. In their human experiments, Fabing and Hawkins describe numerous dramatic cardiovascular, visual and gastrointestinal effects from intravenous administration of bufotenine. Among these were increased respiratory rate, heaviness in the chest, purpling of the head and neck skin (like the color of a diluted eggplant), visual disturbances and color hallucinations, vomiting, nausea, and retching. They also report that within a few minutes of stopping the injection, these symptoms began clearing, leading to a period of mental awareness and continued perceptual changes. McLeod and Sitaram administered bufotenine intranasally with no effects. They administered bufotenine intravenously and reported no cardiovascular or gastrointestinal effects, and their subject did not exhibit the breathing difficulties and intense skin flushing as reported by Fabing and Hawkins. However, profound emotional and perceptual changes, as well as bizarre visual effects, were reported when intravenous dosages were increased. Interestingly, all of the nonpsychoactive symptoms that these researchers reported might be attributed to bufotenine's effect at multiple serotonin receptors throughout various organ systems, as described by Borne (1994). In addition, it is clear that by increasing dosages as cited in both of these reports, any central effects elicited by the drug might be masked by exacerbation of peripheral effects.

While classical hallucination reactions, as reviewed by Glennon (1994), seem lacking as described by these researchers and their subjects, enough evidence seems present to pursue reasons why some psychoactive effects are taking place. By reviewing the current molecular pharmacology of bufotenine, including activity at serotonin receptors in the central nervous system, insight may be gained as to the drug's purported actions.

TABLE 1
Binding Affinities at the 5-HT2A & 5-HT2C Receptors (uM Concentrations)

	5-HT2A	5-HT2C	Reference
d-LSD	< 10	< 10	Peroutka 1991
	0.38 ± 0.05*		Almaula et al., 1996a
	0.24 ± 0.05	6.4 ± 0.7	Almaula et al. 1996b
Bufotenine	2.7 ±1.3**		Roth et al. 1997a
	< 10	10-1,000	Peroutka 1991
	162 ±14*		Almaula et al. 1996a
	182 ± 35	234±27	Almaula et al. 1996b
	337 ±91*		Roth et al. 1997a
	649 ±52		Choudhary et al. 1993
5-MeO-DMT	15 ±2**		Glennon et al. 1994
	620 ± 40*	960 ±180	Glennon et al. 1994
Psilocin	81 ±12*	140 ±12	Almaula et al. 1996b

*Measured at [^{3}H] Ketanserin-labeled 5-HT2A receptors (low affinity state).
**Measured at [^{125}I]DOI-labeled 5-HT2A receptors (high affinity state).

SEROTONIN ANALOGS AND THEIR RECEPTORS: CLUES TO THE HALLUCINOGENIC SIGNATURE

The study of serotonin (5-hydroxytryptamine, 5-HT) and its receptor sites are currently one of the most dynamic areas in drug research due to the lengthy and diverse list of physiological effects that serotonin has on the body. Some of these effects moderated by serotonin include cardiovascular effects, gastrointestinal motility, mood and behavior control, appetite and sleep control, and sexual and hallucinogenic behaviors (Borne 1994). Comprehensive reviews of serotonin receptors and ligands are found in Hardman and Limbird (1996), Glennon and Doukat (1995), Glennon, Westkaemper and Bartyzel (1991), and Peroutka (1991).

Since very early in the development of serotonin research, LSD, psilocin, 5-MeO-DMT, as well as other purported hallucinogens such as bufotenine, have been used in numerous experimental models to characterize 5-HT receptors and activity (Peroutka 1985; Aghajanian & Hailgler 1975; Hungen, Roberts & Hill 1975). This is due to the nonspecific nature of LSD, bufotenine and other indolealkylamines when binding at multiple 5-HT receptors (Peroutka 1991, 1985; McClue, Brazell & Stahl 1989).

The potent hallucinogenic nature of LSD has long been established and its effects serve as the model of classic hallucinogenic response (Glennon 1994). Psilocin is an indolealkylamine metabolite of psilocybin, found in the hallucinogenic mushroom genus *Psilocybe*, as well as other mushroom families. The botany of psilocybin mushrooms is reviewed by Schultes (1990), and the hallucinogenic effects of psilocin are vividly depicted by R. Gordon Wasson (1990, 1980) in his ethnomycolatry accounts of Mexican mushroom rituals. Likewise, Davis and Weil (1992) experimented with 5-MeO-DMT, an indolealkylamine derived from the toxin of the Sonora Desert Toad, *Bufo alvarius*. They reported profound hallucinogenic responses by smoking the toad's dried toxin. These known hallucinogens may serve as pharmacological models to directly compare with bufotenine.

At least 14 distinct 5-HT receptors have been pharmacologically and physiologically characterized (Glennon & Doukat 1995; Peroutka 1991). However, for this review of hallucinogenic activity, comparisons will be limited to activities at the 5-HT2A and 5-HT2C receptors, formerly named 5-HT2 and 5-HT1C. Of the many possible modes of comparison of the agents in question, the current review will compare receptor binding activity, second messenger production and possible binding mechanisms as cited in the current literature. These criteria currently serve as some of the initial biochemical tools which are being used to measure possible hallucinogenic potential.

Serotonin-2 (5-HT2) receptors belong to the super family of G protein-coupled receptors (GPCRs) linked to the activation of Phospholipase C (PLC) as an intermediate step in neural transmission (See reviews by Sanders-Bush & Canton 1995; Trumpp-Kallmeyer et al. 1992; Huang & Julius 1991). This is in contrast to other classes of 5-HT receptors which are linked to the activation of adenyl cyclase as their corresponding intermediate step or "second messenger," and do not appear to serve a role in hallucinogenisis. The cascade of intracellular mechanisms involving PLC activation is generally characterized as "PI hydrolysis" and may be a more important measurement of receptor-ligand activity than binding affinity.

Correlation between 5-HT receptor binding affinities and human hallucinogenic potency has suggested that 5-HT2A receptors mediate the hallucinogenic effects of LSD, phenethylamine hallucinogens, and indolealkylamine hallucinogens (Marek & Aghajanian 1996: Fiorella, Rabin & Winter 1995a; Peroutka 1991; McClue, Brazell & Stahl

TABLE 2
Effects of 5-HT and Hallucinogens at 5-HT Receptors Linked to PI Hydrolysis

	5-HT2A		5-HT2C		
Drug	**pEC_{50}**	**Emax***	**pEC_{50}**	**Emax***	**Reference**
5-HT	6	100	8.1	100	Cornfield & Nelson1991
	-	-	6.47	100	Cornfield & Nelson1991
	7.21± 0.22	100	7.81±0.07	100	Newton et al. 1996
LSD	8.5	25	7.9	34	Cornfield & Nelson1991
	8.79±0.05	38±3	6.55±0.30	25±2	Newton et al. 1996
Bufotenine	6.4	44	6.55	56	Cornfield & Nelson1991
5-MeO-DMT	-	-	6.42	47	Cornfield & Nelson1991
	6.52± 0.13	54±11	6.07±0.09	75±5	Newton et al. 1996

*Emax values are given as percent relative to 5-HT.

TABLE 3
Ability to Activate PI Hydrolysis at the 5-HT2A Receptor

Drug	**K_{act} (uM)**	**V_{max}**	**Reference**
5-HT	47±13	100	Roth et al. 1997b
	62 ±20	100	Roth et al. 1997a
	92 ±18	100	Choudhary et al. 1993
Bufotenine	84 ±2	72 ±1	Roth et al. 1997b
	127 ± 24	90 ±14	Roth et al. 1997a
	182 ±77	80 ± 14	Choudhary et al. 1993
5-MeO-DMT	988 ±169	86 ±2.6	Roth et al. 1997a

Note: V_{max} expressed as the percentage of maximum stimulation of 5-HT

1989). In addition, a major role for the 5-HT2C receptor in hallucinosis has been proposed (Sanders-Bush 1994; Burris, Breeding & Sanders-Bush 1991).

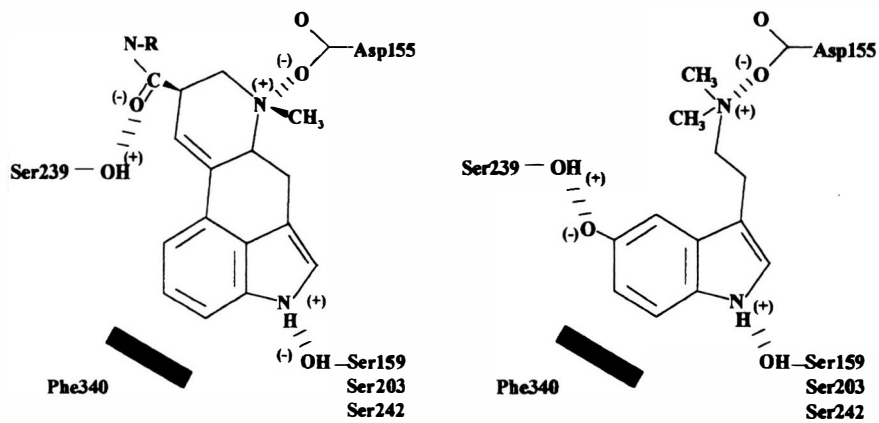
In a series of *in vivo* biochemical and behavioral experiments in rats, Fiorella, Rabin and Winter (1995a, 1995b, 1995c) studied the hallucinogenic effect of LSD and other known hallucinogens and their activity at the 5-HT2A and 5-HT2C receptors. Their data support the hypothesis that agonist activity at both of these receptors is an essential component of the stimulus effect of indolealkylamine hallucinogens (Fiorella, Rabin & Winter 1995a). In addition, their results "... suggest that 5-HT2A agonist activity may be required, but is not in itself sufficient for indolamine ... compounds to elicit hallucinations in humans" (Fiorella, Rabin & Winter 1995b). Finally, they summarize that agonist interactions with 5-HT2A receptors may predominantly mediate the stimulus properties of hallucinogens, while the 5-HT2C receptors play a modulatory role (Fiorella, Rabin & Winter 1995c).

In reviewing results from comparative studies between hallucinogenic and nonhallucinogenic drugs' activities at both the 5-HT2A and 5-HT2C receptors, Newton and colleagues (1996) also conclude that "... it is unlikely that hallucinosis is mediated primarily by activity at the 5-HT2C receptor, whereas activity at the 5-HT2A receptor may represent an important but not unique mechanism associated with hallucinogenic drug action."

Binding activity of LSD, psilocin, 5-MeO-DMT and bufotenine at both the 5-HT2A and 5-HT2C receptors is well established (see Table 1). Current measurements of receptor activity confirm Vogel and Evans' (1977) early reports of brain activity measurement, with the order of activity being LSD > bufotenine > 5-MeO-DMT. In addition, psilocin, bufotenine and 5-MeO-DMT mirror LSD's preferential binding activity at the 5-HT2A receptor over the 5-HT2C receptor.

Comparisons of PI hydrolysis activity at 5-HT2A and 5-HT2C receptors (Tables 2 and 3) demonstrate that bufotenine activates both receptors at levels which closely duplicate or surpass results produced by LSD and 5-MeO-DMT. As stated above, this measure of receptor activation coupled with measures of receptor binding affinities offers evidence toward hallucinogenic potential. While these data offer initial steps in collecting the criteria toward the full hallucinogenic signature, they do not prove nor disprove hallucinogenic activity.

FIGURE 2
Purported 5-HT2A Receptor Binding Sites of LSD (Left) and Bufotenine



To illustrate the possible mechanisms by which LSD and other ligands bind and activate the 5-HT2 receptors, the current article offers the following list of purported 5-HT2A ligand receptor binding or recognition sites. Binding sites are given as the amino acid, its sequence number, and the transmembrane domain of the receptor's protein structure in which it is found. Numerous other binding sites and mechanisms are being studied, hence regular additions and revisions to this list seem likely.

1. Asp155 TMH III: hydrogen bonds with the terminal amine of bufotenine and the amine nitrogen embedded in the heterocycle of LSD (Almaula et al. 1996a; Kristiansen & Dahl 1996; Shih, Chen & Gallaher 1994).
2. Ser239 TMH V: binds the 5-OH of serotonin or bufotenine, or the -Oxy of 5-MeO-DMT (Kristiansen & Dahl 1996). Serine 239 is also in a position to possibly bind the carboxy group of LSD (Westkaemper & Glennon 1994; Wang, Gallaher & Shih 1993)
3. Ser242 TMH V: binds 4-OH group of the hallucinogen psilocin (Shih, Chen & Gallaher 1995, 1994). Almaula and colleagues (1996a) and Johnson and colleagues (1993) suggest that Ser242 binds the N-1 nitrogen on the Indole ring rather than the 4-oxy group of the indolealkylamines. Alternatively, Ser159 TMH III or Ser203 TMH IV has also been suggested as N-1 binding sites (Donnelly, Findlay & Blundell 1994,as cited in Kristiansen & Dahl 1996; Trumpp-Kallmeyer et al. 1992).
4. Phe340 TMH VI: interacts via *pi-pi* stacking (edge-to-face) with the phenyl moiety of indolealkylamine and ergoline ligands (Roth et al. 1997a, 1997b; Kristiansen & Dahl 1996; Choudhary et al. 1995).

The graphic representations of chemical structures and binding mechanisms of LSD and bufotenine at the 5-HT2A receptor derived from this list are shown in Figure 2. The chemical structures are derived from Pfaff and colleagues (1994), Westkaemper and Glennon (1994), Johnson and colleagues (1993), and Glennon, Westkaemper and Bartyzel (1991). These representations show the possibility of identically favorable binding sites for LSD and bufotenine.

In summary, using the criteria of receptor binding activity correlated with measurements of PI hydrolysis activity, and adding the illustration of similarities of binding geometry, when bufotenine is compared with other known hallucinogens, there is a significant amount of evidence that bufotenine possesses similar or identical properties. It follows that if bufotenine is present at therapeutic concentrations at the 5-HT2A and 5-HT2C receptors in the brain, its neurological response should mirror that of LSD, 5-MeO-DMT or psilocin. This evidence might both confirm and narrow the argument of bufotenine's hallucinogenic potential to the question of its ability to cross the blood brain barrier, not its activity at the purported hallucinogenic receptors.

BLOOD BRAIN BARRIER (BBB) AND PARTITION COEFFICIENTS

In correlating 5-MeO-DMT's and psilocin's hallucinogenic actions with possible reasons for bufotenine's purported psychoactivity despite its poor ability to cross the BBB, an understanding of the mechanisms of drug permeability and impermeability is required. In particular, mechanisms by which the BBB is compromised may prove helpful in considering possible mechanisms for bufotenine's psychoactive potential.

Guyton (1991) states "In general, the blood-cerebrospinal fluid and the blood-brain barriers are highly permeable to water, carbon dioxide, oxygen, and most lipid-soluble substances such as alcohol and most anesthetics, . . . and almost totally impermeable to plasma proteins and many large organic molecules. Therefore, the blood-cerebrospinal fluid and the blood-brain barriers often make it impossible to achieve effective concentrations of . . . some non-lipid-soluble drugs in the cerebrospinal fluid or parenchyma of the brain."

The correlation between polarity, degree of ionization, lipid solubility, and membrane permeability is discussed in Gennaro (1990: 709-711). It has long been recognized that a drug's degree of lipid solubility generally correlates to ability to cross the BBB and other biological membranes if an active transport mechanism is lacking.

Although lipid solubility of a drug might be an important factor in determining its ability to cross the BBB, a more important criteria seems to be its partition coefficient. "It is more logical to use partition coefficients rather than solubility in a single solvent for structure-activity correlations since, in a biological system, one is dealing with a heterogeneous system rather than a simple solution. Partition coefficients have been used in the study of drug absorption, distribution, metabolism, toxicity and structure-activity correlation" (Gennaro 1990: 170-171). Table 4 shows experimentally observed partition coefficient values for 5-MeO-DMT, psilocin and bufotenine, with higher values equating to increased ease in passage through various lipoprotein barriers. The values shown in Table 4 appear to correlate with Barfknecht & Nichols 1975), who proposed a value of 1.40 as the lower limit required to obtain in vivo hallucinogenic activity in man, with an optimum value of 3.14.

The structure-activity relationships of classical hallucinogens are reviewed by Jacob and Shulgin (1994). About the indolealkylamines, they state, "The 5-hydroxylation of DMT . . . yields bufotenine, which is probably not a hallucinogen." They go on to state that O-methylation (yielding 5-MeO-DMT) allows entry into the CNS, again implying that bufotenine's hallucinogenic inactivity may be due to inability to cross into the brain. Confirmation of 5-MeO-DMT's ability to accumulate in the brain is documented by Takahashi and colleagues (1985) and Berger and colleagues (1978).

As cited above, numerous investigators hypothesize that the lack of experimental confirmation of the hallucinogenicity of bufotenine is due to its low lipid solubility leading to poor penetration into the brain (Migliaccio et al. 1981; Kantor, Dudlettes & Shulgin 1980; Chilton, Bigwood & Jensen 1979; Glennon et al. 1979; Vogel & Evans 1977). This poor distribution of bufotenine into the brain has been confirmed, although minor, presumably subefficacious levels do accumulate there (Fuller, Snoddy & Perry 1995; Sanders-Bush, Oates & Bush 1976).

TABLE 4
Comparative Observed Partition Coefficients

Drug	Part. Coef.
5-MeO-DMT	3.30*
Psilocin	3.30*
Bufotenine	0.06**

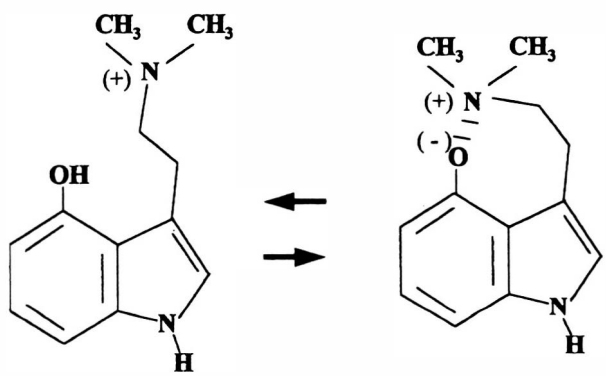
*Migliaccio et al. 1981.
**Migliaccio et al. 1981; Glennon et al. 1979.

In correlating structure-activity relationships between bufotenine and psilocin, both are hydroxylated at adjacent points on the indole ring system. It follows that psilocin should have the same partition coefficient as bufotenine, with marginal central activity. If the assumption is made that bufotenine's lack of hallucinogenic activity is mainly due to its poor ability to cross the BBB, then the same should hold for psilocin. However, numerous investigators (McKenna & Towers 1984; Kantor, Dudlettes & Shulgin 1980), have proposed that psilocin may form a pseudo-ring system, a configuration which bufotenine is not able to achieve (Migliaccio et al. 1981; see Figure 3). Kantor, Dudlettes & Shulgin (1980) comment that this ring conformation may allow oral efficacy of 4-hydroxyl substituted drugs such as psilocin, presumably by increasing permeability across the BBB, as well as inhibition of enzymatic catabolism by monoamine oxidase (MAO).

In this proposed system, the charged terminal nitrogen of the amine group and the anionic 4-hydroxyl group interact through ionic bonding. Thereby, the molecule becomes much less polar and its partition coefficient may increase to a value comparable to 5-MeO-DMT. This is supported by values reported by Migliaccio and colleagues (1981), who noted identical observed values of 3.30 for psilocin and 5-MeO-DMT, as well as a much lower observed value of 0.06 for bufotenine. They also note that psilocin's high partition coefficient is due to lower dissociation (presumably the 4-oxy function being "covered" by the charged nitrogen), yielding a configuration which is less basic by an order of magnitude when compared with bufotenine. It is possible that the molecule readily reorients from this ring system to its binding shape since the bond strength between the amine nitrogen and either the 4-oxy group of the indole or the Asp155-oxy group of the purported binding site is approximately the same (Gennaro 1990: 170). Taken together with the binding activity at the 5-HT2A and 5-HT2C receptors shown above, this feature of high BBB permeability may be part of an explanation for psilocin's documented hallucinogenic activity.

Similarly, the substitution of the methyl group at the 5-oxy of bufotenine, yielding 5-MeO-DMT, results in a poorly ionized, nonpolar molecule with a relatively high observed partition coefficient (Table 4). The correlation between this high partition coefficient and ability to cross

FIGURE 3
Psilocin as a Pseudo-Ring System



the BBB is reported by Berger and colleagues (1978), whose animal studies demonstrate significant accumulation of 5-MeO-DMT in brain tissues. It is most noteworthy that the 5-methyl substitution does not enhance 5-HT receptor affinity (Glennon, Westkaemper & Bartyzel 1991; Glennon et al. 1979). This may lead to the conclusion that the methyl substitution, while allowing the molecule to cross the BBB more readily than bufotenine, might in fact lower the binding activity and PI hydrolysis at the 5-HT2A receptor as shown in Tables 1 and 3.

In summary, when compared with psilocin and 5-MeO-DMT, bufotenine's lack of ability to readily cross the blood brain barrier seems to be the main correlation to its lack of hallucinogenic activity. However, to explain the reported psychoactive effects of the drug, other mechanisms may be considered and combined with the evidence that it shows significant activity at the 5-HT2 receptors.

DISRUPTION OF THE BBB

To answer the question of the reported psychoactive properties of bufotenine, part of the solution is suggested by physiological events which disrupt the blood brain barrier (BBB).

The BBB serves as one of the most important protective mechanisms in the body. By isolating the brain from fluctuations in body chemistry, foreign chemicals (drugs), and infectious bacteria and viruses, the internal environment of the brain is stabilized for normal electrical activities (Marieb 1992). The BBB is essentially constructed of the walls of the endothelial cells of the brain capillaries, joined by tight, impermeable junctions (Marieb 1992; Guyton 1991). This is in contrast to the relatively loose junctions and ready permeability of capillaries throughout the rest of the body (Guyton 1991).

However, the BBB is compromised during certain physiological events in the body, in particular during acute hypertensive episodes. This may be due to the mechanical stretching and distention of the lumen of the microvessels during times of increased fluid pressure (Johansson 1989).

During periods of acute hypertension, the permeability of the BBB to a number of compounds is increased. "Opening of the BBB allows uncontrolled influx of plasma into the interstitial space which modifies the physiological micro environment of the brain and might bring biologically active factors in contact with the neurons" (Sokrab et al. 1988). Experimentally, these hypertensive states are achieved through administration of vasopressors such as epinephrine. In numerous studies, the sharp rise in blood pressure caused the BBB to leak otherwise impermeable molecules into the brain tissue (Johansson 1989; Sokrab et al. 1988; Hardebo & Ownman 1980; Johansson & Martinsson 1980, 1979).

The use of hyperosmolar intra-arterial solutions of mannitol replicates the sharp increase in fluid pressure seen in acute hypertensive insults. Using this technique, Zunkeler and colleagues (1996) demonstrated the rapid rise in arterial pressure increased BBB permeability to Methotrexate, a chemotherapeutic drug "which is exemplary of drugs with low permeability." Methotrexate is also described as "practically insoluble in water, alcohol, chloroform or ether . . ." (Gennaro 1990: 1155), implying a remarkably low partition coefficient.

In studies where epinephrine was used as the hypertensive agent, albumin, fibrinogen and other blood components which would normally not cross the BBB, leaked into brain tissues (Johansson 1989; Sokrab et al. 1988; Johansson & Martinsson 1980, 1979).

It is interesting to note that in this and many other studies, epinephrine was used as the vasopressor of choice to disrupt the BBB. Its ability to compromise the BBB is greater than other vasopressors such as norepinephrine and angiotensin (Sokrab et al. 1988; Johansson & Martinsson 1979). In a review by Hardebo & Ownman (1980), the

authors show evidence that once the BBB is compromised during hyperosmolar or hypertensive insult, monoamine neurotransmitters can enter the brain. They state that "once the barrier is open, systemically administered monoamines enter the brain parenchyma, where they can induce pronounced changes in cerebral blood flow and metabolism." The monoamine neurotransmitter models that they used are 5-HT, epinephrine, and dopamine, none of which normally crosses the BBB. Additional experimental results by Johansson & Martinsson (1979) showed that once the BBB is opened with epinephrine, entry of epinephrine itself caused significant alteration of brain activity.

These BBB studies may begin to offer some evidence toward an understanding of some dynamics of the reported psychoactive properties of bufotenine. While no specific BBB study seems to exist using bufotenine as the experimental drug crossing the compromised BBB, some inference might be drawn from the Methotrexate and monoamine neurotransmitter observations. Each of these drugs apparently crosses the intact BBB less readily than bufotenine, however, during hypertensive insults, each crosses into the brain.

DISCUSSION

In summarizing the results of the reviewed data correlating 5-HT2 receptor activity and BBB permeability studies, we are left with the conclusion that in order to elicit possible hallucinogenic responses in humans, bufotenine cannot be used as a sole agent. Furthermore, many of the known or purported indolealkylamine hallucinogens such as 5-MeO-DMT, DMT and bufotenine were shown to be ineffective when taken orally. Psilocin, with its ability to form a pseudo-ring structure is the lone example of oral activity in this group of reviewed compounds. Hence, any further experimental models which might test the possibility of bufotenine's hallucinogenic properties would have to incorporate an agent which would compromise the BBB as described above. Additionally, if a catecholamine such as epinephrine is used to open the BBB, both it and bufotenine would have to be administered parenterally, since both are inactive through the oral route of administration.

It is essential to note that in the human hallucinogenic experiments by Fabings and Hawkins, and McLeod and Sitaram, bufotenine was used as the sole active agent. Although in both of these reports bufotenine was injected parenterally, the absence of an agent to open the BBB yielded ambiguous results. This might lead to an updated experimental model in which epinephrine or a similar vasopressor is added to the mixture. While suggesting that this model may overcome the shortcomings of these previous human experiments, two factors might reconcile the uncertain results that were reported. If given as a single entity, while exhibiting other serotonergic responses, small amounts of bufotenine have been shown to accumulate in the brain (Fuller, Snoddy & Perry 1995; Sanders-Bush, Oates & Bush 1976). Additionally, although significant blood pressure changes were not noted, local vasopressor actions of high doses of bufotenine may have partially compromised the BBB to allow at least a partially effective dose of the drug to enter the brain in addition to the natural accumulation which occurs. While potentially being masked by other serotonergic responses, these accumulations may have caused some psychoactive manifestations, although not a full hallucinogenic response.

These sole-agent experiments also took the drug out of its natural context of being in a mixture with other bioactive ingredients such as in *Bufo* toad toxin. Most of the anecdotal reports that link bufotenine to hallucinogenic activity have involved the use of *B. marinus* dried skins or toxin. The main components of the natural products derived from *Bufo sp.* toads are cardioactive sterols (bufotoxins and bufagins), catecholamines such as epinephrine, and indolealkylamines such as bufotenine, serotonin, bufothionine, cinobufotenine and 5-MeO-DMT (Daly, Myers & Whittaker 1987; Chen & Kovarikova 1967). The cardiotoxic activity of the bufotoxins and bufagins contained in toad toxins is well documented, although it is beyond the scope of this review (See references in Lyttle, Goldstein & Gartz 1996; Hitt & Ettinger 1986).

The indolealkylamine component of toad toxins is recognized as the potentially hallucinogenic part of the mixture. While *Bufo alvarius* toxin has been shown to be hallucinogenic through its 5-MeO-DMT content, *B. bufo bufo* and *B marinus* have been anecdotally linked to hallucinogenic activity through the bufotenine contained in their toxins. In comparison, *B. viridis* toxin is not mentioned as being psychoactive. Accordingly, *B. viridis* toxin contains bufothionine, which is not mentioned as being hallucinogenic.

Also important to this review is that major components of toad toxins and toad skins are catecholamines such as epinephrine. The toxin of *B. marinus* may contain up to 5% epinephrine (Chen & Kovarikova 1967). When looking for explanations of reported psychoactivity through toad toxin use, while the harmful effects of the cardiotoxic sterols must not be overlooked or discounted, the potential effects of high concentrations of epinephrine and other vasopressors likewise cannot be omitted. Additionally, bufotenine itself has been described as a vasopressor (Kantor, Dudlettes & Shulgin 1980), although Fabing and Hawkins (1956) reported no changes in their subjects' blood pressure.

The implication of toad toxin psychoactive effects here are twofold. First, in a dose-dependent manner of administration, if the toxic effects of the cardiotoxic sterols were somehow avoided or diminished by smoking or other parenteral routes, and the hypertensive effect of the epinephrine component was left intact, there is a possible physiological scenario of epinephrine causing an acute hypertensive episode. Second, subsequent to this hypertensive

insult, bufotenine may cross the compromised BBB, and enter the brain in sufficient concentrations to bind and activate the 5-HT2A and 5-HT2C receptors and cause a psychoactive response.

Although they did not experiment with the toxin of *Bufo marinus*, with its high concentrations of bufotenine and epinephrine, Davis and Weil (1992) reported that smoking the toxin of *Bufo alvarius* with its high concentrations of 5-MeO-DMT caused profound hallucinations, an apparent indication that at least some indolealkylamines may be heated without loss of potency. Additionally, epinephrine administered by inhalation has long been recognized as a rapid, potent vasoconstrictor and vasopressor, although no evidence seems to have been reported on epinephrine's efficacy when heated through smoking.

From an ethnopharmacological viewpoint, an experimental route of administration through enema solutions might be explored. A number of sources report that in numerous Mesoamerican and South American cultures, many psychoactive agents have been taken rectally. Peter de Smet (1985) gives a comprehensive pharmacological review of snuffs and enema preparations used by ancient and modern New World peoples. In particular, he describes enema self-administration of DMT, an indolealkylamine relative of bufotenine. He reports no effects from the DMT, and attributes this to possible first-pass metabolism of the drug through the liver. A interesting experimental model would be the application of a bufotenine and epinephrine combination enema. This might test whether other indole alkaloids show the same results, along with whether epinephrine is therapeutic through rectal administration, and finally whether the combination would produce any effect on the BBB leading to psychoactive response.

In summary, we are left with possible future experimental research which might be performed to confirm or disprove bufotenine's true psychoactivity. Animal studies might be performed using epinephrine and bufotenine to determine if bufotenine actually crosses the BBB if it is opened with epinephrine. Proposed human experiments in a controlled setting might include a mixture of bufotenine and epinephrine administered either through inhalation, enema or injection. Additionally, *Bufo marinus* toxin might be experimentally smoked to duplicate the experiments performed by Davis and Weil (1992), or likewise given as an enema. While any psychoactive effects could be monitored and recorded, a record of blood pressure fluctuations would be useful in determining the acuity of the hypertensive insult needed to open the BBB to allow fully psychoactive concentrations of bufotenine to cross into the brain.

A controlled experimental setting would achieve the goals of accurately recording results while offering protection against the potentially harmful effects of the experimental agents. Especially careful consideration must be given to the potential toxicity from the bufotoxins contained in *B. marinus* toxin used in experimental models and in further discussions of toad use. Questions of dosage, route of administration and MAO metabolism might be resolved through these prospective experiments.

CONCLUSION

This article has attempted to bring three topics into focus as they apply not only to the consideration of bufotenine as a possible psychoactive agent, but also as they apply to known hallucinogens. These topics are activity at the purported hallucinogenic receptors, ability to cross the BBB, and events which disrupt the BBB.

Current neuropharmacology research uses the parameters of receptor binding activity and activation of second messenger production as basic molecular functions of possible hallucinogenic response. In reviewing the current literature and its accepted parameters for measuring possible hallucinogenic potential, this article has attempted to introduce aspects of molecular pharmacology to the question of bufotenine's purported hallucinogenic activity. These recent discoveries of the molecular level of hallucinogenic activity do not appear to have been included in any previous discussion of bufotenine's psychoactivity or lack thereof. For future reviews of any purported hallucinogen, the issues of appropriate receptor binding and activation should not be overlooked.

To help illustrate experimental results and to further pursue activation mechanisms, computer molecular modeling of 5-HT2 receptors and their ligands is being actively developed. Ensuing reviews of hallucinogens might consider these aspects as important parts of discussion of psychoactivity.

Additionally, an attempt has been made to identify pharmacologically possible scenarios to reconcile reports of psychoactivity described in published human experimental reports, as well as anecdotal reports of toad toxin and toad skin use. While questions concerning possible toxic consequences of toad toxin use remain, this article has attempted to show a possible psychoactive link between two of their naturally occurring components, bufotenine and epinephrine.

Finally, this article has attempted to address reasons why the ability to cross the BBB may not be an immutable reason for a drug's purported central nervous system activity or lack thereof. When considering natural products, the context of their use must be taken into account, especially if they are presented in combination with other potentially active agents in their natural setting. The bulk of reasoning behind the rejection of bufotenine as a hallucinogen seems linked to its poor ability to cross the BBB, and disregards its natural context. The current review of events and agents which compromise the BBB may stimulate further consideration of this aspect of bufotenine's neuropharmacology through some of the suggested experimental models.

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