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THE NATURE OF THE PULMONARY RECEPTORS EXCITED BY ANTIHISTAMINES

BY

J. V. JONES

From the Nuffield Institute for Medical Research, University of Oxford

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In 1950 Aviado, Pontius, and Li showed that a number of antihistamine compounds, injected intravenously into dogs, caused a transient inhibition of respiratory movements, followed by a longer period of rapid shallow breathing. This response was abolished by cutting or cooling the vagi; it was attributed to an action on receptors in the lungs, since injection into the cavity of the left ventricle was ineffective. In 1951 Dawes, Mott, and Widdicombe showed that there are at least two types of pulmonary receptors in the cat which may be stimulated by the injection of drugs, and which alter breathing. Veratridine stimulates the pulmonary stretch endings (whose afferent nerves are blocked by cooling the vagi to 10° C.) and causes an arrest of breathing in the expiratory position. Phenyldiguanide and 2-α-naphthylethyl*iso*thiourea cause a similar response, followed by a period of rapid shallow breathing. These effects are not abolished until the vagi are cooled below 3° C.

In the experiments described in this paper the methods employed by Dawes, Mott, and Widdicombe (1951) have been used to analyse further the mode of action of the antihistamines diphenhydramine hydrochloride (Benadryl) and mepyramine maleate (Anthisan). It has been found that they do not stimulate the pulmonary stretch endings, but act on some other receptors in the lungs.

METHODS

Cats, dogs, and rabbits were used in these experiments. The cats were anaesthetized with chloralose (60 mg./kg.), and the dogs and rabbits with pentobarbital (32 mg./kg.). The animals were tracheotomized, and enclosed from the neck downwards in an air-tight box, whose volume was recorded on a kymograph. The blood pressure was recorded from the carotid artery with a mercury manometer, and injections were made through a cannula in the external jugular vein. The left auricle was cannulated in five cats, through an incision between the third and fourth, or fourth and fifth ribs. These animals breathed spontaneously after the chest had been closed and air had been removed from the intrapleural space. Action potentials were recorded from slips dissected from the phrenic and vagus nerves by means of a conventional resistance-capacity differential amplifier. In some experiments the electrocardiogram and respiratory movements were photographed simultaneously. The vagi were cooled on silver thermodes 1–2 cm. long through which alcohol from a freezing reservoir was circulated. The temperature was recorded by thermocouples incorporated in each thermode and connected to mirror galvanometers.

RESULTS

In cats, rabbits, and dogs, mepyramine and diphenhydramine produced a sharp fall of blood pressure lasting about a minute, and often followed by a slight rise; and an inhibition of breathing in the expiratory position, which may last 20–30 seconds (Fig. 1). This is usually followed by rapid shallow breathing with an increased expiratory volume (see Dawes, Mott, and Widdicombe, 1951). In all animals the respiratory effects were abolished either by cooling or cutting the vagi. The fall in blood pressure was not abolished by cutting the vagi. The doses required for a reproducible respiratory effect were 0.5–3.0 mg./kg. of diphenhydramine, and 5–10 mg./kg. of mepyramine. In a few experiments in which the respiratory responses were compared with those produced by phenyldiguanide, there was a close resemblance.

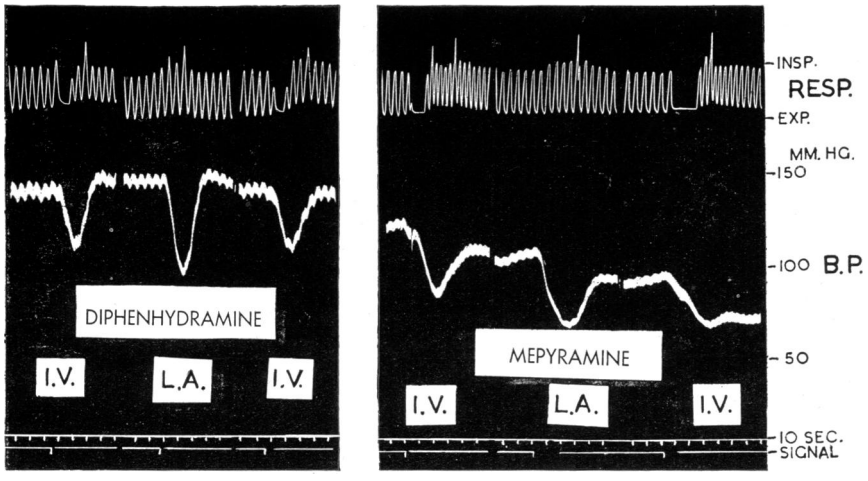

FIG. 1.—Cat, 3.0 kg.; chloralose. Records of respiratory movements (above), and blood pressure (below). Injections of 10 mg. diphenhydramine and mepyramine were made intravenously (I.V.) and into left auricle (L.A.). The intra-auricular injections cause no inhibition of breathing, which must therefore be due to an action of the higher concentration within the lungs.

In five cats the left auricle was cannulated, and natural breathing was re-established after the chest had been closed. It was found that a dose of mepyramine or diphenhydramine which effectively inhibited respiration on intravenous injection, produced little or no respiratory effect when injected into the cavity of the left auricle (Fig. 1). This was also true of phenyldiguanide in the three animals in which this substance was used. The left auricular injections in most experiments produced a greater fall in blood pressure. While, therefore, it would appear that the respiratory action of these drugs in cats is due to an effect on pulmonary receptors, the cardiovascular action must be attributed to other causes.

In order to obtain additional evidence of the action of these two antihistamines on pulmonary receptors, the latency between injection and response was measured. Action potentials were recorded from the phrenic nerve in three cats, while injections were made into the right auricle through a catheter passed down the jugular vein. The average latency between injection and the inhibition of phrenic motoneurones

was from 2 to 2.2 seconds for mepyramine, and from 1.3 to 2.5 seconds for diphenhydramine. The latency for veratridine was always longer, and varied from 3.6 to 5.9 seconds.

In sixteen cats, eleven rabbits, and seven dogs the effect on the respiratory reflex of cooling the vagi to various temperatures was investigated. In all animals, a control response with the vagi uncooled was first established. With the vagi cooled to temperatures between 5 and 10° C. a positive response to diphenhydramine was obtained in each of five cats. Even at 2° C. or below, three of four cats still showed a clear reflex effect. The response to mepyramine was present in five of seven cats at vagal temperatures between 5 and 10° C. In four of five it was absent at 2.5 or 2° C. (Fig. 2). The results with rabbits were less clear, but in two experiments

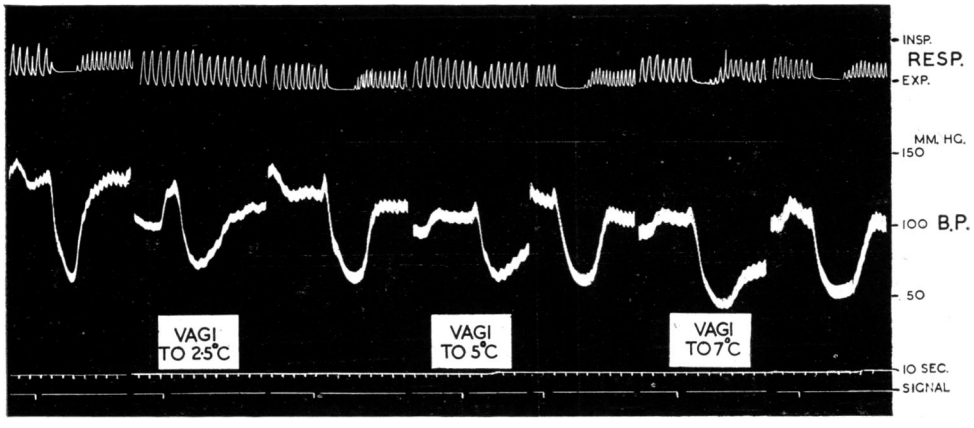

FIG. 2.—Cat, 3.1 kg.; chloralose. Records of respiratory movements (above), and blood pressure (below). Intravenous injections of 10 mg. mepyramine. With both vagi cooled to 2.5° C., the respiratory inhibition is completely blocked. There is a slight effect at 5° C., and a clear inhibition at 7° C. The vagi were cooled for 2 min., and injections were made at intervals of 5 min.

a reflex response to mepyramine and diphenhydramine was observed at vagal temperatures below 5° C. In dogs, diphenhydramine only was used, and it was found that the respiratory reflex persisted at temperatures as low as 2° C., while the reflex effects of veratridine were abolished between 12 and 14° C.

These observations show that in all three species the respiratory reflex which mepyramine and diphenhydramine cause by acting on receptors in the lungs differs from that caused by veratridine, and cannot be explained by an action on pulmonary stretch endings. In addition, the action of massive dose of diphenhydramine on the pulmonary stretch endings has been investigated directly by recording action potentials from the vagus in cats and dogs. The animals were maintained on artificial respiration, the right vagus was cut, and records were made from the left vagus. The sensitization of pulmonary stretch fibres which is typical of veratridine was never observed, and in seven of fourteen fibres in cats, and thirty-three of sixty-four in dogs, diphenhydramine either reduced the frequency of discharge or abolished it altogether (Fig. 3). The fact that diphenhydramine is a local anaesthetic (Dutta, 1949) may explain the disappearance of the discharge.

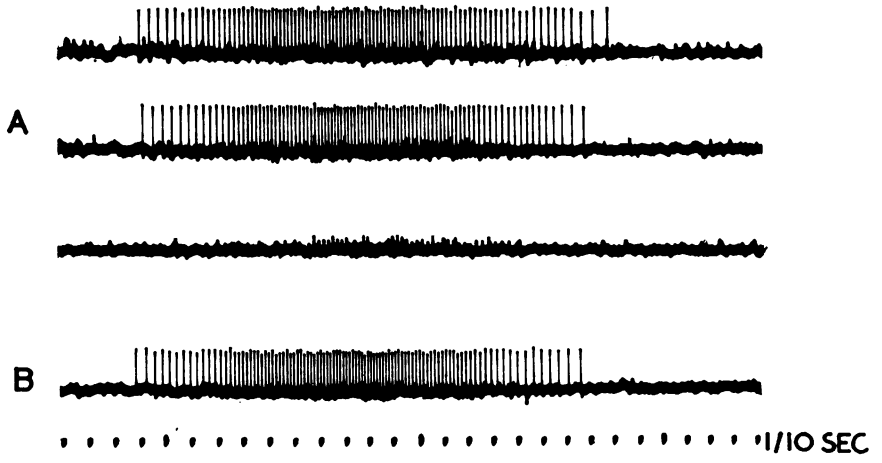

FIG. 3.—Cat, 3.4 kg.; chloralose. Action potentials recorded from left vagus (artificial respiration). A, tracings continuous, injection of 20 mg. mepyramine during second breath. The fibre discharge is abolished. B, record made 2 min. later, when discharge has returned.

DISCUSSION

The results show that the reflex apnoea and subsequent rapid shallow breathing caused by mepyramine and diphenhydramine is different from that caused by veratridine. The antihistamines do not sensitize the pulmonary stretch endings, and the respiratory reflex survives at vagal temperatures below 5° C., whereas the stretch fibres are blocked and the veratridine reflex abolished at temperatures of 10 to 12° C. The latency of the reflex is also considerably shorter than that of veratridine. These conclusions are in agreement with those reached by Aviado, Pontius, and Li (1950), who showed that, in dogs, antihistamines caused a respiratory reflex after tachyphylaxis to veratridine had developed, and that veratridine could cause respiratory inhibition on inhalation, whereas the antihistamines would not. These observations, in conjunction with those recorded in this paper, suggest that the receptors for diphenhydramine and mepyramine are considerably nearer the pulmonary valves than those for veratridine; they may even be on the arterial side of the pulmonary vascular bed.

In all these respects, the antihistamines closely resemble the amidines, and it seems likely that the reflexes involved in cats and rabbits are the same. If this is so, the results in dogs are of particular interest. Dawes, Mott, and Widdicombe (1952) find that in this species certain amidines excite the chemoreceptors of the carotid and aortic bodies, and cause no respiratory reflex from pulmonary receptors.

Here, then, is further evidence for the existence of a second set of reflex afferent endings in the lungs, which are sensitive to the action of certain drugs, and which are capable of producing an inhibition of respiration. Their physiological function still remains an open question.

SUMMARY

1. The action of the antihistamine compounds mepyramine and diphenhydramine on respiratory reflexes has been investigated in cats, rabbits, and dogs. The transient

apnoea and subsequent rapid shallow breathing which they cause are due to an action on receptors in the lung.

2. Mepyramine and diphenhydramine decrease the discharge frequency or abolish the activity of the pulmonary stretch endings. But since their reflex action on breathing persists when the vagi are cooled to a temperature at which the pulmonary stretch fibres are blocked, this action must be due to an effect on other receptors in the lung not yet identified.

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References

Aviado, D. M., Pontius, R. G., and Li, T. H. (1950). *J. Pharmacol.*, **99**, 425.
Dawes, G. S., Mott, J. C., and Widdicombe, J. G. (1951). *J. Physiol.*, **115**, 258.
Dawes, G. S., Mott, J. C., and Widdicombe, J. G. (1952). *Arch. int. Pharmacodyn.* (in press).
Dutta, N. K. (1949). *Brit. J. Pharmacol.*, **4**, 281.