ist necessary if misinterpretations of experimental results are to be avoided. We thank Prof. Dr. Schümann for allowing us to conclude these experiments in his institute.

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Arachidonic acid lowers and indomethacin increases the blood pressure of the rabbit

Studies on the effects of exogenous prostaglandins (PG) of the E and A-type on vascular resistance have shown them to be among the most potent of all naturally occurring vasodilatators (Karim & Somers, 1972) Normally, the prostaglandins do not act on a tissue after release into the blood stream but are formed locally. They are inactivated by the ubiquitous 15-hydroxy prostaglandin dehydrogenase (PGDH) and other enzymes, either close to the site of action or in the lung and other tissues following release into the blood (Änggård, 1971). It might therefore be more interesting from a physiological view point to study the effects of locally produced endogenous prostaglandins. It has been proposed that since the availability of the precursor acid at its site of formation appears to be the rate limiting factor in the formation of PG (Samuelsson, 1970), the endogenous formation of PG might be enhanced by the administration of large doses of the C_{20} polyenoic precursor acids (Änggård, 1970). Conversely the formation of endogenous prostaglandins can be blocked by indomethacin and related compounds (Smith & Willis, 1971; Vane, 1971; Hamberg & Samuelsson, 1972). We now report that intra-arterial infusion of arachidonic acid in rabbits lowers the blood pressure. This is prevented by indomethacin or 5,8,11,14-eicosatetraynoic acid (TYA), two PG synthesis inhibitors, which conversely produce an increase in the resting blood pressure.

Five male white New Zealand rabbits (2·5–3·5 kg) were anaesthetized with 1–2 g kg^{-1} of urethane. A polyethylene catheter was inserted from the femoral artery into the descending aorta above the origin of the renal arteries for infusion of arachidonic acid and indomethacin. Blood pressure was monitored from the right femoral artery, from which arterial blood was also sampled. Urine was collected from catheters inserted into the urethers. Arachidonic acid was stored frozen under nitrogen as the methyl ester. One to two hours before use the ester was hydrolysed, the acid purified by

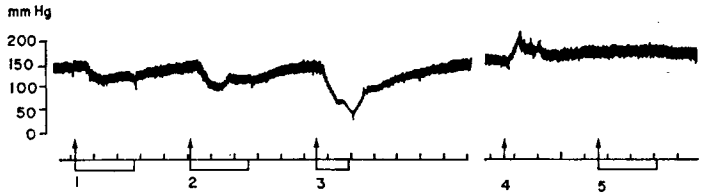

FIG. 1. The effects of arachidonic acid and indomethacin on the rabbit blood pressure. Arachidonic acid was infused intra-arterially at rates of 33 μg kg^{-1} min^{-1}(3 and 5), 55 μg kg^{-1} min^{-1} (2) and 100 μg kg^{-1} min^{-1} (3). Indomethacin (15 mg kg^{-1}) was injected intra-arterially at 4. The time interval was indicated every two min.

silicic acid chromatography, converted to the sodium salt in saline and diluted to a final concentration of 2 mg ml^{-1} with an equal volume of rabbit plasma. Indomethacin (Merck, Sharp and Dohme) was given in a dose of 10–20 mg kg^{-1} dissolved (10 mg ml^{-1}) in 0·1 M potassium phosphate buffer pH 8 and TYA (Roche) in a dose of 10 mg μg^{-1} dissolved like arachidonic acid. Prostaglandins were isolated from urine using XAD-2 (Gréen, 1971) and silicic acid chromatography and estimated by bioassay in combination with prostaglandin dehydrogenase inactivation (Ånggård & Jonsson, 1971).

Arachidonate induced a dose-dependent decrease in the blood pressure. Infusion rates of 15–25 μg kg^{-1} min^{-1} reduced the blood pressure by 10·4 $\pm$ 1·7% (s.d.), 30–45 μg kg^{-1} min^{-1} by 21 $\pm$ 3%, 50–90 μg^{-1} kg min^{-1} by 34 $\pm$ 5·7%, and 95–150 μg kg^{-1} min^{-1} by 61 $\pm$ 8·7%. The infusion of arachidonate was associated by an increase (70%$\pm$) in the urinary output of prostaglandins mainly PGE_2. Following the intra-arterial injection of indomethacin, or of TYA, the blood pressure increased by 19·5 $\pm$ 1·3% ($P<0.001$) and subsequent infusions of the arachidonate (50–200 μg kg^{-1} min^{-1}) failed to elicit any hypotensive effects or an increase in the urinary output of PG. The injection of vehicle for arachidoate, indomethacin or TYA had no effect on the blood pressure. A representative experiment is shown in Fig. 1.

That the hypotensive effect of arachidonate observed in this study was mediated by the formation of prostaglandins was suggested by the findings that (1) the fall of blood pressure was associated with an increased output of renal prostaglandins, which is an index of endogenous renal prostaglandin synthesis (Fröhlich, Sweetman & others, 1973), and that (2) the effects of arachidonate on the blood pressure and on the urinary output of prostaglandins were blocked by indomethacin and TYA, two structurally different PG-synthesis inhibitors. Arachidonic acid is thus a pharmacological tool which by enhancing local PG synthesis may be used to study the physiological role of the PG system, assuming that this is the precursor at the site involved.

The observation that the administration of indomethacin or TYA regularly had a hypertensive effect suggests a role for endogenous prostaglandins in regulating the blood pressure in the rabbit.

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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.