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Studies on the renin response to vasoactive intestinal polyeptide (VIP) in the conscious rabbit

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Vasoactive intestinal polypeptide (VIP) has been found within the renal cortex and is believed to be a neurotransmitter. Although it produces systemic vasodilatation and renin release, the exact mechanism of the latter response is uncertain. When infused into conscious rabbits, VIP elicits a rise in plasma renin activity (PRA) and an increase in heart rate. The rise in PRA is unaltered by pretreatment with propranolol, but is attenuated by indomethacin. The tachycardia is inhibited by propranolol, but unaffected by indomethacin. We conclude that the renin response to VIP is in part prostaglandin-dependent and that the heart rate response is due to direct or reflex β-adrènoceptor stimulation.

Introduction Vasoactive intestinal polypeptide (VIP)-like material has been found within nerves of the renal cortex (Hökfelt, Schultzberg, Elde, Nilsson, Terenius, Said & Goldstein, 1979) and VIP is a potent stimulus to renin release (Porter, Reid, Said & Ganong, 1980). The mechanism of the renin response is unknown, but vasodilator substances like VIP (Said, 1981) can produce renin release through reflex sympathetic stimulation (Pettinger, Campbell & Keeton, 1973), as well as activation of the intrarenal baroreceptor (Peart, 1978). The baroreceptor mechanism (afferent arteriole stretch) is thought to be prostaglandin-dependent, but whether or not the adrenergic pathway involves local prostaglandin release is controversial (Oates, Whorton, Gerkens, Branch, Hollifield & Frölich, 1979; Weber & Wolfgang, 1982).

In this study, we examined the relative importance of prostaglandins and reflex sympathetic activation in the haemodynamic and renin responses to VIP. We studied the effects of β-adrenoceptor blockade and cyclo-oxygenase inhibition on VIP-induced changes in pulse, blood pressure and renin release in conscious rabbits.

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Methods Studies were performed in 9 Sandy Halflop rabbits. Each rabbit underwent 3 separate infusions in random order and at intervals of at least 7 days. The animals were prepared for study in identical fashion. They were fed a standard laboratory diet (RHM R14, Labsure Animal Diets) until 3 h before each infusion. An ear vein and artery were cannulated under lignocaine local anaesthesia. Heart rate and arterial blood pressure were recorded continuously. Each rabbit rested quietly for at least 1 h before infusion. An intravenous dose of 25 pmol kg^{-1} min^{-1} VIP was used in all experiments.

VIP alone (n = 9) Each rabbit received an intravenous infusion of the vehicle alone for 30 min. The vehicle consisted of 1 g l^{-1} rabbit albumin in 50 g l^{-1} glucose solution (isotonic). The volume rate in all experiments was 13.33 ml h^{-1}. VIP was then infused for 30 min. Arterial blood samples were taken 5 min before the end of the vehicle and VIP infusions respectively.

VIP after propranolol (n = 7) Vehicle was infused together with (±)-propranolol (Inderal, ICI Ltd.), 3.2 mg kg^{-1} over 30 min. This dose has been previously shown to produce complete β-adrenoceptor blockade in the rabbit (Gordon, Roddis & Sever, 1980). VIP was then infused for 30 min. Blood samples were taken 5 min before the start and 5 min before the end of the VIP infusion.

VIP after indomethacin (n = 8) Indomethacin (Merck, Sharp and Dohme Ltd.) was infused at a constant rate over 15 min in a dose of 10–15 mg kg^{-1}. The indomethacin was first dissolved in dehydrated ethanol 20 mg ml^{-1}, which was then diluted with NaCl solution (9 g l^{-1}: saline) containing 1 mg sodium bicarbonate per 4.5 ml saline as described by Scott (1980). The final concentration of indomethacin was 3.5 mg ml^{-1}. This dose has been previously shown to inhibit prostaglandin synthesis and depress renin levels (Larsson, Weber & Anggard, 1974) After 15 min, the vehicle was infused for 30 min. This was follwed by a 30 min infusion of VIP. Blood samples were taken for renin estimation be-

Table 1 Range of plasma vasoactive intestinal polypeptide (VIP)-like immunoreactivity concentrations before and during each set of infusions together with changes in plasma renin activity, heart rate and mean arterial blood pressure

		Plasma VIP (pmol l^{-1})		*Plasma renin activity** (ng ml^{-1} h^{-1})		*Heart rate* (beats min^{-1})		*Mean blood pressure* (mmHg)	
	n	Before	During	Before	During	Before	During	Before	During
VIP alone	9	<10	460–1100	4.9±0.8	13.3±4.1[a]	201±6	271±9[a]	80±3	76±5
VIP + propranolol	7	<10	550–850	5.2±1.1	11.6±3.0[a]	187±11	210±7[b]	81±6	78±6
VIP + indomethacin	8	<10	400–720	3.8±0.6	5.3±0.8[ab]	198±10	283±11[a]	76±2	63±2[ab]

Values are given as mean ± s.e., *n* is number of observations. *Geometric mean and s.e. for log normally distributed data. [a] signifies $P<0.01$ comparing 'Before' with 'During' and [b] signifies $P<0.05$ for comparisons *between* each set of infusions *during* VIP infusion.

fore and 45 min after indomethacin, and 5 min before the VIP infusion was stopped. Blood samples were taken for VIP estimation before the start of the VIP infusion and 5 min before it ended.

PRA and plasma VIP were measured by radioimmunoassay (Dimaline & Dockray, 1978; Sever, Peart, Davies, Tunbridge & Gordon, 1979). Mean arterial blood pressure was calculated as 2/3 diastolic pressure plus 1/3 systolic pressure in mmHg. Significance of changes within each set of infusions was assessed by a paired *t* test and between each set of infusions by two-way analysis of variance. PRA was found to approximate the log normal distribution and logarithmic transformations were used in the analysis. The mean value given for this variable is the geometric mean and approximate standard error of mean (s.e.). Other results are expressed as arithmetic mean ± s.e.

Results VIP alone produced a 2–3 fold rise in PRA ($P<0.001$) and a 50% increase in heart rate ($P<0.01$), but little change in mean blood pressure. (Table 1).

Prior treatment with propranolol did not significantly affect the renin response to VIP, but did inhibit the increase in heart rate. This inhibition was significant when compared with the response during VIP alone and after indomethacin ($P<0.001$), Propranolol did not alter the resting blood pressure and heart rate. Adequate β-adrenoceptor blockade was confirmed by the absence of blood pressure and heart rate responses to bolus injections of 10–20μg isoprenaline and lack of renin rise after 6 μg isoprenaline.

Indomethacin did not change the resting mean blood pressure, heart rate or PRA, nor did it influence the VIP-induced tachycardia. It did inhibit the renin response to VIP infusion. VIP after indomethacin produced a small but significant fall in mean blood pressure ($P<0.01$).

Discussion The VIP-induced rise in renin was unaffected by propranolol, but inhibited by indomethacin. This suggests involvement of prostaglandins in the renin response, perhaps through intrarenal baroreceptor stimulation, rather than reflex sympathetic activation and β-adrenoceptor stimulation. Although indomethacin may have actions that are independent of cyclo-oxygenase inhibition, such as phosphodiesterase inhibition (Newcombe, Thanassi & Coisek, 1974), or intrinsic vasoconstrictor activity, at the dose described it has not been found to alter renal function (Dunn & Zambraski, 1980).

Propranolol abolished the VIP-induced tachycardia suggesting that this effect is due to either direct or reflex β-adrenoceptor stimulation. Chatelain, Robberecht, De Neef, Deschodt-Lanckman, Konig & Christophe, 1980 have demonstrated the presence of specific VIP receptors. From our results it seems unlikely that these receptors are involved in the chronotropic action of VIP.

Propranolol and indomethacin did not alter resting blood pressure, but after indomethacin, VIP infusion produced a fall in mean blood pressure. If the adrenergic pathway to renin release is independent of prostaglandin synthesis (Oates *et al.*, 1979), the fall in blood pressure during VIP infusion after indomethacin would be expected to produce renin release through enhanced reflex sympathetic activity. As this did not occur, it seems likely that prostaglandins are involved in the adrenergic pathway. The fall in blood pressure may reflect the reduced renin response, and by inference, diminished circulating levels of angiotensin-II. It is also possible that loss of pressor prostaglandins, e.g. thromboxanes, which are also dependent on the cyclo-oxygenase pathway, might be a factor. Non-steroidal anti-inflammatory agents such as indomethacin are known to inhibit the vascoconstriction produced by thromboxanes and may alter the balance between these and 'depressor prostaglandins', such as prostacyclin (Smith, Schmunk & Lefer, 1981).

The secretory and cerebral vasodilator effects of VIP are also inhibited by indomethacin (Albuquerque, Owens & Bloom, 1979; Wei, Kontos & Said, 1980). This drug may be of value in patients with disorders associated with excess circulating VIP (Friesen, 1982).

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