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Inhibition of human platelet 5-hydroxytryptamine uptake by β-phenethylamine derivatives

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Forty-eight derivatives of β-phenethylamine have been studied as inhibitors of 5-hydroxytryptamine uptake by human blood platelets *in vitro*. Inhibitory potency was found to be increased by *para*-substitution with electronegative groups, by α-methylation in the D-configuration and by addition of *N*-alkyl groups, and to be reduced by saturation of the ring, by *ortho*-methoxylation, *meta*- or β-hydroxylation and by hydrazine formation. It is suggested that optimal affinity involves folding of the molecule to fit a cleft-like carrier site. The structural requirements for activity show features of similarity to those of tryptamine and tricyclic antidepressant derivatives and some resemblance with requirements for inhibition of the adrenergic uptake$_1$ mechanism of the heart. No obvious correlation exists between the activity of these drugs as inhibitors of platelet 5-HT uptake and their ability to exert effects thought to involve central tryptaminergic mechanisms.

It has been suggested that some of the actions of the anorexic agent fenfluramine on the brain and on the peripheral nervous system are exerted by a stimulant effect on tryptamine receptors. Evidence for this comes from observations that methysergide antagonizes fenfluramine-induced hypothermia in dogs (Jespersen & Scheel-Krüger, 1970) and contraction of the isolated human saphenous vein strip (Kirby & Turner, 1971) and that another 5-hydroxytryptamine (5-HT) antagonist, AHR 3009 (8β-carbobenzyloxy-aminomethyl-1-methyl-10α-ergoline), inhibits fenfluramine-induced appetite suppression in rats (Funderburk, Hazelwood & others, 1971).

The possible action of fenfluramine on tryptamine receptors suggested to us that the drug might also influence 5-HT uptake by blood platelets, which is only weakly antagonized by other derivatives of β-phenethylamine (Stacey, 1961). The present work involves a study of structure-activity relations in antagonism of human platelet 5-HT uptake *in vitro* by a number of such derivatives and related compounds with anorexic activity. One object of the study is to characterize the transport carrier site, which is already known to show affinity for compounds of widely different structures, tricyclic antidepressants (Marshall, Stirling & others, 1960; Todrick & Tait, 1969; Ahtee & Saarnivaara, 1971), narcotic analgesics (Ahtee & Saarnivaara, 1973), adrenoceptor blocking drugs (Bygdeman & Johnsen, 1969) and others (Stacey, 1961).

MATERIALS AND METHODS

Procedure

All experiments were done on platelet-rich plasma obtained from volunteers of

either sex. Preparation of platelet-rich plasma, using EDTA Na_2 as anticoagulant, the measurement of 5-HT (incorporating ^{14}C-5-HT as label) uptake *in vitro* and of inhibition by drugs were made as described by Stacey (1961) using the following modifications: (i) preincubation and incubation with 5-HT were at 29° to slow uptake. Preliminary experiments indicated that uptake at this temperature was linear against time over the period of incubation; (ii) the concentration of 5-HT was 10^{-6}M; (iii) the incubation time was 10 min. Radioactivity of the platelets, separated by centrifugation, was measured in a liquid scintillation spectrometer.

Test drugs, dissolved in physiological saline, were adjusted to neutral pH with NaOH and added to the incubation mixtures at 3 or more different concentrations. Concentrations producing 50% inhibition of 5-HT uptake (IC50) were interpolated from log concentration/probit inhibition lines calculated by the method of least squares. Inhibitory potency, calculated as the reciprocal of IC50, is expressed relative to that of β-phenethylamine (=100). In a few instances in which one individual drug isomer or the racemate was unavailable its potency was calculated from the measurements done on the other forms.

Drugs. Sources of the compounds used were: (±)-, (+)- and (−)-fenfluramine HCl, (±)-, (+)- and (−)-norfenfluramine HCl, (±)-*p*-fenfluramine HCl, (±)-N-hydroxyethylnorfenfluramine HCl, (±)- and (−)-amphetamine HCl, (±) and (−) methylamphetamine HCl, (±)-, (+)- and (−)-ethylamphetamine HCl, S 1513 methane sulphonate (Servier Laboratories Ltd.), (±)- and (−)-propylhexedrine HCl, (+)- and (−)-*trans*-, and *cis*-tranylcypromine HCl, tranylcypromine sulphate, (±)-4-hydroxyamphetamine HBr (Smith Kline & French Laboratories), (±)-4-chloroamphetamine HCl, (±)-4-chloromethylamphetamine HBr, (+)- and (−)-4-chloromethylamphetamine HCl, (±)-4-chloroethylamphetamine HCl (Roche Products Ltd.), chlorphentermine HCl, phenelzine sulphate, phenylpropanolamine HCl (William R. Warner & Co. Ltd.), diethylpropion HCl, mephentermine sulphate (John Wyeth & Brother Ltd), phenmetrazine HCl (Boehringer Ingelheim Ltd), (−)*pseudo*ephedrine HCl (Wellcome Research Ltd), (±)-3-hydroxyamphetamine HCl (Merck Sharp & Dohme Research Laboratories), (±)-pheniprazine HCl (Fisons Pharmaceuticals Ltd), (±)-cyclopentamine HCl (Eli Lilly & Co. Ltd), phentermine base (Riker Laboratories Ltd), 5-hydroxytryptamine creatinine sulphate (May & Baker Ltd), dopamine HCl (Calbiochem), 5-hydroxyptamine-3-[^{14}C]-creatinine sulphate (Radiochemical Centre, 55 mCi mmol^{-1} Batch 49), 2-phenethylamine base, tyramine HCl, (−)-ephedrine HCl (British Drug Houses), (±)- and (−)-methoxyphenamine HCl, (+)- and (−)-benzphetamine HCl (Upjohn Ltd), (±)-methylphenidate HCl (Ciba Laboratories Ltd), (+)-amphetamine sulphate B.P., (+)-methylamphetamine HCl B.P.

RESULTS

The results of the experiments yielded satisfactory log concentration/probit lines for all the drugs studied; some are shown in Fig. 1. The results for the different drugs yielded similar slopes within the range 1·11 to 1·97 (Mean ± s.d.: 1·48 ± 0·16). The slope for β-phenethylamine (1·11) was flatter and those for diethylpropion (1·97) and *cis*-tranylcypromine (1·87) steeper than the remainder, the values lying more than two standard deviations from the mean.

The values of IC50 with 95% confidence limits and the relative potencies of the

Table 1. *Inhibition of platelet 5-HT uptake by derivatives of β-phenethylamine.*

Drug	n	IC50 ($\times 10^{-5}$M)[a] mean	95% confidence limits		Relative potency[b]
(−)-4-Chloromethylamphetamine	17	0·17	0·15	0·19	16,847
(±)-4-Chloroethylamphetamine	11	0·17	0·14	0·21	16,847
(±)-*p*-Fenfluramine	10	0·23	0·18	0·29	12,452
Chlorphentermine	11	0·26	0·24	0·29	11,015
(±)-4-Chloromethylamphetamine	11	0·31	0·26	0·38	9,239
(±)-4-Chloroamphetamine	11	0·32	0·28	0·38	8,950
(+)-Fenfluramine	10	0·41	0·34	0·50	6,985
(±)-Fenfluramine	12	0·59	0·47	0·73	4,854
(+)-Norfenfluramine	27	0·70	0·57	0·86	4,091
(+)-4-Chloromethylamphetamine	12	0·91	0·72	1·17	3,147
(±)-Norfenfluramine	18	1·02	0·76	1·37	2,808
(−)-Fenfluramine	11	1·30	1·04	1·64	2,203
(+)-Ethylamphetamine	16	1·66	0·93	2·93	1,725
(±)-4-Hydroxyamphetamine	18	1·98	1·75	2·24	1,446
(±)-Ethylamphetamine[c]		(2·98			961)
(+)-Methylamphetamine	9	3·15	2·73	3·63	909
(−)-Norfenfluramine	20	3·19	2·69	3·77	898
(±)-Hydroxyethylnorfenfluramine	11	3·38	3·04	3·75	847
(±)-Methylamphetamine	31	5·41	3·56	8·24	529
(+)-Amphetamine	10	5·51	4·46	6·80	520
p-Tyramine	13	5·63	4·53	6·97	509
(+)-Methoxyphenamine[c]		(5·70			502)
(+)-Benzphetamine	12	5·90	5·04	6·89	485
(±)-Benzphetamine[c]		(6·79			422)
(±)-S1513[d]	11	7·30	6·15	8·68	392
(−)-Benzphetamine	13	8·00	6·96	9·19	358
Mephentermine	11	8·02	7·35	8·75	357
(±)-Amphetamine	16	8·79	5·87	13·18	326
(±)-Methoxyphenamine	13	9·39	8·41	10·49	305
(+)-Propylhexedrine	11	9·78	7·27	13·11	293
Phenmetrazine	13	10·67	8·41	13·52	268
(±)-3-Hydroxyamphetamine	11	12·72	11·41	14·19	225
(±)-Propylhexedrine[c]		(12·86			223)
Phentermine	12	13·52	11·45	16·00	212
(−)-Ethylamphetamine	22	14·58	8·03	26·95	196
(+)-*trans*-Tranylcypromine	14	15·04	12·99	17·25	190
Tranylcypromine	14	18·60	13·08	25·56	154
(−)-Propylhexedrine	11	18·78	14·19	24·76	152
(−)-Methylamphetamine[c]		(19·15			149)
(±)-Methylphenidate	14	22·83	18·14	28·89	125
Dopamine	11	22·94	20·00	26·26	125
(−)-Methoxyphenamine	12	26·65	23·68	29·99	107
(±)-Cyclopentamine	11	27·62	23·87	31·95	104
(−)-Amphetamine	10	28·11	21·27	37·36	102
β-PHENETHYLAMINE	13	28·64	22·53	36·42	100
(−)-Ephedrine	9	33·76	31·36	36·35	85
(−)-*trans*-Tranylcypromine	11	34·92	20·71	60·16	82
(±)-Pheniprazine	12	44·56	35·38	55·63	64
Phenylpropanolamine	15	61·46	55·07	68·63	46
(−)-Pseudoephedrine	12	75·71	66·54	86·08	38
Phenelzine	11	88·18	78·63	98·68	32
Diethylpropion	11	103·45	90·25	118·28	28
cis-Tranylcypromine	17	138·78	111·47	172·81	21

a. IC50 is the drug concentration producing 50% inhibition of uptake.
b. Potency is expressed relative to β-phenethylamine (=100).
c. Calculated values.
d. 1-(3-Trifluoromethylphenyl), 2-(β-benzoyloxyethylamino) propane = *N*-oxyethylbenzoyl-norfenfluramine.

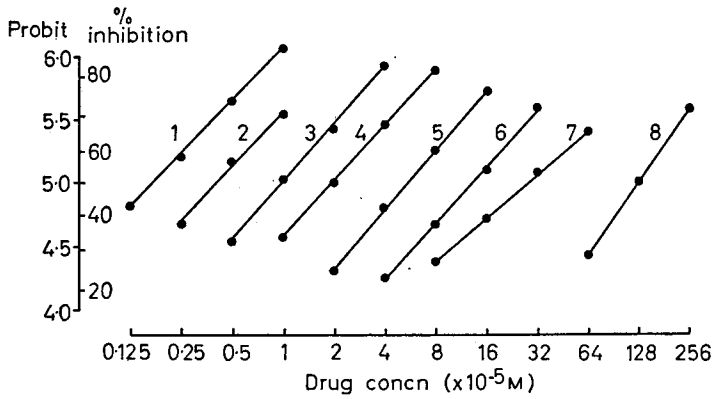
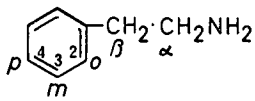


FIG. 1. Inhibition of platelet 5-HT uptake by β-phenethylamine derivatives. Abscissa: drug concentration (log scale). Ordinate: % inhibition (probit scale). 1. (−)-4-Chloromethylamphetamine. 2. (+)-Fenfluramine, 3. (±)-Norfenfluramine. 4. (±)-4-Hydroxyamphetamine. 5. (+)-Amphetamine. 6. Phentermine. 7. β-Phenethylamine. 8. *cis*-Tranylcypromine.

drugs tested are listed in Table 1. In Tables 2 to 4 the results are grouped to illustrate the influence of various molecular structural features in the β-phenethylamine skeleton.



Structure-activity relations

Effects of ring substitution (*Table 2*). In the *ortho*-position, methoxylation (as in methoxyphenamine) reduced activity. In the *meta*-position, a trifluoromethane group (as in norfenfluramine) increased activity whereas hydroxylation (as in 3-hydroxyamphetamine) reduced it. In the *para*-position, chloro- (as in 4-chloroamphetamine), trifluoromethyl-(as in *p*-fenfluramine) or hydroxyl- (as in *p*-tyramine) substituents increased activity in descending order. *Meta*- and *para*-hydroxylation together (as in the catecholamine dopamine) had negligible effect, indicating that the influences of the groups were mutually exclusive. Replacement of the benzene ring by saturated six- or five-membered rings (as in propylhexedrine and cyclopentamine respectively) reduced activity.

Effects of side chain substitution (*Table 3*). Substitution with an α-methyl group increased activity, but in the case of amphetamine this effect was found only in the (+)-isomer. Addition of a second methyl group (as in phentermine) reduced the activity of the (+)-isomers of amphetamine and methylamphetamine but increased that of the (−)-isomers. Phentermine had approximately twice the potency of β-phenethylamine. β-Hydroxylation reduced activity of the α-methylated derivatives, but the information here is limited because the drugs studied cover only half the possible conformations at these sites.

Table 2. *Effects of ring substitution on inhibition of platelet 5-HT uptake.*

Substituent	Parent drug (P)	Derivative (D)	Potency ratio (D/P)
o-Position			
OCH_3	Methylamphetamine	Methoxyphenamine	(±) 0·6
			(+) 0·5
			(−) 0·7
m-Position			
CF_3	Amphetamine	Norfenfluramine	(±) 8·6
			(+) 7·9
			(−) 8·8
	Ethylamphetamine	Fenfluramine	(±) 5·1
			(+) 4·0
			(−) 11
OH	*p*-Tyramine	Dopamine	0·2
	Amphetamine	3-Hydroxyamphetamine	(±) 0·7
p-Position			
Cl	Amphetamine	4-Chloroamphetamine	(±) 27
	Methylamphetamine	4-Chloromethylamphetamine	(±) 17
			(+) 3·5
			(−) 113
	Ethylamphetamine	4-Chloroethylamphetamine	(±) 17
	Phentermine	Chlorphentermine	52
CF_3	Ethylamphetamine	*p*-Fenfluramine	(±) 13
OH	β-Phenethylamine	*p*-Tyramine	5·1
	Amphetamine	4-Hydroxyamphetamine	(±) 4·4
Catechol			
3,4-Dihydroxy	β-Phenethylamine	Dopamine	1·2
C_6H_{11}	Methylamphetamine	Propylhexedrine	(±) 0·5
			(+) 0·3
			(−) 1·0
C_5H_9	Methylamphetamine	Cyclopentamine	(±) 0·2

Table 3. *Effects of side chain substitution on inhibition of platelet 5-HT uptake.*

Substituent	Parent drug (P)	Derivative (D)	Potency ratio (D/P)
α-Methylation	β-Phenethylamine	Amphetamine	(±) 3·3
			(+) 5·2
			(−) 1·0
	p-Tyramine	4-Hydroxyamphetamine	(±) 2·8
	Phenelzine	Pheniprazine	(±) 2·0
α-Dimethylation	Amphetamine	Phentermine	(±) 0·6
			(+) 0·4
			(−) 2·1
	Methylamphetamine	Mephentermine	(±) 0·7
			(+) 0·4
			(−) 2·4
	4-Chloroamphetamine	Chlorphentermine	(±) 1·5
	β-Phenethylamine	Phentermine	2·1
β-Hydroxylation	Amphetamine	Phenylpropanolamine	(±) 0·1
	(+)-Methylamphetamine	(−)-Ephedrine	0·1
	(−)-Methylamphetamine	(−)-Pseudoephedrine	0·2

Effects of N-*substitution* (*Table 4*). Amine substitution with alkyl groups (as in methyl- and ethylamphetamine) increased activity, the effect of an ethyl group being marginally greater than that of a methyl group. Further, hydroxylation of this ethyl group (as in hydroxyethylnorfenfluramine) reduced activity, whether by com-

Table 4. *Effects of* N-*substitution on inhibition of platelet 5-HT uptake.*

Substituent	Parent drug (P)	Derivative (D)	Potency ratio (D/P)
Alkyl			
CH_3	Amphetamine	Methylamphetamine	(±) 1·6
			(+) 1·7
			(−) 1·5
	Phentermine	Mephentermine	1·5
	4-Chloroamphetamine	4-Chloromethylamphetamine	(±) 1·0
CH_2CH_3	Amphetamine	Ethylamphetamine	(±) 2·9
			(+) 3·3
			(−) 1·9
	4-Chloroamphetamine	4-Chloroethylamphetamine	(±) 1·9
	Norfenfluramine	Fenfluramine	(±) 1·7
			(+) 1·7
			(−) 2·5
CH_2CH_2OH	Norfenfluramine	Hydroxyethylnorfenfluramine	(±) 0·3
	Fenfluramine	Hydroxyethylnorfenfluramine	(±) 0·2
Aryl			
$<^{CH_3}_{CH_2\ C_6H_5}$	Amphetamine	Benzphetamine	(±) 1·5
			(+) 0·9
			(−) 3·5
$CH_2\ C_6H_5$	Methylamphetamine	Benzphetamine	(±) 0·8
			(+) 0·5
			(−) 2·5
$CH_2CH_2OC{=}O\ C_6H_5$	Norfenfluramine	S1513	(±) 0·1
Hydrazine			
NH_2	β-Phenethylamine	Phenelzine	0·3
	Amphetamine	Pheniprazine	(±) 0·2

parison with the appropriate primary or secondary amine. Aryl substituents tended to reduce activity, though the (−)-isomer of benzphetamine was more potent than (−)-amphetamine or (−)-methylamphetamine, with both of which it can appropriately be compared. The hydrazine derivatives phenelzine and pheniprazine were less potent than their primary amine equivalents.

Stereoisomers. In nine of ten pairs of optical isomers studied the (+)-isomer (D configuration) was more potent than the (−)-isomer, the potency ratio being highest for ethylamphetamine and lowest for benzphetamine. In the case of 4-chloromethylamphetamine the (−)-isomer was more potent than the (+)-isomer. The absolute configurations of these latter isomers are unknown.

DISCUSSION

All the derivatives of β-phenethylamine studied showed inhibitory actions against platelet 5-HT transport. Their potency is not great, however, because even (−)-4-chloromethylamphetamine, the most active, is much less potent than the tricyclic antidepressant agents. Under our experimental conditions, imipramine is approximately 20 times, and chlorimipramine 140 times, more potent. It must be concluded, therefore, that β-phenethylamine derivatives have less affinity for the transport carrier involved. Nevertheless, the experimental results provide evidence about the structural requirements for attachment to the carrier.

Electronegative substituents in the *para-* or *meta*-positions of the ring, α-methyl-groups in the D-configuration and *N*-alkyl groups all appear to be favourable for such attachment, while in general *ortho*, β and *N*-aryl substituents are unfavourable or without influence. These findings are in keeping with observations on the actions

of tryptamine derivatives (Stacey, 1961; Lessin, Long & Parkes, 1965) and tricyclic antidepressants (Todrick & Tait, 1969; Tuck & Punell, 1973) on the same transport system and with the ability of the β-phenethylamine derivatives to deplete brain 5-HT (Pletscher, Bartholini & others, 1964), to inhibit brain 5-HT synthesis (Sanders-Bush & Sulser, 1970) and to cause contraction of the rat stomach strip (Frey, 1970). The significance of these observations is hard to evaluate but two aspects are of interest. First, there is approximate parallelism between potency and the degree of electronegativity in the *para*- and *meta*-ring positions which indicates that such groups probably attach to the carrier at the point which binds the negatively charged hydroxyl group of 5-HT. This group is essential for transport by this system (Stacey, 1961) and for the action on at least one type of tryptamine receptor (Vane, 1959). Secondly, the favourable influence of lipophilic groups of modest bulk (i.e. alkyl rather than aryl) in the side chain and the detrimental effect of β-hydroxylation suggest that folding of the molecule makes it more appropriate for carrier attachment. This observation suggests that the carrier site may be cleft-like in shape.

The characteristics discussed show superficial similarities to those shown by the same compounds as inhibitors of the noradrenaline uptake$_1$ mechanism of the isolated heart (Iversen, 1964; Burgen & Iversen, 1965). A comparison of relative affinities of 16 derivatives for the two systems reveals some similarity of rank order, though the potencies differ greatly and there are some exceptions to the ranking. Some similarity of carrier conformation is indicated.

The assumption has been made that all the drugs tested inhibit 5-HT uptake by competitive affinity for the same site of action. This assumption is supported by the finding that the log concentration/inhibition lines are parallel except in the case of the weakest inhibitors which may have different mechanisms of action at the high concentrations tested (*ca* 10^{-3}M). It is pertinent also that the site of action of all the compounds studied, whether on the cell membrane or on the storage granules, is unknown. More than one site of action could be involved. Some work suggests that 4-chloromethylamphetamine is taken up by platelets and stored in the granules (Pletscher, Da Prada & Burkard, 1970). Preliminary experiments in which platelets were incubated with (±)-fenfluramine 10^{-5} or 10^{-4}M and their fenfluramine content subsequently analysed by gas-liquid chromatography (Campbell, 1970) have revealed that the drug is absorbed by the cells to reach concentration ratios of 16 and 7 repectively. The absorption was, however, immediate, and did not increase with time. Further, the apparent Km of the system (*ca* 65×10^{-5}M) is many times higher than the IC50 against 5-HT uptake ($0{\cdot}59 \times 10^{-5}$M), so that the relevance of these findings to the action of the drug on 5-HT uptake is not clear.

It has been suggested that the blood platelet could be studied as a model of brain tryptaminergic (Paasonen, 1968) and adrenergic (Abrams & Solomon, 1969) neurons, evidence for which has recently been reviewed (Sneddon, 1973). It is of obvious interest to see whether parallelism exists between the ability of the compounds studied to influence 5-HT uptake and to exert various centrally mediated effects which might involve tryptaminergic neurons or receptors. Though selected results reveal some parallelism, it is apparent that no real correlation exists over a wide range of drugs, presumably because the central actions of these drugs depend as much on their ability to penetrate the blood-brain barrier and reach their site of action as on their intrinsic potency. Thus in general we find no agreement with

anorexic activity (Le Douarec & Schmitt, 1964; Le Douarec, Schmitt & Laubie, 1966; Abdallah & White, 1970; Mantegazza, Müller & others, 1970), nor with analeptic or central depressant activity (Le Douarec & Schmitt, 1964; Boissier, Simon & others, 1965; Biel, 1970; Beregi, Hugon & others, 1970), nor with hypothalamic 5-HT depleting ability (Fuller, Hines & Mills, 1965; Opitz, 1967; Nielsen & Dubnick, 1970).

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