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Renal Control of the Peripheral Uptake of Exogenous Gastrin in the Dog

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Abstract. The extraction of plasma gastrin during intravenous infusion of exogenous hormone has been measured in the head, gastrointestinal tract, or kidney of dogs submitted to sham surgery, evisceration, or binephrectomy without or with subsequent kidney transplantation. A significant gastrin extraction was demonstrated not only in the kidney, but also in the head and in the gastrointestinal tract; moreover, plasma gastrin extraction in the head and the bowel was considerably reduced by binephrectomy and was brought back to control values after subsequent kidney transplantation. A non-specific effect of surgery and a variation in peripheral blood flow seem to be excluded. Thus a control by the kidney of the peripheral removal of blood gastrin is evidenced, the mechanism of which remains hypothetical.

Key words: Gastrin metabolism – Kidney

Introduction

Many clinical and experimental investigations have demonstrated that the kidney plays a major part in the removal of gastrin from the blood (Korman et al. 1972; Becker et al. 1973; Booth et al. 1973; Clendinnen et al. 1973; Davidson et al. 1973, 1974; Gedde-Dahl 1975; Gedde-Dahl and Flatmark 1975; Thompson et al. 1975; Rayford et al. 1977; El Munshid et al. 1976; Taylor and Dockray 1976; Yamagata et al. 1976; Lundqvist et al. 1978a, b; Hohnke and Wilder 1978; Buijs 1979; Hansky 1979; Christensen et al. 1979; Hallgren et al. 1979; Muolo et al. 1979; Gold et al. 1980; Nielsen et al. 1980).

In the meantime, several authors have shown that gastrin is inactivated by other organs: lung (Rayford and Thompson 1977; Clendinnen et al. 1973); small bowel (Becker et al. 1973; Buijs 1979; Rayford and Thompson 1977; Thompson et al. 1975; Hartung et al. 1978; McGuigan 1977; Strauss et al. 1974; Wickbom et al. 1975), liver (Rayford and Thompson 1977; Clendinnen et al. 1973; Greco et al. 1979; Shiu 1976; Thompson et al. 1969), gastric fundus (Evans et al. 1974), whereas results from studies on hepatic uptake were contradictory (Thompson et al. 1975; Dencker et al. 1973; Reeder et al. 1972). Strunz et al. (1978) have provided evidence that gastrin is removed from the blood by various organs without predominant kidney uptake; these results have been confirmed for exogenous and endogenous gastrin by Thompson et al. (1979). Strunz et al. (1978) did not detect an inactivation of gastrin in the blood; this hormone does not seem to be secluded out of the capillary bed; the authors suggest that gastrin might be catabolized in the vascular endothelium or in the tissues.

If the kidney uptake of gastrin is not predominant as compared with other areas of the body, the magnitude of the effects of nephrectomy or of renal failure on the overall gastrin uptake are somewhat surprising. An explanation might be that the extrarenal removal of blood gastrin is also controlled to some degree by the kidney. The present experiments have been performed in order to test this hypothesis.

Methods

Mongrel dogs (10 – 22 kg) were anesthetized by intravenous injection of sodium pentobarbital (30 mg · kg^{-1}) followed by periodical supplementation under control of corneal reflexes. The trachea was cannulated and connected to a breathing pump. Body temperature was kept at 37.5° C with warming blankets. A continuous i.v. infusion of saline (154 mMol sodium chloride, 1 ml · min^{-1}) was established throughout the experiments. The femoral arterial pressure was recorded continuously with a mercury manometer. Six groups of experiments were performed. In *groups 1* (11 dogs) *and 2* (6 dogs), an initial laparotomy was made without other surgery; these groups served as references. In *group 3* (13 dogs), the animals were submitted to an initial binephrectomy; the adrenals were left in place with their vascular connections. In *group 4* (7 dogs), the gastrointestinal tract was removed from the cardia to the rectum together with the pancreas and the spleen; the liver was not removed but the portal vein and the hepatic arteries were tied; kidneys and adrenals were left in place ("eviscerated dogs"). In *group 5* (7 dogs), an initial binephrectomy was performed as in group 3, carotid artery and jugular vein were dissected in one side of the neck and were tied; two hours later, one kidney taken from a donor dog was transplanted by anastomosing the proximal end of the aorta to the carotid artery initially tied and the proximal end of the vena cava to the jugular vein with Pear's cannulas, thus avoiding the use of anticoagulants (Lichardus and Nizet 1972); the interruption of renal blood flow did not exceed 5 min. In this group the body weight of nephrectomized dogs and of kidney donors was comprized between 10 and 15 kg. In *group 6* (4 dogs), an initial laparotomy was performed as in groups 1 and 2; 90 min later, the animals were submitted to binephrectomy.

In *groups 1 – 5*, human purified gastrin 17 (Imperial Chemical Industries), dissolved in a solution containing 154 mMol sodium chloride and 0.05 mMol ammonium bicar-

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bonate, was infused intravenously at a constant flow rate of 1 ml · min^{-1}. In *groups 1, 2, 3 and 4*, the gastrin infusion started 1 h before the measurements of gastrin removal. In *groups 3 and 4*, the concentration of gastrin solution was reduced in order to reach comparable plasma levels despite the reduction in gastrin clearance in nephrectomized animals, or mass reduction in the eviscerated ones. The measurements of gastrin removal were made 90 min after induction of narcosis in group 1, and after 6 h in the groups 2, 3 and 4. In *group 5*, a priming dose of gastrin (0.03 µg · kg^{-1}) was injected intravenously 1 h after completion of binephrectomy and was followed by the continuous infusion at a rate of 0.12 µg · kg^{-1} · h^{-1}. In this group, the measurements of plasma gastrin removal were made 30 min before and 2 h after kidney transplantation.

In the five first groups, arterial plasma gastrin was measured immediately before gastrin infusion. Blood samples (3 ml) were drawn simultaneously from the femoral artery, and from jugular, portal or renal veins for the measurements of gastrin extraction in the head, bowel or kidney respectively. For each measurement, 6 arterial and venous samples were taken at 1 min intervals and the respective results of blood gastrin assays were pooled. The rate of blood gastrin removal, expressed in percent of arterial value, was calculated as follows:

$$\frac{\text{arterial concentration} - \text{venous concentration}}{\text{arterial concentration}} \times 100.$$

Plasma gastrin concentration was measured in duplicate in each blood sample by radioimmunoassay (Kit Commissariat à l'Energie Atomique, France; Gask, Institut National des Radio-éléments, Fleurus, Belgium). Human gastrin 1–17 was used as standard and ^{125}I labelled human gastrin as tracer; an antihuman gastrin was used as antibody and the separation of free and antibody-labelled hormone was performed using dextran charcoal. The identity of reactivity between dog and human gastrin was assayed by verifying the parallelism of dilution curves. The specificity of the antiserum supplied in the kit with respect to the immunoreactive gastrin species and circulating substances was shown by the inhibition curves given by the maker. The percentage of cross reactions was calculated, according to Abraham; as $X/Y \times 100$ (where X and Y are respectively the weight of the substance to be assayed and the weight of cross reactant that causes a 50 % inhibition of tracer binding.

1. Gastrin 1–17	100 %
2. Gastrin 2–17	73 %
3. "Big gastrin"	38 %
4. C.C.K.	3.5 %
5. Gastrin like pentapeptide	3.5 %

The sensitivity of the assay defined as the lowest detectable dose measured with an acceptable precision was 10 pg · ml^{-1}.

In *group 6*, cephalic blood flow was evaluated in each dog 45 and 15 min before nephrectomy and 45 and 75 min after removal of the kidneys. The blood flow measurement was performed by bolus injection of 200 µCi of 133 Xe into the common carotid artery, followed by an external detection of the time course of the radioactivity within the head by means of a shielded scintillation probe. Blood flow indexes were determined by a monoexponential fitting in cm^3 per min per unit mass of distribution of 133-Xenon (Sveinsdottir et al. 1970).

The significance of differences between mean values was by Student's t-test (unpaired values).

Results

In the control dogs submitted to laparotomy alone, a significant removal of plasma gastrin was observed in the kidney, the head and the gastrointestinal tract; no significant differences were found between the measurements 90 min (group 1) or 360 min (group 2) after narcosis; after binephrectomy (group 3), the percentage of gastrin removal was reduced to about one fourth of control values; in eviscerated dogs (group 4) the percentage of gastrin removal increased in the head and the kidney (Table 1). In group 5 (Table 2) the percentage of gastrin removal in the head was reduced to the same values as in group 3 and restored to the control values of groups 1 and 2 after the kidney transplantation.

The arterial blood pressure, after induction of narcosis and 6 h later, was 118 ± 5 and 122 ± 7 mm Hg respectively in control dogs, 126 ± 8 and 126 ± 5 mm Hg in the binephrectomized ones, 111 ± 6 and 87 ± 4 in the eviscerated ones, 114 ± 11 and 113 ± 8 mm Hg in the animals submitted to nephrectomy and transplantation. The arterial partial pressure in CO_2 was not significantly modified by binephrectomy.

Table 1. Blood gastrin removal by head, bowel or kidney in laparotomized, binephrectomized or eviscerated dogs

	Laparotomy		Binephrectomy	Evisceration
	Group 1	Group 2	Group 3	Group 4
Time from induction of narcosis (min)	90	360	360	360
Rate of gastrin infusion (µg · kg^{-1} · h^{-1})	0.23	0.24	0.14	0.19
Arterial gastrin concentration (pg · ml^{-1})	102 ± 11	127 ± 9	103 ± 9	130 ± 20
Gastrin removal (%)				
head	28.2 ± 2.2	26 ± 3.2	6.4 ± 1.9	35.7 ± 2
		$P < 0.001$	$P < 0.001$	
		$P < 0.02$		
bowel	29.6 ± 4.7[a]	32.1 ± 4.6	7.6 ± 2.4[b]	
		$P < 0.001$		
kidney		30.4 ± 3		43 ± 3.7
		$P < 0.01$		

Mean values ± SEM, [a] 6 experiments, [b] 7 experiments

Table 2. Effect of kidney transplantation upon peripheral removal of blood gastrin in previously binephrectomized dogs (group 5). Mean values ± SEM

	Before kidney transplantation	2 h after kidney transplantation
Arterial gastrin concentration ($pg \cdot ml^{-1}$)	88 ± 9	115 ± 13
Gastrin removal in the head (%)	8.3 ± 3.6	30.3 ± 4.9
	$P = 0.0025$	

The head blood flow indexes were respectively 34.8 ± 2.6 $cm^3 \cdot min^{-1} \cdot (100\ g)^{-1}$ before nephrectomy and 33.3 ± 2.3 $cm^3 \cdot min^{-1} \cdot (100\ g)^{-1}$ after binephrectomy (non significant difference).

The arterial plasma gastrin concentration, immediately before infusion of exogenous hormone, was 16.6 ± 2.2 pg $\cdot ml^{-1}$ in control dogs, significantly higher in nephrectomized dogs (24.7 ± 3.6 $pg \cdot ml^{-1}$; $P < 0.05$) and lower (although not significantly) in the eviscerated animals (12.8 ± 2.4 pg $\cdot ml^{-1}$).

Discussion

These results confirm the previous studies which provided evidence that gastrin is removed from the blood in several body areas of the dog (Strunz et al. 1978; Thompson et al. 1979). Moreover, the results point to a renal control of the extrarenal removal since its reduction was observed within 90 min after binephrectomy and since it was restored to control levels after subsequent kidney transplantation. The fall of peripheral removal cannot be due to the surgical trauma itself: the control animals were submitted to sham surgery and the very drastic procedure of evisceration increased the arterio-venous difference in gastrin concentration instead of reducing it; the best argument against a non-specific consequence of experimental procedure was provided by the correcting effect of kidney transplantation. One limitation of these experiments could be that no absolute measurements of plasma gastrin extraction were made since regional blood flows were not known; thus an evaluation of quantitative gastrin balance was not possible. However, if the decrease in arterio-venous differences were due to an increased blood flow and not to lower extraction rates, a fourfold increase in the blood flow should have been required to account for the observed values. Such a possibility was very unlikely since the arterial pressure remained stable throughout the experiments, with the exception of the eviscerated animals; in this latter group, a decrease in blood flow may have been responsible for the higher arterio-venous differences. An additional control was given by the experiments of group 6: the comparative measurements of cephalic blood flow demonstrated no significant change after binephrectomy.

It is worthwhile to point out that, in the experiments involving kidney transplantation, the neck vessels were tied initially; thus the correction effect of transplantation was not explainable by hemodynamic changes in cephalic circulation induced eventually by the unilateral interruption of blood flow in the carotid artery and in the jugular vein.

The higher levels of plasma gastrin concentration in nephrectomized dogs, before infusion of the hormone, are explainable by a decrease in overall extraction. Lower levels were to be expected after evisceration; it may be assumed that the decrease did not reach the level of significance because more individual measurements should be required at these low plasma hormone concentrations.

In additional, unpublished observations, we have controlled the fact that gastrin added to the blood in vitro is not significantly destroyed after 60 min incubation at 37° C; moreover, after Sephadex G_{50} chromatography of dog's blood enriched in human gastrin 1–17 by intravenous continuous infusion, we found the same peak of immunoreactivity in blood samples drawn from femoral artery, jugular, portal and renal veins.

The mechanism by which the kidney modulates the peripheral removal of blood gastrin is not known. Perhaps, the kidney releases an activator or eliminates an inhibitor of peripheral hormone catabolism; perhaps the rate of escape of gastrin out of the vascular space is under renal control. These points are under present investigation.

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