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DRUGS WHICH ANTAGONIZE 5-HYDROXYTRYPTAMINE

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A specific antagonist for 5-hydroxytryptamine (HT) might be valuable in various ways. It might provide evidence for the identification of HT in tissue extracts. It might help those who are interested in other pharmacologically active substances by suppressing interference due to HT. It might also have direct actions of its own which would provide a clue to the physiological function of HT which is found in tissues. This paper describes part of the search for such an antagonist. Some of these results were communicated to the British Pharmacological Society in July, 1952.

METHODS

Rats' uteri were prepared by the subcutaneous injection of stilboestrol (10 μg. per 100 g. wt.) the day before the experiment. Ovariectomy (Erspamer, 1952a) did not seem to be necessary. The uteri were suspended in a 2 ml. bath at 30° C. and the solution was that recommended by Gaddum, Peart, and Vogt (1949). Their contractions were recorded with a lever on a smoked drum with a magnification of about 5. Drugs were added to the bath in small measured volumes, and the concentrations recorded here were the final concentrations in the bath. Either acetylcholine (ACh) or carbachol was given in alternate doses to control the specificity of the effect of antagonist drugs.

Isolated pieces of guinea-pig's ileum were suspended in a 2 ml. bath containing Tyrode's solution maintained at 37° C. and the movements of the longitudinal muscle recorded with a lever. The portion of the ileum adjacent to the caecum was found to be most sensitive to HT. Histamine and choline esters were used as control drugs.

Isolated rabbits' ears were perfused at room temperature through a cannula in the central artery. A special injection cannula, as described by Gaddum and Kwiatkowski (1938), was interposed between the reservoir containing the perfusion fluid and the arterial cannula. The drugs were injected through the rubber cap of this cannula. Two reservoirs were connected with the injection cannula, one containing the ordinary perfusion fluid and the other containing the antagonist. The preliminary steps of dissection and cannulation of the artery were the same as described by Page and Green (1948). The ear was placed on a draining plate and the perfusate from the cut surface was led to a small collecting funnel which led into a capillary. This capillary end was connected to a drop-timer (Gaddum and Kwiatkowski, 1938). In the tracings, the height of the record measures the interval between successive drops. The perfusion fluid was that recommended by Page and Green (1948) for the study of serum vasoconstrictor, and had the following composition (g./l.):

NaCl, 8.2; KCl, 0.84; $CaCl_2,2H_2O$, 0.04; $MgCl_2,6H_2O$, 0.06; $NaHCO_3$, 0.4; glucose, 1. To each litre was added 10 ml. of phosphate buffer containing 4 parts of 1 M-K_2HPO_4 to 1 part of 1 M-KH_2PO_4.

When this solution was used, the ear was much more sensitive to vasoconstrictor substances than when Locke's solution was used. The ear was always more sensitive on the next day after being kept overnight in the refrigerator. Adrenaline was used as a control drug.

We are indebted to various manufacturers and others for preparations of the following drugs—5-hydroxytryptamine creatine sulphate (Messrs. Upjohn), tryptamine hydrochloride (British Drug Houses), various ergot alkaloids (Sandoz Products), piperoxane (May & Baker, Ltd.), mescaline sulphate (Roche Products, Ltd.), gramine (L. Light & Co., Ltd.), dibenamine (Smith, Kline & French Research Laboratories), cinobufotenine (Dr. K. K. Chen). Doses are given in terms of the bases.

RESULTS

HT was found to cause contractions of the uterus, duodenum, and colon of rats; the uterus, duodenum, and jejunum of rabbits; and the uterus, duodenum, jejunum, and ileum of guinea-pigs. It caused vasoconstriction in the perfused ears of rabbits. The most sensitive of these tissues were the rat's uterus (Erspamer, 1952a), the guinea-pig's ileum (Gaddum, 1953a; Robertson, 1953; Rocha e Silva, Valle, and Picarelli, 1953), and the rabbit's ear (Rapport, Green, and Page, 1948), all of which have been used before for experiments with HT.

There is evidence that some of the actions of HT and tryptamine are due to combination with

special receptors, which are not identical with the receptors for histamine, adrenaline, or ACh, and which have been called tryptamine-receptors (Gaddum, 1953a). These other drugs all have effects like those of HT on some tissues but not on all tissues. Histamine and adrenaline do not stimulate the rat's uterus, adrenaline does not stimulate the guinea-pig's ileum, and ACh causes vasodilatation rather than vasoconstriction in the freshly prepared rabbit's ear (Burn and Robinson, 1951).

In every case a test of specificity was carried out by comparing the effect of HT with that of a suitable dose of some other drug before and after the addition of the antagonist. When the effects of both drugs were depressed the antagonism was considered unspecific and unimportant. Such effects may be caused by depression or poisoning of the contractile mechanism. The statement that an antagonism was specific means that the effect of HT was depressed while the effect of the control drug was not. This test does not prove that HT and its antagonist are competing for the same receptor, but does exclude some cases in which they are not.

Guinea-pig's ileum can be specifically desensitized to HT by exposure to high concentrations of this drug or tryptamine (Gaddum, 1953a ; Rocha e Silva *et al.*, 1953). Similar results may sometimes be obtained with the rat's uterus. In one experiment, for example, HT (75 μg./l.) and tryptamine (7,500 μg./l.) caused effects similar to those of carbachol (750 μg./l.). A high concentration of HT (15,000 μg./l.) was then added to the bath for 43 min. This caused strong contractions, which disappeared after 13 min. The muscle now gave no response to HT or tryptamine, but the effect of carbachol was unchanged. This desensitization persisted for 15 min. after the high concentration of HT had been removed ; the muscle then again gave a response to tryptamine. In some experiments the effect was obscured by the persistence of muscular contractions in the presence of HT ; the inhibitory effect of high concentrations of HT was much less clearly shown on the rat's uterus than on the guinea-pig's ileum. It would not be easy to do similar experiments with the rabbit's ear, because large doses of HT stop the flow completely.

Specific antagonisms are commonly due to the competitive action of drugs similar in structure to the active drug, and tests have therefore been made with a number of compounds which, like HT, contain an indole nucleus. Most of these were specially prepared by Messrs. Glaxo, and the results will be published in a separate paper.

Gramine (3-dimethylaminomethyl-indole) acted as the prototype for a number of active synthetic anti-HT compounds, and its effect on the rat's uterus is shown in Fig. 1. It abolished the response to HT without affecting the response to carbachol. Erspamer has observed the same effect (1954). In a concentration of 10 mg./l. it decreased the sensitivity of the rabbit's ear to HT by more than 2,000-fold and that to adrenaline by about 15-fold. On the other hand it had no definite effect on the response of the guinea-pig's ileum.

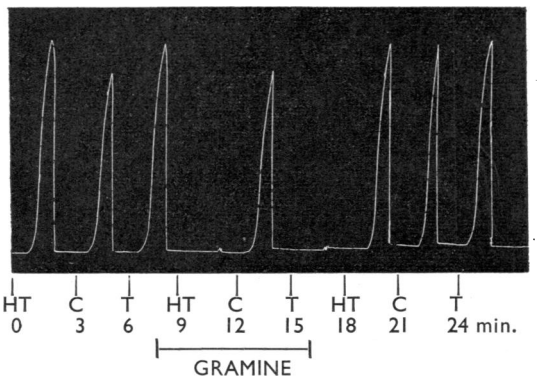


FIG. 1.—Rat's uterus. 2 ml. bath. Interval 3 min. HT, 5-hydroxytryptamine 20 ng. C, Carbachol 100 ng. T, Tryptamine 4,000 ng. Gramine (20 μg.) specifically inhibited tryptamine receptors.

Ergot Alkaloids.—Tryptamine forms part of the molecule of lysergic acid, certain derivatives of which are very active antagonists of HT on the rat's uterus and the rabbit's ear.

The antagonism of ergotoxine and tryptamine was described by Laidlaw (1911) and that of ergotamine and α-methyltryptamine by Seki (1929). Heymans, Bouckaert, and Moraes (1932) found that ergotamine antagonized the vasoconstrictor action of defibrinated blood, which was presumably due mainly to HT. Gaddum, Peart, and Vogt (1949) obtained similar results with dihydroergotamine and made the additional observation that suitable concentrations of this drug suppressed the response of the rabbit's ear to cat's plasma without altering the response to adrenaline. This fact seemed surprising at the time but is now explained, since the response to HT can also be suppressed without altering the response to adrenaline.

The results recorded below confirm and extend those obtained by various workers who have studied the antagonism of HT and ergot alkaloids during recent years (Erspamer, 1952a ; Woolley and Shaw, 1953 ; Fingl and Gaddum, 1953 ; Page and McCubbin, 1953).

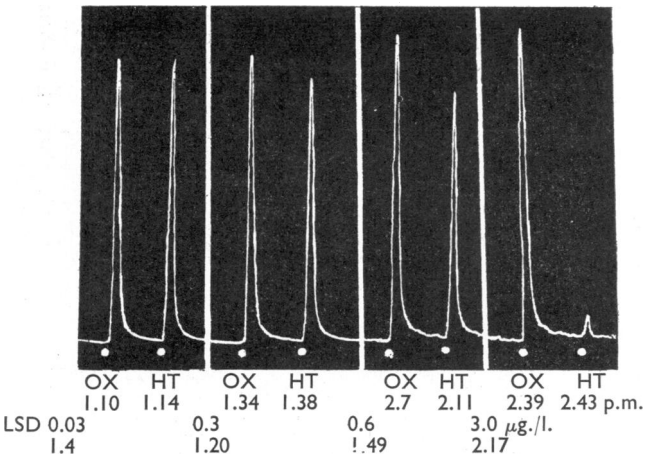
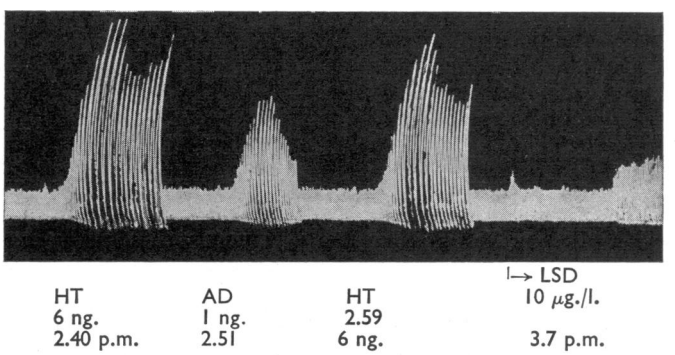


FIG. 2.—Rat's uterus. 3 ml. bath. OX, oxytocin 30 mu./l. HT, 5-hydroxytryptamine 16 μg./l. LSD specifically inhibited tryptamine receptors.

The most active and specific of these derivatives which has been tested is lysergic acid diethylamide (LSD). A preliminary account of this action has already been published (Gaddum, 1953b). Fig. 2 shows the result of an experiment on the rat's uterus in which LSD (0.3 μg./l.) caused a small decrease in the effect of HT (16 μg./l.) while a higher concentration (3 μg./l.) inhibited the effect almost completely. Control doses of oxytocin (30 mu./l.) gave effects which were not altered by the LSD. When the LSD was removed from the bath and the administration of the other drugs continued, the response to HT returned almost to its original value in about an hour. A concentration of 0.6 μg./l. of LSD reduced the effect of HT (15 μg./l.) so that after 10 min. the dose of HT had to be doubled to reproduce the original effect. It was thus estimated that the pA_2 (10 min.) was about 8.7 (Schild, 1947). This indicates that LSD had about the same activity in this experiment as atropine had when tested by Schild as an antagonist for ACh on guinea-pig's intestine. When the LSD was left in the bath its action continued to increase for at least 20 min.

Various derivatives of lysergic acid have been compared for their effects on the rat's uterus as antagonists of HT and placed in the following descending order of potencies—lysergic acid



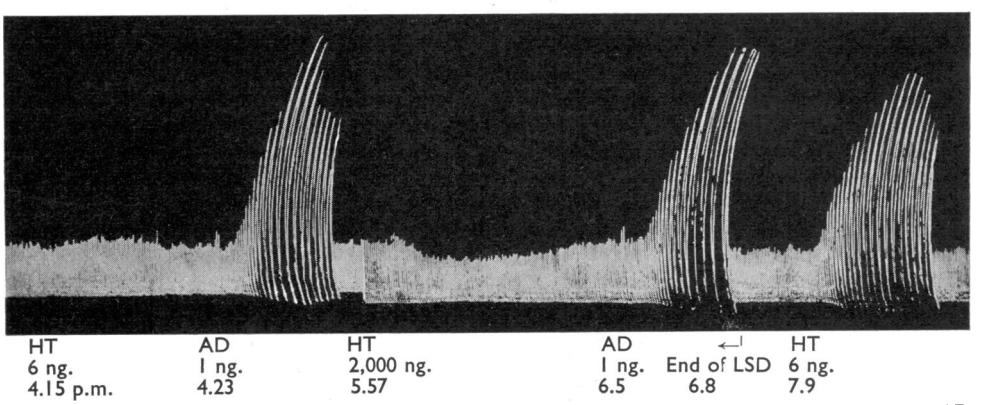


FIG. 3.—Rabbit's ear perfused. Height of record shows interval between drops. HT, 5-hydroxytryptamine. AD, adrenaline (doses in ng.). LSD (10 μg./l.) specifically inhibited response to HT.

diethylamide, dihydroergotamine dihydroergocornine, and dihydroergokryptine. Ergotamine, ergotoxine, and ergometrine generally caused much spontaneous activity in the concentrations used, but in all cases there was some evidence of a fall in the response to HT in conditions where there was no change in the response to a choline ester. Dihydroergocristine caused marked inhibition, but this was not specific.

Some of these substances were also tested on the rabbit's ear. With this tissue it is possible to compare their actions against HT and adrenaline, both of which cause vasoconstriction; whenever this comparison has been made the response to HT has been depressed more than the response to adrenaline.

Fig. 3 shows the results of an experiment where HT (6 ng.) had more vasoconstrictor action than adrenaline (1 ng.). LSD was then perfused in a concentration of 10 μg./l., and this abolished the constrictor effect of HT even when the dose was increased to 2,000 ng. At the same time the response to adrenaline showed a gradual increase.

Fig. 4 shows the results of a similar experiment with dihydroergotamine. A concentration of 20 μg./l. of this drug abolished the response to HT and greatly diminished that to adrenaline, but when the doses were increased adrenaline was again effective. It was evident that dihydroergotamine was more active as an antagonist to HT than as an antagonist to adrenaline, but its action was not so specific as that of LSD.

In a concentration of 20 μg./l. ergotamine did not produce any significant inhibition of the response of the rabbit's ear to HT. In a concentration of 40 μg./l. the responses to both HT and adrenaline were abolished, but a four-fold dose of adrenaline was effective, while a 100-fold dose of HT was not. Ergometrine, even in a concentration of 100 μg./l., had no significant effect on the response to HT or adrenaline.

The antagonism between HT and the ergot alkaloids on the guinea-pig's ileum is comparatively feeble and less clearly specific. In a concentration of 100 μg./l. LSD reduced the response to HT by 50%, but much higher concentrations (10,000 μg./l.) appeared to have no more effect. The responses to histamine and ACh were not altered in these experiments.

Low concentrations of dihydroergotamine had no effect, but when higher concentrations (2,500–25,000 μg./l.) were used the response to HT was depressed. In these conditions the response to histamine was also depressed, sometimes even more than that to HT. Similar results were obtained with rabbit's duodenum.

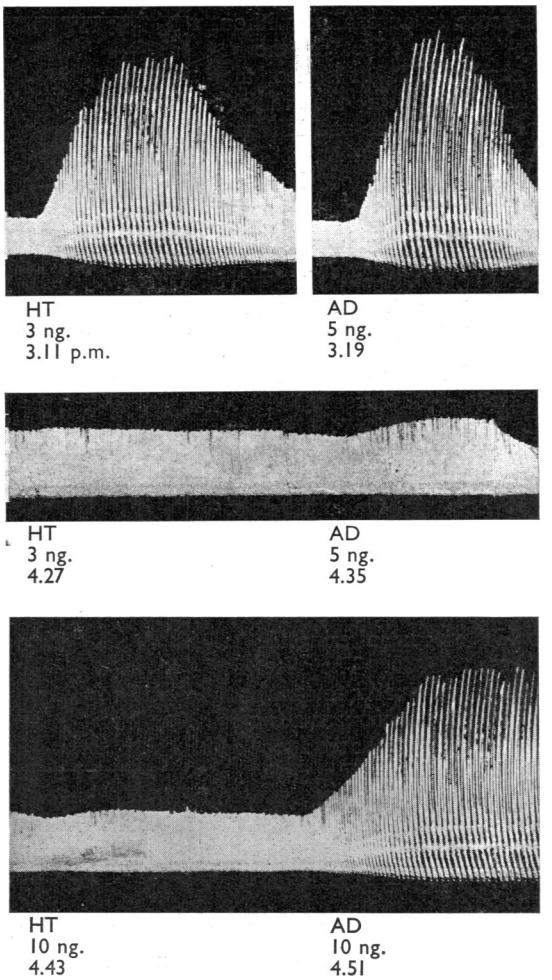


FIG. 4.—Rabbit's ear perfused as in Fig. 3. Top: control doses of 5-hydroxytryptamine (3 ng.) and adrenaline (5 ng.). From 3.25 dihydroergotamine (20 μg./l.) was continuously present in the perfusion fluid. Both drugs antagonized, but HT more than adrenaline.

Piperoxane (933F, piperidylmethylbenzodioxane).—Piperoxane is known as an antagonist of adrenaline, but it had no antagonistic action to HT on the rat's uterus (50 mg./l.) or the rabbit's ear (400 μg./l.). This result confirms those of Erspamer (1953) and Fingl and Gaddum (1953). Fig. 5 shows the results of an experiment in which HT was first compared with adrenaline and found to be about 1.5 times as active. The perfusion fluid was then replaced by a similar fluid containing piperoxane (400 μg./l.). This abolished the

response to adrenaline without any definite effect on the response to HT. It is clear that antagonisms on the rabbit's ear to adrenaline and HT may vary independently. LSD is more active against HT and piperoxane is more active against adrenaline.

Dibenamine (*NN*-dibenzyl-β-chloroethylamine) is known as an antagonist of adrenaline with a very prolonged action. It also has some antihistamine activity (Nickerson, 1949; Fleckenstein, 1952). It antagonized the action of HT on all of the three tissues used in the present experiments.

A concentration of 5 μg./l. of dibenamine greatly reduced the response of a rat's uterus to HT without altering the response to ACh. The effect developed gradually for an hour or more. A concentration of 100 μg./l. abolished the response to HT and slightly reduced that to ACh. With higher concentrations the response to HT was immediately, completely, and irreversibly blocked.

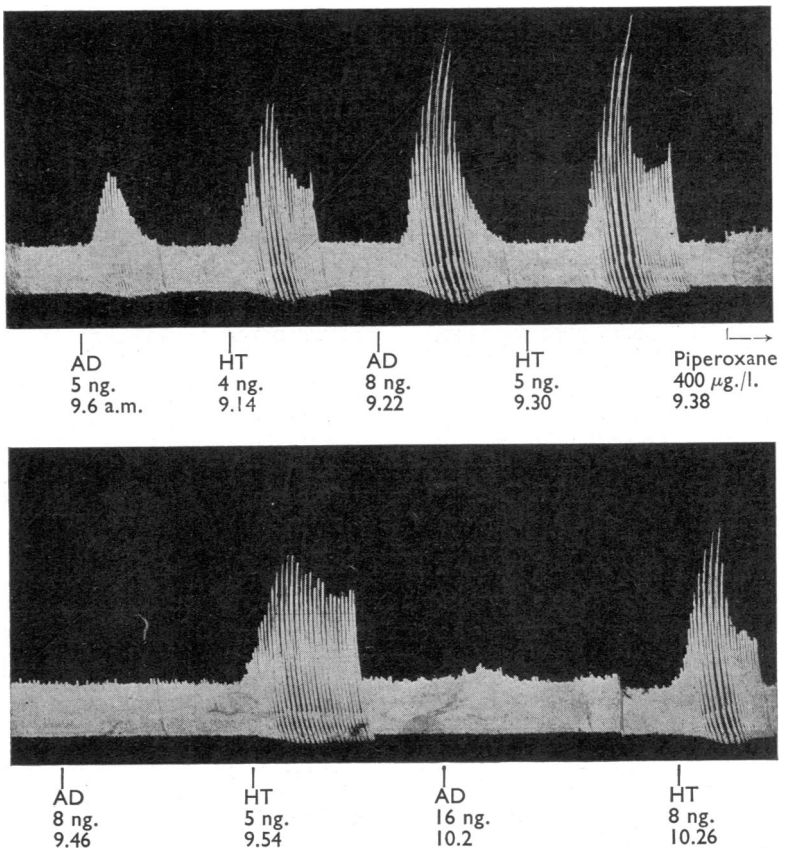


FIG. 5.—Rabbit's ear perfused as in Fig. 3. Piperoxane (400 μg./l.) abolished the response to adrenaline without much effect on the response to HT.

The receptors in the rabbit's ear were less sensitive to dibenamine. A concentration of 100 μg./l. caused 75% inhibition of the response to adrenaline and 64% inhibition of the response to HT. Both effects persisted when the dibenamine was washed away.

The guinea-pig's ileum was less sensitive than the rabbit's ear. Dibenamine (1,000 μg./l.) reduced the responses to histamine and HT about equally without affecting that to ACh. When the dibenamine was washed away the response to HT returned, but not that to histamine. Dibenamine was thus found to be a powerful antagonist for HT on the rat's uterus (Erspamer, 1952a, 1953). On the other two tissues its action against HT was feebler, and less than its actions against adrenaline and histamine (Fingl and Gaddum, 1953).

Inhibitors of Amine Oxidase.—In low concentrations ephedrine potentiates some of the actions of adrenaline and in higher concentrations it antagonizes them (Gaddum and Kwiatkowski, 1938). The first action has been attributed to the inhibition of amine oxidase, which ephedrine is known to cause, and since HT is destroyed by amine oxidase (Blaschko, 1952; Freyburger, Graham, Rapport, Seay, Govier, Swoap, and Vander Brook, 1952) it was thought possible that some of its effects might be increased by ephedrine and allied drugs. Experiments with ephedrine and amphetamine on the rat's uterus and the guinea-pig's ileum did not show any significant action of this kind, but it was found that the response of the perfused rabbit's ear to HT was greatly increased when ephedrine (10 mg./l.) was present in the perfusion fluid. In these experiments the response to adrenaline was actually depressed by this concentration of ephedrine (Fig. 6). The potentiation of the effect of HT is presumably due to the inhibition of amine oxidase. The inhibition of the response to adrenaline by higher concentrations of ephedrine has been attributed to blockade of the adrenaline

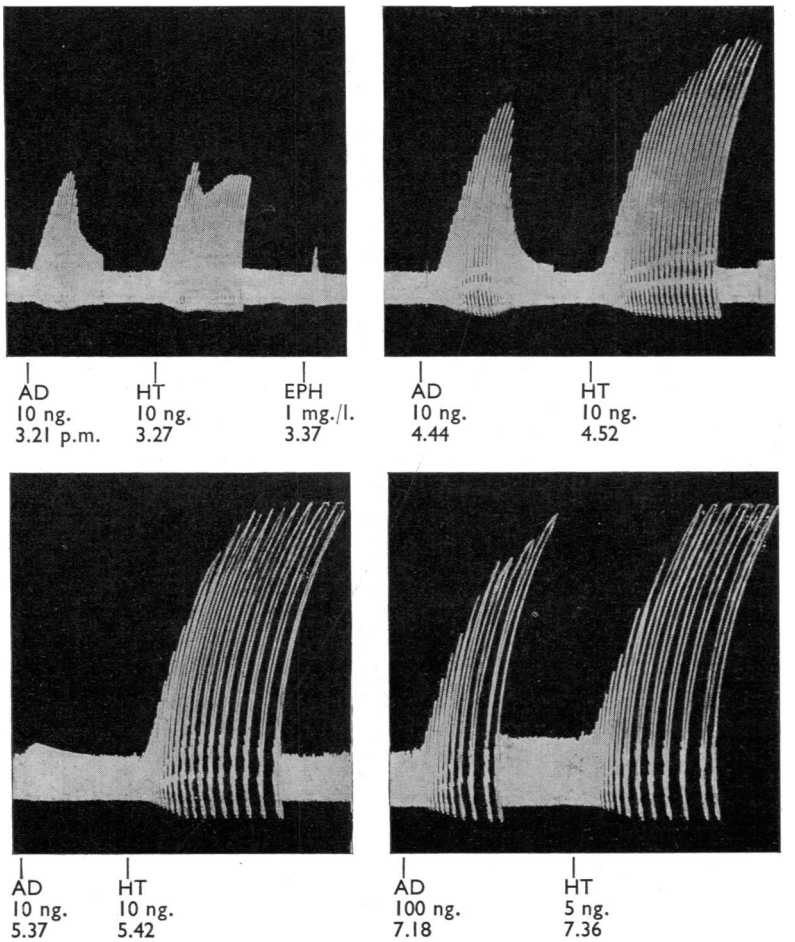


FIG. 6.—Rabbit's ear perfused as in Fig. 3. Doses in ng. Ephedrine (1 mg./l.; 3.37–5.7) increased the responses to adrenaline (AD) and 5-hydroxytryptamine (HT). In a higher concentration (10 mg./l.; 5.7–7.50) ephedrine diminished the response to adrenaline, but increased the response to HT still more.

receptors (Gaddum and Kwiatkowski, 1938). The tryptamine receptors do not appear to be blocked by the concentrations of ephedrine used in these experiments.

The theory that this potentiation of the response to HT is due to the inhibition of amine oxidase was confirmed by the results of one experiment with choline-*p*-tolyl ether bromide (Brown and Hey, 1952; Hey, 1952). This drug, which is known to inhibit amine oxidase, was added to the fluid perfused in a rabbit's ear in a concentration of 1 mg./l. This increased the effects of both adrenaline and HT; a higher concentration (10 mg./l.) decreased both effects.

Cocaine.—Cocaine is not only a local anaesthetic but also an inhibitor of amine oxidase (Philpot, 1940). Reid and Rand (1952) found that it increased the effect of HT on a strip of sheep's carotid artery, but reported no experiments to test whether this was a specific effect, or an unspecific increase in the contractile power of the muscle. In our experiments cocaine did not show any effects which could be attributed with confidence to the inhibition of amine oxidase. In a concentration of 5–10 mg./l. it increased the effects of both HT and ACh on the rat's uterus. When it was washed away the effects gradually returned to their original level. Lower concentrations had no significant action. A higher concentration (50 mg./l.) temporarily inhibited the effects of both HT and ACh (Fig. 7).

The action of HT on the rabbit's ear was not significantly changed by cocaine (10 mg./l.), although the action of adrenaline was much increased in the same experiment. It has been suggested that the effect of cocaine on the response to adrenaline is due to the inhibition of amine oxidase (Philpot, 1940; Blaschko, 1952). If this is so, it is perhaps surprising that the cocaine did not increase the effect of HT in this experiment. It might be suggested that the effect of HT on the rabbit's ear does not depend on amine oxidase, but if so the potentiating action of ephedrine cannot be explained in the way that has been suggested above.

Cocaine (5–10 mg./l.) inhibited the response of the guinea-pig's ileum to HT reversibly without much effect on the responses to histamine and ACh. The response to nicotine was inhibited to the same extent as the response to HT. This inhibition has been observed by others (Sinha and West, 1953; Rocha e Silva *et al.*, 1953) and explained on the theory that HT acts on the nervous tissues in the intestine and that cocaine inhibits its action by paralysing these nerves.

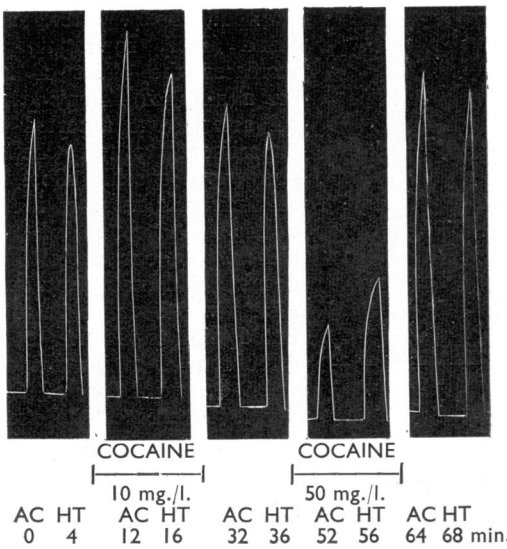


FIG. 7.—Rat's uterus. 2 ml. bath. AC, acetylcholine, 500 ng.; HT, 5-hydroxytryptamine, 10 ng. Cocaine (10 mg./l.; 5–17 min.) increased both effects. A higher concentration of cocaine (50 mg./l.; 37–57 min.) decreased both effects.

The actions of cocaine on these three tissues were thus different. The response of the rat's uterus was unspecifically increased by low concentrations and unspecifically decreased by higher concentrations. The response of the rabbit's ear was unaffected and the response of the guinea-pig's ileum was inhibited, like the response to nicotine, before the responses to histamine or ACh. The generalization of Sinha and West (1953), that local anaesthetics antagonize the actions of HT, does not give all the facts.

Atropine.—In concentrations of 5–100 μg./l. atropine completely abolished the effect of carbachol (50 μg./l.) on the rat's uterus, while leaving the effect of HT unchanged. A higher concentration (1,000 μg./l.) diminished the effect of HT by 50%.

Atropine (5 μg./l.) abolished the response of the guinea-pig's ileum to carbachol (5 μg./l.) but not that to HT (50 μg./l.) (Fig. 8). Higher concentrations of atropine (100 μg./l.) diminished the effect of HT and abolished the effect of ACh (3–5 μg./l.) while leaving that of histamine (3–5 μg./l.) unchanged. These results confirm those of previous workers (Gaddum, 1953a; Rapport and Koelle, 1953; Robertson, 1953; Rocha e Silva *et al.*, 1953). Atropine inhibits the effect of HT on this tissue more than that of histamine, but less than those of choline esters. The actions of atropine on the guinea-pig's ileum are thus similar to those on the rat's uterus, but there was less difference between the doses effective against HT and ACh.

Atropine (100–1,000 μg./l.) had no action on the effect of HT on the rabbit's ear.

Antihistamines.—Experiments were done with mepyramine and diphenhydramine. The first is one of the most specific antihistamines, and the second is less specific since it has some action against ACh (Schild, 1947).

The effect of HT on the rat's uterus was partially blocked by either drug in a concentration of 100 μg./l. and completely blocked by 1,000 μg./l. With diphenhydramine the response to ACh was inhibited to approximately the same extent as the response to HT.

Mepyramine (1,000 μg./l.) had little or no effect on the response of the guinea-pig's ileum to HT or ACh, though a concentration of 5 μg./l. was sufficient to abolish the response to histamine. Diphenhydramine (25–1,000 μg./l.) produced partial inhibition of the responses to both HT and ACh, and abolished the response to histamine almost completely.

These two antihistamines thus produced much the same effect on the responses of both tissues to HT as on their responses to ACh. The experiment with the guinea-pig's ileum provides another example confirming the generalization that mepyramine is a more active and more specific antihistamine than diphenhydramine.

These results are in general agreement with those of Reid and Rand (1951, 1952), Rapport and Koelle (1953), and Erspamer (1952b).

Inactive or Unspecific Antagonists.—Hexamethonium (10 mg./l.) inhibited the effect of

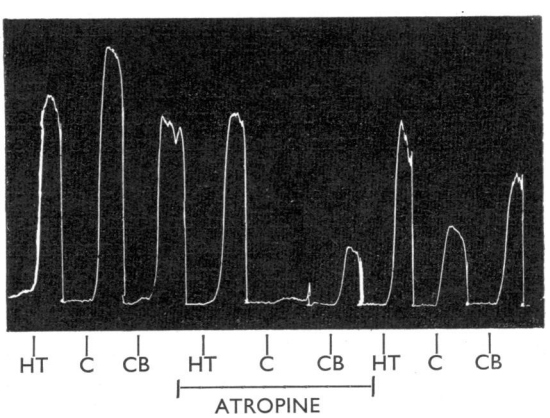


FIG. 8.—Guinea-pig's ileum. 2 ml. bath. Interval 3 min. HT, 5-hydroxytryptamine 100 ng. C, carbachol 10 ng. CB, cinobufotenine (*N*-trimethyl-5-hydroxytryptamine) 1,200 ng. Atropine (10 ng. during time signal) suppressed the response to carbachol but not that to HT. With CB the effect was intermediate.

nicotine on the guinea-pig's ileum without altering the effect of HT. This confirms the results of Robertson (1953) and Rocha e Silva *et al.* (1953).

Mescaline (50 mg./l.) did not affect the response of the rat's uterus to HT. Mescaline is thought by some to resemble lysergic acid diethylamide in its effects on the central nervous system. These two drugs might therefore have been expected to have similar effects as antagonists of HT, but this was not the case.

Yohimbine (5 mg./l.) markedly depressed the response of the rat's uterus to HT and tryptamine. The response to ACh was also depressed, though less, and the antagonism was thus not very specific (cf. Erspamer, 1953). The antagonism between yohimbine and HT on isolated strips of carotid artery has been described by Reid and Rand (1952), Woolley and Shaw (1953), and Shaw and Woolley (1953). These authors obtained effects with concentrations as low as 0.1 mg./l., but give no evidence that the inhibition was specific.

Eserine in low concentrations (100–1,000 μg./l.) caused a small increase in the response of the rat's uterus to HT and higher concentrations sometimes caused a decrease, but the effects were feeble.

Although both yohimbine and eserine contain an indole ring there is as yet no evidence that either of them is a specific antagonist of HT.

Discussion

Experiments with specific antagonists confirm the conclusion that HT produces some of its effects by acting on specific receptors. With mepyramine, piperoxane, and atropine it is possible to abolish the effects of histamine, adrenaline, and ACh respectively, without altering the effects of HT. Higher concentrations of these drugs may antagonize HT, but this does not invalidate the evidence given by the experiments with low concentrations, which show that some at least of the effects of HT are due to combination with receptors which are not identical with the receptors for histamine, adrenaline, or ACh.

The drugs which do antagonize HT have given different results when tested on different tissues. LSD is a very active and specific antagonist for HT in experiments on the rat's uterus or the rabbit's ear, but had little effect in experiments on the guinea-pig's ileum even when high concentrations were used. Other ergot alkaloids and gramine gave similar though less striking results. These drugs were more effective on the rat's uterus and the rabbit's ear than on the guinea-pig's ileum, but the reverse is true of atropine, cocaine, or excess of HT itself.

Other workers (Robertson, 1953 ; Rocha e Silva *et al.*, 1953) have obtained similar results with the last three drugs on guinea-pig's ileum, and have suggested a theory to account for them. The effect of HT on this tissue resembles that of nicotine in that both effects are blocked by similar concentrations of atropine and cocaine. It is therefore suggested that HT acts, like nicotine, at some point in the nervous tissues in the intestine. Hexamethonium, or sufficient excess of nicotine, blocks the response to small doses of nicotine without blocking the response to HT. These facts are explained on the theory that HT acts on the postganglionic nerve fibres whereas nicotine acts on the nerve cells.

This theory does not provide a satisfactory explanation of the observation of Rocha e Silva *et al.* (1953), that when the guinea-pig's ileum is desensitized to HT by excess of HT itself, it still gives a normal response to nicotine. If the site of action of HT is peripheral to that of nicotine and is paralysed, it is surprising that the response to nicotine is normal. Nicotine and HT appear to behave similarly to one another but independently ; if the bath contains excess of either of these drugs the muscle gives no response to that drug, but a normal response to the other drug. There is nothing to suggest an anatomical difference between the sites of action of the two drugs. It is possible that the ganglion cells in the intestine contain two types of receptor, one of which is stimulated by ACh or nicotine and inhibited by excess of nicotine or hexamethonium, while the other type is stimulated by HT and inhibited by excess of HT. These cells would then be comparable with various plain muscle cells which are believed to have specific receptors for both histamine and ACh. It is also possible that there are two types of cell, one of which is stimulated by nicotine and the other by HT.

Whatever may be the explanation of the behaviour of the guinea-pig's ileum, it is clear that the other two tissues behave differently. The results can be explained on the theory that there are two types of tryptamine receptor:

(*a*) Receptors in the plain muscle of the rat's uterus and rabbit's ear which are easily paralysed by LSD but not so easily paralysed by excess of HT.

(*b*) Receptors in the ganglia of the intestine which are easily paralysed by excess of HT but not easily paralysed by LSD.

If this theory is correct, the relation between LSD and HT is similar to the relation between ACh and atropine. In both cases the receptors in smooth muscle are more easily inhibited by the antagonist, and the receptors in the nervous tissues are more easily desensitized by excess of the active drug.

Summary

1. The effects of 5-hydroxytryptamine (HT) and various possible antagonists were tested on rat's uterus, rabbit's perfused ear, and guinea-pig's ileum.

2. With suitable concentrations of mepyramine, piperoxane, and atropine it is possible to inhibit the effects of histamine, adrenaline, and acetylcholine without altering the effects of HT. This supports the view that HT acts on specific receptors, which have been called tryptamine receptors.

3. The effects of various HT antagonists can be explained on the theory that there are two types of tryptamine receptor. One type is present in the smooth muscle of the uterus and ear and is specifically inhibited by low concentrations of lysergic acid diethylamide (LSD). The second type is present in the nervous tissues in the ileum and is not inhibited by LSD.

4. The effect of HT on the ileum is inhibited by atropine or cocaine in the same way that the effect of nicotine is inhibited. The known facts can be explained on the theory that the ganglia in the guinea-pig's intestine contain two types of receptor, one of which is stimulated by nicotine and the other by HT.

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