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Indolealkylamine and Phenalkylamine Hallucinogens: A Brief Overview

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GLENNON, R. A. AND J. A. ROSECRANS. *Indolealkylamine and phenalkylamine hallucinogens: A brief overview.* NEUROSCI. BIOBEHAV. REV. 6(4) 489–497, 1982.—Various indolealkylamine and phenalkylamine derivatives are hallucinogenic in man and/or are behaviorally active in animals. This overview is divided into two parts. The first part attempts to bring together information concerning the activity of indolealkylamines (i.e., tryptamines, α-methyltryptamines, N,N-dimethyltryptamines, N-alkyltryptamines, lysergic acid derivatives and β-carbolines) and phenalkylamines (i.e., phenethylamines, phenylisopropylamines) along with major key references, and with emphasis on those agents not recently reviewed. The latter portion of this overview describes some of the work being conducted in our laboratories in an effort to elucidate the role of the neurotransmitter serotonin in the mechanism of action of various indolealkylamine and phenalkylamine hallucinogens.

Indolealkylamine hallucinogens Phenalkylamine hallucinogens Discriminative stimulus properties Phenylisopropylamines Phenethylamines Tryptamine derivatives LSD β-Carbolines α-Alkyltryptamines Serotonin

THE use of hallucinogenic agents, particularly of the indolealkylamine type, pre-dates early Aztec culture [13,58]. Yet, today, the term "hallucinogen" still lacks an incisive definition. Hoffer *et al.* [33] introduced "hallucinogen" in 1954; this was followed, shortly thereafter, by the introduction of the term "psychotomimetic." These terminology are somewhat ambiguous in that hallucinogenic agents do not always produce hallucinations nor do psychotomimetic agents necessarily produce psychoses. Kety has noted that hallucinogens produce true hallucinations in only a small percentage of individuals and that a more interesting observation is that they produce a wide variety of mental changes including delusions, hallucinations, thought disturbances, paranoid states and affective changes in different individuals at different times [39]. This is consistent with the generally accepted notion that such agents can produce alterations in thought, mood, perception and behavior. See Brimblecombe and Pinder [8] for a more lengthy discussion of nomenclature and classification. Here, the terms "hallucinogen" and "psychotomimetic" will be used synonymously. However, it is not being implied that all hallucinogenic/psychotomimetic agents produce the same (or similar) effects in man and/or in animals.

Hallucinogenic agents can be divided into a number of categories; perhaps the two largest categories with respect to possible variety of derivatives are the indolealkylamines (tryptamine-derived agents, lysergic acid derivatives and β-carbolines) and phenalkylamines (phenethylamines and phenylisopropylamines). Both human and animal data exist which support the suggestion that certain derivatives in each of the above categories are capable of producing similar behavioral effects; data also exist which indicate that other derivatives produce non-similar effects and, further, that yet other derivatives are behaviorally inactive.

The discussion which follows is divided into (a) a brief review of indolealkylamine and phenalkylamine hallucinogens, and (b) speculations with respect to their mechanism of action. The review section is by no means exhaustive. Rather, an attempt has been made to sort through the existing literature to determine which agents are behaviorally active. Where possible, human data have been included; where such data are unavailable, animal data are quoted. As a note of caution, hallucinogenic activity is a species-specific phenomenon in the sense that only man can actually determine whether or not a compound is hallucinogenic. Animal data should be taken at face value; yet, there are instances where such data have proved remarkably reliable in terms of predictive value. The review will place emphasis on those agents and issues which have previously received relatively little attention and will attempt to highlight the more recent literature. Selected, but representative, references will be cited. Several more detailed, general reviews on older, more established, and miscellaneous hallucinogenic agents are available [7, 8, 11, 16, 21, 51, 61, 75]. A considerable amount of effort has been directed toward elucidation of the mechanism of action of hallucinogenic agents. Without attempting to survey the literature in this regard (refer to the general references cited above), the final section deals with some of our work on the involvement of serotonin in the mechanism of action of these agents.

INDOLEALKYLAMINES

(1) Tryptamines

Though not necessarily without central effects, tryptamines have not been found to possess significant behavioral activity. As a class, however, tryptamines have received relatively little attention. Curtis and Davis examined the effect of a large series of tryptamines on neurones of cat lateral geniculate nucleus [12]. Results of other animal studies are also available [46]. Martin and Sloan have reported that tryptamine (*1*a), itself, produces little central effect in man [43]. Its 5-methoxy derivative (i.e., 5-methoxytryptamine, 5-OMeT; *1*b) produces some behavioral effects in rats [19] and, at high doses, in non-human primates [31]. On the other hand, in tests of discriminative stimulus (DS) control, generalization does not occur when either tryptamine (*1*a) or 5-OMeT (*1*b) is administered to groups of rats trained to discriminate the hallucinogenic agent 5-methoxy-N,N-dimethyltryptamine (5-OMe DMT) from saline [23]. The finding of little or no activity for tryptamine derivatives which are unsubstituted on the α-carbon or terminal amine may be a consequence of rapid metabolism in vivo by, for example, oxidative deamination. Metabolism can be hindered, and activity enhanced, when the tryptamines bear an α-methyl group or are N-alkylated. Furthermore, evidence suggests that certain tryptamines penetrate the blood-brain barrier only with great difficulty. Vogel and Evans have introduced the concept of "minimal effective brain level" (MEBL) and have compared the effects produced in animals by certain agents as a function of the concentration of these agents in the brain (see [76] and references therein). They suggest, based on the amount of drug that actually gets into the brain, that 5-OMeT (*1*b) is actually more potent than either DMT (*3*a) or 5-OMe DMT (*3*e) and that, in fact, it may be equipotent with LSD; alkylation of the terminal amine of *1*b reduces activity but increases the ability of the compound to penetrate the blood-brain barrier. Administration of larger doses of *1*b, in order to achieve greater brain levels, manifests itself in disruption of behavior, which may be a peripherally-mediated event [76].

(2) α-Methyltryptamines

Numerous α-methyltryptamines have been synthesized, but, with a few exceptions, relatively little has been published on their animal pharmacology, and even less on their human activity. α-Methyltryptamine (α-MeT; *2*a) is hallucinogenic in man. Early studies on the effects of *2*a in humans have been reported by Hollister *et al.* [34] and by Murphree *et al.* [49]; their results have been supported by a more recent study [65].

In animal studies, generalization occurs between the stimulus produced by 5-OMe DMT and that produced by α-MeT [27]. The most potent of the tryptamine-derived hallucinogens is 5-methoxy α-MeT (*2*b), which, in man, is about ten times more active than α-MeT (*2*a) [38,63]. A number of other α-alkyl tryptamines have been prepared; for example, Heath-Brown and Philpott [30] have synthesized a series of such compounds for which there are some animal [41], but no human data. Ho and co-workers [32] have conducted animal studies on additional derivatives. Recently, Marsden has studied the involvement of dopamine and serotonin in the effects produced by α-MeT [42]. Also, because of its chiral center, α-MeT can exist as R(−) and S(+) isomers; Repke and Ferguson [53] have recently reported the synthesis of each of the enantiomers from the appropriate ethyl tryptophanate. The entire subclass of α-methyltryptamines deserves further attention.

(3) N,N-Dimethyltryptamines

This subclass is perhaps the best studied of the indolealkylamines. DMT (*3*a) and its 5-methoxy derivative (5-OMe DMT; *3*e), and, to a lesser extent, other tryptamine-derived compounds, have been identified as constituents of hallucinogenic plant substances used by Central and South American natives in pre-Columbian times [35]. Yet, only recently have these compounds been studied in a controlled clinical setting. In 1956, Szara [68] reported on the activity of DMT in man. It might be noted that unlike tryptamine, both its α-methyl (*2*a) and N,N-dimethyl (*3*a) derivatives are hallucinogenic, with the latter being approximately half as active as α-MeT (*2*a).

Psilocin (*3*b), the 4-hydroxy derivative of DMT is about five times as active as the parent compound. Being one of the better known members of this subclass, its pharmacology has been reviewed in detail [8]. The phosphate ester of psilocin (i.e., psilocybin), like psilocin, is naturally-occurring. Psilocybin, which is approximately equiactive with psilocin, is probably rapidly hydrolyzed to psilocin in vivo. The O-methyl ether of psilocin, 4-OMe DMT (*3*c) has not been evaluated in man under controlled conditions, although results from animal studies are available (e.g., [73,77]). In rats trained to discriminate 5-OMe DMT from saline, 4-OMe DMT was found to be about as active as DMT [27,73].

Bufotenine (5-hydroxy DMT or N,N-dimethylserotonin; *3*d) has been a subject of controversy for a number of years. In one human study bufotenine was found to be active in total doses of 4–16 mg (IV) [15]; however, Turner and Merlis [72], who investigated the effects of bufotenine in fourteen schizophrenic patients, report that the drug was not hallucinogenic at doses of up to 20 mg (IV). The latter publication also mentions that Isbell found bufotenine, at doses of 10–12.5 mg (IM) to produce elementary visual hallucinations in an unspecified number of subjects. When administered to animals, only small amounts of bufotenine penetrate the blood-brain barrier [56], a finding which is consistent with its low lipid solubility [20]. Based on minimally effective brain levels, Vogel and Evans conclude that bufotenine may actually be two to three times more active than 5-OMe DMT (*3*e), but that only a small fraction of an administered dose ever reaches the brain [76]. In an effort to overcome this problem of poor lipid solubility, Gessner *et al.* [20] prepared 5-acetoxy DMT (i.e., O-acetyl bufotenine), which was found to possess a greater lipid solubility than bufotenine, and, which should be hydrolyzed to bufotenine once it has entered the brain. Animal studies reveal that 5-acetoxy DMT is behaviorally active, and more active than either DMT or 5-OMe DMT [17]. No human studies have been performed with 5-acetoxy bufotenine. Because this acetyl derivative is probably hydrolyzed quite rapidly in vivo, several other 5-acyloxy derivatives have been prepared; detailed pharmacology is not yet available on these compounds, although the pivalyl derivative (5-PB) has been found to be behaviorally active in animals [25]. It might also be noted that bufotenine has been demonstrated to be active in several other animal studies when it was administered in such a manner as to by-pass the blood-brain barrier (see discussion in [23] and [25]).

Gessner *et al.* [18,20] and Benington *et al.* [4], in another attempt to overcome lipid solubility problem of bufotenine, prepared and evaluated 5-OMe DMT (*3*e). Although *3*e was assumed to be hallucinogenic, based on the results of animal studies, it was only recently demonstrated to be active in man [65]. 5-OMe DMT is about ten times more active than DMT, and, as such, is thus far the most potent member of the dimethyltryptamine subclass of hallucinogenic indolealkylamines.

6-Hydroxy DMT (*3*f) displays only weak behavioral activity in animals [10, 73, 74] and is not hallucinogenic in man [55]. It may be argued that the lipid solubility of 6-hydroxy DMT, like that of bufotenine, will not allow it to penetrate into the brain; this might account for its inactivity. The hydroxylated derivatives of DMT present an interesting problem. It has been speculated that psilocin, the 4-hydroxy analog of DMT, can form an intramolecular hydrogen bond between its hydroxyl group and terminal amine, thereby enhancing its lipid solubility. The lipid solubility of psilocin, as measured by chloroform-buffer partition coefficient, is indeed not as low as that of bufotenine [20]. Migliaccio *et al.* [48] have recently studied the conformational aspects of bufotenine and psilocin using high-resolution NMR spectroscopy.

It might be speculated that 6-hydroxy DMT, like bufotenine, would display more activity if it were made more lipid soluble by, for example, acylation of the hydroxyl group. Although this is an intriguing possibility, its likelihood is not supported by the low order of activity of its O-methyl ether 6-OMe DMT (*3*g) [20,27]. 7-Hydroxy DMT (*3*h) has not been the object of much study although some animal data are available [10,12]. 7-Methoxy DMT (*3*i) displays a definite, but low order of, activity in animals [20, 27, 37].

Several novel derivatives of N,N-dimethyltryptamine have also shown interesting behavioral activity in animal studies. For example, using rats as subjects, 7-methyl DMT (7-TMT; *3*j) appears to produce effects similar to those of other hallucinogenic agents [27]. Benington, Morin and Kline (unpublished data) have recently prepared the 4-methylthio and 5-methylthio analogs of DMT, i.e., 4-SMe DMT (*3*k) and 5-SMe DMT (*3*l), respectively. In the discriminative stimulus assay, generalization occurs between 5-OMe DMT and both 4-SMe DMT and 5-SMe DMT, with the sulfur compounds being only slightly less active than their corresponding methoxy derivatives [29]. Animal data are also available on a number of other related compounds such as 4,5,6-trimethoxy and 5,6,7-trimethoxy DMT, 5-OMe-6-OH DMT and dimethylhomotryptamine [52, 70, 71, 74], but human data are unavailable.

(4) Miscellaneous N-Alkylated Tryptamines

The N,N-diethyl derivative of tryptamine (DET; *4*a) is hallucinogenic in man [5] and is approximately equipotent with DMT (*3*a). Based on minimal effective brain levels in animal studies, however, Vogel and Evans [76] have concluded that DET may only be one-half as potent as DMT. With respect to human studies, activity appears to decrease with increasing steric bulk about the terminal amine of these alkylated tryptamine derivatives, though this has not been well documented. For example, DPT (*4*c) is somewhat more active than DMT, although DMT is apparently shorter acting than either DET or DPT [69]. DPT has been employed as an adjunct to psychotherapy, in doses of 10 to 165 mg [67]. Although di-isopropyltryptamine (*4*e) is still hallucinogenic [38,64], further increase in the size of the alkyl substituent to di-butyl or di-hexyl reduces dramatically, or abolishes, activity. Related derivatives such as 4-hydroxy DET (*4*b) and 5-OMe DiPT (*4*f) are active in man [38,64]. As far as substitution on the indole nucleus is concerned, it is probable that the structure-activity relationships of these higher homologs will follow those of DMT. A variety of such derivatives have been prepared, and some animal data are available (e.g., [9,36]).

Table 1 lists those tryptamine-derived agents for which reliable human hallucinogenic potencies are available. It might be noted that the doses for DMT, 5-OMe DMT, and DPT are from parenteral administration; the remaining data are from oral administration.

Some generalizations which may be made regarding the behavioral activity of these compounds are as follows: (a) tryptamines, when compared with α-methyltryptamines or N,N-dialkyltryptamines are behaviorally-inactive, or at best, only weakly active (b) α-methylation and N,N-dimethylation of tryptamine results in hallucinogenic agents (the former being somewhat more active than the latter), (c) with respect to methoxy-substituted compounds, the 5-OMe are more potent than the 4-OMe; both of these are more active than either the 6-OMe or 7-OMe derivatives, (d) increasing the size of the alkyl substituent on the terminal amine, from dimethyl to larger alkyl groups, eventually diminishes activity.

(5) Lysergic Acid Derivatives

The individual hallucinogenic agent which has received the most attention is, without doubt, lysergic acid diethylamide (LSD). LSD is the most potent of the hallucinogens, active at the microgram level. Several recent reviews have discussed LSD and its derivatives in depth [16,57] and the reader is referred to these. Most of the structural modification of LSD has taken place at the amide group; replacement of the diethyl amide with larger alkyl groups diminishes or abolishes activity. With the exception of 2-bromo LSD (BOL) and 1-acetyl LSD, other nuclear-substituted derivatives of LSD have not been extensively investigated. This is rather surprising when one considers the popularity of LSD as an object of scientific research; on the other hand, the total synthesis of derivatives of LSD is a time-consuming task, requiring a number of synthetic steps. A variety of partial structures of LSD have been prepared in an attempt to simplify this task and to study structure-activity relationships; yet, for the most part, these derivatives have not been tested in behavioral assays or have not displayed significant activity. Work in this area continues.

(6) β-Carbolines

Several β-carboline derivatives have been isolated from plant sources (e.g., harmine, *6*a; harmaline, *6*b), and other molecular modifications have been prepared synthetically (e.g., 6-methoxyharman, *6*c; 6-methoxyharmalan, *6*d) (Fig. 1). Most of the human data on these compounds is from a study by Naranjo [50]. While these compounds are active in man, none has been found to be significantly more potent than DMT (*3*a).

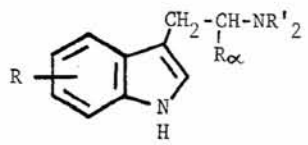
PHENALKYLAMINES

(7) Phenethylamines

Mescaline (*7*a) is by far the most recognized member of

TABLE 1

HALLUCINOGENIC INDOLEALKYLAMINES



Compound	R	R′	Approximate Human Hallucinogenic Dose (mg)	pA_2¶
Tryptamines (R′=Rα=H)				
*1*a Tryptamine	H		I*	6.27
*1*b 5-OMeT	5-OMe		—	7.54
α-Methyltryptamines (R′=H; Rα=Me)				
*2*a α-MeT	H		30	6.25
*2*b 5-OMe α-MeT	5-OMe		3	7.66
N,N-Dimethyltryptamines (R′=Me; Rα=H)				
*3*a DMT	H		75–100	6.00
*3*b Psilocin	4-OH		12	6.84
*3*c 4-OMe DMT	4-OMe		—	6.17
*3*d Bufotenine	5-OH		—‡	7.41
*3*e 5-OMe DMT	5-OMe		6	7.08
*3*f 6-OH DMT	6-OH		I*	—
*3*g 6-OMe DMT	6-OMe		—	5.77
*3*h 7-OH DMT	7-OH		—	4.88
*3*i 7-OMe DMT	7-OMe		—	5.33
*3*j 7-TMT	7-Me		—	6.29
*3*k 4-SMe DMT§	4-SMe		—	6.21
*3*l 5-SMe DMT§	5-SMe		—	6.84
Miscellaneous N-Alkylated Tryptamine (Rα=H)				
*4*a DET	H	Et	50–75	5.79
*4*b 4-OH DET	4-OH	Et	15#	—
*4*c DPT	H	Pr	30–70	—
*4*d 5-OMe DPT	5-OMe	Pr	—	6.53
*4*e DiPT	H	iPr	20–50	—
*4*f 5-OMe DiPT	5-OMe	iPr	6–10	—

*I=inactive.

†Where value not given, human data are unavailable.

‡See text for explanation.

§Unpublished compounds, prepared by Drs. Benington, Morin and Kline.

¶Affinity for 5-HT receptors of isolated fundus preparation [22–24].

#Threshold affects noted at 10–15 mg; loss of reality contact over 30 mg [67].

this subclass, and is active in humans at doses of 300–500 mg. Various methoxylated phenethylamines and positional isomers have been evaluated and few are more active than mescaline. Escaline (*7*b) and proscaline (*7*c), see Fig. 1, where the 4-methoxy group of mescaline has been replaced by an ethoxy or propoxy group are notable exceptions; these agents are active in man at the 40–80 mg level [6]. The 4-methyl and 4-bromo analogs of 2,5-dimethoxyphenethylamine, 7d and 7e, respectively, have been found to be active in man at about 10–15 mg, but appear to produce an effect which is qualitatively dissimilar to that of mescaline [61]. The corresponding 4-iodo derivative has also been reported [26]. The structure-activity relationships of other phenethylamines have been reviewed in detail [60,61].

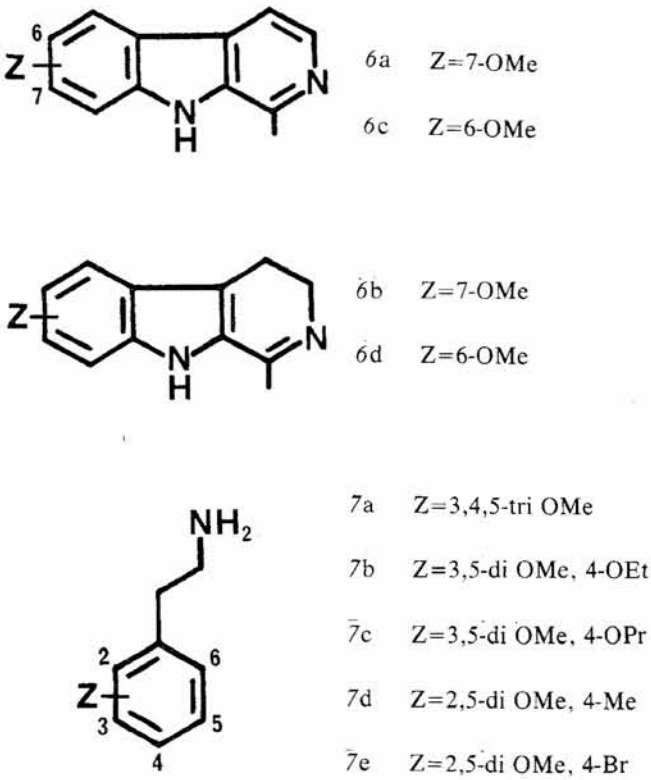


FIG. 1. Structures of several β-carbolines and phenethylamines.

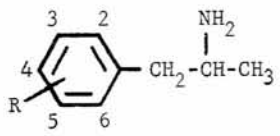
(8) Phenylisopropylamines

The human pharmacology of phenylisopropylamine derivatives has been reviewed in great depth by Shulgin [61]. More recently, Nichols [51] has reviewed the structure-activity relationships of these agents. For this reason, a detailed survey of this topic will be omitted and the interested reader is referred to one of the above reviews. For purposes of discussion, Shulgin has further subdivided the phenylisopropylamines (PIA's), or α-methyl phenethylamines, into several categories: (a) methoxy, (b) methylenedioxy, (c) alkoxy, (d) alkyl and (e) halogenated and sulfurated PIA's. For the sake of completeness, data on some compounds which have been reported to be active (in more than one individual or single experiment) are listed in Table 2. Also included in this table are some of the more recent data published by Shulgin and co-workers.

The phenylisopropylamines, like the α-methyltryptamines, possess a chiral center; hence, the possibility of a pair of isomers exists. For those hallucinogenic PIA derivatives studied to date, the R(−)-isoisomers appear to be more active than their S(+)-isomers [3]. The introduction of this α-methyl group, in addition to creating the chiral center, should also hinder or somewhat protect the terminal amine from oxidative deamination. As a consequence (although other factors can not be ruled out at this

TABLE 2

SOME HALLUCINOGENIC PHENYLISOPROPYLAMINES



	Compound	R	Approximate Human Hallucinogenic Dose (mg)*	pA_2†
*8*b	(±) DOI	2,5-di OMe, 4-I	0.8–2.0	—
*8*c	R(−) DOB	2,5-di OMe, 4-Br	0.5	—‡
*8*d	(±) DOB		0.8–2.0	7.35
*8*e	S(+) DOB		5.0	6.93
*8*f	(±) DOPR	2,5-di OMe, 4-Pr	1.0–2.0	7.17
*8*g	(±) DOET	2,5-di OMe, 4-Et	1.0–4.0	7.18
*8*h	R(−) DOM	2,5-di OMe, 4-Me	1.0–2.5	7.16§
*8*i	(±) DOM		2.0–5.0	7.12
*8*j	S(+) DOM		—¶	6.41
*8*k	(±) 2,4,5-TMA	2,4,5-tri OMe	20	6.81
*8*l	(±) 2,5-DMA	2,5-di OMe	40–50	6.83
*8*m	(±) MMDA-2	2-OMe 4-OCH_2O-5	30–50	6.65
*8*n	(±) 2,4,6-TMA	2,4,6-tri OMe	30–40	6.28
*8*o	R(−) MDA	3-OCH_2O-4	70	6.61
*8*p	(±) MDA		100–125	6.45
*8*q	S(+) MDA		225	6.08
*8*r	(±) 3,4,5-TMA	3,4,5-tri OMe	160–220	5.60
*8*s	(±) 3,4-DMA	3,4-di OMe	400–700(?)	5.45
*8*t	(±) 2,3,5-TMA	2,3,5-tri OMe	Inactive (?)#	5.38
*8*u	(±) 2,3,4-TMA	2,3,4-tri OMe	Inactive#	5.07
*8*a	(±) Amphetamine	H	(5–50)**	5.27
*8*v	(±) PMA	4-OMe	(60–80)	5.15

*Human data from [3] and [61].

†pA_2 Values=affinity for 5-HT receptors [22,24].

‡Agonistic effect precluded determination of pA_2.

§Some agonism observed at higher concentrations.

¶The R-isomer of DOM is more active than the racemic mixture; the S-isomer is inactive at four times the dose of the R-isomer, and has not been evaluated at higher doses.

#Inactive at low doses, higher doses have not been evaluated.

**Single doses are not usually hallucinogenic.

time), the racemic phenylisopropylamines are two to ten times more active than their corresponding phenethylamine counterparts. (This difference may be qualitative as well as quantitative and further investigation is necessary.)

One of the most potent hallucinogens in this subclass is probably the 2,5-dimethoxy-4-methyl derivative of PIA (or DOM; *8*i). This agent bears a methyl group at the 4-position; extension of this methyl group to an ethyl group (DOET; *8*g) or a propyl group (DOPR; *8*f) results in compounds which are quite potent. However, the psychotomimetic effects produced by DOM may not be qualitatively similar to those produced by DOET. This remains to be determined. The 4-brominated analog, DOB (*8*d) is also quite active and at higher doses appears to increase intellectual and emotional stimulation; the corresponding iodinated derivative DOI (*8*b) displays the same potency and duration of action as DOB. The 4-chloro [1], as well as the 4-fluoro and 4-nitro derivatives (Glennon, Young, Benington and Morin; unpublished data) of 2,5-DMA have been prepared and are active in animal studies, although human data are unavailable.

DOM and DOB possess methoxy groups at the 2- and 5-positions and either a methyl or bromo group at the 4-position. Rearranged isomers of DOM and DOB (i.e., where the 4-position substituent has been shifted to either the 2- or 5-position) have been prepared by Anderson *et al.* [2]. These isomers are much less active than either DOM or DOB [2,14]. Anderson and co-workers have also found that N-mono-methylation of several methoxy-substituted

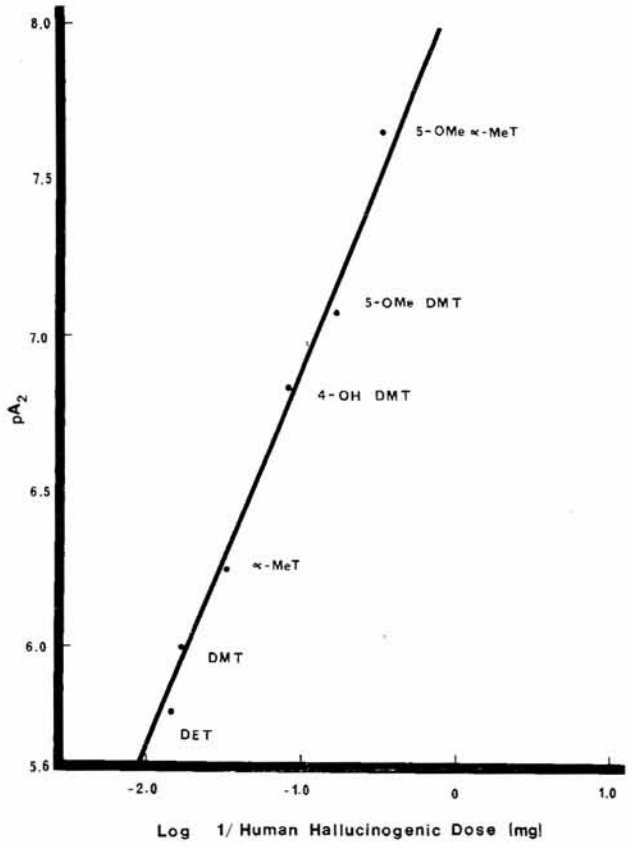


FIG. 2. Relationship between log human hallucinogenic (total mg) dose and serotonin receptor affinity (pA_2).

phenylisopropylamines reduces their potency; for example, the results of human studies reveal that N-mono-methylation of racemic DOM (*8*i) and DOB (*8*d) reduces their activity by tenfold [3,59].

MECHANISTIC SPECULATIONS

The mechanism of action of these hallucinogenic agents is probably far from simple and a complete literature survey on work done in this area is beyond the scope of this review. Nevertheless, various investigators have made an effort to study the mechanism of action of these compounds by comparing their hallucinogenic/psychotomimetic potencies with their quantum chemical parameters, physicochemical and spectral properties, biochemical consequences and behavioral effects in animals. On occasion, correlations may have been found which adequately account for activity, but, only if one or more compounds is deleted from the correlation equation. Although deletion of data points is usually frowned upon, it may be justified in studies on hallucinogenic agents, at least until the following question has been answered. Do all of these indolealkylamine and phenalkylamine hallucinogens produce the same qualitative behavioral effect?

Martin and co-workers [44,45] have addressed this question and have divided many of the hallucinogenic agents into several categories depending upon whether or not their behavioral effects, antagonism, etc., are similar to those of LSD. For example, agents (a) that are LSD-like, or probably LSD-like, include: psilocin (*3*b), mescaline (*7*a), DOM (*8*i), DMT (*3*a) and 2,5-DMA (*8*l); (b) that are probably LSD-like with other properties include: MDA (*8*p); and (c) that are not LSD-like include: amphetamine (*8*a) and DOET (*8*g). If agents are not producing similar effects in human and/or animal studies, is it valid to assume they possess identical mechanism(s) of action?

LSD is known to have an effect on a variety of neurotransmitter systems; the effect of LSD on any one (or more) of these systems may be related to its mechanism of action. Although each of the above classes (and, indeed, individual members within these classes) may elicit unique behavioral responses, an investigation of a common component of their activity might afford useful data [40]. Numerous investigators have demonstrated or suggested that the neurotransmitter serotonin (5-HT) might be involved in the actions of LSD and other hallucinogenic substances. Thus, we have attempted to determine the role which 5-HT might play in the mechanism of action of each of these agents. The approach we have taken is (a) to determine the 5-HT receptor affinities (pA_2 values) of a number of these agents using the isolated rat fundus preparation, and (b) to determine which of these agents will produce generalization in tests of discriminative stimulus control in rats using, for example, 5-OMe DMT as the training drug. Specific experimental details, methodologies and rationale have been discussed [22, 23, 54]. What we have found, briefly, is that indolealkylamine and phenethylamine derivatives possess a 5-HT receptor affinity dependent upon the presence and location of various substituent groups. Affinity data (pA_2 values) are included in Tables 1 and 2. Those compounds which are the most behaviorally active in man possess the highest 5-HT receptor affinities; however, it is not valid to conclude that those agents which possess a high 5-HT receptor affinity will be hallucinogenic in man. This finding by no means excludes the involvement of other neurotransmitters; it does suggest, however, that 5-HT might play a role in their mechanism of action. Rather than (or, in addition to) using Martin's terminology of "LSD-like," these agents can be ranked on the basis of their ability to interact with 5-HT receptors (i.e., on their "serotonergic component"). The result of plotting the human hallucinogenic potencies of the tryptamine-derived compounds from Table 1 against their receptor affinities (where data are available) supports the above statements (Fig. 2). Those tryptamine-derived compounds which are less active in animal studies (e.g., 6-OMe DMT; *3*g and 7-OMe DMT; *3*i) possess lower affinities. Compounds which might undergo metabolism at a faster rate, or, which do not readily enter the brain (e.g., *1*a and *3*d) do not adhere to this generalization [23].

In the discriminative stimulus studies using animals trained to discriminate 5-OMe DMT from saline, generalization has been shown to occur between the stimuli produced by all of the DMT analogs, *3*a–*3*l (except *3*d, *3*f and *3*h), and by 5-OMe DMT. Each of these agents apparently produces interoceptive cues similar to those produced by 5-OMe DMT. Because the stimulus produced by 5-OMe DMT (as well as LSD) can be attenuated by pretreatment of the animal with a 5-HT antagonist, it appears that 5-HT is involved in the mechanism of action of these agents. Indeed, there is a direct correlation between 5-HT receptor affinity and the ED_{50} for those compounds which generalized [27]. We have recently found that 5-HT antagonists, but not the dopamine antagonist haloperidol, attenuates 5-OMe DMT

discriminative responding [79]. Interestingly, Meltzer and co-workers have found that the 5-HT antagonist cyproheptadine partially blocks the psychotomimetic effect of DMT in two out of three normal human subjects while haloperidol was without effect on the psychotomimetic response [47].

The PIA derivatives have not been completely investigated, however, preliminary results are quite interesting. Using 5-OMe DMT (*3*e) as a training-drug, we have investigated the behavioral (discriminative stimulus) properties of thirty-six substituted phenylisopropylamines and/or optical isomers. Results of this study reveal that, in general, the PIA derivatives can be differentiated into several broad categories, i.e., those which (a) produce effects similar to that of 5-OMe DMT, (b) result in partial generalization, followed by disruption of behavior at higher doses, (c) produce negligible 5-OMe DMT-appropriate responding, followed by disruption of behavior at higher doses, and (d) produce saline-like responding at the highest dose tested [28]. As our work has progressed, we have found that DOM is a more suitable training-drug for the evaluation of substituted phenylisopropylamines. Furthermore, stimulus generalization occurs when 5-OMe DMT (*3*e) is administered to these DOM-trained animals [78], and the effects of DOM can be attenuated by pretreatment of the animals with 5-HT antagonists [66,78], but not by pretreatment, as has been shown by Silverman and Ho, with haloperidol [66].

Taken together, these findings suggest that the behavioral effects of certain indolealkylamine and phenalkylamine hallucinogens may be ultimately mediated via a serotonergic mechanism. Furthermore, our work basically supports the contention of Martin *et al.* [44,45] in that these hallucinogens can most likely be divided into several behavioral (and, perhaps, mechanistic) subtypes.

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