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The action of pharmacologically active substances on the flow and composition of cat hind-limb lymph

G. P. LEWIS and N. J. P. WINSEY, *CIBA Laboratories, Horsham*

It has been shown in cats (Lewis, 1967) and rabbits (Lewis & Westcott, 1968) that during tissue injury there is an increase in the flow of lymph and in the concentration of intracellular enzyme systems as well as protein in the lymph draining the injured area. In the present experiments in anaesthetized cats a modification of the method used by Edery & Lewis (1963) and Sturmer & Cerletti (1967) in dogs has been used to study the effects on the flow and composition of lymph of pharmacologically active substances which might be involved in tissue reactions.

Cats were anaesthetized with pentobarbitone sodium (40 mg/kg intraperitoneally). The central stump of the pudendal artery was cannulated with a polythene cannula for retrograde close arterial infusions into the hind limb using a Palmer continuous infusion pump. Venous outflow from the femoral vein was measured by a photoelectric drop-counter, the blood being returned to the animal via the contralateral femoral vein.

To facilitate the cannulation of one of the femoral lymphatics, the connective tissue surrounding the femoral artery and vein was ligated and the limb was passively flexed to fill the lymphatics. One of the vessels was then dissected free and a polythene cannula inserted, tied and glued with Eastman 910 adhesive. As the lymph flow stops in an immobilized animal the resting flow was maintained by passive movements of the limb, obtained by attaching the foot to a motor-driven eccentric wheel. Intracellular enzymes and protein were measured according to methods described by Lewis (1967).

None of the substances infused into the hind limb—histamine, acetylcholine, bradykinin, 5-hydroxytryptamine or prostaglandin (PGE_1 or $PGF_{2\alpha}$)—caused an increase in the concentration of any of the intracellular enzymes in the lymph. Histamine, acetylcholine and bradykinin, however, caused vasodilatation and an increase of lymph flow which was usually accompanied by an increase of protein concentration in the lymph.

Histamine increased blood flow when infused in a concentration of 0.1 μg/min, acetylcholine in a concentration of 1 μg/min, and bradykinin 0.05 μg/min. Both lymph flow and protein concentration increased following infusions of histamine

(1.0–3.0 μg/min), acetylcholine (3.0 μg/min) and bradykinin (0.3–1.0 μg/min). With a second or third infusion the responses to histamine or bradykinin were reduced, due to the development of tachyphylaxis.

In some experiments infusion of histamine or acetylcholine was followed by an increase in lymph flow without a concomitant increase in protein concentration. A further dissociation between these two parameters was more evident when the substance were infused together with the inhibitor Glyvenol® (ethyl-3,5,6-tri-*O*-benzyl-D-glucofuranoside) (Jaques, Huber, Neipp, Rossi, Schär & Meier, 1967). During such a combined infusion, although there was little change in the vascular or lymphatic response, the increase of protein concentration in the lymph was not as great as when histamine or bradykinin were infused alone.

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Catecholamine excretion in mice subjected to the stress of a test for anti-inflammatory activity

K. L. GREEN (introduced by B. J. NORTHOVER), *School of Pharmacy, Leicester Regional College of Technology, Leicester*

Cocaine and a number of α-receptor blocking agents have been shown to reduce the permeability of the mouse peritoneal vascular bed to plasma albumin. The effect was antagonized by β-receptor blocking agents, so it was suggested that cocaine-like drugs reduced vascular permeability by potentiating the effects of endogenous catecholamines. As a continuation of this study, the urinary excretion of adrenaline and noradrenaline has been examined in mice subjected to the stresses involved in a test for anti-inflammatory activity similar to that described by Northover (1963).

Female Schofield mice (25–30 g) were injected intraperitoneally with 4 ml. of 0.05% acetic acid in normal saline at 39°, and intravenously with 0.2 ml. of 0.5% Evans blue in normal saline; urine was collected over the next 4 hr. Catecholamines were extracted by a modification of the method of Anton & Sayre (1962). The adrenaline and noradrenaline contents were estimated by a differential assay using the propranolol- and cocaine-treated pithed rat, and the electrically stimulated isolated rat uterus. The average recovery of adrenaline added to urine was 74%, and for noradrenaline the recovery was 68%.

During the 4 hr period of collection, normal mice excreted adrenaline 0.12 ± 0.02 (S.E.) μg/kg and noradrenaline 0.52 ± 0.07 μg/kg. Mice injected with Evans