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A QUANTITATIVE STUDY OF ANTAGONISTS OF ADRENALINE ON THE VESSELS OF THE RABBIT'S EAR

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A large number of substances can act as antagonists of adrenaline on the vessels of the rabbit's ear. Among them are some agents, such as the ergot alkaloids, yohimbine, F933, and dibenamine, which are generally considered as specific inhibitors of adrenaline, but in addition there are others usually classed as antihistamine substances or as local anaesthetics, etc. It is well known that Bovet discovered antihistamine substances in a search for anti-adrenaline compounds, and Burn and Dutta (1948), working on rabbit ear vessels, found that procaine, atropine, quinidine, pethidine, and other substances were able to abolish the vasoconstrictor effect of adrenaline and of histamine. The vasoconstrictor effect of adrenaline was even reversed when the ears were perfused with quinidine, diphenhydramine (Benadryl), or procaine.

These findings showed that adrenaline is antagonized, on the isolated rabbit's ears, by many substances other than those which could be expected to act as inhibitors from the results of simple blood pressure experiments. Thus the question arose whether it was possible to make a clear distinction on the vessels of the rabbit ear between substances commonly regarded as having an anti-adrenaline action and those better known as having other properties, such as antihistamine and local anaesthetic action.

A quantitative study has therefore been made of the abolition of the constrictor action of adrenaline by various substances when perfused in Locke's solution through the rabbit ear vessels, and also of the rate of return of the constrictor action after perfusing once more with Locke's solution alone. The rabbit ear vessels have been found to be well suited to making quantitative studies of this kind when the outflow recorder of Stephenson (1948) was used.

It is increasingly believed that inhibition or reversal of the constrictor effect of adrenaline is due to competition by the inhibiting or reversing agent for the receptors to which adrenaline attaches itself. Presumably an inhibiting substance may be said to be specific when it has an especially high affinity for the adrenaline receptors. It should then block these receptor groups in higher dilution than that in which it blocks other receptors. Perhaps also the combination of the specific inhibitor with the receptor must be relatively stable and not quickly reversible.

METHOD

The experimental procedure was the same as in the previous work of Burn and Dutta (1948) and Burn and Robinson (1951). A fine glass cannula was tied into the central artery at the base of the ears severed from the head. Then the ears were perfused with Locke's solution, saturated with oxygen + 5 per cent CO_2, at room temperature and at a constant pressure which produced an outflow of about 3 ml./min. Injections of test doses of adrenaline were made into a small rubber-capped chamber, through which the perfusion fluid passed just before entering the cannula. These test doses of adrenaline were given in a constant volume of 0.1 ml. Locke's solution and varied from 0.001 to 0.05 μg., depending on the sensitivity of the ear vessels. The dose of adrenaline most frequently used was 0.01 μg. The final dilutions of adrenaline in Locke's solution were prepared just before each injection. As in the previous experiments of Burn and his colleagues, Stephenson's outflow recorder was found to be most satisfactory in registering very small changes of the vascular tone.

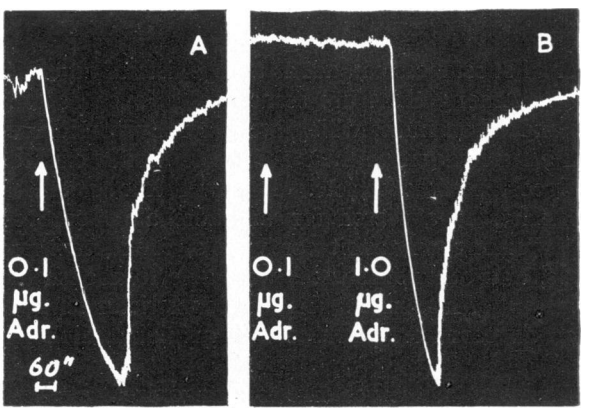

FIG. 1.—The anti-adrenaline activity of ergotoxine ethanesulphonate. A. Normal constrictor effect of 0.1 μg. adrenaline. B. A dose of adrenaline (1 μg.) 10 times greater than the initial test dose produces the same degree of constriction when ergotoxine ethanesulphonate (0.02 μg./ml.) has been perfused for 30 min.

When constant responses to several injections of a certain test dose of adrenaline had been obtained, perfusion with pure Locke's solution was discontinued and changed for Locke's solution containing an anti-adrenaline substance. Then the decrease of the vascular response to adrenaline was determined after 30 min. of perfusion. By a number of such experiments the exact concentration of substance was found which reduced the effect of adrenaline to 1/10 of the initial effect; thus after perfusion with an anti-adrenaline substance a dose of adrenaline 10 times greater than the initial test dose produced the same constriction as the initial test dose before perfusion, as shown in Fig. 1.

When pure Locke's solution was perfused again the initial sensitivity to adrenaline returned more or less quickly. The period required for complete recovery was determined in each experiment. The ears were generally used for two days, and several experiments were made in this time. As already observed by Burn and Dutta the vessels became more sensitive to adrenaline with continued perfusion so that at a later stage a given dose produced more constriction than before. The opposite change was never found. Thus a decrease of the constrictor effect of adrenaline was always due to the drug perfused. The potency of the anti-adrenaline substances, on the other hand, was about the same on the first and on the second day of perfusion and differed only slightly on different ears.

RESULTS

Comparison of the anti-adrenaline potency on the rabbit ear vessels.—The anti-adrenaline potency of various compounds was first investigated. Table I shows the results. Most of the substances commonly regarded as anti-adrenaline compounds were found to act in the lowest concentration. The most powerful were the substances " ergotoxine ethanesulphonate " (B.P. 1932) and ergotamine tartrate. Twelve experiments were performed. " Ergotoxine ethanesulphonate " (0.02 μg./ml.) and ergotamine tartrate (M/10,000,000) produced a considerable decrease of the outflow without completely blocking adrenaline. It was sometimes quite difficult to determine whether adrenaline was inhibited by these substances or whether its action on the ear vessels was no longer visible because they were so constricted. Nevertheless, in four experiments with 0.02 μg./ml. of " ergotoxine ethanesulphonate " in the perfusion fluid, a reduction of the adrenaline effect to about 1/10–1/5 was obtained, roughly comparable with the effect of the other adrenaline inhibitors; in these experiments the recovery took more than 100 min. These results are not included in Table I. After these ergot alkaloids, the substance Regitine (CIBA 7337; 2-(N′-*p*-tolyl-N′-*m*-hydroxyphenylaminomethyl)-imidazoline hydrochloride) was found to be the most potent, and next in order was dibenamine. The degree of inhibition with dibenamine was found to depend on the duration of the perfusion much more than with other substances. As a rule no further change in the action of adrenaline was obtained by prolonging the perfusion with the anti-adrenaline compound beyond 30 min. With dibenamine, however, the change was progressive,

TABLE I

ANTI-ADRENALINE EFFECTS OF VARIOUS DRUGS IN THE PERFUSED RABBIT-EAR PREPARATION

Substance	Molar concn. required to reduce constrictor action of adrenaline to 1/10th	No. of exps.	Time of washing required for complete recovery (min.)
Regitine (C7337)	M/6 million	7	60
Dibenamine	M/4 million	9	Almost irreversible in 20 hr.
Phenindamine (Thephorin)	M/640,000	4	25
Promethazine (Phenergan)	M/640,000	4	25
Yohimbine	M/320,000	10	120–180 (or more)
Lergigan (RP3389)*	M/320,000	4	15
F933	M/275,000	12	25–45
Antazoline (Antistin)	M/128,000	6	15
Tripelennamine (Pyribenzamine)	M/64,000	4	25
Mepyramine (Neoantergan)	M/32,000	12	20
Tolazoline (Priscol)	M/32,000	19	20
Quinidine	M/32,000	6	15–30
Quinine	M/32,000	4	30–45
Cinchocaine (Nupercaine)	M/32,000–M/16,000	6	20–30
Diphenhydramine (Benadryl)	M/16,000	9	40
Atropine	M/16,000	12	30–40
Pethidine	M/4,000	6	30–40
Amethocaine (Pontocaine)	M/2,000	4	20
Strychnine	M/2,000	11	25–30
Procaine	M/500	4	15
Cocaine	M/250	8	20

* Lergigan is regarded as being 10-(1′-dimethylamine-2′-propyl)-phenothiazine.

the anti-adrenaline action becoming more pronounced even after removing the dibenamine from the perfusing fluid; thus the concentration given in Table I for dibenamine must be regarded as approximate and was obtained when it had been applied for 30 min. The concentration would have been different if the time of perfusion had been different. The very high anti-adrenaline effect of the antihistamine compounds was most striking. Thus Phenindamine (Thephorin) and promethazine (Phenergan) were more active than yohimbine and F933. Other antihistamine compounds were weaker. It is interesting that a similar order for the anti-adrenaline activity of some of these antihistamine compounds was found on the isolated seminal vesicle of guinea-pigs (Haas, 1951). The comparison of the active concentration on the seminal vesicle with the present results on the ear vessels is shown in Table II.

TABLE II

ANTI-ADRENALINE POTENCY OF SOME ANTIHISTAMINE COMPOUNDS ON THE ISOLATED SEMINAL VESICLE OF GUINEA-PIGS AND ON THE RABBIT'S EAR VESSELS

Substance	Seminal vesicle conc. required for complete inhibition of adrenaline (Haas, 1951) (mg./litre)	Rabbit's ear vessels conc. required for reducing the constrictor effect to 1/10th (mg./litre)*
Promethazine	0.4	0.5
Antazoline	4.0	2.3
Tripelennamine	5.0	4.5
Mepyramine	10.0	12.0

* Absolute concentrations corresponding to the mol. concentrations of Table I.

2-Benzylimidazoline (tolazoline, Priscol), which is an anti-adrenaline substance, was about 20 times less active than Phenindamine or promethazine and was equal in potency to quinine, quinidine, and cinchocaine. Diphenhydramine and atropine were tested and found to be half as effective as tolazoline. From these observations it was clear that substances commonly regarded as specific inhibitors of adrenaline, such as F933 and tolazoline, do not always have a powerful action on the perfused rabbit's ear vessels.

Other drugs tested were pethidine, amethocaine (pontocaine), and strychnine, which proved to be antagonists of moderate potency. Weakest of all was cocaine; the inhibition produced by this substance was 2,000–3,000 times less than the inhibition exerted by phenindamine or promethazine. Procaine was twice as strong as cocaine. It is known that some antihistamine compounds may cause a short and sometimes dangerous fall of the cat's blood pressure if injected intravenously. A similar but long-lasting hypotension is observed after intravenous administration of yohimbine and of Regitine. Atropine has also a hypotensive action in ether anaesthesia (Bussell, 1940). The same is true for quinine and quinidine. Sollmann (1945) states that this brief fall of blood pressure is a constant characteristic of the intravenous injection of quinidine or quinine and occurs " apparently quite independent of the cardiac effect " and possibly as an " anaphylactoid phenomenon." Our findings suggest that this hypotensive property, common to the stronger adrenaline inhibitors in Table I, is due to their anti-adrenaline action on the peripheral blood vessels.

Comparison of the reversibility of the anti-adrenaline effect.—From the foregoing results it was clear that anti-adrenaline compounds are not always those which inhibit adrenaline in the lowest concentration. Concentration alone does not suffice to distinguish anti-adrenaline from antihistamine compounds. If the specific inhibition is due to a more stable combination of the antagonistic agent with the adrenaline receptors, then this should become obvious by a slower return to normal, when Locke's solution only is perfused again. Therefore it seemed that the time of elimination might indicate the pharmacological affinity of a competing substance for the receptor group better than the concentration.

The speed of recovery after stopping the perfusion of an anti-adrenaline substance was found to depend on the concentration applied. When a high concentration was used, sometimes many hours were required for the elimination at a constant outflow of about 3 ml./min. Therefore the reversibility of the inhibition produced by different substances was compared when the degree of " saturation " of the adrenaline receptors was the same, that is to say, when equally effective concentrations of the different inhibitors had been used. Thus the time of recovery was investigated for the equally effective concentrations given in Table I. The effect of " ergotoxine ethanesulphonate " when examined in a concentration of 0.02 μg. per ml. (which is 1 in 50 million) persisted for about 100 min. after the perfusion of Locke's solution only. The action of dibenamine was found to be almost irreversible even after 20 hr. The action of yohimbine was prolonged for 2–3 hr., and the action of Regitine for about 1 hr. For the other compounds, however, even for the more potent antihistamine substances, a complete restoration of the sensitivity to adrenaline was obtained after 15–45 min. On the whole, therefore, the anti-adrenaline substances persisted in their effect longer than the antihistamine substances as shown in Fig. 2; however, F933 and tolazoline were exceptions, since their effect was removed by perfusion with Locke's solution after 20–45 min.

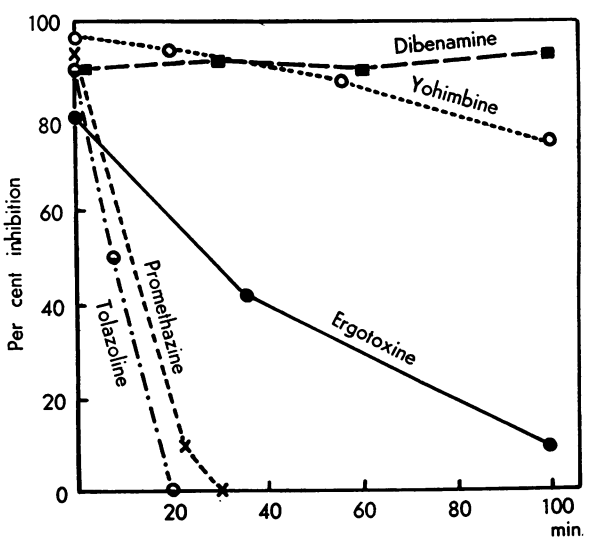

FIG. 2.—The ordinate represents the percentage of inhibition of the constrictor action of adrenaline. The abscissa is time in min. after the change from perfusion with the inhibiting substance back to Locke's solution only. Tolazoline (Priscol) was used as M/32,000. Promethazine was used in M/640,000. Yohimbine was used as M/320,000. Ergotoxine ethanesulphonate was used as 0.02 μg./ml. Dibenamine was used in M/4 million.

Comparison of the affinities for different receptors.—Histamine also produces constriction in the rabbit's ear vessels. This constriction can be abolished by antihistamine compounds, and by other substances such as atropine, pethidine, procaine, and quinidine; thus on rabbit ears it is very easy to determine whether a perfused inhibitor has a greater action against equiconstrictor doses of adrenaline or histamine.

When Regitine was used in a concentration of M/3 million, the equiconstrictor doses were 0.02 μg. adrenaline and 2.0 μg. histamine (Fig. 3). After perfusion with Regitine for 30 min., the effect of adrenaline was reversed while the effect of histamine was greatly reduced. When this was followed by perfusion for 10 min. with Locke's

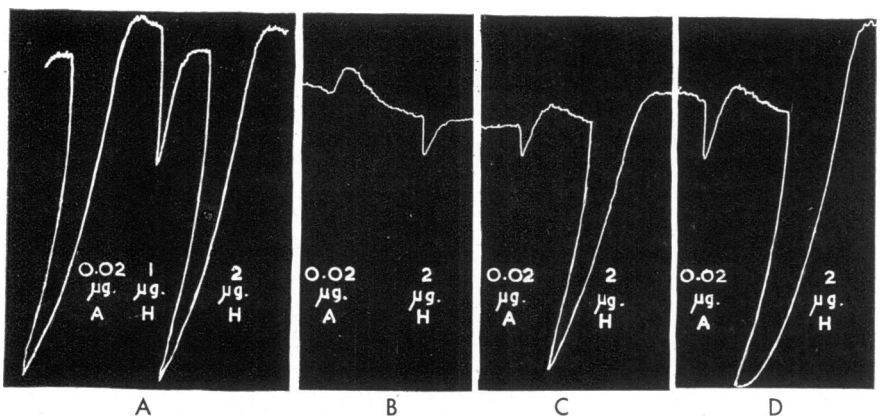

FIG. 3.—To demonstrate the slow disappearance of the anti-adrenaline action and the quick reversibility of the antihistamine action of Regitine. A. Adrenaline (0.02 μg.) and histamine (2 μg.) are equally constrictor. B. Reversal of the constrictor effect of adrenaline by perfusion of Locke's solution containing Regitine (M/3 million) for 30 min. The action of histamine is greatly inhibited. C. After removal of the Regitine from the perfusion fluid for 10 min., adrenaline causes a small vasoconstriction, while the sensitivity of the vessels for histamine has almost recovered to normal. D. Full restoration of the sensitivity to histamine by washing for 25 min. The adrenaline effect remains still very reduced.

solution only, the effect of adrenaline was a very small constriction, while the effect of histamine had returned to more than half the original effect. After perfusion for 25 min. with Locke's solution only, the adrenaline effect was still very small, while the histamine effect was fully restored.

When yohimbine was used, the effects of adrenaline and histamine were equally inhibited, but when yohimbine was washed out the histamine effect returned to normal, whereas the response to adrenaline did not recover for 2–3 hr.

In Fig. 4 it will be seen that yohimbine (M/320,000) reduced the constrictor actions of both adrenaline and of histamine to 1/10th. After removing the yohimbine from the perfusion fluid, the original constrictor effect of histamine returned in 50 min., but the effect of adrenaline remained reduced.

When dibenamine was used the concentrations which sufficed to reduce the constrictor action of adrenaline to 1/10th reduced the constrictor action of histamine even more. Three experiments were carried out in which the effect of dibenamine on the constrictor actions of adrenaline and histamine were compared, and in two of these, after removal of the dibenamine, the histamine constriction began to return

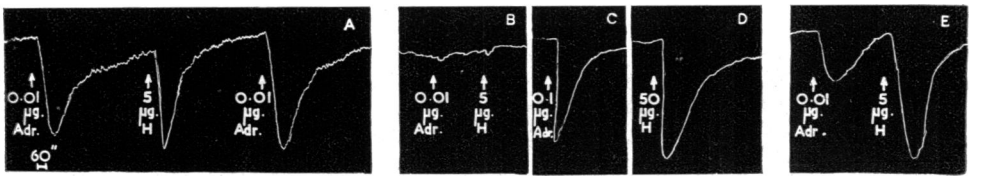

FIG. 4.—The different reversibility of the anti-adrenaline and antihistamine effect of yohimbine. A. Adrenaline (0.01 µg.) and histamine acid phosphate (5 µg.) are equally constrictor. B. The response to these test doses of adrenaline and histamine are abolished by perfusion of yohimbine HCl (M/320,000). C, D. Doses 10 times greater (0.1 µg. adrenaline, 50 µg. histamine) have nearly the same effect as the initial test doses before the perfusion of yohimbine. This indicates that yohimbine reduces the action of adrenaline and histamine to about 1/10th. E. After 50 min. of washing with Locke's solution the full sensitivity to histamine returns whereas the response to adrenaline is still reduced.

before the adrenaline constriction, though the histamine constriction remained depressed. In the third experiment, both the histamine and the adrenaline effects were similarly reduced for 2 hr. after the dibenamine had been washed out.

When F933 was used in a concentration of M/250,000 only the effect of adrenaline was reduced; the action of histamine was not inhibited.

On the other hand, the antihistamine compounds were much more effective against histamine than against adrenaline, in spite of their powerful anti-adrenaline action. Concentrations one-tenth of those required to reduce the effect of adrenaline to 1/10th blocked the histamine receptors completely. When the perfusion was stopped, in contrast to the quick recovery of the adrenaline sensitivity, the histamine effect remained greatly reduced sometimes for many hours as shown in Table III.

TABLE III

STRENGTH AND DURATION OF THE ANTIHISTAMINE EFFECTS OF SOME ANTIHISTAMINE COMPOUNDS ON PERFUSED RABBIT'S EARS, COMPARED WITH THEIR ANTI-ADRENALINE ACTIVITIES

The test doses injected were 0.005 µg.–0.01 µg. adrenaline and equally constrictor doses of histamine acid phosphate

Substance	Mol. conc.	Effect against adrenaline			Effect against histamine		
		Inhibition %	Recovery %	Time of washing (min.)	Inhibition %	Recovery %	Time of washing (min.)
Tripelennamine..	M/64,000	90	100	25	100	5–10	100
	M/640,000	0	—	—	100	100	50
Mepyramine ..	M/32,000	90	100	20	100	0	600
	M/320,000	0	—	—	100	10–20	600
Promethazine ..	M/640,000	ca. 90	100	25	100	0	360
	M/6,400,000	Slightly reduced	—	—	100	25–50	360

DISCUSSION

Previous work has shown that the constrictor action of adrenaline on the vessels of the rabbit ear is not only reduced or reversed by substances well known to depress or reverse the action of adrenaline on the blood pressure, but also by other sub-

stances, some of which are antihistamine compounds and some local anaesthetics, etc. A study has now been made to see what differences there are between these different classes of compounds. The concentration of each compound sufficient to reduce the constrictor action of adrenaline to 1/10th was first determined, as it seemed likely that substances commonly regarded as adrenaline inhibitors would act in a much lower concentration than the others. To some extent this was found to be true; thus the substances acting in the lowest concentration were " ergotoxine " and ergotamine, Regitine, and dibenamine. On the other hand, some antihistamine compounds acted in lower concentration than yohimbine and tolazoline (Priscol). Thus concentration by itself was not a sufficient guide to distinguish substances as anti-adrenaline compounds.

An attempt was then made to measure the reversibility of the anti-adrenaline effect. After the constrictor action of adrenaline had been reduced to 1/10th of the original by perfusing the compound for 30 min., the perfusion was continued with Locke's solution alone, and the time of recovery of the adrenaline effect was determined. The effect of dibenamine was found to be almost irreversible. The effect of yohimbine persisted for 2–3 hr. or more, while the effects of " ergotoxine " and of Regitine persisted for 1–2 hr. In contrast with these substances, the action of all the other substances was completely reversed in periods from 15–45 min. This group of substances included F933 and tolazoline (Priscol). On the whole, it appeared that prolonged attachment to the adrenaline receptors was characteristic of the well-known anti-adrenaline compounds.

Finally, the anti-adrenaline action of many of these compounds was compared with their antihistamine action, comparison being made of the effective concentrations and of the rates of elimination. F933 did not modify the constrictor action of histamine in concentrations which reduced the constrictor action of adrenaline to 1/10th. Regitine reduced the action of histamine in a concentration which reversed the action of adrenaline. Yohimbine reduced the constrictor action of the two substances equally. Dibenamine also seemed to act equally against histamine and adrenaline. Thus the behaviour of these substances towards adrenaline and histamine differed according to the substance. With Regitine, yohimbine, and dibenamine, however, the constrictor effect of histamine returned more rapidly than that of adrenaline after the antagonist had been washed out.

The reverse was true of the antihistamine substances. They abolished the constrictor action of histamine in lower concentrations than that of adrenaline, and after they had been washed out their effect on the histamine response lasted longer. " Specificity " of an inhibiting substance is obviously due to a preference for a certain type of receptor. This preference may show itself in two ways: (*a*) By the concentration in which one type of receptor is blocked, while other receptors are not affected. This type of inhibition may be quickly reversed; F933 is an example. (*b*) By a specially close and stable combination with one type of receptor, whereas the attachment to other receptors is more labile. Yohimbine, Regitine, and dibenamine are examples.

This second type of specific inhibition is reversed slowly. It may be missed if the effective concentrations only are determined. If injected into an animal such a substance may be expected to attach itself to those receptors only which form a stable combination with it.

Highly specific inhibitors may, however, also show a capacity for unspecific blocking at higher concentrations, and a general overlapping may occur; thus, antihistamine compounds block adrenaline and acetylcholine receptors, whereas atropine and other specific acetylcholine antagonists may combine with histamine and adrenaline receptors. Under these conditions two fundamentally different categories can be distinguished on isolated organs: substances which may be called agonists, such as adrenaline, acetylcholine, and histamine; and their common antagonists, antihistamine and anti-adrenaline drugs, acetylcholine antagonists, and simple local anaesthetics. It must be emphasized that this classification is not only the result of pharmacological findings, but also of physicochemical considerations. All " agonists " or " antagonistic " agents included in this study are nitrogen-containing compounds, with ability to act as cations under physiological conditions and to be adsorbed on negatively charged groups (receptors) of the cell surface. Thus, if the " antagonists " act by competition, a greater affinity of the inhibitory cations for the negative receptors must be assumed. In a recent study, Fleckenstein, Guenther, and Winker (1951) used the artificial collodion membrane in order to measure electrically the adsorption and retention of about sixty nitrogen-containing organic cations. Clear differences between the " agonist " and " antagonist " categories were found. All " agonist " substances (adrenaline and other sympathomimetic compounds, acetylcholine and related drugs, histamine, coniine, nicotine, veratrine) were found to be adsorbed loosely on the negative structures of the membrane and to be washed out again very quickly. On the other hand, the " antagonistic " substances (anti-adrenaline, anti-acetylcholine, and antihistamine compounds as well as quinine, pethidine, and simple local anaesthetics) had a much greater affinity for these negative receptors, and were much less readily washed out; indeed, their adsorption on the collodion membrane was frequently irreversible. Therefore it is suggested that the unspecific action of " antagonists " against all types of loosely adsorbed " agonists " may be a simple physicochemical consequence of differences in adsorbability.

It can also be understood why many basic dyestuffs, well known for their affinity for the collodion membrane (Mond and Hoffmann, 1928; Wilbrandt, 1935), exhibit a powerful anti-acetylcholine and antinicotine effect on the isolated frog rectus (Fleckenstein *et al.*, 1951). Most of these basic dyestuffs were considerably stronger than methylene blue, which was first described by Cook (1926) as an acetylcholine antagonist. Furthermore, some recent results with basic fuchsine on rabbit ears show that a similar activity can be exerted against adrenaline. Strychnine is another substance which is strongly adsorbed on the collodion membrane and is an adrenaline inhibitor as well (see Table I).

Whatever the significance of these physicochemical results may be, adrenaline, acetylcholine, and histamine are, however, in some respect related drugs, having common antagonists on certain isolated organs. This conception, put forward first by Burn and co-workers, is given further support by the new results presented.

SUMMARY

1. The anti-adrenaline potencies of various substances, including anti-adrenaline and antihistamine compounds, simple local anaesthetics, and substances like atropine, pethidine, quinine, quinidine, tolazoline (Priscol), and strychnine, have been

investigated in a comparative study on the perfused vessels of the rabbit's ear. Stephenson's outflow recorder was used, and proved to be a satisfactory method of registering very small changes of vascular tone.

2. Ergot alkaloids (" ergotoxine ethanesulphonate," ergotamine tartrate), Regitine and dibenamine, which are generally considered as " specific " inhibitors of adrenaline, were active at very low concentrations. Some antihistamine compounds also exhibit a high anti-adrenaline action: promethazine (Phenergan) and phenindamine (Thephorin) surpass the anti-adrenaline substances yohimbine and F933, and most antihistamine compounds were stronger than tolazoline (Priscol).

3. When the sensitivity of the vessels to adrenaline has been abolished by ergot alkaloids, Regitine or yohimbine, a slow return to normal is seen when pure Locke's solution is perfused afterwards. The action of dibenamine is almost irreversible. The effect of " unspecific " adrenaline antagonists, such as antihistamine and other compounds, is quickly abolished when the antagonist is washed out. Tolazoline (Priscol) and F933 do not differ in this respect from unspecific adrenaline inhibitors.

4. Many of the compounds tested for their anti-adrenaline potency inhibit the constrictor action of histamine too. This is true for yohimbine, Regitine, tolazoline, and dibenamine, and, as already pointed out by Burn and Dutta, for atropine, pethidine, quinidine, and simple local anaesthetics. Antihistamine compounds block the histamine receptors in extremely small concentrations which are ineffective against adrenaline.

5. Yohimbine, Regitine, and dibenamine, which are regarded as specific adrenaline inhibitors, antagonize the vascular constriction produced by adrenaline and histamine to a similar extent, but when they are washed out, the response to adrenaline remains reduced for a much longer time than the response to histamine. Antihistamine compounds, on the contrary, block the histamine effect for a long time and allow a quick recovery of the sensitivity to adrenaline.

6. These observations justify the assumption that " specific " inhibition is due to a preference for a certain type of receptor. This preference may be obvious (*a*) by the low concentration at which one type of receptor is blocked while other receptors are not affected, or (*b*) by a specially close and stable combination with one type of receptor, whereas the attachment to other receptors is more labile.

7. It is suggested that the action of unspecific antagonists of adrenaline or histamine may be due, if they are present in sufficiently high concentration, to their being more firmly bound by adsorptive forces to the negatively charged structures of the cell membrane than either agonist is.

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