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Lack of influence of indomethacin on neurogenic vasodilatation in the hind-limb and spleen of the dog

Prostaglandins can be extracted from the hind-limb of the dog (Dunham, Rolewicz & Zimmerman, 1968) and released from the spleen by electrical stimulation of the splenic nerves (Ferreira & Vane, 1967; Davies, Horton & Withrington, 1968; Gilmore, Vane & Wylie, 1969).

Since catecholamines induce neurogenic vasodilatation in the perfused hind-limb of the dog and are able to release prostaglandins, I have investigated possible correlations between the presence of prostaglandins and neurogenic vasodilatation, as well as the influence of indomethacin, a potent inhibitor of prostaglandin synthesis (Vane, 1971), on neurogenic vasodilatation.

The hind-limb of pentobarbitone anaesthetized dogs (n = 5) was perfused through the femoral artery with blood from the femoral artery of the opposite leg, with a Harvard Peristaltic Pump (model 1210), at a constant flow rate (80–150 ml min^{-1}). In another series of experiments (n = 6) the spleen was perfused with blood from the femoral artery and the flow rate was kept constant throughout the experiment (20–40 ml min^{-1}). Care was taken not to damage the innervation of the spleen. The perfusion pressure of the hind-limb and of the spleen was set at a slightly higher value (10–20 mm Hg) than systemic blood pressure, measured in the carotid artery. No mass ligatures were applied to the leg; vascular connections of the spleen other than the splenic artery were kept intact.

Intravenous injections of noradrenaline (0·5–4 $\mu g\ kg^{-1}$), adrenaline (0·5–2 $\mu g\ kg^{-1}$) and dopamine (10–40 $\mu g\ kg^{-1}$) caused a rapid and transient fall of the perfusion pressure of the hind-limb which reached its maximal values (30 to 120 mm Hg) 20 to 30 s after injection. This neurogenic vasodilatation had the characteristics described in full by Osswald (1969), and was abolished by ergotamine (5–20 $\mu g\ kg^{-1}$). Neither the interruption of the circulation of the paw by ligation nor intravenous administration of indomethacin (5–15 mg kg^{-1}) induced any significant change in the vasodilator response or in the secondary increase in perfusion pressure, due to the direct vasoconstrictor action of the amines.

The perfused spleen also showed neurogenic vasodilatation after injection of the catecholamines, although it did not reach the magnitude of the response observed in the hind-limb. After a delay of 30 to 45 s, a secondary dilatation was observed, which lasted for 3 to 5 min. Administration of indomethacin (5–20 mg kg^{-1}, i.v.) did not change the first (neurogenic) vasodilatation, but instead of the secondary fall of perfusion pressure, a rise was observed (Fig. 1). This increase in perfusion-pressure was proportional to the dose of catecholamine used and was very marked for the higher dose-range. Ergotamine (up to 100 $\mu g\ kg^{-1}$) did not alter the neurogenic vasodilatation of the spleen.

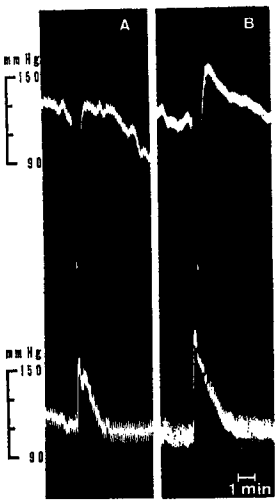

FIG. 1. Perfusion pressure of the spleen (top) and cartoid blood pressure (bottom) of a pentobarbitone anaesthetized dog. Panels A and B show the effects of intravenous injections of noradrenaline 1 μg kg^{-1}; between A and B. indomethacin 5 mg kg^{-1} was intravenously injected.

Since a neurohumoral mediation of neurogenic vasodilatation in the hind-limb has been postulated (see for example Brody, 1966; Osswald, 1969), prostaglandins would be candidates for this function; however, my results do not support this possibility, because indomethacin did not change the neurogenic dilatation in hind-limb or spleen. However, it reversed the secondary dilatation of the spleen vessels. It may be concluded that intravenously injected catecholamines release prostaglandins when they reach the perfused spleen and that the amount released is sufficient to antagonize the vasconstrictor effects of the amines and even to cause a fall of the perfusion pressure; after indomethacin, lack of prostaglandin synthesis and release allows the catecholamines to exert their vasconstrictor effects, causing the perfusion pressure to increase substantially. In the isolated and perfused spleen of the dog the effects of adrenaline infusions were generally increased after indomethacin (Ferreira, Moncada & Vane, 1971), and in the cat spleen responses to noradrenaline were augmented after indomethacin (Ferreira, Moncada & Vane, 1973).

Regarding the nature of neurogenic vasodilatation in the spleen and in the hind-limb, it may be concluded that, since ergotamine did not affect the former but abolished the latter, the mechanisms involved appear to be different.

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