Sodium flufenamate antagonises the potentiation by prostaglandins of noradrenaline-induced vasoconstriction in rat mesentery

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Arachidonic acid or prostaglandins (PGs) of the A, E and F series can potentiate noradrenaline-induced vasoconstriction in rat isolated perfused mesenteric blood vessels (Malik, Ryan & McGiff, 1976; Manku, Mtabaji & Horrobin, 1977). Sodium meclofenamate inhibits PG synthesis and also blocks some excitatory vascular responses to PGs (Levy & Lindner, 1971; Burka & Eyre, 1974). We have studied sodium flufenamate, a drug used clinically, on noradrenaline-induced vasoconstriction in rat isolated mesenteric blood vessels. Rats of either sex weighing 250–300 g were stunned and bled. The mesentery was cut from the intestine and perfused via a cannula in the superior mesenteric artery (2 ml/min, Krebs solution at 37°C). Perfusion pressure was monitored using a transducer and pen recorder. Dose-response curves were constructed for 0.25 to at least 50 μg noradrenaline, injected in 0.05–0.1 ml 0.9% saline containing 20 μg/ml ethylenediaminetetra-acetate and 10 μg/ml ascorbic acid to protect the noradrenaline. Flufenamate and/or PGs were added to the Krebs solution, and the repeat dose-response curves to noradrenaline were expressed as a percentage of the maximal response to noradenaline alone. The results were analysed using the Student's t-test for paired data. Those presented here are on the response to noradrenaline (5 μg) which gave 60 ± 4 (mean $\pm$ s.e. mean)% of maximum vasoconstriction ($n = 22$), but similar results were obtained throughout the dose range.

Sodium flufenamate (2 μg/ml) did not significantly affect the response to noradrenaline (5 μg, $n = 4$, $P > 0.8$). Endogenously synthesised PG may therefore be unimportant in modulating responses to noradrenaline in this preparation.

PGE_2 (20–50 ng/ml) or the PGH_2 analogues (15S)-hydroxy-9α,11α- and (15S)-hydroxy-11α,9α-epoxymethano)-prosta-5Z,13E-dienoic acids (U-44069 and U-46619 each 10 ng/ml) did not affect the basal perfusion pressure, but potentiated the response to noradrenaline throughout the dose range, including the maximum ($P < 0.05$ to < 0.01, $n = 6$, 5 and 6 respectively with 5 μg/ml noradrenaline). Sodium flufenamate (2 μg/ml) antagonised this potentiation (respectively $P < 0.05$ to < 0.02).

Sodium flufenamate reduces calcium uptake by human umbilical venous endothelial cells (Northover, 1973), so that the antagonism of potentiation by PGs may involve inhibition of calcium uptake. However, noradrenaline can induce vasoconstriction in a calcium-free perfusate (Manku & Horrobin, 1976), and in our experiments this was not significantly affected by sodium flufenamate.

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