The nociceptive activity of bradykinin in dog spleen is blocked by a peripheral action of aspirin-like drugs (Lim, Guzman, Rodgers, Goto, Braun, Dickerson & Engle, 1964). We have, therefore, investigated the interactions between bradykinin, prostaglandins and aspirin-like drugs in dog spleen.

Dogs were anaesthetized with pentobarbitone sodium (20 mg/kg I.V.). A small branch of the splenic artery was cannulated retrogradely with polyethylene tubing for intra-arterial injections; the splenic vein was also cannulated for removal of blood. Splenic venous blood was withdrawn at 10 ml/min to superfuse a series of isolated assay tissues to detect prostaglandins (a rat stomach strip, chick rectum and rat colon) and bradykinin (a cat terminal ileum) by the blood-bathed organ technique (Vane, 1964; 1969). After superfusing the assay tissues the blood was returned to the animal intravenously.

Intra-arterial injections of bradykinin (5–20 μg) released prostaglandin-like activity into the splenic venous blood, in amounts (in terms of E_2) varying from 1–5 ng/ml. The release was blocked by indomethacin (2–5 mg/kg intravenously).

Other dogs were lightly anaesthetized with thiopentone (30 mg/kg) and chloralose (30–50 mg/kg) intravenously. Bradykinin (0·1–2 μg) intra-arterially into the spleen produced increases in arterial blood pressure proportional to the dose. This reflex pressor effect of bradykinin is due to stimulation of sensory nerves and is an index of the nociceptive activity of bradykinin (Hashimoto, Kumakura & Taira, 1964). Prostaglandin E_1 or E_2 (5–20 μg) injected together with bradykinin potentiated the reflex pressor response although prostaglandins by themselves were vasodepressor. Indomethacin (1–8 mg/kg) reduced the effect of intra-splenic bradykinin so that four times the dose had to be used to induce the same pressor effect. After indomethacin, prostaglandin E_1 or E_2 given as intra-splenic injections (5–20 μg) or slow infusions (50 ng/min) increased once more the sensitivity to bradykinin.

These results add force to the theory that the analgesic action of aspirin-like drugs is peripheral and is due to inhibition of prostaglandin formation. The prostaglandin released within the spleen sensitizes sensory nerve endings to the nociceptive action of bradykinin. This facilitation may also apply to other chemical or mechanical stimuli. The action of aspirin would then be due to the removal of the prostaglandin-induced facilitation, which accounts for the fact that aspirin is only a weak analgesic.

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The actions of prostaglandins A_1 and A_2 on airway resistance and compliance in the cat

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Main (1964) showed that prostaglandin E_1 (PGE_1) increased the 'resistance to inflation' of cat lungs studied by the method of Konzett & Rössler. This could be interpreted as either an increase in airway resistance or a decrease in compliance. Rosenthale, Dervinis

& Kassarich (1971) found that PGE_1 reduced the resistance and increased the compliance of cat lungs in which airway smooth muscle tone had been induced with neostigmine.

In our experiments open chested cats under pentobarbitone anaesthesia were used. Tracheal pressure and air flow were recorded on magnetic tape, and resistance and compliance were later computed using a modification of the method of Mead & Whittenberger (1953).

Prostaglandins were given by rapid intravenous injection
(i) to cats with no airway tone
(ii) in the presence of airway tone induced by continuous intravenous infusion of neostigmine
(iii) in the presence of airway tone induced by continuous intravenous infusion of methacholine.

In the absence of airway tone in each of thirteen tests, in three cats, PGA_1 and PGA_2 raised the resistance and lowered the compliance. The rise in resistance in response to PGA_1 was dose-dependent over the range from 1 to 25 μg/kg, giving increases in resistance from 10% to 80%. The fall in compliance ranged from 4 to 20%. In response to PGA_2 the rises in resistance were about double those to similar doses of PGA_1, and falls in compliance ranged from 10 to 40%.

In three cats neostigmine methyl sulphate infused at 100 μg/min raised airway resistance by 170 to 200%. Compliance fell by 40%. In each of four tests PGA_2 at 10 μg/kg lowered the resistance by 20 to 40%, and also lowered the compliance by 8 to 50%.

In two cats, methacholine chloride was infused at two rates, 10 μg/min and 400 μg/min, giving increases in resistance of 20% and 300% respectively with falls in compliance of 20% and 55 to 70%. In six tests PGA_2 at 25 μg/kg further raised the resistance and further lowered the compliance at both high and low infusion rates of methacholine.

We infer from these results that PGA_1 and PGA_2 have qualitatively similar actions. Their primary effect on the lungs is to increase airway resistance and to reduce compliance. This effects is still seen when methacholine is used to induce tone in the airway smooth muscle. Tone induced by neostigmine is inhibited by PGA, but a reduction of compliance is still seen. This bronchodilator action of PGA must be related to the mechanism by which neostigmine induces tone, insofar as that differs from the mechanism for methacholine. A direct or indirect action on release of acetylcholine could be involved. The use of neostigmine to induce airway tone may thus provide an unsatisfactory model for the study of potential bronchodilator drugs.

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Determination of the number of muscarinic receptors in chick amnion muscle

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Studies on the binding of the irreversible muscarinic blocking drug propylbenzilylcholine mustard (PrBCM) to the non-innervated smooth muscle of the chick amnion have been made and the results compared to those for ileum. Further, the amnion muscle is suitable for measuring drug responses, the results of which can be compared to those from binding studies (Cuthbert, 1962).

Experiments were made with groups of 6–8 amniotic membranes dissected from fertile hens' eggs incubated for 11 days. The membranes were incubated with ^{3}H-PrBCM (2·4 nM, 1·45 Ci/mmol) in Hank's solution at 30° C for various times. Binding to muscarinic receptors was taken as the difference in the amount of label bound in the