Laboratorium voor Biofarmacie der Universiteit van Amsterdam, W. LAMEIJER
Amsterdam, Roetersstraat 1, P. A. VAN ZWIETEN
Netherlands.

November 3, 1972

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Selective inhibition of angiotensin-induced contractions of smooth muscle by indomethacin

Angiotensin has been shown to release prostaglandin-like substances from the dog kidney (McGiff, Crowshaw, & others, 1970; Aiken & Vane, 1971).

Indomethacin is known to be a potent inhibitor of prostaglandin synthesis (Vane, 1971) and will abolish prostaglandin release from the dog spleen (Ferreira, Moncada & Vane, 1971). Indomethacin has also been shown to cause a direct relaxation of rabbit isolated ileum, an action which appears related to its ability to inhibit prostaglandin synthesis (Ferreira, Herman & Vane, 1972).

In view of these observations it was considered pertinent to examine the effect of indomethacin on the ability of angiotensin to contract smooth muscle. Indomethacin will antagonize the contractions of a number of smooth muscle preparations to a variety of other agonists (Northover, 1967), an action that appears to be related to an inhibition of the entry of calcium ions into the muscle cells (Northover, 1971).

We have examined indomethacin for its effect on the increases in tension, produced by angiotensin, of isolated preparations of guinea-pig ileum and aorta, rat ileum, colon and fundus strip and rabbit aortic strip. Indomethacin (28–112 μM), kept in contact with the preparations for a minimum period of 20 min caused a selective blockade of angiotensin contractions in all tissues with the exception of the rat colon, where it was without effect.

In the guinea-pig ileum, indomethacin (56 μM) caused a $67{\cdot}1 \pm 4{\cdot}0\%$ ($n = 7$) reduction of a submaximal contraction to angiotensin. The corresponding reductions for the other agonists were $16{\cdot}8 \pm 3{\cdot}5\%$ ($n = 6$) for acetylcholine; $19{\cdot}3 \pm 4{\cdot}7\%$ ($n = 7$) for histamine and $31{\cdot}7 \pm 2{\cdot}3\%$ ($n = 6$) for bradykinin. Similar results were obtained with the rat ileum and the rat fundus strip.

On the guinea-pig ileum indomethacin (56 μM) depressed the responses to all effective concentrations of angiotensin with a $61{\cdot}8 \pm 2{\cdot}0\%$ ($n = 6$) depression of the maximum response (Fig. 1a) whereas the only effect seen on the dose response curve for acetylcholine was a small ($20{\cdot}3 \pm 4{\cdot}7\%$; $n = 5$) depression of the maximum response (Fig. 1b).

The same concentration of indomethacin caused a similar depression of the angiotensin dose-response curve on the rabbit aortic strip with a $38{\cdot}5 \pm 3{\cdot}3\%$ ($n = 6$) depression of the maximum response but was without effect on the dose response curve for noradrenaline on the preparation.

These reductions of angiotensin responses did not appear to be due to tachyphylaxis since no decreases in sensitivity to angiotensin were observed in adjacent pieces of tissue dosed concurrently.

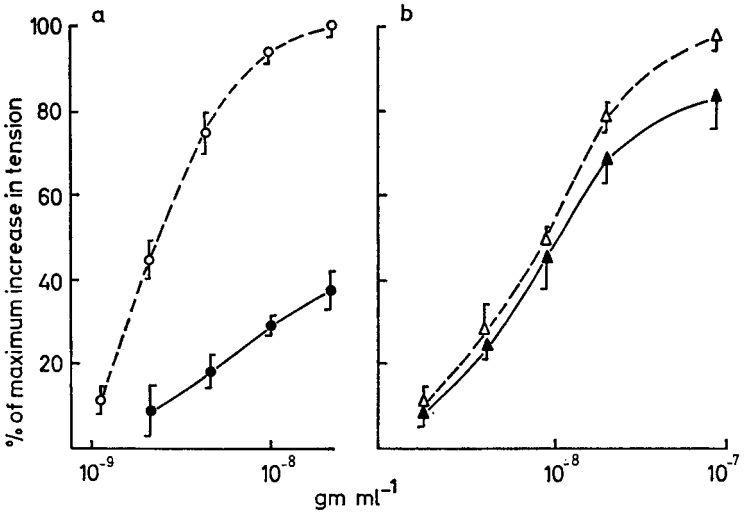

FIG. 1. Effect of indomethacin on the increase in tension of guinea-pig ileum preparations to a) angiotensin and b) acetylcholine. ○—○; △—△; control responses to angiotensin and acetylcholine respectively. ●—●; ▲—▲; responses to angiotensin and acetylcholine in the presence of indomethacin (56 μM) which had been left in contact with the tissue for a minimum period of 20 min.

Intestinal and vascular smooth muscle preparations which were depolarized with KCl or K_2SO_4 produced contractions to angiotensin and a variety of other agonists. The contractions obtained were smaller in amplitude and of a slower time course. Under these conditions indomethacin (56 μM) had no effect on the contractions produced by angiotensin or any of the other agonists except on the guinea-pig ileum (where a small reduction in the amplitude of the angiotensin contractions was observed).

The present results suggest that indomethacin selectively antagonizes the action of angiotensin on the smooth muscle preparations used, furthermore this action appears to be restricted to the cell membrane.

The relatively low concentrations of indomethacin used, the necessity to use a long contact time and the selectivity for angiotensin all suggest that indomethacin may be acting here by preventing prostaglandin synthesis. Experiments are in progress to determine if this is correct and to investigate the role played by calcium ions.

Department of Pharmacy,
The University of Aston in Birmingham,
Birmingham, B4 7ET,
Warwickshire, U.K.
November 15, 1972

E. K. S. CHONG
O. A. DOWNING

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