BRONCHOCONSTRICCTOR EFFECT OF HISTAMINE IN CATS

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It has been reported that bronchoconstrictor effect of a certain spasmogen is modified by release of catecholamines. According to McCulloch et al. (1), these catecholamines are released in guinea pigs by histamine as a result of a sympathetic bronchodilator reflex. Collier et al. (2) assumed that bradykinin or angiotensin directly liberates catecholamines from the adrenal glands of guinea pigs. In cats, Colebatch (3) proposed similar mechanism to that of Collier et al. (2) on the constriction of alveolar ducts produced by histamine. Thus it seems that the source of catecholamines, which affect the bronchoconstriction, varies with sort of spasmogens or with species of animals.

The present experiments were undertaken to examine the role of autonomic nervous system or humoral regulation involved in the bronchoconstriction induced in cats by histamine, which was administered intravenously (4, 5). Besides histamine, acetylcholine and serotonin were also used as bronchoconstrictor agents. In addition, bronchoconstriction induced in guinea pigs by histamine was studied and the results were compared with that of cats.

MATERIALS AND METHODS

1. Bronchoconstrictions in cats

Adults cats of either sex, weighing 1.8 to 4 kg, were anesthetized with sodium pentobarbital (35 mg/kg, i.p.). Artificial ventilation was carried out with a constant volume respiratory pump through a tracheal cannula. The ventilation rate was 26 strokes/min and the stroke volume was about 15 ml/kg. Animals were then immobilized with intravenous injection of gallamine triethiodide (5 mg/kg). Intratracheal pressure, the increase of which denotes the bronchoconstriction, was measured by means of a pressure transducer connected to the side arm of tracheal cannula. The bronchoconstriction was induced by intravenous injection of histamine, acetylcholine or serotonin.

Blood pressure was recorded from the femoral artery by means of a pressure transducer. Heart rate was measured by cardiotachography, triggered by the arterial pulse.

All responses were recorded simultaneously on the ink-writing oscillograph.

2. Pithed and adrenalectomized cats

Pithed cats were prepared according to the method of Pulchino and Trenderenberg (6).

Either in normal or in pithed cat, bilateral adrenalectomy was performed during the...
experiments under artificial respiration.

3. Contraction of nictitating membrane

The contraction of nictitating membrane in pithed cats was measured by means of a strain gauge transducer. The unilateral common carotid artery supplying the nictitating membrane was left intact. The initial tension of 2 g was applied to the membrane. Blood pressure, heart rate and intratracheal pressure were recorded simultaneously.

4. Bronchoconstrictions in guinea pigs

Guinea pigs (about 300 g), anesthetized with intraperitoneal injection of urethane 1.25 g/kg, were artificially ventilated with a respiratory pump delivering 72 strokes/min at a constant stroke volume of 2-4 ml and then immobilized with gallamine triethiodide (2 mg/kg, i.v.).

Intratracheal pressure was measured with a pressure transducer by the same procedure mentioned above. Bilateral adrenalectomy was carried out during the experiments. In some cases, guinea pigs were pithed with a wire, passed through the orbital fossa.

In each experiment, at least five animals were used.

RESULTS

1. Histamine-induced bronchoconstriction in cats

Under the present experimental conditions, the mean basal value of intratracheal pressure was 7.56 ± 0.23 cm H₂O. After intravenous administration of histamine (5 μg/
kg), the intratracheal pressure increased by 1.22 ± 0.12 cm H₂O and the half-duration time of bronchoconstriction was 36 ± 2.84 seconds.

1) Effect of atropine

Intravenous injection of 0.1 mg/kg of atropine, a dose which completely inhibited the bronchoconstriction induced by vagal stimulation, had no influence on the histamine-induced bronchoconstriction.

2) Effect of propranolol

As shown in Fig. 1, the histamine-induced bronchoconstriction was potentiated by pretreatment with propranolol. The potentiation was more pronounced in the duration than in the maximum response to histamine. It was also ob-

![Graph](image-url)

**Fig. 2.** Half-duration time of the histamine-induced bronchoconstriction of cat under the influence of propranolol. Histamine (5 μg/kg) was administered intravenously. The values are means ± standard error of six experiments. ■ = control, □ = after propranolol.

![Graph](image-url)

**Fig. 3.** Effect of histamine on the blood pressure (B.P.), heart rate (H.R.) and intratracheal pressure (I.T.P.) in a pithed cat. Propranolol (1 mg/kg) was administered intravenously after pithing.
served that propranolol had no influence on the basal intratracheal pressure without histamine.

Fig. 2 represents the effect of various doses of propranolol on the duration of bronchospasm induced by histamine. Even at a low dose of propranolol (10μg/kg, i.v.), strong prolongation effect was observed.

3) Bronchoconstrictions in pithed cats

To investigate whether the neurogenic catecholamines are involved or not in the bronchospasm produced by histamine, experiments were carried out with pithed cats. An example of the experiments is shown in Fig. 3. Table 1 summarizes results of five experiments. As shown in these results, the increases in intratracheal pressure and its duration

| Treatment                        | Intratracheal pressure | Intratracheal pressure |
|----------------------------------|------------------------|------------------------|
|                                  | Maximum response (cmH₂O) | Duration (sec)         |
| Control                          | 1.38±0.19              | 31.0±2.3               |
| Pithing                          | 1.24±0.31              | 25.0±3.9               |
| Propranolol after pithing        | 1.70±0.31              | 444.0±90**             |
| Control                          | 1.86±0.27              | 32.5±2.5               |
| Adrenalectomy                    | 2.01±0.32              | 264.2±48.5**           |
| Propranolol after adrenalectomy  | 2.15±0.29              | 288.7±45.3**           |

**P<0.01

![Table 1](image)

Fig. 4. Effect of adrenalectomy on the bronchoconstriction induced by various doses of histamine in a cat. Propranolol (1mg/kg) was administered intravenously after adrenalectomy. I.T.P. = intratracheal pressure.
caused by histamine were not affected by pithing the cat. As with the case of intact cats, propranolol (1 mg/kg, i.v.) considerably enhanced the duration of histamine-induced bronchoconstriction in pithed cats.

4) Effect of bilateral adrenalectomy

Fig. 4 shows the effect of acute bilateral adrenalectomy on the response to histamine. After adrenalectomy, the duration of histamine-induced bronchoconstriction was conspicuously prolonged, whereas the maximum response to histamine was little affected. Unlike in intact or pithed cat, propranolol did not potentiate the response to histamine in adrenalectomized cats (Table 1).

These results suggest that catecholamines, released by histamine from the adrenal medulla, counteract the bronchoconstriction induced by histamine. The possibility that histamine would liberate catecholamines from the adrenal medulla was also examined in the following experiments on heart rate, blood pressure and nictitating membrane.

2. Positive chronotropic action of histamine

The intravenous administration of histamine caused positive chronotropic effect in the anesthetized cat. As shown in Fig. 3 and Table 2, the increase in heart rate produced by histamine was not affected by pithing, whereas it was inhibited by bilateral adrenalectomy. Propranolol markedly depressed the positive chronotropic action of histamine in both pithed and adrenalectomized cats (Table 2). When bilateral adrenalectomy was carried out in pithed cats, the positive chronotropic action of histamine was completely inhibited (Fig. 6).

| Table 2. Changes in heart rate induced by histamine after pithing or adrenalectomy of cats. The heart rate was measured simultaneously with the change in intratracheal pressure in the same animal (Table 1). Histamine (5 μg/kg) or propranolol (1 mg/kg) was administered intravenously. The values are means ± standard error of five (pithing) and eight (adrenalectomy) experiments. |
|-------------------------------------------------|
| Treatment                                      | Heart rate |
|                                                | beats/min  |
| Control                                        | 41.0 ± 7.0 |
| Pithing                                        | 40.0 ± 8.5 |
| Propranolol after pithing                      | 3.0 ± 1.7* |
|                                                |
| Control                                        | 38.3 ± 5.2 |
| Adrenalectomy                                  | 19.9 ± 4.3** |
| Propranolol after adrenalectomy                | 5.4 ± 0.99** |

**P < 0.01

3. Secondary pressor effect of histamine

As shown in Fig. 3, the secondary pressor effect of histamine became distinct by pithing the cat. This pressor response was not antagonized by pretreatment with propranolol. On the other hand, phentolamine or adrenalectomy caused inhibition of the secondary pressor effect (Figs. 5, 6).
FIG. 5. Effect of histamine and adrenaline on the nictitating membrane (N.M.), blood pressure (B.P.) and heart rate (H.R.) before and after treatment with phentolamine in a pithed cat. Drugs were injected into the femoral vein.

FIG. 6. Effect of histamine and adrenaline on the nictitating membrane (N.M.), blood pressure (B.P.) and heart rate (H.R.) before and after adrenalectomy of a pithed cat. Drugs were injected into the femoral vein.

4. Contraction of nictitating membrane

The contraction of nictitating membrane produced by histamine or adrenaline was inhibited by pretreatment with phentolamine (Fig. 5). As shown in Fig. 5, phentolamine
did not influence the effects of histamine on the heart rate and intratracheal pressure.

Just as the case of pressor response or positive chronotropic effect, the contraction of nictitating membrane of pithed cat induced by histamine was markedly suppressed by adrenalectomy (Fig. 6).

5. Acetylcholine- and serotonin-induced bronchoconstrictions in cats

Fig. 7 shows the effect of adrenalectomy on the bronchoconstriction induced by acetylcholine and serotonin. Unlike histamine, the increase in intratracheal pressure caused by these spasmogens was not affected by adrenalectomy. Propranolol, administered after adrenalectomy, produced hardly any effect on the acetylcholine- and serotonin-induced bronchoconstrictions. In addition, it was shown in Fig. 7 that the bronchoconstrictor effect of serotonin was longer-lasting than that of histamine or acetylcholine.

![Fig. 7](image1)

**Fig. 7.** Effect of adrenalectomy and propranolol on the bronchoconstriction induced by acetylcholine (ACh) or serotonin (5-HT) in a cat. Propranolol (1 mg.kg) was administered intravenously after adrenalectomy. I.T.P. = intratracheal pressure.

![Fig. 8](image2)

**Fig. 8.** Effect of adrenalectomy and propranolol on the histamine-induced bronchoconstriction in a guinea pig. Propranolol (1 mg.kg) was administered intravenously after adrenalectomy. I.T.P. = intratracheal pressure.
6. Histamine-induced bronchoconstriction in guinea pigs

Fig. 8 shows an experimental result in guinea pig. The bronchoconstriction produced by histamine was little affected by bilateral adrenalectomy, whereas propranolol markedly potentiated the maximum response of histamine-induced constriction in adrenalectomized preparation. When propranolol was administered to the pithed guinea pig, no potentiation was observed (Fig. 9). In addition, it was found that the bronchoconstrictor effect of histamine was intensified by pithing.

![Fig. 9. Effect of propranolol on the histamine-induced bronchoconstriction in a pithed guinea pig. I.T.P.—intratracheal pressure: Hist.—histamine.](image)

**DISCUSSION**

Colebatch et al. (7) have reported that vagotomy of cats produced no appreciable effect on the decreases in lung compliance and in airway conductance caused by histamine. In the present experiment, it was demonstrated that the histamine-induced bronchoconstriction, which was measured as an increase in intratracheal pressure, and, which involves the reduction of lung compliance as well as the decrease in airway conductance, was not affected by pithing the cat or by intravenous administration of atropine. In addition, it was found that hexamethonium had no influence on the bronchoconstriction induced by histamine. According to Trendelenberg (8), the pressor response of cats to histamine was not abolished by hexamethonium. Staszewska-Barczak et al. (9) showed that hexamethonium did not inhibit the liberation of catecholamines by histamine from adrenal medulla of cats. From these facts, it may be concluded that the effect of vagus or sympathetic nerve was not involved in the bronchoconstrictor response to histamine in cats.

In cats, histamine-induced bronchoconstriction was potentiated by pretreatment with propranolol. This potentiation was more pronounced in the duration than in the maximum response to histamine. Like propranolol, bilateral adrenalectomy strongly prolonged
the duration of histamine-induced bronchoconstriction. When administered to adrenalectomized cats, propranolol could not potentiate the constriction produced by histamine. On the contrary, pithing the cat had no influence on the response to histamine, while propranolol considerably prolonged the duration of the constriction in pithed cats.

These results may indicate that histamine directly releases catecholamines from adrenal medulla and that these catecholamines tend to reduce the bronchoconstrictor action of histamine. The conclusion supports the view of Colebatch (3).

In this connection, it has been reported by Stazewska-Barczak et al. (9) and Trendelenberg (10) that histamine liberated adrenaline from adrenal medulla in cats. In the present study, it was found that the contraction of nictitating membrane and secondary pressor response induced by intravenous injection of histamine, at a dose which caused bronchoconstrictor effect, were inhibited or abolished by phentolamine or bilateral adrenalectomy in pithed cats. The increase in heart rate produced by histamine was also inhibited by adrenalectomy after pithing. These facts suggest that catecholamines released by histamine from adrenal medulla are involved in pharmacological effects.

Unlike the effect of histamine, acetylcholine- and serotonin-induced bronchoconstrictions in cats were not affected by adrenalectomy. Propranolol, administered after adrenalectomy, produced hardly any effect on these constrictions. Therefore, it seems likely that in cats humoral effect is not concerned in bronchospasm induced by acetylcholine or serotonin.

In guinea pigs, propranolol potentiated the histamine-induced bronchoconstriction especially in its maximum response. The potentiation of propranolol was still observed in adrenalectomized guinea pigs but not occurred in pithed preparations. It was further observed that adrenalectomy had little influence on the bronchoconstrictor response of histamine. In isolated tracheal preparation of guinea pigs, propranolol did not potentiate the histamine-induced constriction. These results are basically the same as that of McCulloch et al. (1) who concluded that propranolol antagonized bronchodilator effect of catecholamines which were released from sympathetic nerve endings by homeostatic reflex.

To summarize the data obtained so far, it can be said that histamine administered intravenously liberates catecholamines, which tend to reduce the bronchoconstrictor action of histamine. These catecholamines are released directly from adrenal medulla in cats, while they are liberated reflexly from sympathetic nerve ending in guinea pigs. On the other hand, bronchoconstriction induced by acetylcholine or serotonin seems not to be modified by endogenous catecholamines in cats.

**SUMMARY**

The bronchoconstrictor effect of histamine in cats was studied and compared with that in guinea pigs. The actions of acetylcholine and serotonin were also examined in cats.

1. The bronchoconstriction induced by histamine is modified and reduced by release
of catecholamines. In cats, these catecholamines are liberated by histamine directly from adrenal medulla. In guinea pigs, they are released reflexly from sympathetic nerve endings by histamine.

2. The bronchoconstriction induced by acetylcholine or serotonin in cats seems not to be modified by endogenous catecholamines.

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