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

J. R. PARRATT* and R. STURGESS

*Department of Pharmacology, Royal College, University of Strathclyde, Glasgow G1 1XW*

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 $19 \pm 1$ mmHg (systolic) and $11 \pm 1$ mmHg (diastolic) to $36 \pm 6$ mmHg (systolic) and $21 \pm 3$ 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 $18 \pm 2$ mmHg (systolic) and $10 \pm 1$ mmHg (diastolic) and, 3 min after endotoxin, $20 \pm 1$ and $12 \pm 1$ mmHg. Indomethacin also appeared to prevent, or delay, the onset of the shock phase. In control animals the systolic blood pressure 2h

after endotoxin was a mean of 30 mmHg below the pre-endotoxin levels of 115±10 mmHg whilst the diastolic blood pressure at this time had fallen by a mean of 37 mmHg (from 86±9 mmHg). The arterial pH was reduced from 7·468±0·035 to 7·172±0·043 units 2h post-endotoxin. In the indomethacin treated animals the blood pressure 2h after endotoxin was between 40 and 50 mmHg higher than it was before the endotoxin was administered whilst the decrease in arterial pH (from 7·513±0·038 to 7·375±0·030 units) was not as pronounced as in the animals administered endotoxin alone.

These results indicate that indomethacin not only abolishes the initial acute pulmonary vasoconstriction which follows *E. coli* endotoxin administration in the cat but that it also delays the onset of the shock phase. Possible explanations for these effects include stabilization of mast cells and lysosomes, and the inhibition of the synthesis and release, or antagonism of the vascular effects, of humoral agents such as histamine, 5-hydroxytryptamine and the prostaglandins.

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## Inhibition by cinnarizine of calcium channels opening in depolarized smooth muscle

T. GODFRAIND*, A. KABA and R. ROJAS

*Laboratoire de Pharmacodynamie Générale, Université de Louvain, 4, Van Evenstraat 3000 Louvain, Belgium*

Previous studies have shown that cinnarizine is an antagonist of several vasoactive drugs including adrenaline, angiotensin and 5-hydroxytryptamine. Cinnarizine inhibits the contraction induced by adrenaline in physiological solution but not that in a calcium-free depolarizing solution. It also inhibits the contraction induced by calcium in depolarizing solution (Godfraind & Kaba, 1969, 1972). The present experiments were designed to determine whether such inhibition is due to reduction of the permeability of the vascular smooth muscle membrane to $Ca^{++}$ions.

Strips 4 cm long were prepared by spiral section of rat aorta. They were bathed either in a physiological solution (NaCl 122, $NaHCO_3$ 15, KCl 5·9, $CaCl_2$ 1·25, $MgCl_2$ 1·25 and glucose 11 mM) or in a depolarizing solution (similar but containing 100 mM KCl instead of NaCl and with $CaCl_2$ added according to the concentration required).

In the presence of increasing dosages of cinnarizine ($3\times10^{-9}$M to $2\times10^{-5}$M), the noradrenaline dose-effect curves were depressed non competitively whereas $Ca^{++}$-dose effect curves were progressively displaced to the right; this displacement reached a maximum for cinnarizine $10^{-5}$M and was not characteristic of a competitive antagonism. The contraction evoked by noradrenaline in $Ca^{++}$-free solution containing EGTA was not depressed by cinnarizine.

In the presence of cinnarizine $10^{-5}$M, there was no change in $Na^+$, $K^+$ or $Ca^{++}$ content of rat aorta. Total $^{45}Ca^{++}$ content, determined after equilibration in radioactive solution, was not changed either in physiological solution or in depolarizing solution. Cytoplasmic $^{45}Ca^{++}$ content was estimated by measuring residual radioactivity of muscles washed in a $Ca^{++}$-free solution containing 2 mM $La^{3+}$ (van Breemen, Farinas, Gerba & McNaughton, 1972). As shown in Table 1, an increase of $^{45}Ca^{++}$ content in the tissue compartment blocked by lanthanum was induced by depolarization and by noradrenaline $10^{-5}$M; this increase was prevented by cinnarizine.