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Indolealkylamine analogs share 5-HT_2 binding characteristics with phenylalkylamine hallucinogens

Robert A. Lyon [1], Milt Titeler [1,*], Mark R. Seggel [2] and Richard A. Glennon [2]

[1] *Department of Pharmacology and Toxicology, Neil Hellman Medical Research Building, Albany Medical College, Albany, NY 12208, and* [2] *Department of Medicinal Chemistry, School of Pharmacy, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298, U.S.A.*

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Twenty-one indolealkylamines, some of which are known to be psychoactive in man, were examined for their binding interactions with rat brain cortical 5-HT_2 receptors labeled with the antagonist radioligand [^{3}H]ketanserin in order to develop structure-activity relationships for binding at these sites. Features investigated included aromatic, α-methyl and terminal amine substituents. 4-Methoxy and 5-methoxy substitution impart a higher affinity than 6- or 7-methoxy substitution; a 7-hydroxyl group essentially abolishes affinity whereas a 7-methyl or 7-bromo group enhances affinity. α-Methylation has little effect on affinity and, in the one case examined, the S(+) isomer of α-methyltryptamine was essentially equipotent with its racemate and twice as potent as its R(−) enantiomer. Terminal amine methylation results in a small but progressive decrease in affinity in the order: primary amine > dimethylamine > diethylamine. Similarities were noted between these structural requirements for binding and those of the phenalkylamines. Selected compounds (5-methoxytryptamine, N,N-dimethyltryptamine, 5-methoxy-N,N-diethyltryptamine and 5-methoxy-N,N-dimethyltryptamine) were further examined by two-site analysis of displacement studies for [^{3}H]ketanserin specific binding. Hill co-efficients were significantly less than unity and computer-assisted analysis indicated that a two-site model better fit the data than a one-site model. In displacement studies using the putative agonist radioligand [^{3}H]DOB to label 5-HT_2 receptors affinities were 10-100-fold higher than those using [^{3}H]ketanserin. These results are also consistent with earlier findings using psychoactive phenalkylamines in competition studies for radiolabelled 5-HT_2 receptors. In summary, the interactions of indolealkylamines and phenalkylamines with 5-HT_2 receptors have many characteristics in common, supporting the hypothesis that 5-HT_2 receptors may mediate the psychoactive properties of indolealkylamines.

5-HT_2; Serotonin; Indolealkylamine; 4-Bromo-2,5-dimethoxyphenylisopropylamine (DOB)

1. Introduction

Various psychoactive indolealkylamines have been demonstrated to interact with [^{3}H]5-HT-labelled serotonin (5-hydroxytryptamine, 5-HT) binding sites (i.e. 5-HT_1 sites) (Leysen, 1985; Arvidsson et al., 1986). As might be anticipated, binding is sensitive to the nature and location of certain substituent groups; these structural features also seem to play a role in the binding of indolealkylamines to subpopulations (i.e. 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1C}) of 5-HT_1 binding sites (Engel et al., 1983; 1986). Although 5-HT itself is an indolealkylamine, the 5-HT_2 binding characteristics of indolealkylamine derivatives have received surprisingly little attention. In the present investigation we examined the binding of a group of indolealkylamine derivatives at [^{3}H]ketanserin-labelled 5-HT_2 receptors in order to determine the relative importance of various substituents, and to formulate structure-activity relationships. One of

* To whom all correspondence should be addressed.

the goals of the present study was to determine whether or not structural similarities exist between the indolealkylamines and phenalkylamines with respect to their 5-HT_2 receptor interactions. Another goal of this study was to determine if selected indolealkylamines shared similar binding properties with phenalkylamines at ^{3}H-agonist- and ^{3}H-antagonist-labelled 5-HT_2 receptors.

2. Materials and methods

Radioligand binding assays were conducted in essentially the same manner as reported earlier (Shannon et al., 1984). Taconic Farms Sprague-Dawley rats (ca. 220 g) were decapitated and their brains were immediately placed in ice-cold 0.9% saline. Dissecting over ice, the frontal cortices were removed using the anterior border of the corpus callosum as a landmark. Tissue was either used immediately or was frozen at − 30 °C until needed. No differences in binding were noted between these preparations. Membrane homogenates were prepared in a 50 mM Tris HCl (pH 7.4 at 37 °C) buffer containing 10 mM $MgSO_4$ and 0.5 mM Na_2EDTA. Assays were performed in 2.0 ml of buffer containing 50 mM Tris HCl, 0.5 mM Na_2EDTA, 10 mM $MgSO_4$, 0.1% ascorbate and 10 μM pargyline to which membranes (3 mg wet weight for [^{3}H]ketanserin binding or 20 mg for [^{3}H]DOB binding) were added last. Displacement experiments at eleven concentrations of non-labeled drug were performed with tritiated agents obtained from New England Nuclear; 0.4 nM [^{3}H]ketanserin (90.4 Ci/mmol) and 0.4 nM [^{3}H]DOB (40 Ci/mmol). Specific binding was defined using 1 μM cinanserin. Solutions of the indolealkylamines were made fresh daily in assay buffer and each displacement assay was repeated three times. Following incubation at 37 °C for 15 min, membranes were rapidly filtered over glass fiber filters (Schleicher and Schuell) which had been pre-soaked in 0.1% polyethyleneimine, followed by a 10 ml wash with ice-cold buffer. Following a 6 h equilibration in Scintiverse (Fisher) samples were counted in a Beckman 3801 counter at an efficiency of 45%. Displacement data were first analyzed using a computer-assisted iterative program (EBDA) to obtain IC_{50} values and pseudo Hill co-efficients (MacPherson, 1983). K_i values were calculated using the Cheng-Prusoff equation (Cheng and Prusoff, 1973). The non-linear regression program LIGAND was used for two-site analysis of the binding data (Munson and Rodbard, 1980). Each indolealkylamine was tested three times in individual displacement assays on separate days. Computer analysis (one- and two-site modelling) was performed on each displacement curve. Thus, the mean and S.E.M. are the result of three independent displacement assays and computer analyses of these assays.

With the exceptions mentioned below, all of the indolealkylamines used in this study (see table 1) were synthesized earlier in the laboratories of Dr. R.A. Glennon. These include: 5-methoxytryptamine as the hydrogen oxalate (HOx) salt (5-OMe T), 5-benzyloxytryptamine (O-benzylserotonin) HCl (5-OBzl T), S(+)α-methyltryptamine mesylate and R(−)α-methyltryptamine mesylate (α-MeT), racemic 5-methoxy-α-methyltryptamine HCl and (+)5-methoxy-α-methyltryptamine free base (5-OMe α-MeT), N,N-dimethyltryptamine HOx (DMT), 1,N,N-trimethyltryptamine HOx (1-TMT), 4-methoxy-N,N-dimethyltryptamine HOx (4-OMe DMT), 5-methoxy-N,N-dimethyltryptamine HOx (5-OMe DMT), 6-methoxy-N,N-dimethyltryptamine HOx (6-OMe DMT), 6,N,N-trimethyltryptamine HOx (6-TMT), 7-methoxy-N,N-dimethyltryptamine HCl (7-OMe DMT), 5-methoxy-7-methyl-N,N-dimethyltryptamine HOx (5-OMe, 7Me DMT) and 5-methoxy-N,N-diethyltryptamine HCl (5-OMe DET). 7-Hydroxy-N,N-dimethyltryptamine HOx (7-OH DMT) was a gift from the Psychopharmacology Research Branch, NIMH, and bufotenine (5-OH DMT) and serotonin HCl were purchased from Sigma. 4-(2-Aminopropyl)indole or α-methylisotryptamine (as the free base) was synthesized from 4-cyanoindole essentially according to the method of Troxler and coworkers (1968). Melting point = 157-159 °C; literature melting point = 157-159 °C (Troxler et al., 1968).

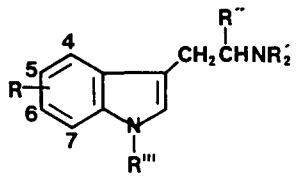
3. Results

The structures of the agents examined are shown in table 1 and in figs. 1 and 2 and the results of

TABLE 1

Structures of indolealkylamines used in this study. Agents were prepared as described in Materials and methods.

Agent



	R4	R5	R6	R7	R′	R″	R‴
5-HT	H	OH	H	H	H	H	H
5-OMe T	H	OCH_3	H	H	H	H	H
5-OBzl T	H	OBzl	H	H	H	H	H
(+)α-MeT	H	H	H	H	H	CH_3	H
(−)α-MeT	H	H	H	H	H	CH_3	H
5-OMe-α-MeT	H	OCH_3	H	H	H	CH_3	H
(+) 5-OMe-α-MeT	H	OCH_3	H	H	H	CH_3	H
DMT	H	H	H	H	CH_3	H	H
1-TMT	H	H	H	H	CH_3	H	CH_3
4-OMe DMT	OCH_3	H	H	H	CH_3	H	H
5-OH DMT	H	OH	H	H	CH_3	H	H
5-OMe DMT	H	OCH_3	H	H	CH_3	H	H
6-TMT	H	H	CH_3	H	CH_3	H	H
6-OMe DMT	H	H	OCH_3	H	CH_3	H	H
7-OMe DMT	H	H	H	OCH_3	CH_3	H	H
7-OH DMT	H	H	H	OH	CH_3	H	H
7-Br DMT	H	H	H	Br	CH_3	H	H
5-OMe,7-Me DMT	H	OCH_3	H	CH_3	CH_3	H	H
5-OMe DET	H	OCH_3	H	H	C_2H_5	H	H

the displacement studies using [^{3}H]ketanserin are shown in table 2. Table 3 lists the two-site analysis of selected displacement studies using [^{3}H]ketanserin and the affinities of these compounds in displacing the 5-HT_2 receptor agonist ligand [^{3}H]DOB.

Structural modification of 5-HT can result in either an increase or a decrease in affinity depending upon the particular alteration. O-methylation has relatively little effect on affinity; for example compare in table 2 the K_i values for 5-HT vs.

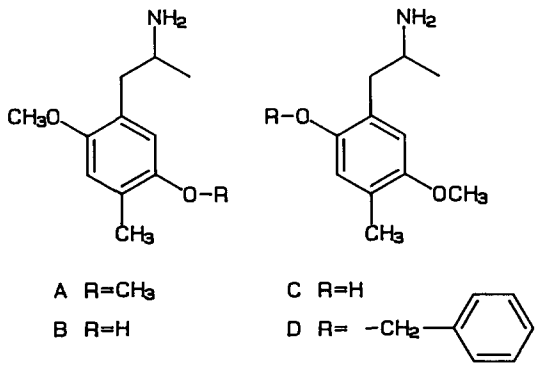


Fig. 1. Structures of DOM (A), 5-HMMP (B), hydroxy DOB (C) and benzyloxy DOB (D).

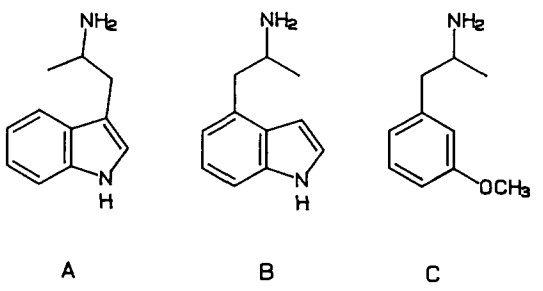


Fig. 2. Structures of racemic α-MeT (A), α-Me isotryptamine (B) and 3-methoxyphenylisopropylamine (C).

TABLE 2

Results of radioligand binding studies using [^{3}H]ketanserin to label 5-HT_2 receptors. Agents were used in displacement experiments for [^{3}H]ketanserin specific binding as described in Materials and methods. (a) S.E.M. are reported following K_i and Hill values and are the result of three independent displacement assays and individual computer analysis of these assays; (b) value obtained from Shannon et al. (1984); (c) value obtained from Glennon et al. (1986). It should be noted that IC_{50} conversion to K_i values is accurate only when the Hill coefficient equals unity.

Agent	K_i (nM)	Hill slope
5-HT	560 (20) [a]	0.75 (0.02)
5-OMe T	300 (20)	0.75 (0.02)
5-OBzl T	360 (30)	0.98 (0.03)
α-MeT	2500 (170)	0.74 (0.03)
(+)α-MeT	3100 (500)	0.89 (0.07)
(−)α-MeT	5000 (300)	0.94 (0.05)
α-Me isoT	5000 (250)	0.95 (0.05)
5-OMe-α-MeT	320 (20)	0.71 (0.02)
(+)5-OMe-α-MeT	310 (20)	0.72 (0.02)
DMT	1200 (40)	0.86 (0.02)
1-TMT	400 (90)	0.99 (0.03)
4-OMe DMT	1300 (50)	0.95 (0.03)
5-OH DMT	480 (20)	0.78 (0.05)
5-OMe DMT	600 (40)	0.85 (0.03)
6-OMe DMT	7300 (380)	0.93 (0.05)
6-TMT	2500 (300)	0.77 (0.01)
7-OMe DMT	5400 (100)	0.92 (0.03)
7-OH DMT	>10000	ND
7-Br DMT	170 (15)	0.95 (0.02)
5-OMe,7-Me DMT	360 (60)	0.81 (0.04)
5-OMe DET	1120 (135)	0.71 (0.08)
DOM	100 [b]	0.71 (0.04)
5-HMMP	200 (50)	0.92 (0.09)
Hydroxy DOB	210 [c]	0.77 (0.06)
Benzyloxy DOB	140 (15)	0.85 (0.05)

TABLE 3

Two-site analysis of indolealkylamine displacement studies and affinities for [^{3}H]DOB-labelled 5-HT_2 receptors. Two-site analysis performed as described in Materials and methods. K_H is the high affinity inhibition constant, $\%R_H$ is the % of receptors in the high affinity state and K_L is the low affinity inhibition constant. Two-site fit was significantly better than a one-site model ($P < 0.01$). [^{3}H]DOB assays are described in Materials and methods. In each case three independent displacement assays were performed. These assays were individually computer-analyzed. Mean and S.E.M. are the result of these three analyses.

Agent	K_H (nM)	$\%R_H$	K_L (nM)	K_i ([^{3}H]DOB)
DMT	84 (18)	19 (3)	1856 (141)	64 (10)
5-OMe T	3 (1)	23 (4)	647 (86)	3 (0.7)
5-OMe DMT	6 (2)	14 (2)	1640 (139)	15 (3)
5-OMe DET	13 (1)	14 (2)	883 (64)	54 (9)

5-OMe T, and bufotenine vs. 5-OMe DMT. Interestingly, the affinity of the O-benzyl derivative of 5-HT (5-OBzl T) is not very different from that of 5-HT itself, suggesting that the binding site might posses an area of bulk tolerance able to accomodate this large substituent. α-Methylation of 5-OMe T, to afford racemic 5-methoxy-α-methyltryptamine, has no effect on affinity; the (+) isomer is equiactive with the racemic mixture. The isomers of α-methyltryptamine were examined in order to be able to make an enantiomeric potency comparison; S(+)αMe T appears to be about twice as potent as its R(−) enantiomer. The affinity of racemic α-MeT is similar to that of racemic α-Me isoT.

Comparing 5-OMe T, 5-OMe DMT and 5-OMe DET, it is found that as the terminal-amine substituent is increased in size from primary amine to dimethylamine to diethylamine, 5-HT_2 site affinity decreases slightly. Substituents on the aromatic nucleus can also alter affinity. Clearly, the 6- and 7-methoxy derivatives of DMT posses a lower affinity than do 4-OMe DMT and 5-OMe DMT. Demethylation of 7-OMe DMT, to afford 7-OH DMT, results in an even further decrease in affinity. 7-Br DMT posseses about 10 times the affinity of DMT and greater than 50 times the affinity of 7-OH DMT. Because of the possibility that this portion of the molecule might interact with a hydrophobic region of the binding site (which would explain the low affinity of 7-OH DMT and the enhanced affinity of 7-Br DMT), 5-OMe-7 Me-DMT was examined and was found to possess about twice the affinity of 5-OMe DMT. Introduction of a methyl group at the 6 position (i.e. 6-TMT) results in a slight decrease in affinity whereas introduction of a methyl group at the indole N1 position (i.e. 1-TMT) results in a 3-fold increase in affinity as compared with DMT.

Generally, indolealkylamine displacement of [^{3}H]ketanserin from 5-HT_2 receptors resulted in

shallow (less than unity) Hill coefficients (table 2). Analysis of the displacement curves of selected compounds fit a two-site model significantly better than a one-site model (table 3). These compounds also showed a 10-100-fold higher affinity in displacing [^{3}H]DOB (table 3). For example, 5-OMe DMT displaced [^{3}H]ketanserin with a K_i of 600 nM and Hill coefficient of 0.85. Two-site analysis of the data indicated a high affinity site with a K_i of 5.7 nM and a low affinity site with a K_i of 1640 nM. 5-OMe DMT displaced [^{3}H]DOB labeled sites with an affinity of 15 nM (table 3). A similar binding pattern was observed with DMT, 5-OMe DET and 5-OMe T.

4. Discussion

The results of this study show that the structural modification of indolealkylamines can make subtle differences in their affinity for [^{3}H]ketanserin-labelled 5-HT_2 receptors. The profile that emerges can be summarized as follows: (a) alkylation of the terminal amine results in in a small but progressive decrease in affinity as the substituent is increased in size from hydrogen to methyl to ethyl, (b) α-methylation of the side chain has relatively little effect on affinity, (c) one optical isomer of an α-methyl derivative (i.e. α-MeT) posseses twice the affinity of its enantiomer; stereochemistry seems to play a role in binding, but the role is small, (d) hydroxy/methoxy groups are better tolerated at the 4- and/or 5-positions than at the 6- and 7-positions of the indolealkylamine nucleus, (e) there may be a hydrophobic region associated with that portion of the binding site that is associated with the 7- and 1-position of the aromatic nucleus (although electronic, steric and other factors cannot be ruled out at this time), and (f) there may be a region of bulk tolerance in the region of the 5-position.

We have recently studied the interactions of various phenalkylamine analogs with 5-HT binding sites; 2,5-dimethoxy-substituted phenalkylamines (depending on what other substituents are present) display a fairly high affinity and selectivity for 5-HT_2 sites (Glennon et al., 1986). If the indolealkylamines and phenalkylamines interact with these binding sites such that they share common aromatic and terminal amine features, there should be similarities in their structure-activity relationships. This is found to be the case. We have already reported that alkylation of the terminal amine of phenalkylamines reduces their affinity for 5-HT_2 sites, that an α-methyl group has little effect on affinity, that one optical isomer (i.e. the R isomer) posseses two to three times the affinity of its enantiomer, that methoxy substitution (at a position that corresponds to the 5-position of the indolealkylamines) results in enhanced affinity and that introduction of methyl and bromo groups (at a position that corresponds to the indole 7-position) increases affinity (Shannon et al., 1984; Glennon et al., 1984; 1986). Based on the results of the present study, there are two additional alterations of the phenalkylamine moiety that we can examine. If the molecules interact with the binding sites as suggested, the N1 indole nitrogen should correspond to the phenalkylamine 5-position. Because N1-methylation enhances the affinity of DMT for 5-HT_2 sites, it might be expected that O-demethylation of the 5-position methoxy group of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) will decrease affinity. As shown in table 2, the O-demethyl derivative of DOM (i.e. 5-HMMP) posseses half the affinity of DOM. Secondly, if there is a region of bulk tolerance associated with the indolealkylamine 5-position, the benzyloxy analog of the appropriate hydroxyphenalkylamine should possess comparable affinity. We recently reported on the affinity (K_i = 210 nM) of the hydroxy analog of DOB (i.e. hydroxy DOB; fig. 1) for 5-HT_2 sites (Glennon et al., 1986). Table 2 shows that the affinity of the corresponding benzyloxy analog (K_i = 140 nM) is similar to that of hydroxy DOB. Thus there are nine different alterations in structure that have qualitatively the same effect in the indolealkylamine and phenalkylamine series. Finally, if the indolealkylamines and phenalkylamines interact with 5-HT_2 sites as proposed, it would be expected that the sidechain-transposed indolealkylamine α-methyl isotryptamine (α-Me isoT; fig. 2) would possess an affinity somewhere between the limits imposed by racemic α-MeT (K_i = 2500 nM) and 3-methoxyphenylisopro-

pylamine) (K_i = 7800 nM). This is found to be the case; the K_i of α-Me isoT for 5-HT_2 sites = 5000 nM (table 2).

Similarities are again observed between the indolealkylamines and phenalkylamines in their mode of binding with 5-HT_2 receptors. Previous reports have demonstrated a guanyl nucleotide dependency of phenalkylamine (Shannon et al., 1984) and indolealkylamine (Battaglia et al., 1984) displacement of [^{3}H]ketanserin binding indicative of an agonist interaction at this receptor. Agonist but not antagonist competition data better fit a two-site computer model indicative of a two-state receptor (Shannon et al., 1984; Battaglia et al., 1984).

We have recently characterized the binding of [^{3}H]DOB, a 5-HT_2 receptor agonist, in rat brain membranes (Titeler et al., 1985; Lyon et al., 1986). [^{3}H]DOB was found to label approximately 5% of the 5-HT_2 receptors labelled by the antagonist radioligand [^{3}H]ketanserin (Lyon et al., 1986). It is not unusual for an agonist radioligand to label a fraction of the sites labelled by an antagonist radioligand (Stiles et al., 1984). 5-HT_2 receptor antagonists had equal affinity for [^{3}H]ketanserin- and [^{3}H]DOB-labelled 5-HT_2 receptors indicating a 5-HT_2 receptor pharmacology while 5-HT_2 receptor agonists competed with 10-100-fold higher affinity for [^{3}H]DOB-labelled receptors (Lyon et al., 1986). We have hypothesized that [^{3}H]DOB labels an agonist high affinity state of the 5-HT_2 receptor (Lyon et al., 1986).

In this study selected indolealkylamines were examined for their interactions with both [^{3}H]ketanserin- and [^{3}H]DOB-labelled 5-HT_2 receptors. In displacement studies using [^{3}H]ketanserin, computer-modelling revealed the presence of two affinity states. The high affinity state corresponds well with the affinity determined in displacement of [^{3}H]DOB-labelled 5-HT_2 receptors. Thus, indolealkylamine displacement of [^{3}H]-DOB-labelled 5-HT_2 receptors appears to correspond to the agonist high affinity state of the 5-HT_2 receptor. Although a relationship is suggested by these data further studies are required to definitively establish a relationship between indolealkylamine displacement of [^{3}H]DOB- and [^{3}H]ketanserin-labelled 5-HT_2 receptors. Such a relationship has been previously shown for other 5-HT_2 receptor agonists (Lyon et al., 1986). It should be noted that two-site computer modelling of the [^{3}H]ketanserin displacement data revealed a population of high affinity sites greater than that determined by the direct binding of [^{3}H]DOB. This finding is unexplainable at this time.

Recent studies have shown that 5-HT_2 agonism may be responsible for the psychoactive effects of hallucinogenic compounds (Glennon et al., 1983; 1984; Rasmussen and Aghajanian, 1986). Indeed, several of the agents listed in table 2 (e.g. 5-OMe α-MeT > 5-OMe DMT > DMT = 4-OMe DMT) are hallucinogenic in humans (see Nichols and Glennon, 1984 for a review). Unfortunately, lack of comparative clinical investigations and differences in routes of administration and in distribution/metabolism, make strict potency comparisons virtually impossible. In addition, certain agents with affinity for 5-HT_2 sites (e.g. 5-OMe T, 5-OH DMT) are behaviorally inactive; probably because of their inability to penetrate the blood-brain barrier and/or due to their rapid metabolism in vivo (Nichols and Glennon, 1984). Nevertheless, the present study indicates that indolealkylamines and phenalkylamines share common structure-activity relationships and a common mode of interaction at 5-HT_2 receptors. If a 5-HT_2 interaction is a mediating event in the hallucinogenic effects of various drugs (Glennon et al., 1984) it is entirely possible that hallucinogenic indolealkylamines can act via a similar mechanism.

Acknowledgements

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