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DOM and Related 2,5-Dimethoxy-4-Alkylphenylisopropylamines: Behavioral and Serotonin Receptor Properties

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GLENNON, R. A., D. LEMING DOOT AND R. YOUNG. *DOM and related 2,5-dimethoxy-4-alkylphenylisopropylamines: Behavioral and serotonin receptor properties.* PHARMAC. BIOCHEM. BEHAV. **14**(3) 287–292, 1981.—Using an isolated rat fundus preparation, the 4-methyl (DOM), ethyl (DOET), propyl (DOPR) butyl (DOBU), tertiary butyl (DOTB) and amyl (DOAM) derivatives of 2,5-dimethoxy-phenylisopropylamine (2,5-DMA) were found to possess quite similar serotonin receptor affinities (pA_2=7.02–7.22). The fundus preparation could not be used to determine pD_2 values because all of the compounds were found to interact in an agonistic manner both with serotonin and PRT (phenoxybenzamine resistant tryptamine) receptors. Administration of DOET, DOPR, DOBU, DOTB and DOAM to animals (rats) trained to discriminate 5-OMe DMT from saline resulted only in partial generalization. While each of these agents possesses a high 5-HT receptor affinity, and while their behavioral effects might, therefore, involve a serotonergic component, the stimulus properties of these compounds are qualitatively dissimilar to those produced by the training dose of 5-OMe DMT.

4-Alkyl-2,5-dimethoxyphenylisopropylamines 4-Alkyl-2,5-dimethoxyamphetamines 5-Methoxy-N,N-dimethyltryptamine Serotonin receptors Discriminative stimulus properties DOM DOET

SEROTONIN (5-hydroxytryptamine, 5-HT) has been implicated as playing a role, at least in part, in the mechanism of action of several classes of hallucinogenic/psychotomimetic agents. Phenalkylamine derivatives, for example, have been demonstrated to interact with 5-HT receptors of various peripheral tissue preparations [5–7, 9, 26] and have also been shown to interact with 5-HT binding sites of rat brain homogenates [2]. Various behavioral assays on methoxylated phenalkylamines further suggest that serotonergic mechanisms may play a significant role [3, 19, 28–30]. While some of these methoxylated phenalkylamines might produce their effects by direct 5-HT receptor interaction [4,23], others appear to exert an indirect effect, e.g. enhancement of 5-HT release, inhibition of 5-HT uptake [14, 22–24].

Neurotransmitter systems other than, or in addition to, 5-HT may also play a role in the behavioral effects observed for some of these compounds (e.g. [13, 14, 21, 22, 24, 27]). However, in our previous studies we have found that both phenethylamine derivatives and phenylisopropylamine derivatives possess varying affinities, dependent upon the presence and location of substituent groups, for the 5-HT receptors of the isolated rat fundus preparation [9]. Of the methoxy derivatives examined, 2,5-dimethoxy substitution appears to be optimal for maximal affinity [9]. Alkyl substitution at the 4-position of 2,5-dimethoxyphenylisopropylamine (2,5-DMA) results in compounds which are potent psychotomimetic agents [17]. For example the 4-methyl (DOM, "STP") and 4-ethyl (DOET) derivatives of 2,5-DMA are approximately 80–100 times more potent than mescaline [17,18]. Although we have previously determined the 5-HT receptor affinity (pA_2) of DOM and DOET, we have not investigated the remainder of the homologous series. In this present study, we wish to determine the pA_2 values for the 4-propyl (DOPR), 4-butyl (DOBU), 4-*tert* butyl (DOTB) and 4-amyl (DOAM) derivatives of 2,5-DMA for comparison with those of DOM and DOET. In addition, because these compounds are partial agonists, i.e. mixed agonist-antagonists, the fundus preparation will be used to study the agonistic effects of the entire series (4-H through 4-amyl).

Another approach which might be useful in studying the possible serotonergic involvement of these agents is to eval-

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uate their discriminative stimulus properties in animals. 5-Methoxy-N,N-dimethyltryptamine (5-OMe DMT) can serve as a discriminative stimulus in rats [10]. Because the behavioral effects (interoceptive cues) produced by 5-OMe DMT are attenuated by pretreatment of the animals with the 5-HT antagonist pizotyline, these cues appear to be (at least partially) mediated via a serotonergic mechanism [10]. Generalization has been shown to occur between the 5-OMe DMT stimulus and both 2,5-DMA [11] and DOM [10,11]. Doses of LSD, DOM and DOET which mimicked mescaline, in mescaline-trained rats, were blocked by the same doses of pizotyline or cinanserin found to be effective against mescaline [29]. Silverman and Ho [19] found that the DOM stimulus generalizes to LSD and DOET. In a companion study, then, the 4-substituted derivatives of 2,5-DMA will be administered to rats, trained to discriminate 5-OMe DMT from saline, in order to determine if common interoceptive cues are produced.

METHOD

pA_2 Assay

Male Sprague-Dawley rats (Flow Labs, Dublin, VA), weighing 200–250 g, were used in this study. The rat stomach fundus preparation employed was essentially that described by Vane [25]; the assay was performed as previously described [9]. The test compounds were examined a minimum of twice, at each of usually four different concentrations, using 5-HT oxalate as agonist. The ED_{50} for 5-HT was determined for each of the dose response curves and the apparent affinities were calculated as pA_2 values by the method of Arunlakshana and Schild [1]. Linear regression analysis provided not only pA_2 values, but also the slopes of the Schild plots.

pD_2 Assay

As a measure of agonist activity, pD_2 values were determined using the same fundus preparation described above. After obtaining an initial cumulative dose response curve to 5-HT, a cumulative dose response curve was obtained, at 10–12 increasing concentrations, for each of the test compounds. Due to the difficulty encountered in washing the fundus preparation free of test compounds, each pair of curves was obtained using a fresh preparation (see results for explanation). The height of the cumulative dose response curves is defined as α; in the present study, α is calculated by dividing the maximal height of the dose response curve of an agonist by the maximal height of the immediately preceding dose response curve to 5-HT. The symbol $\alpha 1$ refers to α before phenoxybenzamine blockade while $\alpha 2$ refers to the α obtained after blockade. The blocking experiments were performed by incubating the fundus strip with phenoxybenzamine hydrochloride (bath concentration of 1.84×10^{-4} molar) for twenty minutes, after an initial dose response curve was first obtained for 5-HT. After the incubation period, the fundus strip was washed several times with Tyrode solution prior to obtaining a dose response curve for one of the test compounds.

Behavioral Assay

Six male Sprague-Dawley rats were trained to discriminate 5-OMe DMT hydrogen oxalate (1.5 mg/kg) from saline in a two-lever operant task as described by Glennon *et al.* [11]. Briefly, administration of saline or 5-OMe DMT, 15 minutes prior to a variable 15-second (VI-15) schedule of reinforcement, served as the discriminative cue for the correct (reinforced) lever. Occasional periods (2.5 min) of nonreinforcement were used to assess the degree of stimulus control exerted over behavior by saline and 5-OMe DMT, and, to evaluate the series of compounds described herein.

Drugs

(±)-2,5-Dimethoxyphenylisopropylamine HCl (2,5-DMA), (±)-4-ethyl-2,5-dimethoxyphenylisopropylamine HCl (DOET) were obtained from NIDA. The hydrochloride salts of the other 4-substituted derivatives of 2,5-DMA, i.e. propyl (DOPR), butyl (DOBU), tertiery butyl (DOTB) and amyl (DOAM) were gifts from Dr. A. T. Shulgin. Phenoxybenzamine HCl (Dibenzyline®) was a gift from Smith Kline and French Laboratories, Philadelphia, PA. All solutions were prepared fresh daily.

RESULTS

We have previously reported pA_2 values for 2,5-DMA, DOM and DOET [9]; pA_2 values for the remaining compounds are listed, along with the slopes of their Schild plots, in Table 1. Some of the compounds occasionally produced a slight agonistic effect (usually less than 10% of the overall height of the total dose response curve) at the higher concentrations tested; if such was the case, the crest of this response would represent the new baseline. Antagonism appears to be competitive, however, as noted by the slopes of the Schild plots.

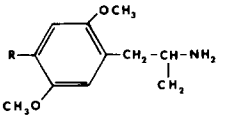
At high enough concentrations, all of the compounds studied are capable of producing an agonistic response in the fundus preparation and may thus be referred to as partial agonists or mixed agonist-antagonists. Consequently, in a separate series of experiments employing the fundus preparation, attempts were made to determine pD_2 values (reported in Table 2 as "apparent" pD_2 values).

Blocking experiments (Table 3) reveal that the test compounds retain varying degrees of agonistic activity even after the 5-HT receptors are irreversibly inhibited by incubation with phenoxybenzamine. These responses are are, however, attenuated after blocking. Because of this effect, valid pD_2 values (in the absence of phenoxybenzamine) can not be determined and the effect of these agents are reported as "apparent" pD_2 values. The pD_2 values in Table 3 are not "apparent" because they reflect the interaction of drug with the PRT receptors (not PRT and/or 5-HT receptors, which is the case in Table 2).

When obtaining pD_2 values, it is customary to obtain several cumulative dose response curves for the agonist on each of several preparations. However, successive cumulative dose response curves could not be obtained for the compounds in this study; this effect was examined in greater detail for DOM than for most of the other agents. After exposure to high concentrations of, for example DOM, the fundus strip could not be completely washed free of compound, i.e. the strip did not relax to the original baseline. In addition, the relaxation that did occur was a very slow process, requiring, on occasion, up to several hours. Offermeier and Ariens [16] have reported observing similar behavior with LSD, for example. As a result of this incomplete washout, successive dose response curves achieve a progressively diminished maximal contraction (α); in addition, pD_2 values were erratic. For these reasons, (a) it was necessary

TABLE 1

pA_2 VALUES FOR 4-SUBSTITUTED 2,5-DIMETHOXYPHENYLISOPROPYLAMINES



Compound	R	pA_2*	Slope†	Number of Determinations‡
2,5-DMA	H	6.83	—	—
DOM	$-CH_3$	7.12	—	—
DOET	$-CH_2CH_3$	7.18	—	—
DOPR	$-(CH_2)_2CH_3$	7.17 (±0.10)	0.90 (±0.14)	3 (15)
DOBU	$-(CH_2)_3CH_3$	7.03 (±0.05)	0.87 (±0.06)	3 (15)
DOTB	$-C(Ch_3)_3$	7.22 (±0.11)	1.09 (±0.09)	3 (14)
DOAM	$-(CH_2)_4CH_3$	7.02 (±0.06)	0.91 (±0.06)	2 (10)

*pA_2 values are followed by standard deviation. The pA_2 values for 2,5-DMA, DOM and DOET have been previously reported [9].

†Negative slope of Schild plot followed by standard deviation.

‡Number of determinations followed by total number of dose response curves.

to obtain each dose response curve, along with its preceding 5-HT control curve, on a fresh preparation, and (b) protection experiments could not be performed, i.e., incubation of the fully contracted strip with, for example, phenoxybenzamine, followed by wash-out and, then, generation of a new dose response curve. The above mentioned problems were not evident when the fundus preparation was exposed to low doses of the test compounds and, therefore, the likelihood of interference during the pA_2 determinations is felt to be, at most, minimal.

During the attempted pD_2 determinations, DOM was found to produce a bi-phasic dose response curve (see Fig. 1 for an example). In four of the seven dose response curves obtained for DOM, the demarcation between the two curves was sufficiently distinct (horizontal) to allow independent determinations of pD_2 and α for each of the two portions of the curve. In Fig. 1, α for the lower curve is the distance represented by A while B is the measured distance to obtain α for the upper curve; these data are listed in Table 2 as DOM-lower curve and DOM-upper curve. In the three remaining bi-phasic curves for DOM, the plateau (A-B junction) was not as horizontal as for the other four curves; as a consequence, it was difficult to determine exactly where the lower curve terminated and where the upper curve began.

As in our previous reports [10,11], the animals trained to discriminate 5-OMe DMT from saline, consistently responded 85–96% on the 5-OMe DMT-correct lever when administered 1.5 mg/kg 5-OMe DMT, and never more than 10% when administered saline. Administration of DOET, DOPR, DOBU and DOAM resulted only in partial gener-

TABLE 2

"APPARENT" pD_2 VALUES FOR 2,5-DMA ANALOGS*

	"Apparent" pD_2	Slope	α1†	Number of Determinations
2,5-DMA	4.52 (±0.33)	0.98 (±0.18)	0.99 (±0.18)	3
DOM	5.63 (±0.52)	0.68 (±0.12)	0.91 (±0.12)	7
DOET	4.82 (±0.10)	1.04 (±0.08)	0.99 (±0.30)	4
DOPR	5.30 (±0.37)	1.53 (±0.55)	0.49 (±0.09)	3
DOBU	5.12 (±0.09)	3.55 (±1.96)	0.23 (±0.10)	3
DOAM	4.39 (±0.13)	1.02 (±0.38)	0.30 (±0.17)	2
DOM‡ (upper curve)	3.92 (±0.28)	2.29 (±0.37)	0.30 (±0.11)	4
DOM‡ (lower curve)	6.50 (±0.14)	1.04 (±0.12)	0.64(±0.18)	4

*pD_2, slope and α values are followed by standard deviation.

†Height of dose response curve divided by height of preceding 5-HT curve.

‡DOM produces a bi-phasic dose response curve (Fig. 1); pD_2 and α values can be independently determined for each section (upper and lower portion) of the curve.

TABLE 3
RESULTS OF PHENOXYBENZAMINE BLOCKING EXPERIMENTS*

	pD_2	$\alpha 2$†	% Block‡	Number of Determinations
2,5-DMA	3.29 (±0.43)	0.21 (±0.18)	79%	3
DOM	3.42 (±0.13)	0.34 (±0.14)	63%	4
DOET	3.84 (±0.21)	0.35 (±0.15)	64%	4
DOPR	3.62 (±0.17)	0.06 (±0.01)	88%	3
DOBU	3.55 (±0.46)	0.09 (±0.08)	61%	5
DOAM	3.51 (±0.15)	0.07 (±0.02)	77%	2

*pD_2, and α values are followed by standard deviation.
†Height of dose response curve divided by height of preceding 5-HT curve.

‡$\frac{\alpha 1 - \alpha 2}{\alpha 1} \times 100$

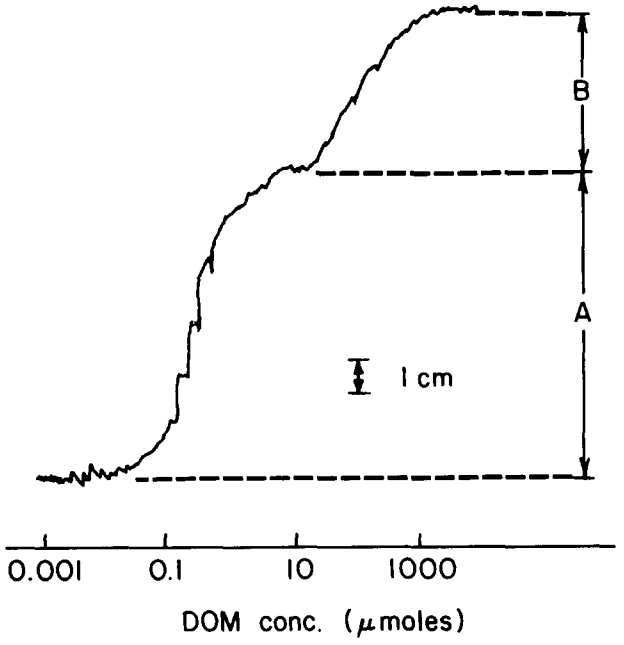


FIG. 1. Bi-phasic dose response curve for DOM (A=DOM-lower curve, B=DOM-upper curve). Increasing concentrations of DOM were added at regular (50–70 sec) intervals.

alization, i.e. 40–48% 5-OMe DMT-appropriate responding; response rates were not dissimilar to those elicited by 5-OMe DMT. DOTB produced saline-like responding (Table 4).

DISCUSSION

Examination of a series of tryptamine derivatives has revealed that those compounds which are the most behaviorally active possess the highest 5-HT receptor affinities (pA_2 values) in the fundus preparation [8,11]; as activity decreases, so does 5-HT receptor affinity. For a series of phenylisopropylamine (amphetamine) derivatives, again, the most behaviorally potent analogs possess a high affinity [9]. An unencumbered 2,5-dimethoxy pattern results in compounds with the highest pA_2 values [9]. Substitution at the 4-position of 2,5-dimethoxyphenylisopropylamine (2,5-DMA) is known to effect psychotomimetic activity as determined both in human and animal experiments [15,17]. Of the compounds we had previously examined, the 4-methyl and 4-ethyl derivatives of 2,5-DMA, i.e. DOM and DOET, possess not only the highest, but nearly identical 5-HT receptor affinities. Interestingly, 4-substitution of 2,5-DMA by a propyl (DOPR), butyl (DOBU), tertiary butyl (DOTB) or amyl (DOAM) group results in pA_2 values which are all in the 7.02 to 7.22 range, values which are similar to the pA_2 values of DOM and DOET (Table 1). With the exception of DOTB, for which human data are unavailable, the compounds listed in Table 1 constitute some of the most behaviorally active phenylisopropylamines known [17]. The results of this investigation suggest that, unlike the tryptamine derivatives where a parallelism exists between pA_2 values and behavioral potency in animals [11], a similar parallelism does not exist for this phenylisopropylamine series. Nevertheless, those phenylisopropylamines which are the most active do possess a relatively high affinity (pA_2) for the 5-HT receptors of the isolated rat fundus preparation.

Another method of determining affinity is by examination of agonistic effects whereby affinity can be expressed as pD_2 values. Although the 5-HT agonistic effects of several of these compounds have been previously examined, pD_2 values have not been reported. The agonistic activity of 2,5-DMA and DOM have been studied using superfused vascular strips of dog dorsal metatarsal vein [5] and sheep umbilical artery [7]. Using the latter preparation, Shulgin and Dyer [18] have studied the agonism produced at 5-HT receptors by the entire series (4-H through 4-amyl 2,5-DMA) which is under investigation herein. With respect to the fundus preparation, Huang and Ho [12] have reported that 100 μg/mL of DOM produces an agonistic response comparable to that produced by 0.05 μg/mL of 5-HT, while Standridge *et al.* [20], have found both R(−)-DOM and S(+)-DOM to be less potent than 5-HT. In this present study, cumulative dose response curves were obtained for all of the test compounds (with the exception of DOBT, where sufficient quantities were unavailable), wherefrom, theoretically, pD_2 values can be de-

TABLE 4

RESULTS OF GENERALIZATION STUDIES

	Dose-range tested (mg/kg)	Number of doses	Total number of animals to receive drug*	Highest 5-OMe DMT-correct responding†
DOM	0.25–1.00	3	18	82%‡
DOET	0.01–0.75	5	18	40%
DOPR	0.05–0.50	7	24	40%
DOBU	0.05–0.75	5	15	44%
DOTB	0.05–1.50	5	15	4%
DOAM	0.10–3.00	5	15	48%

*Three to six (usually three) animals were used per dose of compound.

†Highest correct responding achieved; increasing the dose(s) beyond that giving this percent responding resulted in disruption of behavior (i.e. reduced number, or, no lever-presses). 5-OMe DMT (1.5 mg/kg) typically results in 85–96% responding while saline administration never exceeds 10% responding.

‡The total number of animals used and the highest percent responding have not been previously published, however, we have previously published the ED-50 for generalization in the 5-OMe DMT-trained animals [11].

termined. Winter and Gessner [31] have previously cautioned against using the pD_2 method, when the fundus preparation is employed, because of the existence of contractile phenoxybenzamine-resistant tryptamine (PRT) receptors. Indeed, blocking experiments (Table 3) reveal that the test compounds interact in an agonistic manner with both the 5-HT and PRT receptors. In other words, the contractile responses observed can result from an agonistic interaction with both the 5-HT and PRT receptors and, hence, true pD_2 values for the 5-HT receptor interaction can not be determined. DOM, for example, appears to produce a maximal contraction (α=0.91) similar to that produced by 5-HT itself (α=1.00). A comparison of pD_2 values would suggest that DOM is one hundred-fold less active than 5-HT. However, whereas the action of 5-HT is exclusively at the 5-HT receptors [31], DOM, as well as the other derivatives in Table 2, can produce an agonistic effect even when the 5-HT receptors are blocked (Table 3). While most of the test compounds produced typical dose response curves, DOM produces a bi-phasic curve (Fig. 1). In several cases, the initial (lower) curve appears to reach a plateau prior to the initiation of the second (upper) portion of the curve. From these few curves, pD_2 and α for the upper curve are quite similar to the data obtained in the blocking experiments with DOM (Table 3). Thus, it might be assumed that the upper curve represents the interaction of DOM with the PRT receptors while the lower curve is a more accurate representation of a dose response curve for the interaction of DOM with 5-HT receptors of the fundus preparation. In this manner, DOM is found to be about one-tenth as active an agonist as is 5-HT. Furthermore, DOM possesses a hundred-fold higher affinity for 5-HT receptors than for PRT receptors.

Based on the results of the blocking experiments, which implicate PRT receptor participation, and on the individual pD_2 values for the bi-phasic DOM curve, it is concluded that the rat fundus preparation is inappropriate for studying the 5-HT receptor interactions of these compounds when the pD_2 method is used. The agonistic effects (pD_2 values, ED_{50} values, etc.) of various phenalkylamines have been reported, using the isolated rat fundus preparation, and caution is advised in interpreting these data until PRT receptor involvement has been determined.

Generalization occurs when DOM is administered to 5-OMe DMT-trained rats [10,11]. When the higher homologs are administered, generalization is not observed (Table 4). Responding on the 5-OMe DMT-correct lever never exceeded 50%. These data suggest that DOM and 5-OMe DMT produce similar interoceptive cues but that the effects of DOET, DOPR, DOBU, DOTB and DOAM, under the testing conditions reported, are somewhat dissimilar to those of 1.5 mg/kg of 5-OMe DMT.

Of the 4-substituted derivatives of 2,5-DMA, DOM and DOET have been the best studied; see Shulgin [17] for a recent review. It is interesting to note that, in man, the subjective effects of DOET are consistently different from the psychotomimetic syndrome observed with higher levels of DOM [17]. There are insufficient human data on the qualitative behavioral effects produced by DOPR, DOBU and DOAM to determine whether they should be classified with DOM or with DOET [17]. The results of the discriminative stimulus assay suggest that the interoceptive cues produced by the higher homologs (at the dosage and time constraints of this assay) are not as similar to the interoceptive cues produced by 5-OMe DMT as are those of 2,5-DMA and DOM. However, because generalization occurs between DOM and DOET [19], there may be some sharing of common mechanistic components responsible for the behavioral effects which are produced by these compounds.

The results of this present study may be summarized as follows: (a) although 4-methylation of 2,5-DMA doubles its affinity, replacement of this methyl group by other small alkyl groups has no further effect on pA_2; (b) there is no parallelism between pA_2 and human dose of the phenalkylamines studied (although all of those compounds shown to be active in man also possess a high pA_2); (c) the pD_2 method is not useful for studying the agonistic effects of phenalkylamine derivatives when the rat fundus preparation is being used; and (d) with the exception of DOM, complete generalization does not occur when the 4-alkyl derivatives of 2,5-DMA are administered to 5-OMe DMT-trained rats.

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