The Action of Anti-inflammatory Drugs on the Permeability of Mesenteric Mesothelium to Plasma Protein

SIR,—Mesenteric mesothelium bears a close morphological resemblance to the endothelium of blood vessels and it was of interest to discover whether drugs which reduced vascular permeability would also reduce the permeability of the mesentery to plasma protein. A method has been devised which enables the permeability of the rat mesentery to plasma protein to be measured *in vitro*. A large rat is killed by a blow on the head and a section of small intestinal mesentery is selected which is free from major blood vessels and fat deposits. The mesentery is gently draped over an open end of a 12 mm. diameter glass tube and secured around the rim with a cotton ligature. The piece of mesentery occluding the end of the glass tube is then cut out from the abdomen. In this way it is possible to rapidly complete the preparation without touching the surface of the delicate mesentery with either the fingers or instruments. The mesenteric diaphram is then set up in a 100 ml. beaker containing 70 ml. of Locke's solution, whilst inside the glass tube is placed 2·5 ml. of solution containing 0·5 per cent bovine plasma albumin, 0·5 per cent azovan blue, and 0·9 per cent sodium chloride. Care is taken to maintain the levels of fluid inside and outside the tube the same at all times. The Locke's solution is kept mixed by means of a slowly rotating magnetic stirrer, and the temperature maintained at 26–28°.

Albumin-bound azovan blue slowly diffuses through the mesentery into the Locke's solution, 1 ml. samples of which are withdrawn at 10 min. intervals and their optical extinction measured. Each time a sample is taken 1 ml. of fresh Locke's solution is added to keep the volume constant. Samples are collected in this way for 90 min. and then the substance to be tested is added to the bath as a neutral (pH 7·4) solution, samples being collected for a further 90 min. The rate of entry of dye (G) is calculated by the method of least squares both for the period before, and the period after the addition of the substance under test. The ratio of the rate of diffusion before (G_1) and after (G_2) addition of the drug is a measure of the effect of the drug on the permeability of the mesentery to plasma protein.

TABLE I

ACTION OF DRUGS ON THE PERMEABILITY OF MESENTERY TO PLASMA-PROTEIN

Drug	G_2/G_1 per cent
Control (sodium chloride) ..	91
2,6-Dihydroxybenzoic acid ..	93
m-Hydroxybenzoic acid	86
Salicylic acid	75*
Thymoxyacetic acid	62*

Final concentration of each substance in the bath was 7·5mM.

* Indicates that there is a significant ($P<0·05$) difference between G_1 and G_2.

Table I shows the effects of various substances. Thymoxyacetic acid was the most active of those tested and this is in agreement with the considerable activity of the substance as an anti-inflammatory agent (Northover and Verghese 1962). Among hydroxybenzoates 3 compounds were tested, salicylate being active, *m*-hydroxybenzoate only slightly active, and 2,6-dihydroxybenzoate inactive. This again is in agreement with the anti-inflammatory action of the compounds.

It would seen that the rat mesentery offers a useful *in vitro* system on which the effect of permeability-reducing drugs can be investigated and these preliminary observations suggest that it behaves in some ways like the endothelium of blood vessels.

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REFERENCE

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Effect of Pyrogallol on Acute Learning in Rats

SIR,—Pyrogallol causes an increase in the contents of adrenaline and noradrenaline of the brain of mice (Izquierdo, J. A. and Biscardi, 1961) and rats (Izquierdo, J. A., Juorio and Dezza, unpublished) presumably by inhibition of their *O*-methylation. It seemed to us, therefore, a useful tool for a preliminary approach to the study of adrenergic mechanisms in learning.

At a dose of 200 mg.kg. i.p., in rats, it promoted habituation of investigatory-orienting and of arrest unconditioned reflexes to a buzzer to which there normally was none. The startle reflex was unaffected. The buzzer had a duration of 3 sec. and was presented 50 consecutive times (intervals between buzzes: 30–90 sec.) to 26 animals, 19 of which received pyrogallol and 7 water, 3 min before testing.

In other groups of rats, after 20 "control" presentations of this buzzer alone, it was paired with a shock (0·5 sec. of 150/sec. 100 V × 0·1 msec. rectangular pulses) delivered 1–2 sec. after it to a metallic grid on the floor of the training box. An instrumental response (lifting of one or both forepaws) appeared after 5–15 pairings, and reached a stable level of 50–90 per cent per block of 10 trials after 40–50 trials. The initial rate of appearance of the conditioned reflex was significantly lower in 9 rats to which pyrogallol was given 3 min. before the session began, as compared with 7 water-treated ones. In 8 other rats in which pyrogallol was given later during the reinforcement stage, when the instrumental response was already stabilised, its performance was unaffected.

In 7 rats, pyrogallol was injected 3 min. before beginning an extinction of the conditioned reflex; the rate of the extinction was significantly higher than in 7 other water-treated rats.

Pyrogallol is known to produce a slight increase in blood pressure which is counteracted by phentolamine (Izquierdo, 1962), and an increase in duodenal motility which is blocked by atropine (Izquierdo and Izquierdo, 1961; Izquierdo, 1962), both effects lasting 15–40 min. Neither phentolamine (10 mg./kg., 7 rats) nor atropine (1 mg./kg., 7 rats) given i.p. 1 min. before pyrogallol, modified the effect of the latter on extinction. Phentolamine alone (7 rats) had an effect not different from that of water, but atropine (7 rats) increased the extinction to a level not significantly different from that attained either with pyrogallol alone or with both drugs in combination.

Thus, any reflex influence of blood pressure or increase of duodenal motility by pyrogallol on extinction can be disregarded, and an effect on brain catecholamines is left as the most likely mechanism. But the action of atropine on extinction suggests, nevertheless, some interaction (other than duodenal) between both drugs.