the results of Schneider & Drazen (1980). Since $PGI_2$ was described as a pulmonary vasodilator (Kadowitz et al 1978), the contribution of vascular smooth muscles to the myotropic activity of the lung parenchymal strip appears to be minor. Our results also confirm the relaxant activity of $PGE_2$ on the lung strip (Chand & DeRoth 1979; Schneider & Drazen 1980).

Leukotriene $B_4$ was very active, especially on guinea-pig smooth muscle. Although the duodenum appeared the most sensitive tissue studied, the stability of the lung parenchymal strip afforded better assessment of the biological activity of this lipoxygenase product. The doses we used were high and the response of the lung strips to histamine and $LTB_4$ difficult to compare, but experiments not presented in this paper have shown that $LTB_4$ is 50–100 times more potent than histamine on this preparation.

In conclusion, this report has analysed the comparative myotropic effects of selected mediators on rat, guinea-pig, rabbit and chick smooth muscles. However, tissue concentrations of these substances have to be determined before any conclusions can be drawn on their physiological role in hypersensitivity or inflammatory reactions.

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REFERENCES

Bergstrom, S. Carlson L. A., Weeks, J. R. (1968) Pharmacol. Rev. 20: 1–48

Borgeat, P., Samuelsson, B. (1979a) Proc. Natl. Acad. Sci. USA 76: 2148–2152

Borgeat, P., Samuelsson, B. (1979b) Ibid. USA 76: 3213–3217

Chand, N., DeRoth, L. (1979) J. Pharm. Pharmacol. 31: 712–714

Dept of Pharmacology of the University of Edinburg (1970) Pharmacological experiments on isolated preparations, Churchill Livingstone, Edinburg.

Gagnon, D. J., Sirois, P. (1972) Br. J. Pharmacol. 46: 89–93

Hammarstrom, S., Murphy, R. C., Samuelsson, B., Clark, D. A., Mioskowski, C., Corey, E. J. (1979) Biochem. Biophys. Res. Commun. 91: 1266–1272

Kadowitz, P. J., Chapnick, B. M., Feigen, L. P., Hyman, D. L., Nelson, P. K., Spannhake, E. W. (1978) J. Appl. Physiol. 45: 408–413

Moncada, S., Mugridge, K. G., Whittle, B. J. R. (1977) Br. J. Pharmacol. 61: 451 P-452P

Murphy, R. C., Hammarstrom, S., Samuelsson, B. (1979). Proc. Natl. Acad. Sci. USA 76: 4275–4279

Samuelsson, B., Borgeat, P., Hammarstrom, S., Murphy, R. C. (1980) in: (eds) Samuelsson, B., Ramwell, P. W., Paoletti, R. Advances in Prostaglandin and Thromboxane Research, Vol. 6, 1–18, Raven Press, New York

Schneider, M. W., Drazen, J. M. (1980) Am. Rev. Resp. Dis. 121: 835–842

Sirois, P., Borgeat, P. (1980) Int. J. Immunopharmacol. 2: 281–293

Sirois, P. Borgeat, P., Jeanson, A., Roy, S., Girard, G. (1980) Prostaglandins Med. 5: 429–444

Vane, J. R. (1957) Br. J. Pharmacol. Chemother. 12: 344–349

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# Vascular reactivity to vasopressin in doca-salt hypertensive rats

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Plasma concentrations of arginine vasopressin are elevated in doca-salt hypertensive rats, and their blood pressure is lowered by antagonists of this peptide (Mohring et al 1977; Crofton et al 1979). These observations have prompted the suggestion that vasopressin plays a role in maintaining peripheral resistance in this form of hypertension (Mohring 1978). However, the plasma concentrations of vasopressin in doca-salt hypertensive rats are apparently insufficient to exert a direct vasoconstrictor effect, unless a large increase in 'vascular reactivity' to this peptide has occurred. In the present study, vasoconstrictor responses to vasopressin, noradrenaline and adrenergic nerve stimulation have been compared in isolated mesenteric arteries from doca-salt hypertensive and normotensive rats, to determine whether reactivity to vasopressin is increased and if this increase is of greater magnitude than that seen for other vasoconstrictor stimuli.

Doca-salt hypertension was induced in Alderley Park Wistar rats (80–100 g, either sex), by a subcutaneous implant of desoxycorticosterone acetate (75 mg) and the substitution of 0·8% NaCl for drinking water. Six to eight weeks after this procedure the systolic blood pressure of these rats (196·2 ± 6·4 mmHg, n = 13) was significantly greater ($P < 0.001$) than the blood pressure of untreated control rats (127·7 ± 5·5 mmHg, n = 13, tail cuff method, Gerold & Tschirky 1968). The weights of doca-salt hypertensive (234·9 ± 5·0 g, n = 13) and of control rats (235·6 ± 5·0 g, n = 13) were not significantly different.

Pairs of normotensive and hypertensive animals were anaesthetized (pentobarbitone sodium, 60 mg $kg^{-1}$ i.p.) and their mesenteric arteries cannulated and perfused at a constant flow of 6·0 ml $min^{-1}$ with Krebs solution (37 °C) bubbled with 95% $O_2$ 5% $CO_2$ (McGregor 1965). Arginine vasopressin (Sigma) and (−)-noradren-

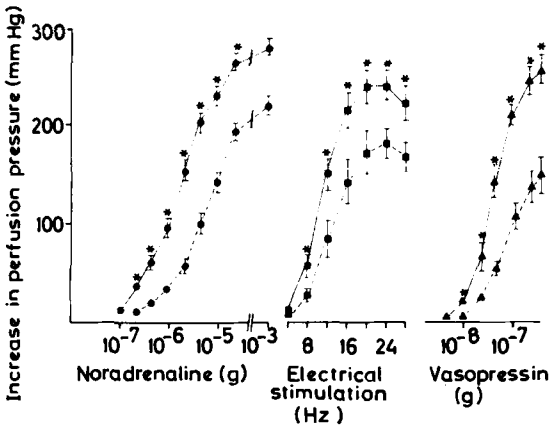


FIG. 1. Log-dose response curves for noradrenaline (n = 12, ●), arginine vasopressin (n = 6, ▲) and frequency response curves to adrenergic nerve stimulation (n = 10, ■) in mesenteric artery preparations from normotensive (- - -) and doca-salt hypertensive rats (——) * response amplitude in preparation from hypertensive rat significantly different ($P < 0.05$) from control.

aline bitartrate (Sigma) were injected in volumes of 0·02–0·08 ml through a rubber tube close to the mesenteric artery cannula. The noradrenergic nerves supplying the mesenteric arteries were electrically stimulated (2 ms pulse width, supramaximal voltage, 28–32 V, 30 s trains of stimuli) via periarterial platinum electrodes.

The basal perfusion pressures (at a flow rate of 6·0 ml $min^{-1}$) of mesenteric artery preparations from doca-salt hypertensive (19·3 ± 1·6 mmHg, n = 13) and from normotensive control rats (19·0 ± 1·5 mmHg, n = 13) were not significantly different. However the amplitudes of vasoconstrictor responses evoked by noradrenaline ($2 \times 10^{-7}$ —$10^{-3}$ g) and by vasopressin ($8 \times 10^{-9}$ —$4 \times 10^{-7}$ g) were significantly greater in preparations from hypertensive than from normotensive animals (Fig. 1). Consequently, the dose-response curves for these two agonists in preparations from hypertensive rats were displaced to the left of the control. The magnitude of this displacement was assessed by the log dose-ratio (control/hypertensive, at a response level of 100 mmHg) and this was not significantly different for the two agonists (noradrenaline log dose-ratio = 0·68 ± 0·10; vasopressin log dose-ratio = 0·48 ± 0·10). Preparations from hypertensive rats exhibited a lower vasoconstrictor threshold for noradrenaline and for vasopressin than those from normotensive rats. Vasoconstrictor responses evoked by electrical stimulation (8–24 Hz) were also of significantly greater amplitude in preparations from hypertensive rats than in those from the control animals (Fig. 1).

These results demonstrate that vascular reactivity to vasopressin is increased in mesenteric artery preparations from doca-salt hypertensive rats. The magnitude of this increase was similar to that observed when noradrenaline or nerve stimulation were used as the vasoconstrictor stimulant (Fig. 1). This non-specific increase in vascular reactivity exhibited characteristics of both an increased vascular wall to lumen ratio (*increased maximum response*), and of vascular supersensitivity (lower vasoconstrictor threshold, Collis & Alps 1975). However, the results do not support the possibility that the concentrations of vasopressin reported to occur in doca-salt hypertensive rats could have a direct pressor action. For this to occur, Mohring (1978) has suggested that a shift to the left of the vasopressin dose-response curve of 14 fold at the threshold dose and of more than 1000-fold at the upper part of the dose-response curve would be necessary. The present study demonstrates only a 2–6 fold shift in the vasopressin curve. Therefore if vasopressin does play a role in maintaining doca-salt hypertension it is not through a direct vasoconstrictor effect.

## REFERENCES

Collis, M. G., Alps, B. J. (1975) Cardiovasc. Res. 9: 118–126

Crofton, J. T., Share, L., Shade, R. E., Lee-Kwon, W. J., Manning, M., Sawyer, W. H. (1979) Hypertension 1: 31–38

Gerold, M., Tschirky, H. (1968) Arzneim. Forsch. 18: 1285–1287

McGregor, D. D. (1965) J. Physiol. (London) 177: 21–30

Mohring, J., Mohring, B., Petin, M., Haack, D. (1977) Am. J. Physiol. 232: F260–269

Mohring, J. (1978) Klin. Wochenschr. 56: (Suppl 1), 71–79