

- FRANKLAND, B. T. B., HOLLENBERG, M. D., HOPE, D. B. & SCHACTER, B. A. (1966). Dissociation of oxytocin and vasopressin from their carrier protein by chromatography on Sephadex G-25. *Br. J. Pharmac. Chemother.*, **26**, 502-510.
- HAWKER, R. W., NORTH, W. G. & ZERNER, B. (1969). The pharmacology of a new oxytocic principle from ox hypothalamus. *Br. J. Pharmac.*, **35**, 175-186.
- HOLTON, P. (1948). A modification of the method of Dale and Laidlaw for standardization of posterior pituitary extract. *Br. J. Pharmac. Chemother.*, **3**, 328-334.

The involvement of histamine in malaria

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An increase in histamine concentration in the blood of *P. knowlesi*-infected rhesus monkeys (*Macaca mulatta*) is primarily concerned, among other vaso-active substances released during the advanced stages of the disease, in the inflammatory "stasis" that often occurs in local vessels. This inflammatory stasis is particularly evident in the brain vessels, and leads to overall disturbances of the blood circulation, which in turn lead to pathophysiological effects such as coma (Maegraith, 1966).

Histamine was extracted from blood of control (non-infected) and infected monkeys by a modification of the method of Barsoum & Gaddum (1935). It was assayed on the guinea-pig isolated ileum suspended in Tyrode solution using histamine acid phosphate (BDH) as a standard.

The histamine extracts were also injected intradermally into guinea-pigs and accumulation of circulating dye (pontamine sky blue, 6BX) at the site of injection was observed as an indication of changes in vascular permeability. The lesions produced by the histamine extracts from five infected monkeys were often more intense in colour than those produced by the same substance extracted from four control monkeys, which, as expected, elicited very weak reactions. The effectiveness of the histamine extracts from the malarial monkey in increasing vascular permeability and causing extensive damage to the endothelial vessel walls was almost completely abolished by pre-treatment of the animals with mepyramine maleate (20 mg/kg), promethazine hydrochloride (20 mg/kg) and diphenhydramine hydrochloride in the same dose.

Diapedesis of leucocytes was observed in 1-2 hr, and cell necrosis was demonstrated in the 24-28 hr old lesions, as evidenced by histological examinations of the skin sections previously fixed in Zenker's fluid.

Histamine has been shown to be one of the factors involved in the widespread breakdown of the blood-brain barrier, since intracranial injections into guinea-pigs (weight 140-200 g) caused exudation of high molecular weight substances such as albumin associated with fluid into the cerebrospinal fluid.

A mean concentration of histamine of 0.15 $\mu\text{g/ml}$. in the circulating blood was found in *P. knowlesi*-infected monkeys during the late stages of the disease, no histamine was detected in the blood of control monkeys. It is therefore concluded that histamine is one of a group of pharmacologically active inflammatory substances liberated into the circulation when the disease becomes relatively severe and produces a widespread disturbance of the blood-brain barrier. Increased net movement of heavy protein molecules such as albumin across the relevant membranes would suggest the occurrence of local "stasis" in the small vessels of the brain substance

during the acute stages of the infection, bringing about impedance of blood flow. Other actions of histamine are being further investigated.

REFERENCES

- BARSOUM, G. S. & GADDUM, J. H. (1935). The pharmacological estimation of adenosine and histamine in blood. *J. Physiol., Lond.*, **85**, 1-14.
- MAEGRAITH, B. G. (1966). Pathogenic processes in malaria. In *The Pathology of Parasitic Diseases*, p. 15, Fourth Symposium of the British Society for Parasitology, 1965. Blackwell: Oxford.

A model to demonstrate the inhibition by dexamethasone of anaphylactic bronchoconstriction

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The efficacy of steroids in the treatment of human bronchial asthma is well known. Their selection for anti-asthmatic use is based on their anti-inflammatory and anti-rheumatic potency, as no satisfactory laboratory test for assessing their effects against allergic bronchoconstriction has been demonstrated. We describe the effect of dexamethasone against anaphylactic bronchoconstriction in the rat.

Wistar rats were infected by subcutaneous injection of 3,000-5,000 larvae of *Nippostrongylus brasiliensis*. Five weeks later, animals were lightly anaesthetized with ether and the brain and spinal cord destroyed by pithing. The trachea was cannulated and the rat ventilated with a Starling miniature respiratory pump of stroke volume 5-7 ml. at a rate of 90 strokes/min. The side arm of the tracheal cannula was connected to a non-return water valve set at a pressure of 7.5 cm water. For intravenous administration of substances the jugular vein was cannulated. Tracheal flow was measured with a pneumotachograph and recorded on a multi-channel electronic recorder. Animals were challenged with *N. brasiliensis* antigen (500 worm equivalents/kg intravenously) (Ogilvie, 1967). The resultant decrease in tracheal flow was used as an assessment of bronchoconstriction and was recorded for 10 min after challenge.

In an experiment using thirty-nine animals, dexamethasone (5 mg/kg) was given intraperitoneally at 1, 4, 24 and 48 hr before challenge to groups of nine to eleven rats. Twelve rats were untreated. The resultant time/response curve showed that the activity of dexamethasone increased with time to a maximum at 24 hr, then waned. The maximum reduction was significantly ($P < 0.025$) different from control. In a further experiment using ninety-four animals, one dose of dexamethasone was given intraperitoneally 24 hr before challenge to each of six groups of twelve to thirteen rats using a dose range of 0.0156 to 16 mg/kg using four-fold dose increments. One further group of nineteen animals received only saline. Dexamethasone reduced the anaphylactic bronchoconstriction in a linear ($P < 0.001$) dose related manner. Significant ($P < 0.05$) reductions were obtained over the dose range 0.25 to 16 mg/kg.

Guinea-pig anaphylaxis may serve as a model of human bronchial asthma (Collier & James, 1967), but steroids have not been conclusively demonstrated to reduce anaphylactic bronchoconstriction in this species (Hicks, 1969). The above