rebound hypertension (20–30 mmHg) above pretreatment levels and also a marked tachycardia.

In conscious renal hypertensive dogs ($n=5$) with blood pressure recorded from chronically implanted arterial cannulae, clonidine pretreatments (3 x 0.15 mg p.o. for 4 or 10 day periods) produced sustained falls in blood pressure and marked bradycardia. In the 3 mongrel dogs a rebound hypertension (40–80 mmHg) and tachycardia was observed after completion of either treatment (day 5 or 11) but rebound hypertension was not observed in beagle dogs ($n=2$). The mechanism of this rebound hypertension on clonidine withdrawal remains to be investigated but it would seem that two experimental models are available for this study.

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The effects of β-adrenoceptor blockade on the development of deoxycorticosterone acetate (DOCA) hypertension in the dog

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Salt-loading in dogs with partial nephrectomy has been shown to produce hypertension which is dependent upon an elevation of cardiac output (Coleman & Guyton, 1969; Cowley & Guyton, 1975) followed by autoregulation and an increase in vascular resistance. It seemed possible therefore to examine this process during the development of DOCA hypertension. We have produced a model of DOCA hypertension in the dog in which it was possible to evaluate the effects of β-adrenoceptor blockade during the developmental stages to determine the role of changes in cardiac output.

Male beagle dogs (13.0–15.5 kg) were chronically implanted with carotid artery and jugular vein vinyl catheters from which blood pressure (BP) and cardiac output (CO dye-dilution) measurements were made. Plasma volume (PV) was measured by the Evans Blue method and extracellular fluid volume (ECFV) by determination of the thiocyanate space. Several weeks after unilateral nephrectomy, DOCA (1.0 g) was implanted subcutaneously in 5 dogs, and 3 days later they were given a drinking solution containing 1.0% NaCl, 0.25% KCl and 0.25% sugar *ad libitum* for a further 15 days. At the end of this period, drinking water containing 0.25% KCl and 0.25% sugar was provided. A group of 4 dogs similarly treated were given atenolol 150 mg twice daily during the saline drinking period to investigate the effect of β-blockade on the development of the hypertension.

In dogs receiving DOCA and saline alone there was an increase over 7 days in systolic BP 149 ± 3.3 to 182 ± 9.0 mmHg ($P<0.01$) and in diastolic BP 86 ± 1.9 to 111 ± 4.6 mmHg ($P<0.01$). These changes were sustained and were accompanied by an initial reduction in heart rate (HR) from 81 ± 4.3 to 60 ± 4.2 bts/min which gradually returned to control values. There was a small increase in CO of approximately 0.48 l/min after 7 days and total peripheral resistance (TPR) increased by 30% after 3 days but these changes were not statistically significant. PV increased from 917 ± 26 to 1116 ± 57 ml and ECFV 4.98 ± 0.20 to 5.94 ± 0.581 ($P<0.05$) at day 7 but returned to control values at day 14.

In the group receiving atenolol along with DOCA and saline, the BP rose as it did in the last group from 138 ± 4.8 to 189 ± 3.8 mmHg systolic ($P<0.01$) and 85 ± 4.5 to 113 ± 4.3 mmHg diastolic ($P<0.01$). HR fell from 90 ± 8.9 to 50 ± 11.6 bts/min (day 14), CO was reduced during the first 7 days from 2.30 ± 0.17 to 1.91 ± 0.29 l/min ($P<0.05$). This effect was more pronounced by day 14 when CO was 1.63 ± 0.07 l/min ($P<0.01$, TPR increased progressively over 14 days from 3696 ± 242 to 6289 ± 356 dynes sec cm^{-1} ($P<0.002$). The changes in PV and ECFV showed a small upward trend which was not statistically significant.

In control experiments in 4 normotensive dogs, atenolol 150 mg p.o. twice daily produced a small fall in BP from 145 ± 7.0 to 130 ± 5.0 mmHg systolic and 80 ± 7.0 to 58 ± 4.0 mmHg diastotic ($P<0.01$) over a period of 24 days.

In conclusion therefore DOCA and saline produced an elevation in blood pressure which was associated with an increase in both cardiac output and peripheral resistance and an expansion of plasma and extracellular fluid volumes. β-Adrenoceptor blockade did not prevent the development of DOCA/saline hypertension in spite of the fact that it prevented a rise in cardiac output.

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The presence of prostaglandin-like material in carrageenin induced rat hind paw inflammation

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The involvement of prostaglandins (PGs) in the delayed phase of carrageenin hind paw oedema (Di Rosa, Giroud & Willoughby, 1971) is generally accepted. Direct evidence for this assumption is based on bioassay of exudate, squeezed out of amputated inflamed paws (Willis, 1969). However, data on non-inflamed paws or on time of collection were not reported. These omissions are important since tissue damage and concomitant platelet aggregation are likely to produce PGs. To avoid this pitfall we used a coaxial perfusion technique (Rocha e Silva & Antonio, 1960) to collect part of the exudate.

Male Wistar rats (180–250 g) were anaesthetized with urethane (25%) – chloralose (2%). Polythene cannulae (diameter 3 mm) were inserted, subcutaneously, through a small incision in the lateral skin of the tarsus, and pushed into the subplantar region. Perfusion with 6% dextran in sterile pyrogen-free saline was carried out with an innercannula (diameter 1 mm) extending 3–4 mm. After removal of traces of blood (30 min, 4 ml/h), the perfusion was continued (30 min, 2 ml/h) to obtain a basal measurement of PG-like activity (PGL). Thereafter, either sodium-carrageenin (0.1 ml, 1%) or saline was injected subplantarly. Biological activities in perfusates, collected (30 min, 2 ml/h) at different times after these injections, were tested directly on a cascade of isolated tissues (rat stomach, rat colon and cat jejunum) in the presence of appropriate antagonists. No serotonin (<1 ng/paw) or bradykinin-like activities (<0.5 ng/paw) were detectable. The results concerning PGL are given in Table 1.

Table 1 Collection of prostaglandin-like activity (PGL) from rat hind paws before (–30 min) and after treatment with carrageenin or saline

Treatment Perfusion time	*Saline PGL (ng PGE_2/paw)*	*Carrageenin PGL (ng PGE_2/paw)*
–0.5–0 h	<1.0 (8)	<1.0 (10) 1.1 (1)
1–1.5 h	<1.0 (2)	<1.0, 1.3 (2)
2–2.5 h	<1.0 (2)	2.0 (1)
4–4.5 h	<1.0 (2)	2.9 ± 0.3 (4)*
6–6.5 h	<1.0 (2)	3.3 ± 1.2 (4)*

The values are expressed as ng PGE_2/paw since the efficiency of the perfusion in removing PGs from the exudate is difficult to estimate. All values are means ± s.e. mean. The numbers of observations are given in brackets. * $P < 0.05$, when compared with zero-time controls. (Mann-Whitney *U* test, one-tailed).

These data directly support the assumption (Di Rosa *et al.*, 1971) that PGs are present in the late phase of carrageenin oedema. However, the total amount *in situ* is probably higher. Since PGL was undetectable in saline pretreated paws it is unlikely that tissue irritation by the prolonged presence of cannulae is a source of PGL under these conditions. Similar results were obtained with lipid extracts from perfusates, collected at 4 h after carrageenin or saline injection when cannulae were installed immediately after sacrificing the rats or immediately after indomethacin pretreatment (2 mg/kg i.v.) of rats under pentobarbitone anaesthesia.

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