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## A Comparison of the Cardiac Stimulating and Bronchodilator Actions of Selected Sympathomimetic Amines. (29239)

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Early investigations by Youmans *et al*(1,2) gave results which indicate the importance of the structural groups of the epinephrine molecule for various excitatory and inhibitory actions. They proposed that there are two or more receptive mechanisms. More recent investigations(3,4) have added further emphasis to the concept of 2 distinct epinephrine-sensitive receptors and have provided additional knowledge of the importance of various structural groups for the effects obtained.

The nature of the receptor in the heart mediating cardio-acceleration has continued to defy easy classification although results obtained with the blocking agent, dichloroisoproterno(5) are in agreement with the hypothesis that these receptors are of the *beta* type which usually subserve inhibitory function in other organs innervated by the sympathetic nervous system. This concept applied to sympathomimetic amines as a class, would lead to the generalization that those which induce cardio acceleration would also cause relaxation of the smooth muscle of the bronchioles. Availability in our laboratories of a large number of structurally diverse sympathomimetic amines has permitted us to extend earlier investigations of cardiac receptor affinity and to correlate these results with action in other organs.

*Material and methods.* Cardiac activity was determined *in vitro* by perfusion of the isolated heart of albino rabbits(6). Inotropic activity was measured with a Grass FT .03 force displacement transducer and recorded on a Grass polygraph. Initial diastolic tension was set at 10 g at the beginning of each experiment and changes in isometric tension recorded. Chronotropic changes were determined from the above described recording. All drugs were administered directly into the aortic cannula at a constant volume of 0.1 ml and the dosage expressed in terms of the base. Unless otherwise indicated, all drugs are the racemic mixture. Each drug was tested on a fresh heart preparation at 3 or more doses. Cardiac responses were plotted on semilog graph paper and the dose producing a 20% increase in force or rate estimated from this plot.

Bronchodilator action was determined by the method of Luduena *et al*(6). Data shown in Table I include also representative values taken from published reports or from earlier experiments carried out in our laboratories and are cited in order to provide a broader comparison with the recent results obtained with the N-cyclopentyl substituted amines.

This investigation includes the following commercially available drugs, in addition to the experimental compounds shown in Table I: 1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol (isoproterenol) *levo*-1-(3,4-dihydroxyphenyl-2-aminoethanol (levarterenol), 1-(3,4-dihydroxyphenyl)-2-amino-1-propanol (nordefrine), 1-(3,4-dihydroxyphenyl)-2-isopropylamino-1-butanol (isoetharine), 3,4-di-

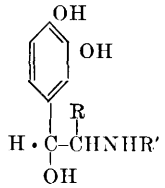

TABLE I. Comparison of Sympathomimetic Amine Effects on Perfused Heart with Effects on Perfused Lung.

| Compound | Structure R | Structure R' | Cardiac effect* (μg/heart) Force | Cardiac effect* (μg/heart) Rate | μg/lung | Bronchodilator action,† relative activity | Reference |
|---|---|---|---|---|---|---|---|
| Levarterenol | H | H | .029 | .029 | 50.0 | 1/69–1/279 | (9,10) |
| Epinephrine | H | methyl | .020 | .060 | | 1/2 –1/10 iso. | (9,10) |
| Isoproterenol | H | *i.* propyl | .0025 | .003 | .50 | | |
| I | H | cyclopentyl | .004 | .005 | .70 | | |
| Nordefrine | methyl | H | .030 | .060 | | 1/100 iso. | (10) |
| II | methyl | cyclopentyl | .040 | .110 | 1.50 | | |
| Ethylnorepinephrine | ethyl | H | 1.000 | 1.500 | | 1/71 epi. | (11) |
| Isoetharine | ethyl | *i.* propyl | .040 | 2.500 | 1.50 | 1/2 iso. | (9) |
| III | ethyl | cyclopentyl | .160 | 6.500 | 1.10 | 1 1/3 iso. | (9) |
| IV | propyl | cyclopentyl | 100.0 ‡ | >100.0 | >1000.0 | >1/2000§ | |
| Phenylephrine | | | 50.0 | 100.0 | | 1/20 epi. | (11) |
| Metaraminol | | | 2.7 | 5.0 | | inactive | |

* Rabbit isolated perfused heart. Dose required to produce a 20% effect.

† Guinea pig isolated perfused lung(6). Approximate $ED_{50}$ doses are indicated. Values cited from the literature, obtained by other experimental procedures, are expressed in terms of the appropriate reference drug.

‡ Larger doses caused depression.

§ A dose of 1200 μg caused 29-32% effect.

hydroxyphenethylamine (dopamine), 1-(3,4-dihydroxyphenethyl-2-amino-1-butanol (ethylnorepinephrine), *levo*-1-(3-hydroxyphenyl)-2-amino-1-propanol (metaraminol) and *levo*-1-(3-hydroxyphenyl)-2-methylaminoethanol (phenylephrine).

*Results.* Cardiac stimulating effects (force and rate) of several sympathomimetic amines have been evaluated by means of the rabbit isolated perfused heart with the results shown in Table I. The presence of a cyclopentyl group on the N increased these actions. Effects were reduced by substitution of a methyl, ethyl or propyl group on the carbon adjacent to the nitrogen (α-carbon), the influence on rate being greater than for changes in force. At the largest doses used in this investigation, there often were some reductions in cardiac stimulation (Table I).

Bronchodilator action in the perfused guinea pig lung, when compared with effect on the heart as described above, does not correlate well. Compounds II and III are more effective bronchodilators than would have been expected from results obtained with the heart. Furthermore, substitution of the N by a cyclopentyl or isopropyl group (I, isoproterenol *vs* levarterenol) increased bronchodilator action more than would be expected from such a comparison. Levarterenol has about 1/70 and 1/100 the bronchodilator and 1/7 and 1/10 the cardiac stimulating actions, respectively, of the N-substituted compounds I and isoproterenol. This difference in relative effectiveness is illustrated also by the results obtained wtih other sympathomimetic amines (Table I). Nordefrine, a potent cardiac stimulant, is not an effective bronchodilator; epinephrine and levarterenol have comparable cardiac stimulating actions but the latter is much less effective as a bronchodilator drug; isoetharine is much less cardiac stimulating than isoproterenol, but about one-half as effective as a bronchodilator drug.

A comparison of the cardiac stimulating action of the drugs shown discloses that the threshold doses for effect on force and rate, which are approximately equal for these two effects in the case of isoproterenol and I, are decreased in different amounts as the length of the side-chain is increased by substitution at the α-carbon. This is apparent also when isoetharine, the N-isopropyl analog of III, is compared with isoproterenol. These results suggest that the rabbit heart receptor system

distinguishes between force and rate and that the structural requirements for optimal actions in this organ differ in turn from those in the guinea pig bronchioles, involved in bronchodilator action.

*Discussion.* The data presented here extend those reported by Youmans *et al*(1,2) on the relative importance of structural variation of the epinephrine molecule for cardiac accelerator action. Comparable data are not available for effects on cardiac force of contraction. Although there is little difference between the cardiac effects of epinephrine and norepinephrine, replacement of the N-methyl with a cyclopentyl or isopropyl group resulted in a distinct increase in potency. Effectiveness was reduced by substitution of the carbon $\alpha$ to the nitrogen by a methyl, ethyl or propyl group.

The data presented here as well as those described previously(7) indicate that the molecular requirements for cardiac receptor action are quite specific. There is some evidence that a second receptor with different structural affinity may be involved for changes in the force of contraction. Comparison with results obtained by lung perfusion indicate further that there are considerable differences in structural requirements for optimal sympathetic effector action. Similarly, other organs show important differences in molecular structural affinity, as shown by the early findings of Youmas *et al* (1) who compared the actions of various sympathomimetic amines on intestinal inhibition with those obtained with the nictitating membrane preparation and by Luduena *et al* (8) who reported that in dogs, levo-nordefrine in equipressor doses with epinephrine is considerably less active than the latter in stimulating the retractor penis.

Results obtained by us, as well as those reviewed above, suggest that the general class of adrenotropic receptors may consist of a population with somewhat different affinities for structurally varied sympathomimetic amines. The demonstration of DCI-sensitive receptors (*beta*-receptors) in contradistinction to those stimulated by epinephrine after such blockade (the *alpha* type) may be another expression of this population difference.

*Summary.* Cardiac stimulating actions of selected sympathomimetic amines have been compared. In the case of the $\beta$-phenethanolamines described here, this effect was increased by substitution of a cyclopentyl or isopropyl group in the N-center. Alkyl (methyl, ethyl or propyl) substitution of the $\alpha$-carbon of the side chain markedly reduced cardiac stimulation and in the case of the N-substituted catecholamines described here, disclosed differences in potency for effects on force as compared to rate. The structural requirements for initiating sympathomimetic cardioacceleration and for increases in the force of contraction differ from those which are optimal for bronchodilator action. The receptors responding to sympathomimetic amines may consist of a population differing in sensitivity to structural variation of the agonist (and possibly also to the various antagonists).

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