**References**

Anton, A. H. (1960). *J. Pharmac. exp. Ther.*, **129**, 282–290.
Brodie, B. B. (1965). In *The Scientific Basis of Drug Therapy in Psychiatry*, Editors: Marks, J. & Pare, C. M. B., pp. 127–146, Oxford: Pergamon.
Hammer, W. M. & Brodie, B. B. (1967). *J. Pharmac. exp. Ther.*, **157**, 503–508.
Schanker, L. S. & Morrison, A. S. (1965). *Int. J. Neuropharm.*, **4**, 27–39.
Sturman, J. A. & Smith, M. J. H. (1967). *J. Pharm. Pharmac.*, **19**, 621–623.

## The dual mode of action of histamine in the cat isolated tracheal chain

SIR,—In the cat isolated tracheal chain, a fully relaxed preparation *in vitro* (Hawkins & Paton, 1944), histamine antagonizes non-specifically the contractions induced by acetylcholine (Akcasu, 1952) and potassium chloride (Akcasu, 1959). Since in the isolated heart histamine effects have been attributed to a direct interaction with mycocardial receptors (Mannaioni, 1960), or to an indirect action based on the release of catecholamines (Went, Szucs, & Feher, 1954), it is of value to establish the mechanism of histamine relaxation of cat tracheal chains.

Tracheal rings of cats, untreated or pretreated with reserpine (0·5 mg/kg, injected intraperitoneally 48 and 24 hr before the experiment), were prepared according to the modification by Akcasu (1959) of the method described by McDougal & West (1953), and studied in Tyrode solution aerated with oxygen 95% and carbon dioxide 5% at 37 ± 0·5°. A dose of carbamylcholine chloride (carbachol), chosen from dose-response curves to produce a 60 to 85% of maximum contraction in a 2-ring chain, was left in contact with the tissue for 6·5 min. Histamine dihydrochloride was added for the last 1·5 min of this time. When antagonists were used they were added with the carbachol. All doses are expressed as μg of salt per 30 ml of bath volume. Responses, magnified 16 times, were recorded on a smoked drum kymograph with an auxotonic pendulum lever (Paton, 1957). Statistical calculations were made according to Snedecor (1957).

Only 7 of the 19 preparations taken from untreated cats showed a relaxation to 50 μg of histamine while all relaxed to 100 μg (Table 1). The relaxation was dose-dependent and reached a maximum with 200 μg of histamine. The relaxing action of histamine was only partially prevented by mepyramine maleate (40 μg). Similarly pronethalol (40 μg), a dose which fully blocked the relaxing effect of 1-(−)-noradrenaline bitartrate (2·5 to 10 μg) was only partially effective against histamine. Neither inhibitor, in the concentrations stated, altered

TABLE 1. DEPRESSION IN MM BY HISTAMINE (H) OF CARBACHOL[1]-CONTRACTIONS[2] OF CAT TRACHEAL RINGS.

| H-Dose: μg/30 ml | 50 | 100 | 200 | 400 | 800 | 1600 | Slope ± s.e. |
|---|---|---|---|---|---|---|---|
| | | | Untreated | | | | |
| Mean ± s.e. (n) | −19·3 ± 4·16 (7) | −28·2 ± 4·97 (19) | −43·5 ± 6·48 (19) | −44·2 ± 6·79 (13) | | | 30·35 ±10·81 |
| | | | Reserpine-pretreated | | | | |
| Mean ± s.e. (n) | | | | −9·7 ± 2·06 (6) | −18·3 ± 2·97 (7) | −33·0 ± 5·24 (7) | 39·35 ± 8·96 |

(1) Mean dose: 1·41 ± 0·081 μg/30 ml (2) Mean contraction height: 92·7 ± 3·45 mm

contraction heights to carbachol, but higher concentrations of either inhibitor reduced them. When both inhibitors were added simultaneously (40 $\mu$g of each) histamine relaxations were fully counteracted, but carbachol contractions were partly suppressed.

Sensitivity to carbachol was unaffected in tracheal rings taken from reserpine-pretreated cats. Despite the catecholamine depletion, histamine relaxed these preparations, but the doses required were much higher (Table 1), the threshold dose of histamine being 400 $\mu$g while the response to 800 $\mu$g was about equivalent to that produced by 50 $\mu$g in tracheal rings from untreated cats. The addition of 3200 $\mu$g of histamine to two of the preparations increased the relaxations further, to $-53$ mm. The slopes of the dose-response curves to histamine in tracheal chains from untreated and reserpine-pretreated cats were parallel, but their x-intercepts were significantly different ($P < 0{\cdot}001$); the x-intercept for the untreated preparations was 10·49 $\mu$g, whereas it was 244·4 $\mu$g for the catecholamine-depleted tracheal rings. Exposure of the catecholamine-depleted tracheal chains to 10 $\mu$g of noradrenaline bitartrate for 10 min, followed by a 5-min washing period, approximately doubled the relaxing potency of histamine.

The observation that mepyramine and pronethalol partly counteracted relaxations to histamine in tracheal rings from untreated cats, together with the ability of histamine to relax catecholamine-depleted tracheae, permit the conclusion that histamine has a dual mode of action in this preparation: (1) it releases catecholamines which stimulate adrenergic $\beta$-receptors to induce relaxation and (2) it combines with its own specific receptors to induce relaxation.

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## References

Akcasu, A. (1952). *J. Pharm. Pharmac.*, **4**, 671.
Akcasu, A. (1959). *Archs int. pharmacodyn. Ther.*, **122**, 201–207.
Hawkins, D. F. & Paton, W. D. M. (1944). *J. Physiol., Lond.*, **144**, 193–219.
Mannaioni, P. F. (1960). *Br. J. Pharmac. Chemother.*, **15**, 500–505.
McDougal, M. D. & West, G. B. (1953). *Ibid.*, **8**, 26–29.
Paton, W. D. M. (1957). *J. Physiol., Lond.*, **137**, 35 P.
Snedecor, G. W. (1957). Statistical Methods, 5th edn, pp. 55–101 and 122–129. Ames, Iowa: The Iowa State College Press.
Went, S., Szucs, E. & Feher, O. (1954). *Acta physiol. hung.*, **5**, 121–130.