A COMPARISON OF THE EFFECTS OF NORADRENALINE, ADRENALINE AND SOME PHENYLEPHRINE DERIVATIVES ON ALPHA-, BETA$_1$- AND BETA$_2$- ADRENERGIC RECEPTORS*

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SUMMARY

The possibility of two types of beta-adrenergic receptors is supported by the results presented. It is shown that the phenylephrine group of compounds have more pronounced affinities towards the beta$_1$-(cardiac) adrenergic receptors than towards the beta$_2$-(bronchial) adrenergic receptors. The cardioselective action is the greatest in the case of ethylnorphenylephrine. It is postulated that the presence of a small substituent on the amino nitrogen and a (only one) meta-hydroxyl group may contribute towards cardioselectivity in the case of phenylethylamine derivatives. Ethylnorphenylephrine has a relatively low affinity towards the alpha-adrenergic receptors.

The nature of the substituent on the amino group of adrenergic catecholamines is known to have a distinct influence on the pattern of effects produced by these compounds. Since two major groups of effects are evident Ahlquist[1] postulated two types of adrenergic receptors, the *alpha*-adrenergic receptors on which effects are easily induced by noradrenaline but not by isoproterenol, and the *beta*-adrenergic receptors on which effects are easily induced by isoproterenol but not by noradrenaline.

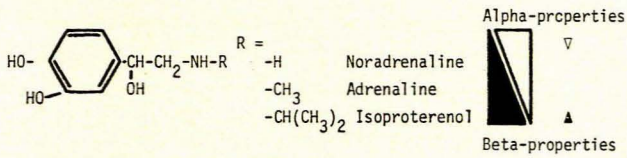

Fig. 1. Decrease in alpha-adrenergic properties and increase in beta-adrenergic properties with increase in size of the substituent on the amino group in the noradrenaline series.

Lands *et al.*[2,3] and others[4-6] have recently pointed out that the beta-adrenergic receptors may further be subdivided in two groups, the beta$_1$-receptors and the beta$_2$-receptors. It was shown that certain beta-adrenergic stimulants, e.g. *l*-α-methylnoradrenaline (*l*-nordefrine), act mainly on the beta$_1$-receptors causing cardiac stimulation (positive inotropic and positive chronotropic effects) and fatty acid mobilization, while other beta-stimulants, e.g. t-butylnoradrenaline, act mainly on beta$_2$-receptors causing bronchodilation and vasodilation.

A number of compounds with bronchial selectivity (beta$_2$-selectivity) have been described recently.[7-9] Little, however, has been published on compounds with cardiac selectivity (beta$_1$-selectivity).

During investigations with a large number of sympathomimetic amines it became evident that the phenylephrine derivates apparently exhibit the most pronounced beta$_1$-selectivity of the compounds we investigated. This article is a report of our findings with this group of drugs.

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METHODS

The action of these compounds on the cardiac (beta$_1$)-receptors were determined by using isolated rat atria suspended in a modified Locke's solution. The chronotropic effects were measured by means of a Grass force-displacement transducer connected to a tachograph unit of a Model 7 Grass Polygraph.

For determination of the effects on the beta$_2$-receptors relaxation of tracheal chain preparations (of guinea-pigs), suspended in Krebs-Henseleit solution, were used according to the technique described by Foster.[10]

The effects of the compounds which were tested for alpha-receptor affinity, were obtained by using the isolated vas deferens of young male rats. This preparation was suspended in Tyrode solution. The temperature throughout all of these experiments was maintained at 37°C.

Cumulative dose-response curves of the compounds tested were obtained in each experiment using the method of Van Rossum[11] (see Fig. 2), and pD$_2$ values and relative intrinsic activity were calculated from the curves. Each of these values presented below is an average of at least 6 experiments.

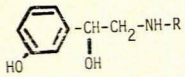
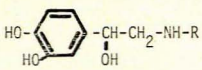
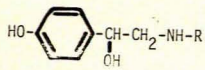
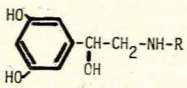
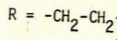
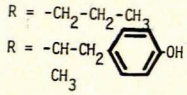
RESULTS

The affinity and intrinsic values of the phenylephrine derivatives for the beta$_1$- and beta$_2$-receptors, are presented in Table I. From this table it can be seen that the relative intrinsic activities of the phenylephrine derivatives (3-hydroxyphenylamines) are generally slightly lower than that of noradrenaline on both types of beta-receptors. Differences in intrinsic activities of the same compound on the two types of beta-receptors are, however, not significant.

The differences in affinity (expressed as pD$_2$ values in Table I) of the same compound on the two types of beta-receptors, however, are significant for phenylephrine, ethylnorphenylephrine (Effortil) and propylnorphenylephrine. These three compounds have a markedly better affinity towards the beta$_1$-receptor, especially ethylnorphenylephrine. The affinities and intrinsic activities of some 3,4-dihydroxyphenylethylamines, 3,5-dihydroxyphenylethylamines and 4-hydroxyphenylethylamines are also presented in Table I. Note that those compounds of the last three series that exhibit higher pD$_2$ values on the beta$_1$-receptors than on the beta$_2$-receptors generally have a substituent smaller than -C$_4$H$_9$ on the amino group.

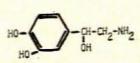
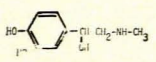
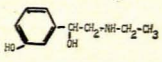
Since ethylnorphenylephrine exhibited the most pronounced selectivity for the beta$_1$-receptors, this compound was compared with noradrenaline and adrenaline on the isolated vas deferens of the rat to compare effects on the alpha-adrenergic receptors. Results of this investigation are presented in Table II and Figs. 2 and 3. Table III gives the relative affinities of adrenaline and ethylnorphenylephrine on the alpha-, beta$_1$- and beta$_2$-receptors when the affinities of noradrenaline to these receptors are taken as 1·0. Note that the affinity of adrenaline is higher than

TABLE I. RELATIVE INTRINSIC ACTIVITIES AND AFFINITIES (GIVEN AS pD_2 VALUES) OF 4 SERIES OF ADRENERGIC COMPOUNDS, TESTED ON THE ISOLATED RAT ATRIUM AND GUINEA-PIG TRACHEAL CHAIN PREPARATION

Compound	*Isolated rat atria (rate)* ($beta_1$-receptor) RIA	pD_2	*Guinea-pig trachea** ($beta_2$-receptor) RIA	pD_2
I. 3-hydroxyphenethylamine series (phenylephrine series)				
				
Norphenylephrine R = –H	0·8	5·9 ± 0·1		
Phenylephrine R = $-CH_3$	0·8	6·9 ± 0·1	0·6	5·2 ± 0·2
Ethylnorphenylephrine R = $-CH_2-CH_3$	0·9	8·9 ± 0·3	0·8	5·4 ± 0·3
Propylnorphenylephrine R = $-CH_2-CH_2-CH_3$	0·7	7·1 ± 0·4	0·7	5·2 ± 0·2
Butylnorphenylephrine R = $-CH_2-CH_2-CH_2-CH_3$	0·7	5·4 ± 0·2	0·7	5·2 ± 0·4
II. 3, 4-dihydroxyphenethylamine series (adrenaline series)				
				
Noradrenaline R = –H	1·0	7·4 ± 0·1	1·0	5·8 ± 0·6
Adrenaline R = $-CH_3$	1·0	8·1 ± 0·2	1·0	6·9 ± 0·3
Isoproterenol R = $-CH(CH_3)_2$	1·0	8·5 ± 0·2	1·0	8·4 ± 0·4
III. 4-hydroxyphenethylamine series (synephrine series)				
				
Synephrine R = $-CH_3$	0·8	5·2 ± 0·1	0·6	4·9 ± 0·4
Ethylnorsynephrine R = $-CH_2-CH_3$	0·8	5·8 ± 0·3	0·7	5·1 ± 0·3
Propylnorsynephrine R = $-CH_2-CH_2-CH_3$	0·7	7·4 ± 0·3	0·9	6·3 ± 0·5
Butylnorsynephrine R = $-CH_2-CH_2-CH_2-CH_3$	0·7	5·7 ± 0·2	0·9	6·8 ± 0·1
IV. 3, 5-dihydroxyphenethylamine series (orciprenaline series)				
				
Orciprenaline R = $-CH(CH_3)_2$	1·0	7·2 ± 0·3	1·0	7·7 ± 0·4
Th 1178 S.U. 	0·7	6·5 ± 0·2	1·0	5·8 ± 0·5
Th 1165 a 	1·0	6·8 ± 0·2	1·0	9·6 ± 0·2

*Values according to Miller.[13]
RIA = relative intrinsic activity.

TABLE II. COMPARISON OF EFFECTS OF NORADRENALINE, ADRENALINE AND ETHYLNORPHENYLEPHRINE ON ALPHA-RECEPTORS

Compound	Structure	*Alpha-receptor (rat vas deferens)* RIA	pD_2
Noradrenaline		1·0	5·4 ± 0·2
Adrenaline		1·0	5·8 ± 0·3
Ethylnorphenylephrine		1·0	4·5 ± 0·2

RIA = relative intrinsic activity.

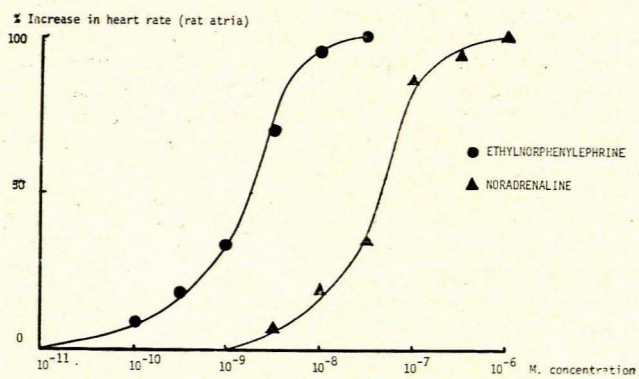


Fig. 2. Cumulative log concentration-response curves for noradrenaline and ethylnorphenylephrine. Note that ethylnorphenylephrine exhibits a much higher affinity than noradrenaline.

that of noradrenaline on the alpha-receptors, the beta$_1$-receptors (confirming the results of Ariëns[12]) and also on the beta$_2$-receptors (confirming the results of Lands *et al.*[3]). The difference between the affinities of noradrenaline and adrenaline is smallest on the alpha-receptors and largest on the beta$_2$-receptors (Lands *et al.*[3] also indicated a larger difference in bronchodilatory activity than in cardiac activity).

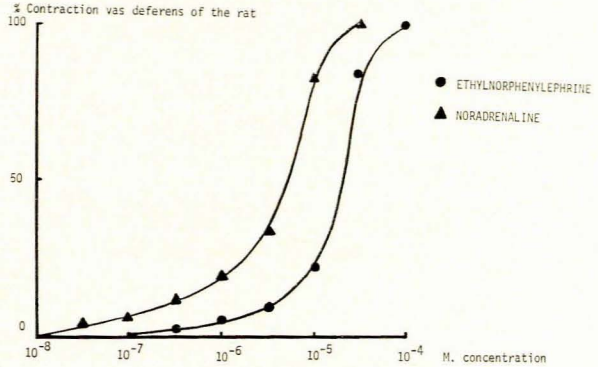


Fig. 3. Cumulative log concentration-response curves for noradrenaline and ethylnorphenylephrine. Note that ethylnorphenylephrine exhibits a lower affinity than noradrenaline.

On the other hand, ethylnorphenylephrine has its highest affinity towards the beta$_1$-receptors. It has a lower affinity than either noradrenaline or adrenaline towards the alpha-receptors and beta$_2$-receptors.

TABLE III. RELATIVE AFFINITIES OF NORADRENALINE, ADRENALINE AND ETHYLNORPHENYLEPHRINE ON ALPHA- AND BETA-RECEPTORS

		Beta-receptors	
Compound	*Alpha-receptor*	*Beta$_1$*	*Beta$_2$*
Noradrenaline	1·0	1·0	1·0
Adrenaline	2·5	5·0	12·5
Ethylnorphenylephrine	0·1	31·0	0·4

DISCUSSION

The results indicate that the phenylephrine derivatives are to a certain extent cardioselective. The only other cardioselective compounds of this type are *l*-nordefrine[3] and metaraminol.[2] The latter compounds, however, have very low activities. Of the phenylephrine derivatives ethylnorphenylephrine exhibits the highest degree of selectivity on cardiac rate.

From the results in Table I it appears that two factors in the series of compounds studied may be responsible for beta$_1$-receptor selectivity. Firstly, it is possible that the 3-hydroxyphenylethylamine (phenylephrine series) structure is more favourable for affinity towards the beta$_1$-receptors than the 3,4- or 3,5-dihydroxyphenylethylamine structure or the 4-hydroxyphenylethylamine structure. Secondly, it appears that the substituent on the amino group should be smaller than -C_4H_9 to favour affinity towards the beta$_1$-receptors. The most pronounced example in this case is in the phenylephrine series where a -C_2H_5 substituent (in the case of ethylnorphenylephrine) is present on the amino group.

Ethylnorphenylephrine also has a relatively low affinity on the alpha-adrenergic receptors (see Tables II and III). The affinity as measured on the beta$_1$-receptors is about 300 times larger than that found on the alpha-receptors. One would therefore hardly expect any significant alpha-adrenergic action of this compound in doses that give a beta$_1$-adrenergic response in the intact animal.

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