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A PHARMACOLOGICAL STUDY ON THE EFFECT OF 5-HYDROXYTRYPTAMINE AND ITS ANTAGONISTS ON THE BRONCHIAL MUSCULATURE

BY

B. K. BHATTACHARYA

(Arch. int. Pharmacodyn.)

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FROM THE DEPARTMENT OF PHARMACOLOGY, UNIVERSITY OF GHENT, (BELGIUM)
DIRECTOR : PROF. DR C. HEYMANS

A PHARMACOLOGICAL STUDY ON THE EFFECT OF 5-HYDROXYTRYPTAMINE AND ITS ANTAGONISTS ON THE BRONCHIAL MUSCULATURU (1)

BY

B. K. BHATTACHARYA

(Received for publication 26-5-1955*)*.

Although much work has been done with the antagonists of 5HT (5-hydroxytryptamine) using isolated tissues and intact animals, little is known on the effect of 5HT and its antagonists on bronchial musculature (ERSPAMER, 10, 11; GADDUM and HAMEED, 15; GADDUM et al. 16). An intravenous injection of 5HT in the cat produces moderate bronchoconstrictor action (REID and RAND, 30, 31; COMROE et al, 4). Guinea-pigs exposed to 1 % aerosol of 5HT develop severe dyspnoea followed by convulsions (HERXHEIMER, 19, 20). Using this technic, HERXHEIMER has studied several antagonists which include atropine, dihydroergotamine and lysergic acid diethylamide. Using isolated tracheal chains of guinea-pig and cat, quantitative assay of the antagonists of 5HT has been attempted by several workers (FREYBURGER et al, 14; SINHA and WEST, 32). Since this method excludes bronchial musculature, it can not be taken into consideration. Using the technic of isolated guinea-pig lung perfusion (BHATTACHARYA and DELAUNOIS, 1) it has become possible to record the changes of bronchial ways and to study the effects of various drugs in small concentration on the bronchial musculature. This paper reports the action of 5HT and its antagonists on the bronchial musculature as studied in isolated guinea-pig lung.

(1) Aided by a grant from the " Centre National d'Anesthésiologie ".

Methods

The preparation for the perfusion of isolated guinea-pig lung is the same as that described by Bhattacharya and Delaunois (1). An interval of about 10 minutes is generally allowed before any injection is given. The injections are made into the rubber tubing and the volume is restricted to within 0.25 cc. Since the drug solution takes about 2 minutes to traverse the distance from the site of injection, the action of the drug will be noticeable after this period. Our routine procedure consists in injecting the spasmogenic dose of 5HT and the antagonist after it when there is complete bronchospasm or acute bronchospasm reducing the bronchial recordings by 75 %. Whenever a lung is not sensitive to the usual dose of 5HT or it takes unusually long time to produce the desired bronchospasm, the preparation is rejected. The average time taken to produce acute bronchospasm is within 5 minutes. In a number of experiments the procedure has been reversed and the antagonist is injected 2 minutes before 5HT. In case where a drug has a delayed action, the interval is extended depending on the individual drug. Though this procedure is the method of choice in antagonistic study of 5HT using various preparations like rat uterus, guinea-pig ileum and rabbit ear, we prefered to induce bronchospasm by 5HT and then observe the bronchodilator effect of the antagonist. This, we feel, is more rational in approach for the lung preparation. We have limited our observation to one drug for one lung at a time, thereby eliminating the problem of drug fixation and its effect on subsequent drug administration.

The drugs used are 5-hydroxytryptamine (Serotonin creatinine sulfate, Abbott), lysergic acid diethylamide (LSD, Sandoz), dihydroergotamine methane sulfonate and ergotamine tartrate (Sandoz), dibenamine (N,N-dibenzyl-β-chlorethylamine hydrochloride), Phenergan (promethazine) and Neoantergan (mepyramine), L-epinephrine bitartrate and L-arterenol bitartrate (Winthrop-Stearns), Isopropylarterenol (isoprenaline, Richter), Regitine (phentolamine, Ciba) and atropine sulphate. All doses of substances injected refer to their salts.

Results

5-Hydroxytryptamine (5HT) produces bronchospasm depending on the intensity of drug action. In doses of less than 5γ, 5HT is found

to be not active. With 10 γ and above, it produces definite broncho-constriction allowing the bronchi to relax slowly. For our experiments we have used a dose of 25 γ which invariably produces complete or acute bronchospasm with at least 80 % decrease in the amplitude of lung contractions (FIG. 1). Thereafter the bronchi generally do not

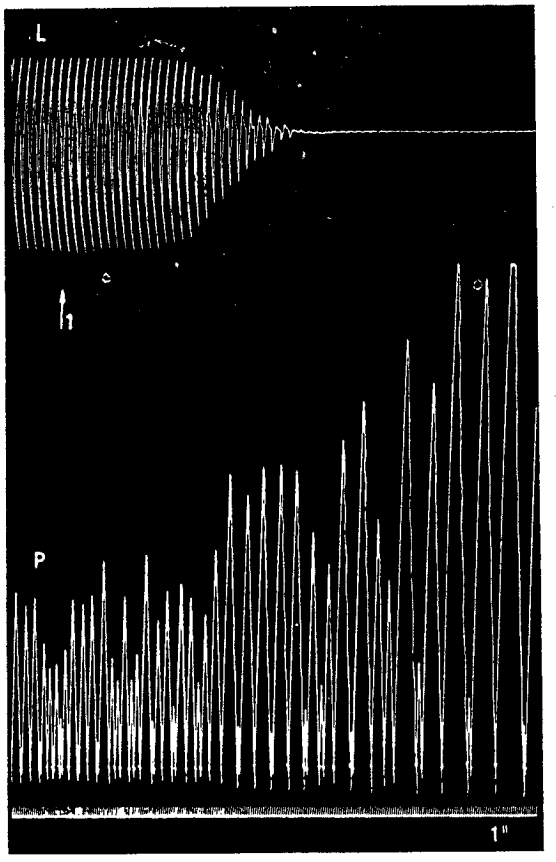

FIG. 1

At ↑ 1, 5HT, 25 γ injected.
The perfusion flow was not increased.
The natural vasoconstrictor effect of 5HT is shown.

L : Bronchial calibre changes
P : Perfusion

relax at all or relax partially after one hour. This has been conclusively demonstrated in several control studies after a single injection of 5HT. There is definite slowing of the flow of perfusion fluid during acute

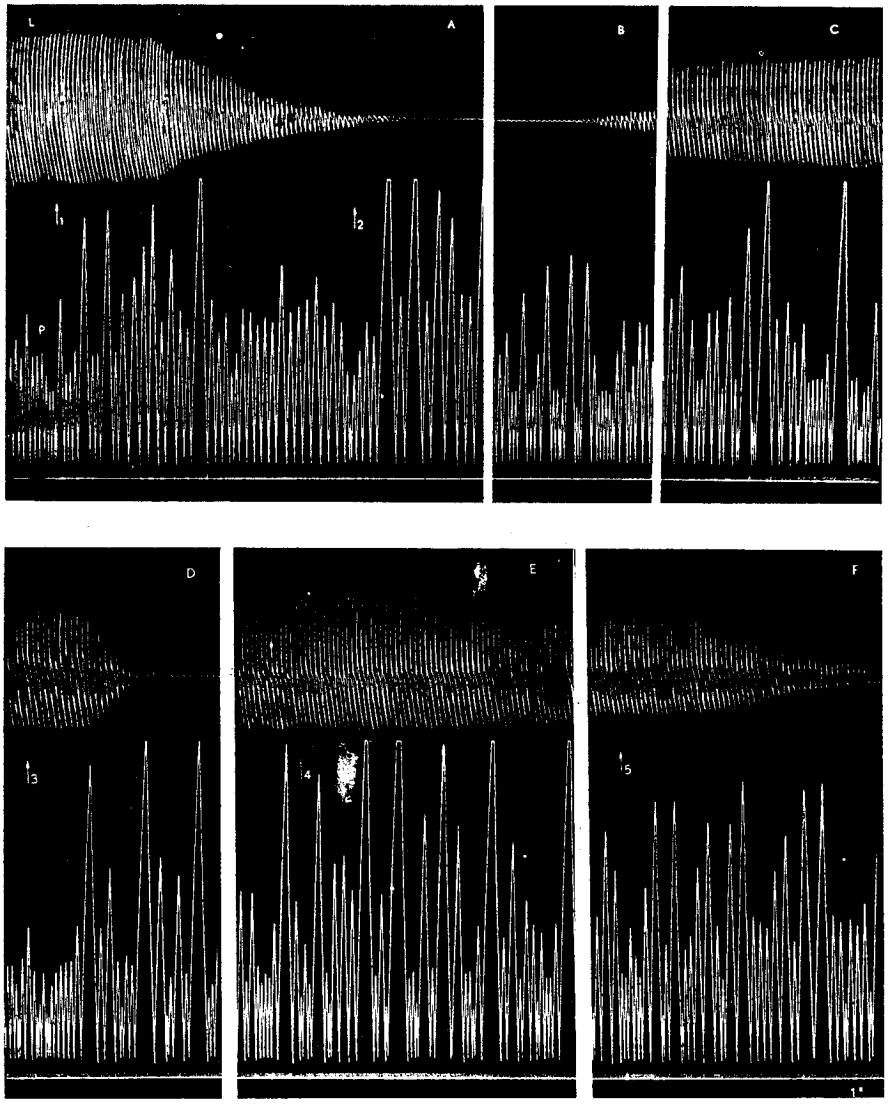

FIG. 2

At ↑ 1, 5HT, 25 γ		4.09 P.m
At ↑ 2, LSD, 2.5 γ		4.14
At ↑ 3, 5HT, 50 γ		4.45
At ↑ 4, 5HT, 25 γ		5.15
At ↑ 5, histamine 5 γ		5.45

Between A and B, 8 minutes.
Between B and C, 5 minutes.
Between C and D, 12 minutes.
Between D and E, 20 minutes.
Between E and F, 24 minutes.

bronchospasm. GINZEL and KOTTEGODA, (17) have also demonstrated vasoconstrictor action of 5HT in perfused cat lung. The intense vasoconstrictor action of 5HT necessitates in increasing the rate of perfusion in many experiments before injecting the antagonist. Otherwise the drug will take a longer period to reach the lung and counteract the effect of 5HT.

Ergot alkaloids : Of the ergot preparations, we have tested lysergic acid diethylamide (LSD), dihydroergotamine and ergotamine. These three are active and they are thus placed in the descending order of potencies. The results confirm those obtained by other workers using different tissues (ERSPAMER, 7; GADDUM and HAMEED, 15). The most active and specific of these three is lysergic acid diethylamide (LSD). The margin between the effective and toxic dose is rather small. Below 0.1 γ it is not active. The range of activity is between 0.25 γ to 4 γ. The optimum dose is 2.5 γ. (FIG. 2). Over 5 γ it is toxic. LSD is very slow acting and takes about 10 minutes before any effect can be observed. Once the lung is completely relaxed with the optimum dose of 2.5 γ LSD, subsequent injections of 25 γ 5HT have no effect. There is no tachyphylaxis with 5HT, if the drug is injected at an interval of 30 minutes and interspersing 5HT with acetylcholine or histamine (our own observation and also SINHA and WEST, 32). In several experiments we injected 50 γ and 100 γ 5HT after total relaxation of bronchi by LSD from complete bronchospasm. LSD can block the single fold but not the double fold increase in the effective dose of 5HT. But the recovery period after the double-fold dose was remarkably small. Dihydroergotamine follows LSD in the same pattern but requires higher dose to be effective. A dose of 25 γ is found to be optimal. It also acts some what slowly. The effects are generally seen 6 to 7 minutes after the injection of the drug (FIG. 3). Like LSD, it blocks the effects of subsequent injections of 5HT. Compared to these two, ergotamine tartrate is feeble in its action as it requires at least 100 γ to relax the bronchi partially from complete bronchospasm.

Adrenaline : The studies on the antagonism of adrenaline has not so far been attempted. Adrenaline relaxes the smooth muscle of bronchi. In normal experimental animal, relaxation of the bronchi has less noticeable effect on respiratory activity. This has been demonstrated by BHATTACHARYA and DELAUNOIS, (1). It is only in the presence of bronchial constriction that relaxation by adrenaline produces an observable increase in the lengthening of tracings on the kymograph.

Since adrenaline is known to reverse or prevent the constriction produced by several agents (CAMERON and TAINTER, 2), we tried adrenaline in

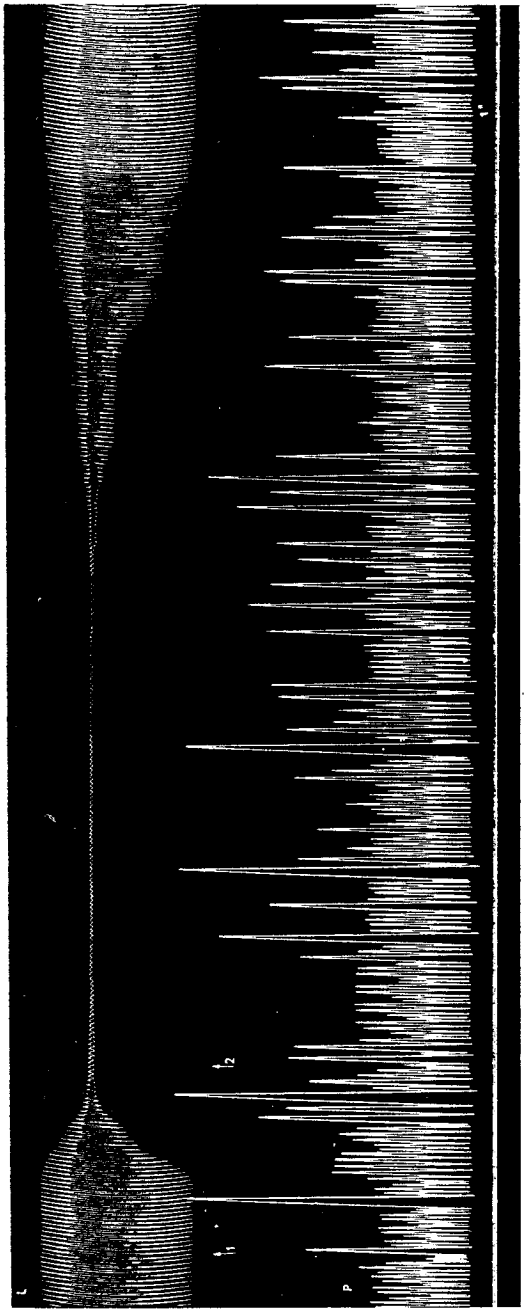

FIG. 3

At ↑ 1, 5HT, 25 γ
At ↑ 2 dihydroergotamine 25, γ.

L : Bronchial calibre changes.
P : Perfusion

5HT-induced bronchospasm. Adrenaline in a dose of 1 γ and 2 γ has practically no effect in relieving the bronchospasm, but a 5 γ dose will relieve the bronchospasm quickly and almost completely (FIG. 4). But the action of adrenaline is short-lived and after 10 minutes, the effect starts to wear off and it is necessary to inject the same dose at an interval of 15 minutes. With a bigger dose of 20 γ and above, adrenaline can antagonise the effect of 25 γ 5HT for the entire period of experimentation of 3 hours. Noradrenaline is known to be much weaker than adrenaline.

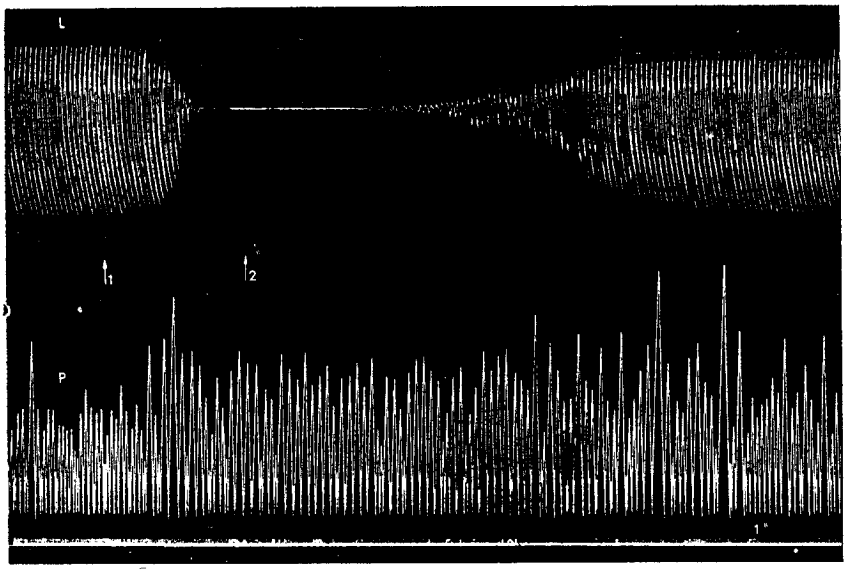

FIG. 4

At ↑ 1, 5HT, 25 γ.
At ↑ 2, Adrenaline 5, γ.

L : Bronchial calibre changes.
P : Perfusion.

The exact ratio of the relative activity of these two amines is different according to different authors. Using the isolated perfused lung of guinea-pig, CAMERON and TAINTER, (2) and LANDS et al, (21) found the ratio to be approximately 1 : 7, but LUDUENA et al, (24) differed from them and fixed the ratio to be 1 : 17. On the other hand MCDOUGAL and WEST, (25) suggested a ratio of 1 : 5, but they used the isolated tracheal chain of cat and guinea-pig. Using the lung perfusion technic of BHATTACHARYA and DELAUNOIS, (1), we find that a dose of 50 γ noradrenaline is required to relax the bronchi though not very effectively. With 100 γ, the relaxation of bronchi is complete, a feature produced by

a 10 γ adrenaline injection. From our observations, we can suggest a ratio of 1 : 10 between adrenaline and noradrenaline, but this is applicable only against 5HT-induced bronchospasm.

Isopropylarterenol (isoprenaline) is known to be the most potent beta adrenergic agent. It is more potent than adrenaline as a bronchodilator (HEBB and KONZETT, 18; LANDS et al, 22). The minimum effective dose of isopropylarterenol is 5 γ which is nearly the same as that of adrenaline (FIG. 5). The action is little bit prolonged over adrenaline

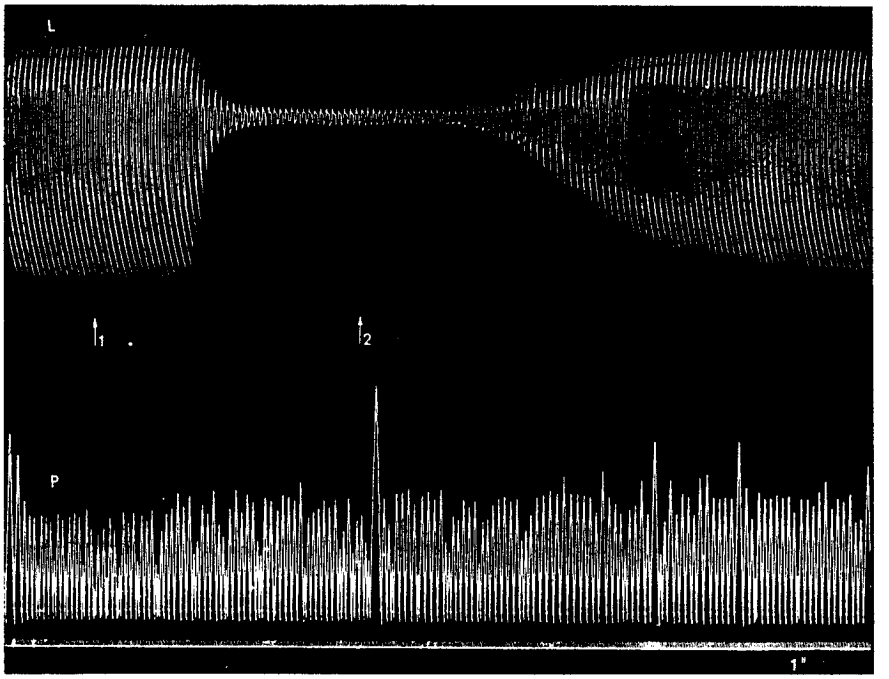

FIG. 5

At ↑ 1, 5HT, 25 γ.
At ↑ 2, Isopropylarterenol, 5 γ.

L : Bronchial calibre changes.
P : Perfusion.

which may account for its superiority. Isopropylarterenol like adrenaline in a high dose of 20 γ and above blocks the bronchospastic effects of a 25 γ injection of 5HT.

Atropine : The antagonistic effect of atropine to 5HT differs from tissue to tissue (GADDUM and HAMEED, 15). It is not a very effective antagonist against 5HT-induced bronchospasm. A dose of 0.5 mg.

and below has no effect at all. With 1 mg., the recovery is 50 %. But a protective dose of 1 mg. can block completely the effect of 25 γ 5HT. A protective dose of 0.5 mg. atropine has no effect. This apparent difference in dose schedule can be explained on the basis of great reduction of pulmonary flow after complete bronchospasm from 5HT. The drug takes a longer time to circulate through the pulmonary system.

Antihistaminics : Certain antihistaminics like mepyramine (Neoantergan) and diphenylhydramine (Benadryl) are found to be antagonist to 5HT, (ERSPAMER, 8; GADDUM and HAMEED, 15; RAPPORT and KOELLE, 28; REID and RAND, 30, 31). But the tests were carried out with isolated rat uterus and guinea-pig ileum. In intact cat, PAGE and McCUBIN, (27) observed moderate antagonistic effect of diphenylhydramine (Benadryl), Phenergan (promethazine) and thenyldiamine (thenfadil). In isolated lung perfusion, we tested Neoantergan (mepyramine) and Phenergan (promethazine) with a dose ranging from 50 γ to 2 mg. but failed to observe any antagonistic effect.

Dibenamine : Like antihistaminics, the antagonistic effect of dibenamine (N,N-dibenzyl-β-chlorethylamine hydrochloride) to 5HT varies from tissue to tissue (ERSPAMER, 7, 8; FINGL and GADDUM, 13). Dibenamine was found to be powerful antagonist to 5HT on rat uterus, while it is less sensitive on guinea-pig ileum and rabbit ear. Since dibenamine is not soluble in water, control experiments are necessary to observe the effect of the solvent on the lung. A 2 to 10 % stock solution is prepared in 95 % ethanol made slightly acid with concentrated H_2SO_4 (NICKERSON and GOODMAN, 26). Immediately prior to administration, the stock solution is diluted 1 : 10 with the perfusion fluid and the volume of the solution to be injected should not exceed 0.05 cc. Further dilution will lead to precipitation of the drug in the perfusion cannula and a large volume will have a deleterious effect on the normal lung. This is a great hindrance in the use of dibenamine in isolated lung preparation. Dibenamine is a feeble antagonist against 5HT and a dose of 125 γ seems to be the optimal dose. In higher doses it depresses the lung.

Regitine (phentolamine) : This adrenolytic compound has not been tested previously in antagonism studies of 5HT. Like dibenamine it is also a weak antagonist. Lower than 0.2 mg. it has no action either as a protective or spasmolytic compound. The optimal dose is 0.5 mg The drug acts quickly and the activity even with 0.5 mg. dose not last for more than 30 minutes. Another injection of 25 γ 5HT at this stage

will produce bronchospasm. Over 1 mg. the drug is harmful to the lung tissue.

Unspecified group : A few compounds of substituted phenyl propylamine group have also been tested. One of the series 2,2-diphenyl-4-diisopropylamino-butyramide methyliodide (R79) is a highly active parasympathicolytic agent (DE JONGH et al., 5). In isolated lung perfusion this compound is also very effective in preventing acetylcholine-induced bronchospasm (our own observation). But against 5HT induced bronchospasm this compound is a feeble antagonist with a dose of 1 mg. There is no antagonistic effect in the range of 50 γ to 0.5 mg. The other compounds of the group are ineffective.

DISCUSSION

The results of these experiments clearly show that no definite conclusion can be drawn as to the exact mechanism of action of 5HT. Most of its known actions involve direct stimulation of plain muscle, although one of its physiological function may be concerned with secretory activity (FELDBERG and TOH, 12). The various drugs which antagonise 5HT have given different results when tested on different tissues. This has led to much speculation which includes the consideration of two sites of action, histaminic sites and cholinergic sites (RAPPORT and KOELLE, 28). This theory is untenable due to the inactivity of antihistaminic compounds and to the feeble action of atropine in antagonising the effect of 5HT in isolated lung of guinea-pig. Complications have also arisen from the effectiveness of adrenaline and adrenolytic compounds like dihydroergotamine, dibenamine and Regitine. Both adrenaline and isopropylarterenol have proved to be the most effective in relieving the acute bronchospasm produced by 5HT. Adrenaline has long been accepted as a potent bronchodilator (WARNANT, 29, SWANSON and WEBSTER, 27). It not only antagonises the constriction produced but dilates the bronchi beyond their initial state. It dilates equally well the constriction produced by histamine, barium and pilocarpine (TAINTER, PEDDER and JAMES, 34). What is said of adrenaline by TAINTER in 1934 still holds good against 5HT-induced bronchospasm. Adrenaline can justly be taken as a standard for comparison. But the effect of adrenaline does not last long unless given in a large dose. It differs from lysergic acid diethylamide (LSD) in this way that the effect of LSD is practically irreversible. This is also true to

a great extent for dihydroergotamine. Yet a high dose of 5HT can produce a definite reaction in LSD or dihydroergotamine treated lung. This leads us to speculate on antagonism due to competitive basis.

Summary

Antagonistic studies against 5-hydroxytryptamine have been conducted using isolated guinea-pig lung. The following is the summary of the findings.

1. 5-Hydroxytryptamine (5HT) is a potent bronchoconstrictor. It reduces the flow of perfusion fluid due to constriction of pulmonary vessels.

2. Adrenaline and isoprolylarterenol are the two most active bronchodilators. Unless given in a large dose, the effect is short-acting. Noradrenaline is much weaker than adrenaline and isopropylarterenol as bronchodilator and antagonist to 5HT.

3. Lysergic acid diethylamide (LSD) is an effective antagonist to 5HT, but the margin between curative and toxic dose is narrow. The antagonism is practically irreversible.

4. Dihydroergotamine requires a larger dose than LSD to be effective as an antagonist to 5HT. It has also a prolonged action. Ergotamine is much weaker than dihydroergotamine as an antagonist to 5HT.

5. Dibenamine and Regitine (phentolamine) are antagonist to 5HT in high concentrations. The effects are temporary and in half hour the response to 5HT reappears.

6. Atropine even in high concentration is a feeble antagonist to 5HT.

7. Antihistamines like Phenergan (promethazine) and Neoantergan (mepyramine) are not active.

8. An anti-cholinergic compound 2,2-diphenyl-4-diisopropylaminobutyramide methyliodide (R79) is a feeble antagonist against 5HT induced bronchospasm.

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