Br. J. Pharmac. (1987), **91**, 307–314

Renal effects of gastrin C-terminal tetrapeptide (as pentagastrin) and cholecystokinin octapeptide in conscious rabbit and man

[1]J. Calam, D. Gordon, W.S. Peart, S.A. Taylor & [2]R.J. Unwin

Medical Unit, St. Mary's Hospital Medical School, Norfolk Place, London W2 1PG

1 Pentagastrin and cholecystokinin octapeptide (CCK8) were infused i.v. at three different doses in two sets of 4 conscious rabbits following a repeated measurements design (130, 1,300 and 13,000 pmol kg^{-1} min^{-1} pentagastrin; 5, 50 and 450 pmol kg^{-1} min^{-1} CCK8). In man, two different doses of pentagastrin (13 and 65 pmol kg^{-1} min^{-1}) were infused in two groups of 6 subjects, and CCK8 (2 pmol kg^{-1} min^{-1}) in a third group. According to published human postprandial levels, plasma CCK8-like immunoreactivity concentrations were supraphysiological at all doses infused.

2 In the rabbit, pentagastrin produced a dose-related fall in urine flow and free water clearance, but no significant change in systemic and renal haemodynamics, electrolyte excretion and measured plasma constituents; however, in human subjects, pentagastrin increased renal sodium excretion and reduced potassium excretion but did not change glomerular filtration rate.

3 In the rabbit, CCK8 produced a dose-related fall in plasma renin activity, plasma calcium concentration and mean arterial blood pressure; dose-dependent increases in effective renal plasma flow, glomerular filtration rate and renal sodium excretion. In man, changes in sodium and potassium excretion similar to pentagastrin were observed; there were no significant changes in plasma renin activity, plasma calcium concentration, blood pressure, effective renal plasma flow or glomerular filtration rate.

4 The pharmacological renal effects of pentagastrin in conscious water-loaded rabbits resemble vasopressin. In contrast, CCK8's most striking effect was vasodilatation and was unusual in inhibiting rather than stimulating renin release. In man the *net* changes in urine composition found during infusion of these peptides are similar to those produced by the potassium-sparing diuretics, amiloride and triamterene. However the generally weak renal effects observed, even at pharmacological doses, indicate that these peptides are unlikely to influence renal function under normal physiological conditions.

Introduction

Several forms of gastrin have been identified which differ according to the number of C-terminal peptide residues: G34, G17 and G14. G34 and G17 are the major forms found in blood and tissue and both are released into the circulation after a meal; they are equipotent in terms of gastric acid stimulation, G34 having a plasma half-life some six times longer than G17 (Eysselein *et al.*, 1984). G17 may also be converted to other active C-terminal fragments (Dockray *et al.*, 1981). The C-terminal tetrapeptide of gastrin has all the biological actions of the whole molecule and is shared by cholecystokinin (CCK) (Gregory, 1974). More recently the biologically active C-terminal octapeptide of CCK (CCK8) has been found in high concentrations in brain and peripheral neurones (Rehfeld *et al.*, 1979). Apart from its presence in myenteric nerves and in some nerves to the urogenital tract (Rehfeld, 1980), neural CCK8 has not been found in the kidney.

The haemodynamic changes observed after feeding in dogs (Fronek & Stahlgren, 1968), in particular the increases in renal blood flow and sodium excretion (independent of dietary sodium), have been attributed

[1] Present address: Department of Gastroenterology, Royal Postgraduate Medical School, Du Cane Road, London W12
[2] Author for correspondence at: Department of Physiology, Yale University School of Medicine, P.O. Box 3333, New Haven, Ct. 06510, U.S.A.

to changes in circulating levels of gastrointestinal hormones such as gastrin (Reinhardt *et al.*, 1975) and glucagon (Premen *et al.*, 1985). Similar changes have been observed in man, with reports of a direct relationship between increased glomerular filtration rate and dietary protein (Pullman *et al.*, 1954): one group postulating mediation by a liver-derived hormone (Alvestrand & Bergström, 1984), but another failing to find any correlation with circulating levels of endogenous gut hormones (Farrington *et al.*, 1984). Thus, there is still no clear hormonal candidate for this response; although both pentagastrin (C-terminal gastrin tetrapeptide amide plus N-t-BOC-β-alanine) and pancreatic glucagon infusion in conscious dogs, increase renal blood flow (Gatzka *et al.*, 1975; Premen *et al.*, 1985).

Continuing this search for possible mediators of postprandial changes in renal function, we have studied the renal effects of pentagastrin and CCK8 infusion in conscious rabbits and human subjects.

Methods

Study protocols

Rabbit study Experiments were performed on male Sandy Half-lop rabbits (3–5 kg wt) chosen for their convenient size. Two different groups of 4 rabbits were infused i.v. with pentagastrin (Peptavlon, ICI, UK) and sulphated CCK8 (CRB, Cambridge, UK) according to a random block or Latin square experimental design, respectively, for each of three doses (pentagastrin: 130, 1,300 and 13,000 pmol kg^{-1} min^{-1}; calculated CCK8: 5, 50 and 450 pmol kg^{-1} min^{-1}, and one control). The detailed protocol has been described previously (Dimaline *et al.*, 1983). Briefly, vascular and urethral catheters were inserted under lignocaine local anaesthesia. Each infusion consisted of an initial fluid load (25 ml kg^{-1} 0.28 M glucose over 20 min) followed by a maintenance infusion (0.57 ml min^{-1}) during which eight 20 min urine collections were made (U1–8), with intervals of 10 min. Renal clearances of the continuously infused radioactive compounds ^{51}Cr-labelled ethylene diaminetetraacetate (EDTA; 0.74 kBq min^{-1}) and sodium *p*-[^{125}I]-aminohippurate (Hippuran; 1.48 kBq min^{-1}) were used to estimate glomerular filtration rate (GFR) and effective renal plasma flow (ERPF), respectively. Each control or treatment infusion was begun at 5 min before the start of the third urine collection (U3) and continued until the end of the sixth urine collection (U6). Arterial blood samples were taken (2–2.5 ml), and arterial blood pressure (BP) and heart rate (HR) recorded at the midpoint of each urine collection.

Human study Three sets of human infusion experiments were completed in three groups of 6 subjects: two with pentagastrin at two different doses and one with CCK8 at a single dose. Each protocol was approved by the local Ethics Committee and all 17 healthy volunteers (4 female: no oral contraception) aged 22–35 years gave informed consent; one male participated in both pentagastrin experiments and only males took part in the CCK8 experiment.

In each experiment there was an initial 3 day equilibrium period during which subjects abstained from alcohol, smoking and vigorous exercise and ate a daily diet providing ca. 150 mmol sodium, 2100 kcal and 2.5 l of water. Subjects then fasted overnight. Before 08 h 30 min on the day of study, a peripheral vein in each arm was cannulated with a Teflon plastic cannula (Abocath, Abbott): one for blood sampling and the other for infusion. During each study subjects stood (female subjects sat or squatted, using a bedpan) to pass urine every 30 min (U1–7), but were otherwise recumbent. Between 08 h 00 min and 08 h 30 min an oral water load of 10 ml kg^{-1} was given; thereafter subjects drank water at a rate equal to their urine flow during the preceding 30 min. Sodium *para*-aminohippurate (PAH) infusion and endogenous creatinine clearance were used to estimate ERPF and GFR, respectively (Calam *et al.*, 1983).

Pentagastrin (13 or 65 pmol kg^{-1} min^{-1}) or sulphated CCK8 (calculated dose: 2 pmol kg^{-1} min^{-1}) was infused i.v. during the three urine collections between 11 h 00 min and 12 h 30 min (U3–5) in a vehicle consisting of 50:50 v/v Haemaccel (degraded gelatine 35 g l^{-1}, average mol. wt. 35,000; Hoechst, UK) as carrier and 0.28 M glucose, at a rate of 13.33 ml h^{-1}. Vehicle alone was given during the four control (two basal and two recovery) urine collections U1–2 and U6–7. At the midpoint of each urine collection venous blood was taken (15 ml); HR and arterial BP were recorded by an automated sphygmomanometer (Dinamapp, Criticon, Florida, U.S.A.). Renal blood flow (RBF) was calculated from packed cell volume (PCV) and ERPF, assuming renal PAH extraction of 0.9.

Laboratory analyses of plasma and urine

Previously described techniques (Calam *et al.*, 1983) were used to measure electrolytes, including calcium and phosphate, PAH, creatinine, PCV and plasma renin activity (PRA; by radioimmunoassay). CCK8-like immunoreactivity concentrations (CCK8-LI) were determined by radioimmunoassay using a C-terminal specific CCK/gastrin antibody (Calam *et al.*, 1982).

Data analysis

Mean arterial BP (MBP) was calculated as 2/3 dias-

tolic plus 1/3 systolic pressures and filtration fraction (FF) as the ratio GFR/ERPF.

Rabbit data Data were analysed by 2-way analysis of variance (ANOVA) (factors: rabbit and treatment) with weight and time as covariates, followed by multiple comparisons with the control if appropriate (Dunnett, 1964); $P < 0.05$ was considered significant. In both studies, the results given are based on the observations made during U4, U5 and U6, when a steady state had been achieved. They are expressed as mean ± s.e.mean, except if lognormally distributed when given as geometric mean ± s.e.mean, as indicated.

Human data Comparisons were made between observations obtained during the basal (control) collection periods U1 and U2, with those obtained during collections U4 and U5, when a steady state had been achieved during peptide infusion. The data were analysed by Student's paired t test; $P < 0.05$ was considered significant. Data presented are based on the observations made during collections U1 and U2, U4 and U5, and collection U7 (second recovery). Results are expressed as mean ± s.e.mean, $n = 6$.

Results

Systemic and renal haemodynamics

Rabbit No consistent dose-dependent changes in MBP (control; 84 ± 4 to high dose; 87 ± 7 mmHg) or HR (control; 228 ± 12 to high dose; 249 ± 15 beats min^{-1}) occurred during pentagastrin infusion. During CCK8 infusion, MBP fell at the middle and high doses (control; 71 ± 2 to 61 ± 3 and 57 ± 3 mmHg, respectively; $P < 0.05$), and HR decreased at the high dose (control; 268 ± 8 to 235 ± 4 beats min^{-1}; $P < 0.05$). Pentagastrin caused no significant changes in ERPF (control; 46.4 ± 6.6 to high dose; 58.6 ± 9.0 ml min^{-1}), GFR (12.5 ± 1.6 to 15.7 ± 2.7 ml min^{-1}) or FF (27.7 ± 0.8 to 26.7 ± 1.6%); CCK8 produced dose-related increases in ERPF and GFR, ca. 30–40% at the high dose (49.3 ± 4.1 to 65.9 ± 2.9 ml min^{-1} and 9.6 ± 1.0 to 13.8 ± 0.4 ml min^{-1}, respectively; $P < 0.05$), but no significant change in FF (19.1 ± 0.8 to 21.7 ± 0.9%).

Man BP and HR were recorded in only two subjects during infusion of 13 and 65 pmol kg^{-1} min^{-1} of pentagastrin (not shown), and did not change. Pen-

Table 1 Plasma composition and renal electrolyte excretion during pentagastrin and cholecystokinin octapeptide (CCK8) infusion in conscious rabbits

	Control (vehicle only)	*Pentagastrin* (pmol kg^{-1} min^{-1}) 130 (low)	1,300 (middle)	13,000 (high)	n
[PNa] (mmol l^{-1})	138.3 ± 0.5	140.6 ± 1.0	138.2 ± 0.4	138.3 ± 1.5	11
[PK] (mmol l^{-1})	3.97 ± 0.02	4.06 ± 0.05	*3.62 ± 0.06	3.64 ± 0.10	11
[PCa] (mmol l^{-1})	2.57 ± 0.14	2.90 ± 0.14	*3.13 ± 0.06	2.96 ± 0.09	7
PCV (%)	34 ± 1	36 ± 1	35 ± 2	35 ± 1	4
# PRA (ng h^{-1} ml^{-1})	19.9 ± 1.7	25.2 ± 1.2	27.2 ± 2.1	24.2 ± 2.7	7
# [UNa]V (μmol min^{-1})	6.6 ± 1.4	6.9 ± 1.5	*3.4 ± 0.7	8.1 ± 1.6	11
# [UK]V (μmol min^{-1})	5.0 ± 0.8	7.2 ± 1.2	6.2 ± 1.0	5.8 ± 0.6	11
# [UCa]V (μmol min^{-1})	1.01 ± 0.31	0.38 ± 0.13	0.64 ± 0.26	0.68 ± 0.21	10
		CCK8 (pmol kg^{-1} min^{-1}) 5	50	450	
CCK8-LI (pmol l^{-1})	< 10	10 – 157	677 – 937	4877 – 15877	4
[PNa] (mmol l^{-1})	135.8 ± 0.5	137.7 ± 1.4	135.8 ± 0.6	134.4 ± 0.6	12
[PK] (mmol l^{-1})	3.52 ± 0.08	**4.04 ± 0.09	*3.20 ± 0.09	**3.21 ± 0.07	12
[PGlu] (mmol l^{-1})	7.6 ± 0.3	8.5 ± 0.5	9.7 ± 1.0	**12.7 ± 1.1	8
PCV (%)	36 ± 1	**33 ± 2	*34 ± 1	35 ± 1	8
# [UNa]V (μmol min^{-1})	5.5 ± 1.7	3.1 ± 0.7	*13.9 ± 1.7	**23.0 ± 6.6	12
# [UK]V (μmol min^{-1})	7.3 ± 1.1	6.5 ± 1.0	5.6 ± 0.6	7.2 ± 0.9	12
# [UCa]V (μmol min^{-1})	1.49 ± 0.62	1.31 ± 0.62	**0.41 ± 0.10	**0.60 ± 0.10	12

Values are mean ± s.e.mean; # log-transformed (geometric mean ± s.e.mean); n = number of repeated observations; ** $P < 0.01$; * $P < 0.05$, compared with control by Dunnett's test after ANOVA. Abbreviations: [PNa], etc., plasma concentration (Glu, glucose); PCV, packed cell volume; PRA, plasma renin activity; CCK8-LI, plasma CCK8-like immunoreactivity; [UNa]V, etc., renal excretion rate.

tagastrin did not alter RBF (low dose; 18.0 ± 1.8 to 15.5 ± 1.6 and high dose; 16.1 ± 1.6 to 17.0 ± 1.1 ml min^{-1} kg^{-1} body wt), nor GFR (2.1 ± 0.1 to 2.1 ± 0.1 and 2.0 ± 0.3 to 2.1 ± 0.1 ml min^{-1} kg^{-1}, respectively). A small, but statistically significant, increase in MBP and HR occurred during CCK8 infusion (92 ± 3 to 96 ± 3 mmHg; $P < 0.05$ and 57 ± 3 to 61 ± 4 beats min^{-1}; $P < 0.02$, respectively), but did not recover after infusion; RBF and GFR did not change (17.8 ± 1.6 to 16.9 ± 2.0 and 2.1 ± 0.1 to 2.0 ± 0.2 ml min^{-1} kg^{-1}, respectively).

Urine composition

Rabbit (Table 1) There was no consistent change in the pattern of renal electrolyte excretion during pentagastrin infusion; although falling at the middle dose, sodium excretion tended to increase at the high dose. A dose-related fall in urine flow and free water clearance occurred (Figure 1), with only a small increase in osmolar clearance (control; 200.5 ± 28.4 to high dose; 292.4 ± 34.3 μl min^{-1}; $P > 0.05$). Excretion of sodium more than doubled during infusion of the middle and high doses of CCK8, but renal potassium excretion was unchanged. Renal chloride excretion (not shown) followed sodium and renal calcium excretion fell by more than half at the middle and high doses; renal phosphate excretion rose slightly (control; 0.41 ± 0.15 to high dose; 0.61 ± 0.14 μmol min^{-1}), but did not reach statistical significance. Urine flow did not change even at the high dose (121.0 ± 36.7 to 123.5 ± 29.1 μl min^{-1}), although there was an increase in osmolar clearance (137.7 ± 38.7 to 388.0 ± 69.2 μl min^{-1}; $P < 0.01$) and thus a fall in calculated free water clearance (29.1 ± 48.1 to − 289.8 ± 42.0 μl min^{-1}; $P < 0.01$).

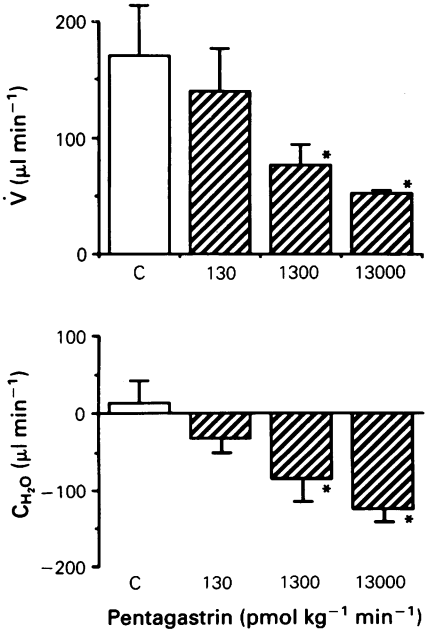

Figure 1 Effect of increasing doses of pentagastrin on rabbit urine flow rate ($\dot{V}$) and free water clearance (C_{H_2O}). $\dot{V}$, log-transformed (geometric mean ± s.e.mean); $n = 11$ repeated observations in each treatment group; $^*P < 0.05$ compared with control by Dunnett's test after ANOVA.

Man (Tables 2 and 3) Mean 24 h renal sodium excretion just before the study was 130 ± 16 mmol ($n = 16$).

Both doses of pentagastrin increased renal sodium excretion and decreased potassium excretion; urine flow, osmolar clearance, free water clearance and calcium excretion were unchanged. CCK8 produced similar effects, with increased sodium and decreased potassium excretions, both by about 15%, approximately half the response to pentagastrin. In each case sodium excretion recovered promptly after infusion. CCK8 also caused a small increase in phosphate excretion.

Plasma composition

Rabbit Table 1 shows the mean values for plasma electrolytes, PCV and PRA during control, pentagastrin and CCK8 infusions, and the range of plasma CCK8-LI levels recorded; plasma pentagastrin concentrations were not measured. There was little change during pentagastrin infusion; CCK8 increased plasma glucose concentration and produced dose-related falls in plasma calcium and phosphate concentrations, and PRA (Figure 2).

Man (Tables 2 and 3) Neither dose of pentagastrin produced significant changes in plasma composition, apart from a small decrease in PRA at the high dose. CCK8 had no effect; the mean rise in CCK8-LI 1 h after the start of CCK8 infusion was 31 ± 7 pmol l^{-1}, some 2–5 times reported postprandial levels (Dockray, 1982).

Discussion

Table 4 summarizes some of the complex renal and hormonal effects observed during pentagastrin and CCK8 infusion in conscious rabbits and man. Despite apparent differences, and although doses were not comparable, there was some similarity of action within, rather than between, species, particularly in man.

Main effects in rabbit and man

In both species it is not easy to separate potentially direct, from indirect, secondary hormonal, effects. In the rabbit, pentagastrin, at much higher molar doses than CCK8, caused significant dose-related falls in urine flow and free water clearance, a vasopressin-like pattern, not produced by CCK8. At high doses, CCK8's actions were largely vascular with systemic and renal vasodilatation, but also renin suppression and an effect on plasma calcium and phosphate levels; this last effect may be through secondary release of calcitonin and parathormone (Stulberg *et al.*, 1976; Vantini *et al.*, 1981). In contrast, both peptides in man had quite similar, yet limited effects, causing small increases in sodium excretion and decreases in potas-

Table 2 Plasma composition, renal electrolyte and water excretion during pentagastrin infusion in man

	Basal (vehicle only)	*Pentagastrin* (13 pmol $kg^{-1} min^{-1}$)	P *value*	*Recovery* (U7)
[PNa] (mmol l^{-1})	138.4 ± 0.7	139.7 ± 1.0	NS	—
[PK] (mmol l^{-1})	4.26 ± 0.08	4.21 ± 0.13	NS	—
# PRA (pg $h^{-1} ml^{-1}$)	1050 ± 409	858 ± 357	NS	—
[UNa]V (μmol $min^{-1} kg^{-1}$)	3.20 ± 0.41	3.97 ± 0.36	<0.01	3.72 ± 0.41
[UK]V (μmol $min^{-1} kg^{-1}$)	1.43 ± 0.21	0.99 ± 0.13	<0.02	0.98 ± 0.09
[UCa]V (μmol $min^{-1} kg^{-1}$)	0.15 ± 0.02	0.16 ± 0.01	NS	—
$\dot{V}$ (μl $min^{-1} kg^{-1}$)	170.6 ± 31.4	184.4 ± 24.7	NS	—
C_{H_2O} (μl $min^{-1} kg^{-1}$)	119.9 ± 29.6	127.2 ± 21.2	NS	—
		(65 pmol $kg^{-1} min^{-1}$)		
[PNa] (mmol l^{-1})	140.8 ± 1.1	141.6 ± 1.3	NS	—
[PK] (mmol l^{-1})	4.29 ± 0.14	4.05 ± 0.14	NS	—
# PRA (pg $h^{-1} ml^{-1}$)	695 ± 187	490 ± 89	<0.01	506 ± 86
# [PAldo] (pmol l^{-1})	262 ± 45	204 ± 18	NS	—
[UNa]V (μmol $min^{-1} kg^{-1}$)	3.32 ± 0.40	4.77 ± 0.51	<0.01	3.68 ± 0.59
[UK]V (μmol $min^{-1} kg^{-1}$)	1.69 ± 0.22	1.07 ± 0.13	<0.01	0.94 ± 0.17
[UCa]V (μmol $min^{-1} kg^{-1}$)	0.15 ± 0.02	0.15 ± 0.02	NS	—
$\dot{V}$ (μl $min^{-1} kg^{-1}$)	166.9 ± 30.2	167.9 ± 27.0	NS	—
C_{H_2O} (μl $min^{-1} kg^{-1}$)	113.3 ± 31.2	115.7 ± 27.2	NS	—

Values mean ± s.e.mean; $n = 6$; # log-transformed (geometric mean ± s.e.mean); P value obtained by paired t test; NS = non-significant ($P > 0.05$). Abbreviations: [PNa], etc., plasma concentration (Aldo, aldosterone); PRA, plasma renin activity; [UNa]V, etc., renal excretion rate; $\dot{V}$ urine flow rate; C_{H_2O}, free water clearance.

Table 3 Plasma composition, renal electrolyte and water excretion during cholecystokinin octapeptide (CCK8) infusion in man

	Basal (vehicle only)	*CCK8* (2 pmol $kg^{-1} min^{-1}$)	P *value*	*Recovery* (U7)
[PNa] (mmol l^{-1})	140.3 ± 0.7	140.5 ± 0.4	NS	—
[PK] (mmol l^{-1})	4.30 ± 0.10	4.28 ± 0.11	NS	—
# PRA (pg $h^{-1} ml^{-1}$)	1037 ± 288	1130 ± 298	NS	—
[UNa]V (μmol $min^{-1} kg^{-1}$)	4.76 ± 0.91	5.44 ± 0.93	<0.02	4.67 ± 0.95
[UK]V (μmol $min^{-1} kg^{-1}$)	1.69 ± 0.37	1.45 ± 0.34	<0.05	1.01 ± 0.24
[UCa]V (μmol $min^{-1} kg^{-1}$)	0.06 ± 0.01	0.05 ± 0.01	NS	—
[UPi]V (μmol $min^{-1} kg^{-1}$)	0.21 ± 0.04	0.27 ± 0.03	<0.01	0.21 ± 0.04
$\dot{V}$ (μl $min^{-1} kg^{-1}$)	153.6 ± 23.9	143.2 ± 25.0	NS	—
C_{H_2O} (μl $min^{-1} kg^{-1}$)	93.2 ± 18.7	81.0 ± 20.8	NS	—

Values mean ± s.e.mean; $n = 6$; # log-transformed (geometric mean ± s.e.mean); P value obtained by paired t test; NS = non-significant ($P > 0.05$). Abbreviations: [PNa], etc., plasma concentration; PRA, plasma renin activity; [UNa]V, etc., renal excretion rate; $\dot{V}$, urine flow rate; C_{H_2O}, free water clearance.

sium excretion; an overall effect resembling the potassium-sparing diuretics, amiloride and triamterene (Reineck & Stein, 1981). The rise in plasma glucose concentration observed during CCK8 infusion in the rabbit may, or may not, be direct (Unger *et al.*, 1967; Dockray, 1981), but could be a factor in CCK8-induced appetite suppression (Dockray, 1982).

Free water clearance, plasma and urinary calcium and phosphate

The vasopressin-like action of pentagastrin in the rabbit, including the lack of change in potassium excretion (Field *et al.*, 1984), suggests either an intrinsic vasopressin-like effect on distal nephron water permeability, or stimulation of endogenous vasopressin release or other vasopressin-like hormone. Both gastrin and CCK have been found in the hypothalmohypophysial system and may regulate anterior and posterior pituitary hormone release (Beinfeld, 1983; Rehfeld *et al.*, 1985; Vanderhaeghan *et al.*, 1985). However, in rabbits, pentagastrin infusion does not seem to increase plasma vasopressin levels (Unwin, Hanson & Lightman, unpublished observations); although unchanged plasma vasopressin concentrations do not exclude endogenous release (Dixey *et al.*, 1986). Free water clearance can also be affected by altered solute transport in the nephron thick ascending limb: (1) in the absence of changes in vasa recta blood flow, and therefore dissipation of the cortico-medullary solute gradient, inhibition of sodium reabsorption in this segment would impair free water generation, and together with an amiloride or triamterene-like effect on distal tubular sodium reabsorption and potassium secretion, could account for some of the net urinary changes observed (Hropot *et al.*, 1985); (2) increased solute reabsorption in this segment together with increased collecting duct water permeability would be more vasopressin-like, with true urine concentration.

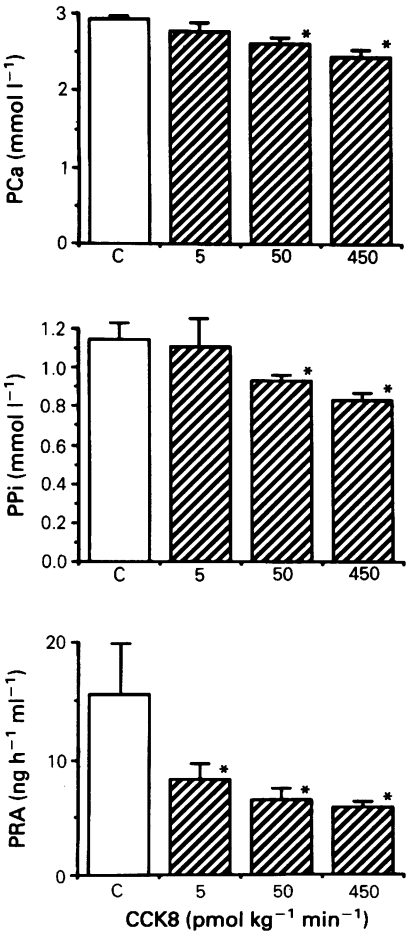

Figure 2 Effect of increasing doses of cholecystokinin octapeptide (CCK8) on plasma calcium and phosphate concentrations (PCa, PPi) and plasma renin activity (PRA). PRA, log-transformed (geometric mean ± s.e.mean); $n = 12$ (PCa, PPi), $n = 8$ (PRA) repeated observations in each treatment group; $*P < 0.05$ compared with control by Dunnett's test after ANOVA.

As indicated above, gastrin-related peptides are potent stimuli to calcitonin and parathromone release, and in the rat calcitonin is antidiuretic, stimulating solute transport (chiefly Mg^{2+}, Ca^{2+} and K^+) in the thick ascending limb and/or increasing collecting duct water permeability (de Rouffignac & Elalouf, 1983; Elalouf *et al.*, 1984); parathormone has no such effect (Elalouf *et al.*, 1986). Calcitonin is also natriuretic and hypocalcaemic (Berndt & Knox, 1980; Austin & Heath, 1981); therefore secondary calcitonin release might well explain some of the effects observed in both species during infusion of these peptides. Unfortunately, in the rabbit, the observations that the effects on plasma and urinary calcium and phosphate were more marked with CCK8, and that phosphaturia is not a useful index of parathormone activity (Peart *et al.*, 1986), make interpretation difficult.

Renal sodium excretion and plasma renin activity

The much greater sodium excretion seen during CCK8 infusion in the rabbit is probably explained by the increase in filtered load (cf. inhibition of intestinal water and electrolyte absorption, and increased mucosal blood flow; Go, 1978) and the fall in PRA, through a consequent effect on the macula densa (increased NaCl delivery; Churchill *et al.*, 1978), or via a more general effect on cellular calcium movement (Peart, 1978; Petersen, 1982). The role of the macula densa in controlling renin release is still not clear;

Table 4 Summary of changes observed during pentagastrin and cholecystokinin octapeptide (CCK8) infusion in conscious rabbits and man

	MBP	*ERPF* (RBF)	*GFR*	*[UNa]V*	*[UK]V*	*[UCa]V*	C_{H_2O}	*PRA*	*[PAldo]*
Pentagastrin									
Rabbit	→	↑	↑	↑	→	↓	↓	→	—
Man	→	→	→	↑	↓	→	→	*↓	*→
CCK8									
Rabbit	↓	↑	↑	↑	→	↓	↓	↓	—
Man	↑	→	→	↑	↓	→	→	→	—

Abbreviations: MBP, mean blood pressure; ERPF(RBF), effective renal plasma flow (rabbit) and renal blood flow (man); [UNa]V, etc., renal excretion rate; C_{H_2O}, free water clearance; PRA, plasma renin activity; [PAldo], plasma aldosterone concentration. Arrows indicate increase, decrease or no change, dashed arrow a non-significant ($P > 0.05$) trend and — not measured; *high dose only.

moreover renal vasodilators usually increase sodium excretion and stimulate renin release (Peart, 1978). Parathormone increases PRA (Smith *et al.*, 1979; Peart *et al.*, 1986), hypocalcaemia and calcitonin have no effect (Llach *et al.*, 1974; Smith *et al.*, 1979), but a direct increase in juxtaglomerular cytosolic calcium would inhibit renin release (Peart, 1978; Fray, 1980). CCK8 is believed to stimulate pancreatic enzyme secretion by a change in acinar cell calcium flux resulting in elevation of intracellular calcium (Christophe & Waelbroeck, 1981; Petersen, 1982). A similar effect on the juxta-glomerular cell might well account for the dose-dependent fall in PRA seen during CCK8 infusion in the rabbit, and the small fall at the higher dose of pentagastrin in man.

Whether pentagastrin and CCK8 have any direct intrinsic effect on distal nephron sodium and potassium reabsorption, and whether any apparent amiloride/triamterene-like effect in man is significant, cannot be deduced from these experiments. To take this analogy further, a comparative study in for example, the rabbit isolated collecting duct, would be necessary.

In conclusion, the effects of these peptides in two different species and at different doses are complicated by several indirect effects. A more specific action on distal tubular sodium and potassium handling cannot be ruled out, but it seems unlikely that these peptides make any significant contribution to postprandial changes in renal function.

We are particularly grateful to Carol Hanson for expert technical assistance, Francis Stone for assaying renin, Guy Rickett for assaying aldosterone and Amabel Shih for help with the Tables and Figures. Thanks also to Professors Giebisch, Green and Berliner for helpful discussion. R.J.U. was an M.R.C. Training Research Fellow and is now a Wellcome Senior Clinical Research Fellow.

References

ALVESTRAND, A. & BERGSTROM, J. (1984). Glomerular hyperfiltration after protein ingestion, during glucagon infusion, and in insulin-dependent diabetes is induced by a liver hormone: deficient production of this hormone in hepatic failure causes hepatorenal syndrome. *Lancet*, **i**, 195–197.

AUSTIN, L.A. & HEATH, H. (1981). Calcitonin: physiology and pathophysiology. *New Engl. J. Med.*, **304**, 269–278.

BEINFELD, M.C. (1983). Cholecystokinin in the central nervous system: a minireview. *Neuropeptides*, **3**, 411–427.

BERNDT, T.J. & KNOX, F.G. (1980). Effects of parathyroid hormone and calcitonin on electrolyte excretion in the rabbit. *Kidney Int.*, **17**, 473–478.

CALAM, J., DIMALINE, R., PEART, W.S., SINGH, J. & UNWIN, R.J. (1983). Effects of vasoactive intestinal polypeptide on renal function in man. *J. Physiol.*, **345**, 469–475.

CALAM, J., ELLIS, A. & DOCKRAY, G.J. (1982). Identification and measurement of molecular variants of cholecystokinin in duodenal mucosa and plasma. Diminished concentrations in patients with coeliac disease. *J. clin. Invest.*, **69**, 218–225.

CHRISTOPHE, J. & WAELBROECK, M. (1981). Receptor theory. In *Gut Hormones*. ed. Bloom, S.R. & Polak, J.M. pp. 127–132. Edinburgh: Churchill Livingstone.

CHURCHILL, P.C., CHURCHILL, M.C. & McDONALD, F.D. (1978). Renin secretion and distal tubule sodium Na^+ in rats. *Am. J. Physiol.*, **235**, F611–616.

DIMALINE, R., PEART, W.S. & UNWIN, R.J. (1983). Effects of vasoactive intestinal polypeptide (VIP) on renal function and plasma renin activity in the conscious rabbit. *J. Physiol.*, **344**, 379–388.

DIXEY, J.J., WILLIAMS, T.D.M., LIGHTMAN, S.L., LANT,

A.F. & BREWERTON, D.A. (1986). The effect of indomethacin on the renal response to arginine vasopressin in man. *Clin. Sci.*, **70**, 409–416.

DOCKRAY, G.J. (1981). Cholecystokinin. In *Gut Hormones*. ed. Bloom, S.R. & Polak, J.M. pp. 228–239. Edinburgh: Churchill Livingstone.

DOCKRAY, G.J. (1982). The physiology of cholecystokinin in brain and gut. *Br. med. Bull.*, **38**, 253–258.

DOCKRAY, G.J., GREGORY, R.A., TRACY, H.J. & ZHU, WEN-YU. (1981). Heptadecapeptide gastrin: conversion to COOH-terminal fragments in dog plasma. *J. Physiol.*, **313**, 22P.

DUNNETT, C.W. (1964). New tables for multiple comparisons with a control. *Biometrics*, **20**, 482–491.

ELALOUF, J.M., ROINEL, N. & DE ROUFFIGNAC, C. (1984). ADH-like effects of calcitonin on electrolyte transport by Henle's loop of rat kidney. *Am. J. Physiol.*, **246**, F213–F220.

ELALOUF, J.M., ROINEL, N. & DE ROUFFIGNAC, C. (1986). Effects of glucagon and PTH on the loop of Henle of rat justamedullary nephrons. *Kidney Int.*, **29**, 807–813.

EYSSELEIN, V.E., MAXWELL, V., REEDY, T., WUNSCH, E. & WALSH, J.H. (1984). Similar acid stimulating potencies of synthetic human big and little gastrins in man. *J. clin. Invest.*, **73**, 1284–1290.

FARRINGTON, K., EL NAHAS, A.M., HILSON, A.J.W., GORNACZ, G., BLOOM, S.R. & MOORHEAD, J.F. (1984). Gut hormones and glomerular hyperfiltration. *Lancet*, **i**, 636.

FIELD, M.J., STANTON, B.A. & GIEBISCH, G.H. (1984). Influence of ADH on renal potassium handling: a micropuncture and microperfusion study. *Kidney Int.*, **25**, 502–511.

FRAY, J.C.S. (1980). Stimulus-secretion coupling of renin. Role of haemodynamic and other factors. *Circulation Res.*, **47**, 485–492.

FRONEK, K. & STAHLGREN, L.H. (1968). Systemic and regional haemodynamic changes during food intake and digestion in non-anaesthetised dogs. *Circulation Res.*, **23**, 687–692.

GATZKA, M., REINHARDT, H.W., FAHRENHORST, K., KACZMARCZYK, G., RIEDEL, J. & KUHL, U. (1975). Effect of pentagastrin on renal blood flow in conscious dogs. *Pflugers Arch* (Suppl.), **359**, 115.

GO, V.L.W. (1978). The physiology of cholecystokinin. In *Gut Hormones*. ed. Bloom, S.R. pp. 203–207. Edinburgh: Churchill Livingstone.

GREGORY, R.A. (1974). The gastrointestinal hormones: a review of recent advances. *J. Physiol.*, **241**, 1–32.

HROPOT, M., FOWLER, N., KARLMARK, B. & GIEBISCH, G. (1985). Tubular action of diuretics: distal effects on electrolyte transport and acidification. *Kidney Int.*, **28**, 477–489.

LLACH, F., WEIDMANN, P., REINHART, R., MAXWELL, M.H., COBURN, J.W. & MASSRY, S.G. (1974). Effect of acute and long-standing hypocalcaemia on blood pressure and plasma renin activity in man. *J. clin. Endocrinol. Metab.*, **38**, 841–847.

PEART, W.S. (1978). Renin release. *Gen. Pharmac.*, **9**, 65–72.

PEART, W.S., RODDIS, S.A. & UNWIN, R.J. (1986). Renal electrolyte excretion and renin release during calcium and parathormone infusions in conscious rabbits. *J. Physiol.*, **373**, 329–341.

PETERSEN, O.H. (1982). Mechanisms of action of hormonal and neuronal peptides on exocrine gland cells. *Br. med. Bull.*, **38**, 297–302.

PREMEN, A.J., HALL, J.E. & SMITH, M.J. (1985). Postprandial regulation of renal haemodynamics: role of pancreatic glucagon. *Am. J. Physiol.*, **248**, F656–F662.

PULLMAN, T.N., ALVING, A.S., DERN, R.J. & LANDOWNE, M. (1954). The influence of dietary protein intake on specific renal functions in normal man. *J. Lab. clin. Med.*, **44**, 320–332.

REHFELD, J.F., HANSEN, H.F., MARLEY, P.D. & STENGAARD-PEDERSEN, K. (1985). Molecular forms of cholecystokinin in the brain and the relationship to neuronal gastrins. In *Neuronal Cholecystokinin*. ed. Vanderhaeghan, J-J. & Crawley, J.N. *Ann. N.Y. Acad. Sci.*, **448**, 11–23.

REHFELD, J.F. (1980). Cholecystokinin. In *Clinics in Gastroenterology, Gastrointestinal Hormones*. ed. Creutzfeldt, W. Vol. 9, pp. 593–607. London: Saunders.

REHFELD, J.F., GOLTERMANN, N., LARSSON, L-I., EMSON, P.M. & LEE, C.M. (1979). Gastrin and cholecystokinin in central and peripheral neurons. *Fedn. Proc.*, **38**, 2325–2329.

REINECK, H.J. & STEIN, J.H. (1981). Mechanisms of action and clinical uses of diuretics. In *The Kidney*. ed. Brenner, B.M. & Rector, F.C. p. 1106. Philadelphia: Saunders.

REINHARDT, H.W., KACZMARCZYK, G., FAHRENHORST, K., BLENDINGER, I., GATZKA, M., KUHL, U. & RIEDEL, J. (1975). Postprandial changes in renal blood flow. Studies on conscious dogs on a high and low sodium intake. *Pflugers Arch.*, **354**, 287–297.

DE ROUFFIGNAC, C. & ELALOUF, J.M. (1983). Effects of calcitonin on the renal concentrating mechanism. *Am. J. Physiol.*, **245**, F506–F511.

SMITH, J.M., MOUW, D.R. & VANDER, A.J. (1979). Effect of parathyroid hormone on plasma renin activity and sodium excretion. *Am. J. Physiol.*, **236**, F311–F319.

STULBERG, B., NORBERG, H.P. & KAPLAN, E.L. (1976). Cholecystokinin, a new hypocalcaemic agent. *Surg. Forum*, **27**, 430–431.

UNGER, R.H., KETTERER, H., DUPRE, J. & EISENTRAUT, A. (1967). Effects of secretin, pancreozymin and gastrin on insulin and glucagon secretion in anaesthetized dogs. *J. clin. Invest.*, **46**, 1630–1642.

VANDERHAEGHAN, J-J., GOLDMAN, F. LOTSTRA, VAN REATH, O., DESCHAPPER, C., ROSSIER, J. & SCHIFFMANN, S. (1985). Co-existence of cholecystokinin- or gastrin-like peptides with other peptides in the hypophysis and the hypothalamus. In *Neuronal Cholecystokinin*. ed. Vanderhaeghan, J-J. & Crawley, J.N. *Ann. N.Y. Acad. Sci.*, **448**, 334–344.

VANTINI, I., COMINACINI, L., PIUBELLO, W., GHIDINI, O., FATTOVICH, G., EDERLE, A., BENINI, L., COCCHETTO, R., CAVALLINI, G., LOCASCIO, V. & SCRURO, L.A. (1981). Effect of gastrointestinal peptides containing the C-terminal tetrapeptide of gastrin on calcium, calcitonin and parathormone serum levels in man. *Hepato-Gastroenterol.*, **28**, 43–48.

(Received August 21, 1986.
Revised January 28, 1987.
Accepted February 18, 1987.)