This work was carried out by the aid of grant B–1914 from the National Institute of Neurological Diseases and Blindness, U.S. Public Health Service.

T. R. Shanthaveerappa
Geoffrey H. Bourne

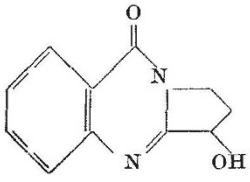
Department of Anatomy,
Emory University,
Atlanta 22, Georgia.

[1] Shanthaveerappa, T. R., thesis, Emory University (1962).
[2] Tewari, H. B., and Bourne, G. H., *Pathologie-Biologie*, **9**, 919 (1961).
[3] Peters, A., *J. Biophys. Biochem. Cytol.*, **9**, 733 (1961).
[4] Robertson, J. D., *Prog. Biophys.*, **10**, 343 (1960).

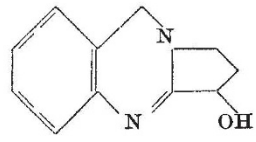
PHARMACOLOGY

Bronchodilating Action of Vasicinone and Related Compounds

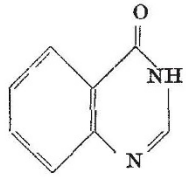
Amin and Mehta have claimed[1] that vasicinone (I), which they obtained by aerial oxidation in sunlight of crude extracts of *Adhatoda vasica* or of pure vasicine (II), the shrub's main alkaloid, has a bronchodilating action. They suggested that this property is attributable to the quinazol-4-one ring system for they found it to be common to the parent substance (III) and various simple derivatives[2]. Vasicine, on the other hand, proved to have a bronchoconstricting action, and the bronchodilator effects variously attributed[3] to preparations containing it they ascribed to contamination by small amounts of vasicinone.



I



II



III

To make some quantitative assessment of these claims we have examined quinazol-4-one (III), *l*-vasicine and *dl*-vasicinone. As we were unable to repeat the photochemical oxidation of vasicine mentioned by the Indian authors we prepared racemic vasicinone in moderate (30 per cent) but reproducible yield by acetylating *l*-vasicine with acetic anhydride, oxidizing the product with chromic oxide in acetic acid and finally removing the protecting acetyl group by alkaline hydrolysis.

In vitro tests on guinea pig tracheal rings showed that vasicinone and quinazol-4-one produced relaxation at 100 μg/ml., thus having about 1/2,000 the activity of adrenaline, whereas vasicine caused slight relaxation at 10 μg/ml. but contraction at higher concentrations.

Against histamine-induced contraction of the isolated tracheal chain vasicinone was about 1/5 as active as 4-quinazolone and about 1/3,800 as active as adrenaline.

In vivo studies on guinea pigs under urethane anæsthesia were made using the Konzett–Rössler[4] technique. Vasicine in doses above 400 μg/kg intravenous produced an increase in resistance of the lungs to inflation, taken as an indication of bronchoconstriction. No evidence of bronchodilation was seen even in the presence of atropine 1 mg/kg (cf. Chopra[3]). This is in agreement with the finding of Southwick and Cremer[5] in the dog and Amin and Mehta[1] in the guinea pig. This bronchoconstrictor action may be related to the reported acetylcholine potentiating properties of vasicine[6].

When given intravenously 4–6 min before the administration of bronchoconstrictor doses of histamine, the alkaloid showed no antagonistic action, but when given 30 sec before, the histamine antagonism was obtained with recovery of the histamine response within 5 min. From dose-response lines it was established that 38 μg of vasicine were required to reduce the response produced by 2 μg of histamine to that elicited originally by 1 μg of histamine. The dose required to produce a similar effect against 5-hydroxytryptamine was 160 μg and the response to acetylcholine could not be blocked with a dose below that which produced bronchoconstriction. The antihistamine effect, although specific, is very weak and of short duration.

With vasicinone and quinazol-4-one the same degree of inhibition of the histamine response could not be achieved as was possible with vasicine. Doses up to 100 μg produced some reduction in response to 2 μg of histamine, but on increasing the dose of either substance a decrease in antagonism was obtained. These doses were well below those required to produce bronchoconstriction.

In summary, therefore, we may say that on isolated tracheal muscle quinazol-4-one and vasicinone are about 1/2,000 as active as adrenaline in producing relaxation and 1/700 and 1/3,800 (respectively) as active against histamine-induced contraction. In the intact guinea pig the compounds showed no bronchodilator activity and were bronchoconstrictor at high doses. Vasicine was the most active compound against histamine-induced bronchospasm; it was fairly specific and had a very short duration of action. Vasicinone and quinazol-4-one showed only slight activity against histamine and antagonism decreased on increasing the dose.

The differences *in vivo* and *in vitro* suggest that we are measuring very different effects and the short duration of action *in vivo* indicates rapid removal or metabolism of these compounds. Their bronchodilator activity is in no way comparable with known bronchodilator drugs.

G. W. Cambridge
A. B. A. Jansen
D. A. Jarman

Research Laboratories,
John Wyeth and Brother, Ltd.,
New Lane,
Havant, Hants.

[1] Amin, A. H., and Mehta, D. R., *Nature*, **184**, 1317 (1959).
[2] Amin, A. H., Mehta, D. R., and Samarth, S. S., *Proc. First Intern. Pharmacol.*, 488 (1961).
[3] *Chopra's Indigenous Drugs of India*, second ed., revised by Chopra, R. N., Chopra, I. C., Hand, K. L., and Kapur, L. D., 265 (Calcutta, 1958).
[4] Holgate, J. A., and Warner, B. T., *Brit. J. Pharmacol.*, **15**, 561 (1960).
[5] Southwick, P. L., and Cremer, S. E., *J. Org. Chem.*, **24**, 753 (1959).
[6] Sharapov, I. M., *Farmakologiya i Toksikologiya*, **22/1**, 67 (1959).