Cysteine, BAL, α-thiol-glycerol or BPP_{5a} (a synthetic pentapeptide similar to the pentapeptide isolated from BPF) potentiate both the bradykinin relaxation and contraction. Cysteine and BAL were up to 10 times more potent at potentiating the bradykinin relaxation than the contraction. There was no potency difference for α-thiol-glycerol or BPP_{5a}. High concentrations of cysteine and BAL produced inconsistent effects, at some concentrations potentiating and others reducing the bradykinin responses. Cysteine at high concentrations potentiated, while BAL reduced the ACh contraction. α-Thiol-glycerol and BPP_{5a} had no effect at any concentration examined.

In similar experiments using phentolamine, we have shown that, although the bradykinin relaxation was reduced, the contraction was either unaffected or potentiated by phentolamine. These results suggested the possibility of separate receptors for the bradykinin-induced relaxation and contraction of the acetylcholine contracted guinea-pig isolated ileum.

We thank Professor H. C. Beyerman (T. H. Delft, The Netherlands) for a gift of BPP_{5a}.

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Potentiation of dibutyryl cyclic 3'5'-AMP-induced gastric acid secretion in rats by non-steroidal anti-inflammatory drugs

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Indomethacin, a potent inhibitor of prostaglandin (PG) synthesis (Vane, 1971), can increase pentagastrin-stimulated acid secretion in the rat (Main & Whittle, 1973). We have now investigated the effects of non-steroidal anti-inflammatory drugs on the secretory response evoked by dibutyryl cyclic 3'5'-AMP (dbcAMP) injected intravenously (Whittle, 1972).

Gastric acid output and gastric mucosal blood flow (MBF) were measured in the urethane-anaesthetized rat (Main & Whittle, 1972). Intravenous injection of indomethacin, in doses which had no effect on basal acid secretion but which lowered resting MBF, caused a dose-dependant potentiation of secretion induced by dbcAMP (10–20 mg/kg I.V.) accompanied by an increase in MBF. Sodium meclofenamate had a similar effect (Table 1). Equilibrium dialysis experiments indicated that these effects

TABLE 1. *Effect of pretreatment with anti-inflammatory drugs on the secretory response to dbcAMP (20 mg/kg) injected intravenously during basal secretion in the rat. Acid output (μ-equiv) is the increase from basal during the 80 min. following injection of dbcAMP. All results, expressed as mean ±S.E.M. where (n) is the number of values, differ significantly from the control ($P < 0.001$).*

Drug	(mg/kg)			Acid output, μ-equiv.	
Control	—			8±1	(16)
Indomethacin	(10)	I.V.	1 h	29±3	(3)
Indomethacin	(20)	I.V.	1 h	34± 6	(3)
Indomethacin	(30)	I.V.	1 h	90±20	(4)
Indomethacin	(15)	S.C.	24 h	55± 3	(3)
Indomethacin	(15)	S.C.	6 h	57± 5	(3)
Indomethacin + Theophylline	(15) S.C. 6 h; (20) I.V. 1 h			123±11	(3)
Phenylbutazone	(100)	S.C.	6 h	52± 4	(2)
Meclofenamate	(30)	I.V.	1 h	52±19	(3)

cannot be attributed to displacement of dbcAMP from plasma protein binding sites by the highly bound anti-inflammatory drugs. Pretreatment with indomethacin or phenylbutazone, injected subcutaneously 6 or 24 h prior to the experiment in doses which produce submaximal gastric ulceration, also increased the dbcAMP responses which were further augmented by theophylline (20 mg/kg I.V.). There was a relationship between the dose of anti-inflammatory drug, the potentiation of dbcAMP-induced secretion (Table 1) and the incidence and severity of mucosal erosions.

We were unable to determine whether these effects were preceded by decreased PG output into the gastric perfusate, since no PG-like activity ($<0{\cdot}1$ ng/min in terms of PGE_1) could be detected during either basal or stimulated secretion (4 experiments). However, pretreatment of rats with indomethacin (15 mg/kg S.C. 6 h) did cause an 80% reduction in the content of PG-like activity in mucosal extracts.

Although we have not established that the observed fall in mucosal PGs is responsible for the increased sensitivity to dbcAMP, or for the reduction in resting MBF, the results raise the possibility that one or more of these effects may be implicated in the production of gastric mucosal erosions.

B. J. R. W. is an MRC scholar.

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The effect of indomethacin on the cardiovascular responses of cats to E. coli endotoxin

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A number of investigators have confirmed the original observation of Northover and Subramanian (1962) that non-steroidal analgesic-antipyretic drugs antagonize the vasodepression elicited by endotoxin administration in the dog (Erdos, Hinshaw & Gill, 1967; Solomon & Hinshaw, 1968; Hall, Hodge, Irvine, Katic & Middleton, 1972). In the cat the response to the administration of a lethal dose of *E. coli* endotoxin consists of an acute phase (manifested by a marked rise in pulmonary artery pressure and transient decreases in systemic arterial pressure and in myocardial contractility) and a delayed (shock) phase characterized by systemic hypotension, a reduced stroke volume and a severe metabolic acidosis (Parratt, 1973). The purpose of the present experiments was to determine the effect of indomethacin on these two quite distinct responses to endotoxin.

Cats were anaesthetized and prepared for the measurement of systemic and pulmonary artery pressures, left ventricular dP/dt, cardiac output and myocardial blood flow as previously described in detail (Parratt, 1973). Within 1–3 min of the intravenous administration of 2 mg/kg *E. coli* endotoxin (Difco Laboratories) there was a marked elevation of pulmonary artery pressure (from 19 ± 1 mmHg (systolic) and 11 ± 1 mmHg (diastolic) to 36 ± 6 mmHg (systolic) and 21 ± 3 mmHg (diastolic) after 3 min) and, usually, transient decreases in systemic arterial pressure and in left ventricular dP/dt max. This acute response was not observed in cats treated with indomethacin (dissolved in a phosphate buffer pH 8 and administered intravenously in a dose of 10 mg/kg 30 min prior to endotoxin). The corresponding pulmonary artery pressures in the indomethacin-treated group were, pre-endotoxin 18 ± 2 mmHg (systolic) and 10 ± 1 mmHg (diastolic) and, 3 min after endotoxin, 20 ± 1 and 12 ± 1 mmHg. Indomethacin also appeared to prevent, or delay, the onset of the shock phase. In control animals the systolic blood pressure 2h