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α-Adrenergic and 5-HT_2-Serotonergic Effects of some β-Phenylethylamines on Isolated Rat Thoracic Aorta

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Abstract—1. 2C-H [2-(2,5-dimethoxyphenyl)ethylamine] ($pD_2 = 6.74$), TMPEA [2-(2,4,5-trimethoxyphenyl)ethylamine] ($pD_2 = 5.83$), 2C-D [2-(2,5-dimethoxy-4-methylphenyl)ethylamine] ($pD_2 = 5.06$), homoveratrylamine [DMPEA, 2-(4,5-dimethoxyphenyl)ethylamine] ($pD_2 = 4.46$) and homopiperonylamine [MDPEA, 2-(3,4-methylenedioxyphenyl)ethylamine] ($pD_2 = 4.19$), elicit concentration-dependent contraction of the isolated rat thoracic aorta.

2. At 9.9×10^{-6} M, 2C-N [2-(2,5-dimethoxy-4-nitrophenyl)ethylamine] behaves as a competitive antagonist to serotonin in this preparation.

3. Considering previous results with the structurally related 2C-B [2-(4-bromo-2,5-dimethoxyphenyl)ethylamine], weak or partial agonistic activity or antagonism of aortic contraction appears to be related to psychedelic properties reported in humans for phenylethylamines.

INTRODUCTION

The phenylisopropylamine hallucinogens are known to interact with α_1-adrenergic, 5-HT_2 and 5-HT_{1C} receptors (Burris and Sanders-Bush, 1988; Luscher and Vanhoutte, 1988; Glennon *et al.*, 1992), and 5-HT_2 and 5-HT_{1C} sites, at least, are believed to be implicated in hallucinogenesis (Titeler *et al.*, 1988; Leysen, 1990; Göthert, 1992). Binding data are available for a fairly large sample of these substances (Shannon *et al.*, 1984; Glennon *et al.*, 1986, 1992; Lyon *et al.*, 1986; Titeler *et al.*, 1988; Seggel *et al.*, 1990), and several have been subjected to behavioral and pharmacological studies (Coutts and Malicky, 1973; Aldous *et al.*, 1974; Glennon *et al.*, 1982, 1983b; Glennon and Hauck, 1985; Heym *et al.*, 1984; Martin and Sloan, 1986; McCall, 1986; Schlemmer and Davis, 1986; Foreman *et al.*, 1989). The potently psychoactive DOB [(±)-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane] and DOI [(±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane], for example, were viewed for several years as 5-HT_2 complete agonists, although they have recently been shown to have similar high affinities for 5-HT_{1C} receptors (Glennon *et al.*, 1992).

In contrast, comparable information regarding the lower, α-demethylated analogues of psychotomimetic amphetamine derivatives, is scarce and quite inconclusive. Among the ring-substituted phenylethylamines, some are known to cause perceptual changes in man at fairly low doses. Others, like mescaline [2-(3,4,5-trimethoxyphenyl)ethylamine], are much less potent, while some appear to be inactive in this regard. Binding studies suggest that a very small number of phenylethylamines bearing a particular pattern of ring substituents exhibit somewhat lower affinities for both 5-HT_2 and 5-HT_{1C} receptors than similarly substituted phenylisopropylamines (Glennon, 1979; Glennon *et al.*, 1980, 1992). Similar studies at other binding sites seem to be lacking. It is well known that the ratio of subjective potencies in humans of pairs of (the stronger) α-methyl and (the weaker) α-demethyl analogues depends strongly on their ring substitution, ranging from less than 2 to at least 25 (Braun *et al.*, 1978; Shulgin and Shulgin, 1991), but the relative importance of affinity and efficacy at relevant receptors, pharmacokinetics and metabolism, has not been assessed.

We have recently shown that 2C-B [2-(4-bromo-2,5-dimethoxyphenyl)ethylamine] (Shulgin and

Table 1. Active concentration range, pD_2 values and relative maximal responses of ring-substituted phenylethylamines

Substance	Range	$pD_2 \pm SD$	Max. response relative to 5-HT	NE	2C-H
2C-H	9.9×10^{-8}–6.1×10^{-5}	6.74 ± 0.5	—	0.89	1.0
TMPEA	7.4×10^{-7}–6.9×10^{-6}	5.83 ± 0.18	0.42	0.36	0.41
2C-D	7.4×10^{-7}–1.4×10^{-3}	5.06 ± 0.02	0.50	0.44	0.50
2C-B*	3.0×10^{-5}–4.0×10^{-4}	4.55 ± 0.11	Not determined		
DMPEA	5.6×10^{-5}–5.3×10^{-4}	4.46 ± 0.21	0.39	0.33	0.37
MDPEA	2.9×10^{-7}–4.7×10^{-4}	4.19 ± 0.12	0.49	0.42	0.47

*Lobos *et al.*, (1992).

Carter, 1975), which is one of the more potently psychoactive members of this group of drugs (Shulgin and Shulgin, 1991), behaves as a fairly weak partial agonist at 5-HT_2 and α_1-adrenergic receptors in the isolated rat thoracic aorta (Lobos *et al.*, 1992). It therefore seemed reasonable to extend these studies to several other representative phenylethylamines to determine whether their expected actions at vascular 5-HT_2 and/or α_1-adrenergic receptors in any way correlate with their activities (or lack of activity) as assayed in volunteers.

MATERIALS AND METHODS

Male Sprague–Dawley rats weighing 300–350 g were killed by cervical contusion. The thoracic aorta was removed, freed of adjacent tissue and cut into 5 mm sections. Each piece of tissue was suspended horizontally in a 10 ml tissue chamber containing modified Krebs solution (Cohen *et al.*, 1986) between a pair of surgical stainless steel supports, one fixed to the bottom of the chamber and the other connected to the transducer. The solution was kept at 37°C and oxygenated with a 95% O_2–5% CO_2 mixture, and the tissue sections were allowed to equilibrate for 2–3 hr under a resting tension of 3*g*.

Cumulative dose–response curves were obtained by stepwise increases in the concentration of NE, 5-HT or the test compound, adding 100 μl aliquots of appropriate solutions of these substances. More drug was added as soon as a steady response was obtained from the preceding dose, until no further contraction was observed. The results were reduced to Hill plots from which apparent pD_2 values were calculated.

The phenylethylamines used in this study were synthesized in our laboratory following published procedures (Shulgin and Shulgin, 1991); their structures were confirmed by ^{1}H-NMR and their purity was checked by TLC. NE [(−)-arterenol bitartrate salt] and 5-HT creatinine sulfate were from Sigma.

RESULTS

Table 1 summarizes the pD_2 values calculated for each compound from the corresponding Hill plots (not shown). Five of the six phenylethylamine analogues studied by us produced concentration-dependent contraction of aortal rings, with data corresponding to norepinephrine controls included for comparison (Figs 1 and 2). The activity ranges indicated in Table 1 reflect the lowest concentrations at which any contractile activity was observed, and the concentrations at which the responses began to decrease. Maximal responses are given relative to NE, 5-HT and 2C-H, which produced slightly stronger contractions than 5-HT.

The present data show that the most active compounds of the group tested are the substances with the aromatic ring substituted at the 2,5 positions (Fig. 1) and varying substitution at C(4), with marked differences in the range of pD_2 values. The 3,4-disubstituted members of the series (Fig. 2) are relatively inactive. 2C-H, the only member of the group without any substituent at C(4), is the most potent compound in the series, showing a pD_2 value slightly

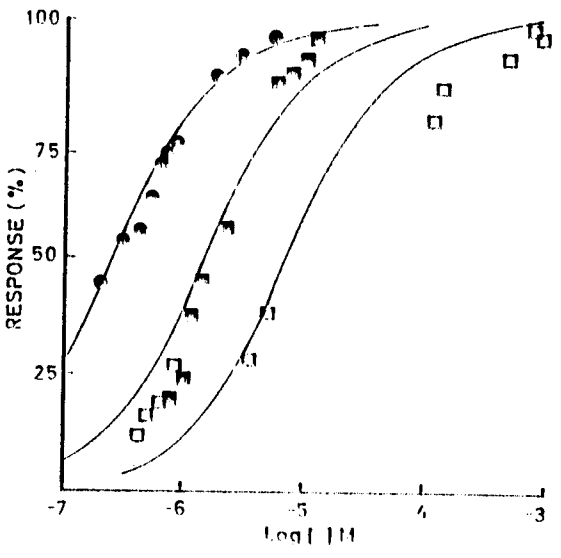


Fig. 1. Cumulative concentration response curves to TMPEA (■), 2C-H (●) and 2C-D (□) in rat aortal rings. The response to each cumulative dose is expressed as a percentage of the maximum contractile response achieved by the drugs. Doses are expressed as the log of the final molar concentration in the bath. Each point in the curves represents the average of 3 measurements.

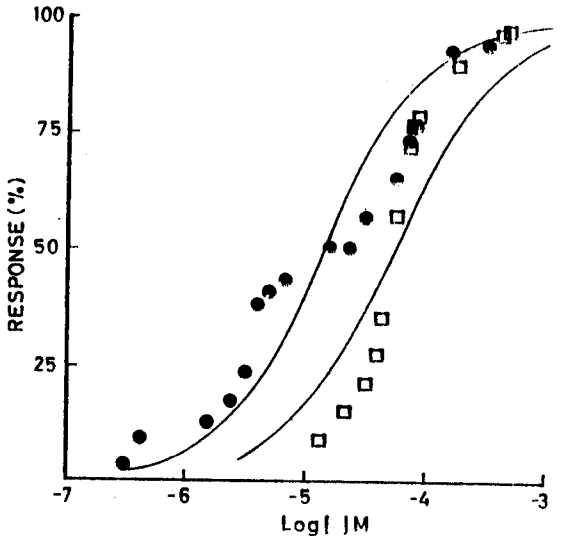


Fig. 2. Cumulative concentration–response curves to MDPEA (□) and DMPEA (●) in rat thoracic aortal rings. The response to each cumulative dose is expressed as a percentage of the maximum contractile response achieved by the drugs. Doses are expressed as the log of the final molar concentration in the bath. Each point in the curves represents the average of 3 measurements.

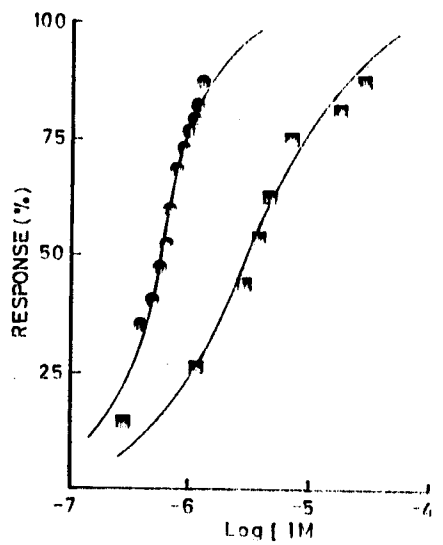


Fig. 4. Cumulative concentration–response curves to 5-HT in rat thoracic aortal rings obtained in the absence (●) and in the presence (■) of 2C-N (9.9×10^{-6} M). Each point in the curves represents the average of 3 measurements.

higher than that calculated for 5-HT, with a maximal response comparable to the latter reference substance tested under the same conditions. All the other compounds able to elicit contraction of the aortal rings exhibited partial agonist behaviour when compared with 5-HT and NE (Table 1).

The sixth compound, 2C-N, did not show any vasoconstrictive activity in this preparation. Nevertheless, after pre-incubating the tissue with a 9.9 μM solution of this substance, the control NE curve was shifted to the right, without any obvious change in its slope or maximal effect ($P > 0.15$) (Fig. 3). 2C-N also shifts the serotonin control curve to the right, but in this case the slope is decreased and the maximal effect is significantly reduced ($P < 0.025$) (Fig. 4).

As the effects of a single concentration of 2C-N were examined, it is not possible to rigorously quantify its pA_2 value. Measuring the shift of the NE concentration–response curve at a specific fraction of the maximal effect, however (Cohen *et al.*, 1986), the

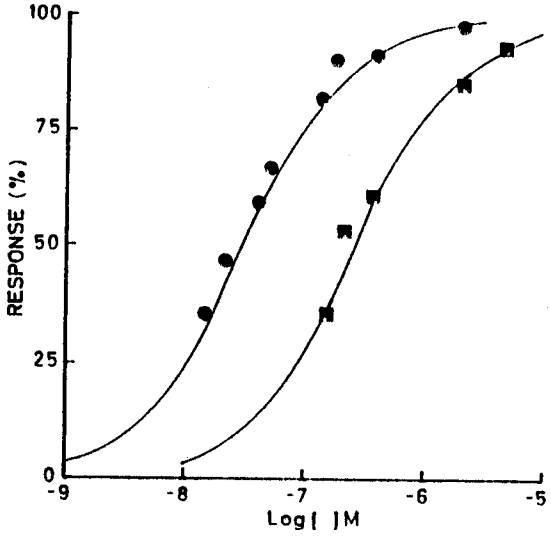
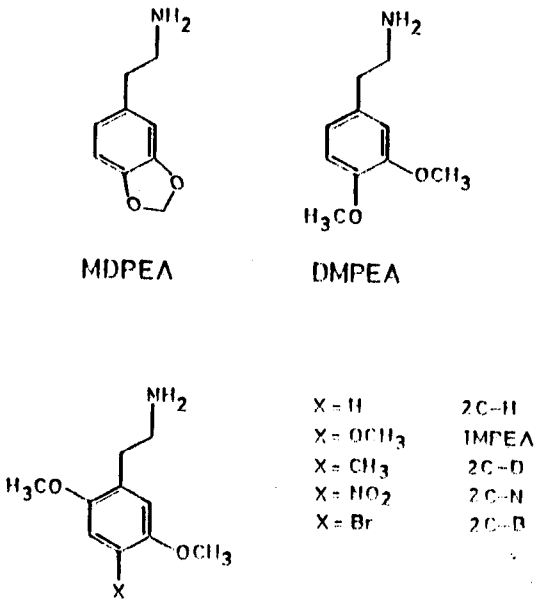


Fig. 3. Cumulative concentration–response curves to NE in rat thoracic aortal rings obtained in the absence (●) and in the presence (■) of 2C-N (9.9×10^{-6} M). Each point in the curves represents the average of 3 measurements.



Scheme 1

apparent dissociation constant of the antagonist can be calculated, and this can be used to estimate the pA_2 value. Comparison of the NE control curve and the graph obtained after incubating with 2C-N thus leads to an apparent $pA_2 = 5.98 \pm 0.09$.

DISCUSSION

2C-N is the only member of this series which, in the rat thoracic aorta preparation, behaved as an antagonist (competitive) to norepinephrine and (non-competitive) to serotonin. All the other phenylethylamines tested by us elicited concentration-dependent contraction of aortal rings. 2C-H, for which no data are available in human volunteers, was the most active agonist, followed by TMPEA. The rather intensely psychoactive 2C-D was a less potent agonist in the aorta preparation, followed by homoveratrylamine (DMPEA) and homopiperonylamine (MDPEA). The psychoactive 2C-B has been shown to contract rat aortal rings at somewhat higher concentrations than 2C-D (Lobos *et al.*, 1992).

Phenylethylamine derivatives, when lacking α-alkyl substituents, are generally believed to be good MAO substrates, and this belief has been invoked as an explanation of the 2-fold greater oral potency of the α-methylated TMA with regard to mescaline in humans, and further generalized to other similar cases. Nevertheless, comparison of the scantily available data for α-unsubstituted and α-methylated phenethylamine pairs indicates that this explanation is quite insufficient. Thus, DON is at least 25 times more potent than 2C-N, while the ratios for the TMA-2/TMPEA, DOB/2C-B and DOM/2C-D, pairs are about 15, 10 and 4, respectively (Braun *et al.*, 1978; Shulgin and Shulgin, 1991), leading to the speculation that the α-methyl group may be more effective in preventing oxidative deamination in the 2,4,5-trisubstituted series (Nichols and Glennon, 1984). Moreover, TMPEA seems to be a poor MAO substrate in comparison with mescaline (Clark *et al.*, 1965), and it could therefore be postulated that a 2-methoxy group renders phenylethylamine derivatives less susceptible to oxidative deamination than their 2-unsubstituted congeners. If this were so, the apparent lack of subjective effects of DMPEA and MDPEA in humans at doses in excess of 300 mg p.o. might well be explained by their rapid metabolic inactivation.

In the remaining members of the series, contractile activity may be compared with subjective potency p.o. as reported by Shulgin and Shulgin (1991). The activity of 2C-H in humans is unknown and presumably low, and TMPEA is inactive at an oral dose of 300 mg; their pD_2 values are 6.7 and 5.8, respectively. 2C-D produces perceptual changes at 20–60 mg, and exhibits a pD_2 of 5.1. 2C-B is active in humans at 12–24 mg, and exhibits a pD_2 of 4.5. These results suggest that, in this set of phenylethylamines, higher subjective activities are associated with lower contractile potencies. It is appropriate to speculate, however, that the activities of these compounds after oral administration may be governed to a great extent by their pharmacokinetics, and that disregarding metabolic differences – the more lipophilic 2C-B would be expected to reach the CNS in higher concentrations than 2C-D, TMPEA or 2C-H.

2C-N, which does not contract the rat aorta preparation, deserves separate comment. Its apparent pA_2 value of 5.98 ± 0.09 vs NE is much lower than that calculated, for example, for prazosin (9.17; Marwood and Stokes, 1983). Although this activity is rather weak this is, to the best of our knowledge, the first time that a phenylethylamine has been shown to behave as an α_1-adrenergic antagonist. Our results also show non-competitive antagonism of serotonin. 2C-N has been reported to produce psychological changes in humans at oral doses in the 100–150 mg range. Unlike its halogen-, alkyl- or alkoxy-substituted congeners, the presence of an aryl nitro group in 2C-N probably results in a low octanol-water partition coefficient and thus diminished penetration of the blood-brain barrier, as has been discussed for its phenylisopropylamine homologue DOH (Gómez-Jeria *et al.*, 1987). In this case, therefore, low subjective potency may also be due to low concentrations in the CNS rather than to low efficacy at the relevant receptors. Obviously, more detailed characterization of the *in vitro* activities of these substituted phenylethylamines is required, as well as an evaluation of their susceptibility to MAO-catalysed destruction and of their transport into the brain.

α-Methyl substitution must also alter the relative stabilities of the drug conformers, and this factor has been mentioned as a possible alternative explanation of the increased potency of phenylisopropylamines over phenylethylamines (Cooper, 1970; Cooper and Walters, 1972). Nevertheless, the few published experimental and theoretical studies of the conformational preferences of related drugs do not indicate the presence of unsurmountable barriers between the more stable conformations (Neville *et al.*, 1971; Makriyannis and Knittel, 1978; Weintraub and Nichols, 1978; DeJong *et al.*, 1982). Moreover, α-methylation of phenylethylamines does not seem to affect their affinities for serotonin gastric fundus, 5-HT_2 or 5-HT_{1C} receptors *in vitro* to any great extent (Glennon, 1979; Glennon *et al.*, 1980, 1992).

Our present results suggest that, insofar as serotonin and/or adrenergic receptors may be involved

in the subjective effects of these drugs, competition with appropriate neurotransmitters for certain binding sites, rather than agonist activity, should be at the root of their action. This idea appears to be in conflict with the 5-HT$_2$/5-HT$_{1C}$ agonist character of the potent hallucinogens DOB and DOI, and thus leads to the hypothesis that other receptors may play a crucial role in the perception-altering activities of α-unsubstituted psychoactive phenylethylamines.

SUMMARY

The contractile actions of homopiperonylamine [MDPEA, 2-(3,4-methylenedioxyphenyl)ethylamine], homoveratrylamine [DMPEA, 2-(4,5-dimethoxyphenyl)ethylamine], 2C-H [2-(2,5-dimethoxyphenyl)-ethylamine], TMPEA [2-(2,4,5-trimethoxyphenyl)-ethylamine] and the psychoactive 2C-D [2-(2,5-dimethoxy-4-methylphenyl)ethylamine] and 2C-N [2-(2,5-dimethoxy-4-nitrophenyl)ethylamine] were assayed in the isolated rat thoracic aorta. All but 2C-N elicited concentration-dependent contraction of this preparation, 2C-H being the most and homopiperonylamine the least potent, while the previously studied 2C-B [2-(4-bromo-2,5-dimethoxyphenyl)-ethylamine] showed activity intermediate between these extremes. 2C-N behaved as a competitive antagonist to norepinephrine and as a non-competitive antagonist to serotonin. In contrast to the tendency expected for hallucinogenic phenylisopropylamines on the basis of receptor binding studies and contractile potency in the isolated sheep umbilical artery, weak or partial agonistic activity or antagonism of aortic contraction by ring-substituted phenylethylamines appears to be related to the psychedelic properties observed in human subjects.

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