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A structure-activity study of sympathomimetic amines on the beta-adrenoceptors of guinea-pig trachea

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Summary

1. The relative activities of a large number of sympathomimetic amines were estimated on the β-adrenoceptors of the guinea-pig tracheal chain preparation. Concentrations which produced half-maximal responses were measured for each drug and the maximum responses were also noted and expressed as a percentage of that produced by isoprenaline.

2. The relative activities of the amines generally decrease with loss of hydroxyl groups from the structure, and amines with less than two hydroxyl groups produce little or no observable response.

3. The affinity constants of the partial agonists and antagonists were measured. The hydroxyl group on the β carbon atom of the side chain, N-alkyl groups and an α carbon methyl group increase affinity, whereas the *p*-phenolic group decreases affinity. The *m*-phenolic group does not seem to affect affinity.

4. By comparing the effects of groups on affinity with their effects on activity, it was deduced that N-alkyl groups, *m*- and *p*-phenolic groups and probably also the β carbon hydroxyl group increase efficacy. Alpha carbon methylation appears to reduce efficacy.

Introduction

There have been many structure-activity studies of sympathomimetic amines but only a few comprehensive studies of actions on β-adrenoceptors. The order of potency on β-adrenoceptors of some of the more potent compounds, such as the catecholamines, has been reported by several workers (e.g. Lands, Luduena, Ananeko & Grant, 1950; Lands, 1951; Foster, 1966; Chahl & O'Donnell, 1967). The potencies of several other phenylethylamines on the β-adrenoceptors of the guinea-pig trachea have also been determined (Chahl & O'Donnell, 1968, 1969, 1971a; Tye, Baldesberger, LaPidus & Patil, 1967).

The purpose of the present work was to compare the activities of a large number of sympathomimetic amines under the same conditions on a tissue containing predominantly β-adrenoceptors, and for this purpose the isolated guinea-pig tracheal chain preparation was chosen. Since the actions of the amines might be complicated by release of noradrenaline or by uptake of the amines by the adrenergic nerve terminals, the potencies of many of the sympathomimetic amines were assessed in the presence of cocaine or on tissues from guinea-pigs pretreated with

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reserpine. The β-adrenoceptor blocking action of propranolol was used to check that the compounds were acting on β-adrenoceptors. Some of the amines were found to be partial agonists or antagonists on β-adrenoceptors and the affinity constants of most of these were measured.

Methods

Isolated guinea-pig tracheal chain preparations were set up in Krebs solution at 37° C as described previously (Chahl & O'Donnell, 1967; 1968). Relaxations against the natural tone were recorded isotonically, usually with a modified Statham 10B strain gauge and a pen recorder, but in later experiments with a lever and a differential transformer. Cumulative concentration–response lines were obtained where possible. The responses were expressed as the percentage of the maximum response of the preparation to isoprenaline and, for those drugs which did not produce the same maximum response as isoprenaline, as the percentage of the maximum response for that drug. For the more potent drugs these results were used to compute a line of best fit expressing a relationship between log concentration and response. From this line the logarithm of the effective concentration producing 50% of the maximum response and its standard deviation (log EC50 ± S.D.) was obtained as described previously (Chahl & O'Donnell, 1967; O'Donnell, 1968). With other compounds the average log EC50's were calculated from individual experimental lines plotted by eye (Chahl & O'Donnell, 1971a). For many of the drugs it was not possible to obtain a complete concentration-response line because of their other interfering actions, and for these drugs a concentration range for the β-adrenoceptor response was calculated.

The drugs were tested in the presence of cocaine (10^{-5}M in contact with the preparation for at least 30 min), and/or propranolol (usually 10^{-6}M for 30 min to 1 h); those drugs which released noradrenaline were tested on preparations from animals pretreated with reserpine, 5 mg/kg, 24 h previously. The log EC50 values in the presence of cocaine were calculated for those drugs potentiated by cocaine and therefore presumably taken up into the adrenergic nerve terminals.

Affinity constants for those drugs which produced a maximum response less than isoprenaline were calculated by the method used by Barlow, Scott & Stephenson (1967) for partial agonists acting at acetylcholine receptors. In this method a plot of the reciprocal of the agonist concentration (1/A) against the reciprocal of the partial agonist concentration (1/P) producing the same response is extrapolated to the 1/P axis to obtain the affinity constant of the partial agonist. In this work isoprenaline was used as the agonist and it was assumed that the drugs had a maximum response less than that of isoprenaline because they were partial agonists and not because they produced other actions such as contractions, at overlapping concentrations. Affinity constants for several substances with very little activity were calculated from their ability to antagonize isoprenaline by the method used by Stephenson (1956) for antagonists of acetylcholine and based on the Gaddum equation (Gaddum, 1937). In these experiments complete concentration–response lines to isoprenaline were obtained before and after addition of the antagonist. The time of contact of the antagonist with the tissue was not less than 30 minutes. Concentrations were tested which produced dose-ratios of between 2 and 100.

The drugs used and their sources are listed in Table 1.

Results

The increase in activity with the increasing size of the substituent on the nitrogen atom for the compounds with three hydroxyl groups is shown by comparing isoprenaline, adrenaline and noradrenaline (Chahl & O'Donnell, 1967) (Table 2). There seems to be a limit, however, because protokylol, which has an even larger substituent group on the nitrogen atom than isoprenaline, was not more potent. Orciprenaline had the lowest potency of these compounds.

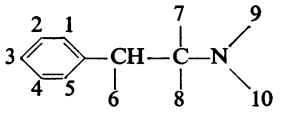
All compounds with two hydroxyl groups had a lower potency than those with three hydroxyl groups, with the exception of nylidrin which had a similar potency to adrenaline (Table 2). Most of these drugs also produced a smaller maximum response than the compounds with three hydroxyl groups. (−)Phenylephrine was more potent than (±)synephrine and even than (−)synephrine, assuming this to be twice as active as the racemate. Greater activity seems to be obtained with the phenolic group in the *m*-position than in the *p*-position. Dopamine was more potent than (±)WIN 5512 and should be more potent than (−)WIN 5512, indicating slight superiority of the catechol combination of hydroxyl groups over the combination of hydroxyls on the β carbon atom and the *p*-phenolic position. The nature of the substituent on the nitrogen atom as well as its size was also important because isoxsuprine had a much lower potency than nylidrin. Dialkyl

TABLE 1. *Sources of drugs*

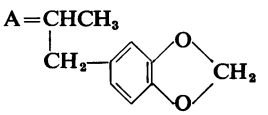
Drug	Source
(±)isoprenaline sulphate	Burroughs-Wellcome
(−)adrenaline acid tartrate	Fluka
(−)noradrenaline acid tartrate	Fluka
(±)orciprenaline sulphate	Boehringer-Ingelheim
protokylol hydrochloride (high m.p. isomer, m.p. 170°–174° C)	Lakeside
(±, erythro)corbasil hydrochloride	Sterling-Winthrop
(±, erythro)ethylnoradrenaline hydrochloride	Sterling-Winthrop
(−)phenylephrine hydrochloride	Sterling-Winthrop
(±)synephrine tartrate	Boehringer-Ingelheim
(±)WIN 5512	Sterling-Winthrop
(±)WIN 5513	Sterling-Winthrop
(±)WIN 5507 acetate	Sterling-Winthrop
dopamine hydrochloride	Sigma
(−)metaraminol bitartrate	Merck, Sharpe & Dohme
(±)nylidrin hydrochloride	Smith & Nephew
(±)isoxsuprine hydrochloride	Mead Johnson
WIN 5565	Sterling-Winthrop
(±)hydroxyamphetamine hydrobromide	Smith, Kline & French
(−)ephedrine hydrochloride	Burroughs-Wellcome
(±)methoxamine hydrochloride	Burroughs-Wellcome
tyramine hydrochloride	Sigma
WIN 5523 hydrochloride	Sterling-Winthrop
(±)amphetamine sulphate	Smith, Kline & French
(+)methamphetamine hydrochloride	Burroughs-Wellcome
(±)methoxyphenamine hydrochloride	Upjohn
mephentermine sulphate	Wyeth
m-tyramine hydrobromide	Dr. R. B. Barlow, University of Edinburgh
(±)2-amino-1-phenyl ethanol	Aldrich
2-phenylethylamine hydrochloride	Koch-Light
cocaine hydrochloride	Drug Houses of Australia
(±)propranolol hydrochloride	Imperial Chemical Industries
reserpine	Ciba ('Serpasil') and Halewood Chemicals

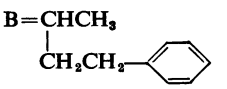
All drugs were obtained as pure powders except for reserpine which was obtained as a solution in ampoules.

TABLE 2. *The structures and activities of sympathomimetic amines*



Drug	Structure 1	2	3	4	5	6	7	8	9	10	Potency (−log EC50)	Maximum response (%)
Isoprenaline	H	H	OH	OH	H	OH	H	H	H	$CH(CH_3)_2$	8·38±0·19 (14)	100
Adrenaline	H	H	OH	OH	H	OH	H	H	H	CH_3	7·77±0·18 (11)	100
Noradrenaline	H	H	OH	OH	H	OH	H	H	H	H	7·37±0·13 (9)	100
Orciprenaline	H	H	OH	H	OH	OH	H	H	H	$CH(CH_3)_2$	6·78±0·24 (16)	100
Protokylol	H	H	OH	OH	H	OH	H	H	H	A	8·37±0·30 (15)	100
Corbasil	H	H	OH	OH	H	OH	H	CH_3	H	H	7·02±0·13 (14)	100
Ethylnoradrenaline	H	H	OH	OH	H	OH	H	CH_2 CH_3	H	H	6·94±0·31 (9)	100
Phenylephrine	H	H	H	OH	H	OH	H	H	H	CH_3	5·73±0·28 (25)	94±6 (46)
Synephrine	H	H	OH	H	H	OH	H	H	H	CH_3	4·95±0·31 (18)	94±7 (21)
WIN 5512	H	H	OH	H	H	OH	H	H	H	H	4·15±0·06 (3)	71±7 (3)
WIN 5513	H	H	OH	H	H	OH	H	H	CH_3	CH_3	No β-receptor response	
WIN 5507	H	H	H	OH	H	OH	H	H	H	$CH(CH_3)_2$	6·41±0·49 (5)	100
Dopamine	H	H	OH	OH	H	H	H	H	H	H	4·93±0·34 (5)	91±11 (12)
Metaraminol	H	H	H	OH	H	OH	H	CH_3	H	H	5·11±0·41 (3)	45±14 (3)
Nylidrin	H	H	OH	H	H	OH	H	CH_3	H	B	7·88±0·39 (9)	98±3 (6)
Isoxsuprine	H	H	OH	H	H	OH	H	CH_3	H	D	6·30±0·37 (5)	90 (1)
WIN 5565	H	H	OH	H	H	H	H	H	H	$CH(CH_3)_2$	4×10^{-5} -1×10^{-4} (6)	<50
Hydroxyamphetamine	H	H	OH	H	H	H	H	CH_3	H	H	1×10^{-6} -5×10^{-6} (15)	<50
Ephedrine	H	H	H	H	H	OH	H	CH_3	H	CH_3	1×10^{-6} -4×10^{-6} (20)	<50
Methoxamine	OCH_3	H	H	OCH_3	H	OH	H	CH_3	H	H	No β-adrenoceptor response	
Tyramine	H	H	OH	H	H	H	H	H	H	H	,,	
WIN 5523	H	H	H	H	H	H	H	H	H	$CH(CH_3)_2$	,,	
Amphetamine	H	H	H	H	H	H	H	CH_3	H	H	,,	
Methamphetamine	H	H	H	H	H	H	H	CH_3	H	CH_3	,,	
Methoxyphenamine	OCH_3	H	H	H	H	H	H	CH_3	H	CH_3	,,	
Mephentermine	H	H	H	H	H	H	CH_3	CH_3	H	CH_3	,,	
m-Tyramine	H	H	H	OH	H	H	H	H	H	H	,,	
2-amino-1-phenyl ethanol	H	H	H	H	H	OH	H	H	H	H	uncertain	
2-phenylethylamine	H	H	H	H	H	H	H	H	H	H	No β-adrenoceptor response	





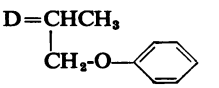


Table 2 *continued*

Potency is expressed as the negative mean log of the effective concentration (M) producing 50% of the maximum response for that drug ± standard deviation. The number of concentration-response lines contributing to each mean log EC50 is shown in parentheses. Where other actions of the drugs prevented calculation of a mean log EC50 a range has been given of molar concentrations between which the direct β-adrenoceptor response on the tissue commenced. The values quoted for all drugs except WIN 5512, metaraminol, nylidrin, isoxsuprine and WIN 5565, were obtained in the presence of cocaine. Values for WIN 5512, metaraminol and WIN 5565 were obtained on preparations from animals pre-treated with reserpine, whereas those for nylidrin and isoxsuprine were from untreated preparations. The average maximum response and its standard deviation (where applicable) of the tissue to the drugs is given as a % of the maximum response to isoprenaline

substitution, as in WIN 5513, produced complete loss of activity on β-adrenoceptors.

The compounds with one hydroxyl group did not all have observable direct agonist action on β-adrenoceptors. Those which did (ephedrine, WIN 5565 and hydroxyamphetamine) produced smaller maximum responses than compounds with two or three hydroxyl groups. The compounds without hydroxyl groups had no observable direct β-adrenoceptor activity (Table 2). Many of the substances examined in this study produced another type of relaxation at high doses, which

TABLE 3. *Mean log affinity constants (log* K)

Drug	Log K ± S.D. Normal		Cocaine	
Phenylephrine	4·6 (P)			
Ephedrine	5·2±0·3 (3) (P)			
	4·5±0·2 (7) (A)			
WIN 5512	3·5, 3·3 (2) (P)			
Metaraminol	4·0, 4·6 (2) (P)		4·3, 4·8 (2)	(P)
WIN 5565	3·7±0·4 (4) (P)			
	2·7±0·5 (3) (A)			
Synephrine	3·9, 3·5 (2) (P)			
Dopamine	4·7, 4·8 (2) (P)			
WIN 5523	3·5±0·4 (3) (A)			
Phenylethylamine			3·1±0·1 (4)	(A)
2-amino-1-phenyl ethanol	3·4±0·1 (4) (A)		3·4±0·4 (5)	(A)
Amphetamine	3·4±0·1 (3) (A)		3·7, 3·7 (2)	(A)
m-Tyramine	2·9 (1) (A)		2·8, 3·3 (2)	(A)
Tyramine	2·5 (1) (A)		2·7, 2·8 (2)	(A)
Hydroxyamphetamine	2·9 (1) (A)		3·1±0·2 (3)	(A)

S.D., standard deviation. (A) or (P) after the drug name indicates whether it was used as an antagonist or partial agonist to obtain the value of log K. Number of experiments is in parentheses. Values obtained in the presence of cocaine are given for some of the drugs. Results for tyramine and some of the results for WIN 5512, metaraminol, WIN 5565 and WIN 5523 were obtained on preparations from guinea-pigs pretreated with reserpine. The result for phenylephrine is quoted without a standard deviation since it was obtained from the computed lines of best fit for isoprenaline and phenylephrine.

was not blocked by propranolol, and some also produced marked contractions (Chahl & O'Donnell, 1971a). It is therefore possible that some reaction of these drugs with β-adrenoceptors might occur at high concentrations but this might be obscured by contractions or non-specific relaxations.

The logarithms of the affinity constants of most of the partial agonists are shown in Table 3 and this table includes the log affinity constants for some compounds related to phenylethylamine which were antagonists. To investigate the possible complications due to axonal uptake, some of these experiments were repeated in the presence of cocaine. Because tyramine produced marked relaxation of normal tissues, the experiments with it had to be performed on tissues from animals pretreated with reserpine.

The logarithm of the affinity constant for phenylethylamine was found to be 3·1 (Table 3). The substitution of a hydroxyl group on the β carbon atom (2-amino-l-phenyl ethanol) produced an increase in the log affinity constant of 0·3 log units. Hydroxyl substitution in the *p*-position produced a loss in affinity. This was shown by comparison of phenylethylamine with tyramine, and amphetamine with hydroxyamphetamine. Substitution of a hydroxyl group in the *m*-position produced no change in affinity as shown by comparison of phenylethylamine and *m*-tyramine. Substitution of a methyl group on the α carbon atom increased affinity as shown by comparison of phenylethylamine with amphetamine, and tyramine with hydroxyamphetamine. It can be seen that the affinity constants for amphetamine and tyramine were somewhat higher in the presence of cocaine. No results were obtained for phenylethylamine in the absence of cocaine. The effects of the various substitutions on the affinity are summarized in Table 4(a).

From the results it should be possible to assess the effects of various substituents on the efficacy of the compounds. Only those compounds which produced an

TABLE 4

(a) *Contributions to affinity of substitutions on the phenylethylamine molecule*

Substitution	Effect on log K	
N-methyl	+0·3	(WIN 5512 and synephrine)
N-isopropyl	+0·4	(phenylethylamine and WIN 5523)
	0·0	(tyramine and WIN 5565)
α-methyl	+0·6	(phenylethylamine and amphetamine)
	+0·3	(tyramine and hydroxyamphetamine)
β-hydroxyl	+0·3	(phenylethylamine and 2-amino-1-phenyl ethanol)
m-phenolic	0·0	(phenylethylamine and *m*-tyramine)
p-phenolic	−0·3	(phenylethylamine and tyramine)
	−0·8	(WIN 5523 and WIN 5565)

(b) *Qualitative effects on efficacy of substitutions on the phenylethylamine molecule*

Substitution	Effect on efficacy	
N-methyl	+	(WIN 5512 and synephrine)
N-methyl to N-isopropyl	+	(phenylephrine and WIN 5507)
α-methyl	− ?	(see discussion)
β-hydroxyl	+ ?	(dopamine and noradrenaline)
m-phenolic	+	(WIN 5512 and noradrenaline)
		(synephrine and adrenaline)
p-phenolic	+	(phenylephrine and adrenaline)
		(metaraminol and corbasil)

Values given are differences between log K values for the pairs of compounds shown in parentheses.

observable response on β-adrenoceptors have been compared since it was felt that the activity of many of the compounds which produced no response might be obscured by other actions occurring at overlapping concentrations and the assumption of no efficacy would then be invalid. The effects on efficacy are shown in Table 4(b).

Discussion

The quantitative estimation of affinity constants on the tracheal chain preparation was difficult. Some of the compounds (e.g. tyramine and hydroxyamphetamine) produced rhythmic activity of the preparations and/or a loss of the natural tone at the concentrations required to produce a shift of the isoprenaline concentration–response line. These difficulties were often more marked when the preparations had been exposed to cocaine or were from animals pre-treated with reserpine. The results might also have been complicated by the effects of monoamine oxidase. No experiments were done with monoamine oxidase inhibitors because it was felt that the results with these used in addition to reserpine would be difficult to interpret. Some idea of the effects of monoamine oxidase can be obtained, however, by comparing values for compounds which are substrates with those for compounds which are not. For tyramine and phenylethylamine the values of log K are 2·8 and 3·1 respectively, whereas for hydroxyamphetamine and amphetamine they are 3·1 and 3·7 respectively. The effect of a *p*-hydroxyl group assessed from the first pair, which are substrates of monoamine oxidase, is to decrease affinity by 0·3 log units, whereas in the second pair, which are not substrates, the decrease is 0·6 log units. Accordingly it seems improbable that the results were greatly modified by the presence of monoamine oxidase.

Another difficulty encountered in this work was that the log affinity constant values obtained for ephedrine (5·2) and WIN 5565 (3·7) as partial agonists were higher than the values obtained by the antagonist method (4·5 and 2·7 respectively). It would appear, therefore, that it is possible only to compare log affinity constants of compounds which have been calculated by the same method. This is well illustrated by consideration of WIN 5565 and WIN 5523. Since WIN 5523 had no apparent efficacy the value for the log affinity constant (3·5) could only be obtained by using it as an antagonist. When this value was compared with that for WIN 5565 tested as a partial agonist (3·7) it seemed that the *p*-hydroxyl group increased affinity, but when it was compared with the value for WIN 5565 calculated as an antagonist (2·7) the results were in agreement with those found for the *p*-hydroxyl substitution in other pairs of compounds (see above).

Even when allowance is made for the difficulties in measuring the affinity of the compounds and for the uncertainty whether they are truly competitive, the effects of substituents on affinity summarized in Table 4(a) seem to be reasonable. Increasing size on the nitrogen atom leads to an increase in affinity of 0·2–0·3 log units/methylene group. This increase was observed in two pairs of compounds (phenylethylamine and WIN 5523, and WIN 5512 and synephrine) but not with tyramine and WIN 5565. It is likely, however, that the accuracy of estimation with these *p*-hydroxy substituted compounds was poor because of their very low affinity. A methyl group on the α carbon atom appeared to produce a greater increase in affinity (0·3–0·6 log units). The alcoholic hydroxyl group increases

affinity by 0·3 log units. It is remarkable, however, that phenolic groups do not increase affinity. In the *m*-position they do not appear to affect it either way and in the *p*-position they seem definitely to reduce it.

The conclusion that there was increase in efficacy with N-alkylation and *m*- and *p*-phenolic substitution (Table 4(b)) rests on the finding that the increases in potency that occur with these substitutions are far greater than can be explained by the increases in affinity alone (Tables 2 & 4(a)). The effects of phenolic groups in increasing efficacy form a marked contrast to their apparent effects on affinity. Stephenson (1956), however, pointed out that high affinity may be incompatible with high efficacy and this is inherent in the rate theory of Paton (1961). The low potency of dopamine compared with noradrenaline would support the conclusion that the β-hydroxyl substitution also increases efficacy (Table 4(b)). There is some doubt, however, whether dopamine is truly a partial agonist because in the presence of the α-adrenoceptor blocking agent phentolamine (0·1 mg/ml) (unpublished observation), it produced the same maximum response as isoprenaline. Thus, the unexpectedly high estimate of log K for dopamine (Table 3) may not be valid. The low maximum response produced by metaraminol compared with compounds such as WIN 5512, phenylephrine and dopamine suggests that α-methyl substitution reduces efficacy. The findings that noradrenaline and corbasil are equipotent (Chahl & O'Donnell, 1971b) could then be explained by supposing that the decrease in efficacy produced by the α-methyl group is offset by the increase in affinity.

Most of the existing theories put forward to explain the interaction of catecholamines with the β-adrenoceptor implicate the catechol group, the β carbon hydroxyl group and the nitrogen atom of the amine group (Bloom & Goldman, 1966; Belleau, 1967). The results from the present study suggest that only the hydroxyl group on the β carbon atom and the substituted nitrogen atom enhance the binding to the receptor (affinity) whereas the hydroxyls of the catechol group, together with the nitrogen atom and perhaps the β carbon hydroxyl group, produce the activation of, or conformational change in the receptor. Although previous speculations have implicated the catechol group in the binding to the β-adrenoceptor (Bloom & Goldman, 1966; Belleau, 1967; and Pratesi, Grana & Villa, 1968), it would seem from the results presented here that the catechol group does not enhance the affinity of the catecholamines but might actually reduce it. The conclusion that the phenolic groups only increase the efficacy, whereas the β carbon hydroxyl group increases affinity is supported by the structures of the β-adrenoceptor blocking drugs. The contribution to efficacy as well as to affinity of the substituted nitrogen atom would indicate that the ring substitutions present in the blocking agents must prevent the effectiveness of other parts of the molecule. The increase in affinity and probable reduction in efficacy which accompanies the substitution of a methyl group on the α carbon atom is of interest since this substitution is present in those blockers which are selective for the β_2-adrenoceptors such as are present in the respiratory tract (Lands, Luduena & Buzzo, 1967). It is likely, therefore, that the effects of the various substitutions on affinity and efficacy are different for β-adrenoceptors of other tissues.

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