Potentiation by prostaglandins of the nociceptive activity of bradykinin in the dog knee joint

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Prostaglandin E_1 or E_2, in concentrations found in inflammatory exudates, increases the pain-producing activity of bradykinin in human skin (Ferreira, 1972) or in dog spleen (Ferreira, Moncada & Vane, 1973). This sensitization is long lasting, for it depends not only on the prostaglandin concentration but also on the duration of infusion. Since aspirin-like drugs block the synthesis of prostaglandins (Vane, 1971; Ferreira, Moncada & Vane, 1971; Smith & Willis, 1971), the removal of such a sensitizing effect could explain their analgesic activity.

We have now developed a method using dog knee joints to investigate this hypothesis further. It measures the reflex hypertension induced by intra-articular injections of bradykinin and compares control and test observations in the same animal by using both knee joints.

Dogs anaesthetized with thiopentone (30 mg/kg) and maintained in a light anaesthesia by intravenous ketamine hydrochloride (Ketalar, Parke Davis) at 0.1-1 (mg/kg)/min were placed in a supine position and the hind legs were fixed at an angle around the knees of about 60°. Polyethylene catheters were inserted into the synovial spaces with the aid of 'intracat' needles. The synovial fluid was washed out with 15 ml tris buffer. Mean blood pressure was recorded from a transducer attached to a cannula in the carotid artery.

Intra-articular injections were made in 1 ml Tris buffer; after 1 min, the catheter was opened and the fluid allowed to escape. Tris buffer injections alone (1-4 ml) had no effect on blood pressure. However, intra-articular bradykinin (0.5-10 μg) induced, after 7-30 s, a dose-dependent rise in blood pressure. Similar effects were produced from either leg.

In five experiments, an infusion of indomethacin (1 μg/min at 0.045 ml/min) was made into one joint. Over 3 h, the untreated joint gradually became more sensitive to the nociceptive effects of bradykinin, but the treated joint did not. These experiments suggested that the sensitization was due to a gradual release of endogenous prostaglandin within the untreated joint. Indomethacin (1 mg) injected into the joint abolished the sensitization, thereby reinforcing the conclusion.

In other dogs, endogenous formation of prostaglandins was prevented by indomethacin injected intravenously (2 mg/kg) and infused (1 μg/min) into both joints. In these dogs higher doses of bradykinin were needed to induce hypertension. Prostaglandin E_1 or E_2 (seven experiments with each) at 50 ng/min was added to the infusion into one knee joint. Within 30 min, that joint became selectively more sensitive to bradykinin. With a lower rate (5 ng/min) of infusion of prostaglandin E_1 or E_2, sensitization to bradykinin developed after 2-3 hours. Prostaglandin F_2 (50 ng/min for 3 h; one experiment) did not produce sensitization.

These results support our contention that aspirin-like drugs produce analgesia by removing the sensitization to physical or chemical stimuli which is induced by the local release of an E prostaglandin.

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