particularly resistant to the inhibitory action of mepyramine. On the other hand the anti-inflammatory agents indomethacin and phenylbutazone (0.1-4 mg/kg) abolished the responses to the prostaglandins and effectively inhibited the AT-induced oedema.

It may be concluded from these observations that the histopathological effects of AT are probably mediated through the release of histamine and $PGF_{2\alpha}$, the latter mediator possibly contributing more to the perivascular and peribronchial oedema.

References

HICKS, R. & SACKEYFIO, A.C. (1972). The nature of adrenergic mechanisms involved in anaphylatoxin activity in the guinea-pig. *Br. J. Pharmac.*, **46**, 260-269.

SACKEYFIO, A.C. (1971). Definition of the histaminic component of the bronchoconstrictor and cardiovascular effects of anaphylatoxin in the guinea-pig. *Br. J. Pharmac.*, **43**, 424-425P.

SACKEYFIO, A.C. (1972). Anaphylatoxin-induced release of a substance with prostaglandin-like activity in isolated perfused guinea-pig lungs. *Br. J. Pharmac.* **46**, 544-545P.

Release of prostaglandins in the knee joint of the dog during local Shwartzman-like reaction

A.G. HERMAN[1]

J.F. & C. Heymans Institute of Pharmacology, University of Gent, De Pintelaan, 135, Gent, Belgium.

The Shwartzmann phenomenon, originally described in the rabbit (Shwartzman, 1928), is a two-stage reaction: the first event consists of a local inflammatory reaction in the skin after an intradermal injection of bacterial endotoxin; the second one consists of a haemorrhagic necrosis of the prepared skin area following an intravenous injection of the endotoxin, 18-24 h after the intradermal injection. Since endotoxin produces an inflammation in the knee joint of the dog (Morgan & Bennett, 1947; Van Arman, Carlson, Kling, Allen & Bondi, 1974) during which prostaglandins (PG) are locally released (Herman & Moncada, 1975), we decided to study the possibility of producing a Shwartzman-like reaction in the dog's knee joint, the release of PG's during its development and the effect of local treatment with indomethacin, which has been shown to inhibit the Shwartzman reaction in rabbit skin (Van Arman, Carlson, Brown & Itkin, 1970).

Mongrel dogs of either sex were anaesthetized with thiopentone (10 mg/kg intravenously). A 'preparatory' injection of endotoxin (E. coli O 111 B4, Difco; 2.5 ng/kg, 9 experiments; 25 ng/kg, 12 experiments) in 0.5 ml of sterile saline was given in one of the knee joint cavities. Symptoms of incapacitation ranging from limping, occasional 3-legged gait to complete 3-legged gait were observed in all animals as described previously (Herman & Moncada, 1975). All animals received an intravenous 'provocative' injection of 250 ng/kg endotoxin 18-24 h later. In 15 out of 21 animals incapacitation occurred which started about 1 h after the injection and lasted for about 3-4 hours. In 12 animals synovial fluid was sampled from the affected joint under light thiopentone anaesthesia and the cavity washed twice with 2 ml of sterile saline. Samples were extracted and bioassayed for PG-like activity (Gilmore, Vane & Wyllie, 1968). In 10 out of 12 animals PG-like activity (range: 4-51 ng PGE_2-equivalents) was detected in the synovial fluid.

In 3 animals indomethacin (200 μg/kg dissolved in phosphate buffer 0.1 M pH 8.9) was injected in the knee joint at the moment of the provocative injection of endotoxin: no symptoms developed in these animals up to 7 h after the injection.

An intravenous injection with endotoxin 24 h after a preparatory injection with concanavalin A (Sigma; 0.1-1 mg/kg, 8 experiments) or lipid A/BSA (supplied by Dr C. Galanos; 5 μg/kg, 2 experiments) gave incapacitation and production of PG's in all animals studied.

These experiments show that a Shwartzman-like reaction can be produced in the knee joint of the dog, during which PG's are released and which can be prevented by local treatment with indomethacin. These findings indicate that PG's may be involved in the local Shwartzman reaction. Furthermore, we think this to be a useful and practical model to study the release of chemical mediators and cells during the local Shwartzman reaction.

[1] Present address: Universitaire Instelling Antwerpen, Universiteitsplein 1, Wilrijk, Belgium.

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References

GILMORE, H., VANE, J.R. & WYLLIE, J.H. (1968). Prostaglandins released by the spleen. *Nature, Lond.*, 218, 1135-1140.

HERMAN, A.G. & MONCADA, S. (1975). Release of prostaglandins and incapacitation after injection of endotoxin in the knee joint of the dog. *Br. J. Pharmac.*, 53, 465P.

MORGAN, H.R. & BENNETT, G.A. (1947). Intra-articular changes induced in rabbits by injection of typhoid somatic antigen. *Arch. Path.*, 44, 609-620.

SHWARTZMAN, G. (1928). A new phenomenon of local skin reactivity to B. Typhosus culture filtrate. *Proc. Soc. exp. Biol. Med.*, 25, 560-561.

VAN ARMAN, C.G., CARLSON, R.P., BROWN, W.R. & ITKIN, A. (1970). Indomethacin inhibits the local Shwartzman reaction. *Proc. Soc. exp. Biol. Med.*, 134, 163-168.

VAN ARMAN, C.G., CARLSON, R.P., KLING, P.J., ALLEN, D.J. & BONDI, J.V. (1974). Experimental gouty synovitis caused by bacterial endotoxin adsorbed onto urate crystals. *Arthritis Rheum.*, 17, 439-449.

Gastric acidity and the mechanisms by which prostaglandins prevent indomethacin-induced gastric erosions

B.J.R. WHITTLE

Department of Pharmacology, Institute of Basic Medical Sciences, Royal College of Surgeons, Lincoln's Inn Fields, London, WC2

Antisecretory prostaglandins inhibit the formation of gastric ulcers and erosions induced by several techniques (Robert, Nezamis & Phillips, 1968). In the present study, the relationship between inhibition of gastric acid secretion and the prevention of indomethacin-induced mucosal erosions by several prostaglandins has been investigated in the rat.

Indomethacin (5-30 mg/kg s.c.) caused the formation of rat gastric mucosal erosions within 1-6 h, the incidence and severity depending on the dose and duration of administration. Prostaglandin E_2 (PGE_2) and its methyl analogues, which are potent inhibitors of rat gastric secretion (Main & Whittle, 1975), reduced erosion formation in a dose and time-dependent manner. The dose reducing the erosion 'score' by 50% (ED_{50}) observed 3 h after indomethacin (15 mg/kg s.c.), was 220, 250, 0.54 and 0.50 μg/kg s.c. for PGE_2, PGA_2, (15S)-15 methyl E_2 and 16, 16, dimethyl E_2 respectively. However, the H_2-receptor antagonist metiamide, in doses which inhibited gastric secretion, also reduced indomethacin erosions; the ED_{50} was 13 mg/kg s.c. The ratio of the ED_{50} for prevention of erosions to the ED_{50} for inhibition of gastric acid secretion in the chronic fistula rat (see Main & Whittle, 1975) was 1.6 for PGE_2 and 0.4 for its methyl analogues, showing a variable relationship. Furthermore, the (15S) methyl analogue of $PGF_{2\alpha}$ also prevented erosion formation (ED_{50} 20 μg/kg s.c.).

The mechanism by which prostaglandins inhibit erosions was further studied by perfusing acidic saline (pH 1-2; 100-10 mM HCl) through the gastric lumen of the urethane-anaesthetized rat. Indomethacin (5-20 mg/kg s.c.) induced a low incidence of erosion formation within 3 h at pH 1.2-2.0, but this effect was greatly potentiated, accompanied by mucus secretion, when the bile salt sodium taurocholate (0.2-5.0 mg/ml) was perfused simultaneously. The time-course and degree of erosion formation, which was followed more closely by enclosing the exteriorized stomach in a transparent chamber (Mersereau & Hinchey, 1973), depended on the acid and taurocholate concentrations and the dose of indomethacin. Administration of the PGE_2 methyl analogues (5 $\mu g\ kg^{-1}\ h^{-1}$ s.c.) prevented indomethacin (20 mg/kg s.c.)-induced erosions during gastric perfusion of taurocholate (1 mg/ml; 2 mM) at pH 1.3 (76 ± 9% inhibition of erosions, n = 4; mean ± s.e.mean) and pH 1 (53 ± 12%, n = 4) for 3 h, and the mucosa appeared hyperaemic. The loss of titratable acid from the gastric lumen, which followed indomethacin administration with taurocholate and acid perfusion, was also reduced by the PGE_2 methyl analogues (20 ± 5% reduction, n = 8).

These results indicate that the formation of indomethacin-induced gastric erosions in the rat depends on the acid concentration in the gastric lumen, and that antisecretory agents such as prostaglandins and metiamide can inhibit their formation. However, the ability of prostaglandins to prevent erosion formation in the presence of exogenous acid indicates that other mechanisms may also be involved. It is not yet known how such mechanisms are related to changes in local blood flow or mucosal permeability.

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