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Effects of Bradykinin on Renal Lymph Flow and Composition

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Summary

It has been reported that bradykinin causes permeability changes with increased vascular leakage in many peripheral tissues, but not in the renal parenchyma. In the present experiments, the effects of bradykinin on renal hilar lymph flow and concentrations of protein and PAH were studied. The results of these experiments show that the protein permeability of the intrarenal vessels from which lymph is derived is not altered by bradykinin. The data presented does, however, suggest that renal lymph may contain tubular reabsorbate, a component from the glomerulus, or both. In addition, data is presented which suggests that a significant amount of lymph may be formed in the renal medulla during renal vasodilation.

Renal lymph flow is known to increase in response to renal artery infusion of acetylcholine (1), prostaglandin E_2 and histamine (2). The mechanism of this response is most likely the result of an increased postglomerular intravascular hydrostatic pressure developed as a result of decreased vascular resistance (2). Changes in the renal lymph to blood plasma concentration ratio (L/P) for protein which would signal alterations in vascular protein permeability were not observed in these studies. Thus, intrarenal vascular structures from which renal lymph protein are derived appear to respond similarly to all three of the above substances, even though one of them (histamine) has notable effects on vascular permeability in non-renal tissues (3, 4). Similarly, bradykinin has been shown to increase vascular leakage in a variety of tissues (4, 5) with no effect on the postglomerular renal vasculature as indicated by colloidal carbon labelling (4). In the present experiments, these observations are extended by studying the effects of renal artery infusion of bradykinin on renal lymph flow and composition.

Methods

Seven mongrel dogs (body wt. = 20 to 30 kg), anesthetized with sodium pentobarbital, were used. The left kidney was exposed through a flank incision, and catheters were secured in the ureter, femoral artery, femoral vein, and renal vein *via* the gonadal vein. An electromagnetic flow meter probe was placed around the renal artery for continuous monitoring of renal blood flow (RBF) (Biotronix BL-613 blood flow meter). Arterial and venous blood pressures were monitored using resistance bridge transducers and a Grass polygraph. A hilar renal lymphatic vessel was catheterized for lymph collections. Renal artery infusion (RAI) was accomplished using a Harvard syringe pump attached to a 20 g hypodermic needle which was inserted through the wall of the renal artery. The RAI was delivered at 0.2 ml/min. During control periods, RAI consisted of 0.9% saline solution, and was changed to saline containing bradykinin (0.25 μg/kg/min) during experimental periods. Each animal received a sustaining infusion of 0.9% saline (2 ml/min) containing sufficient creatinine and PAH to maintain suitable plasma levels of these substances. Timed collections of lymph and urine were made in calibrated containers with midpoint collections of arterial and renal vein blood. In each case, collection time was 60 minutes or less. Sample collections were made during control conditions, during RAI of bradykinin, and during bradykinin infusion with RBF maintained at control by partial occlusion of the renal ar-

tery. For each experiment, one collection period was taken during control and each experimental condition. Restriction of RBF was accomplished by tightening a suture passed around the renal artery and through a short length of polyethylene tubing. Samples were analyzed for creatinine by the Jaffe reaction, for PAH by the method of *Smith* et al. (6) and for protein by a biuret reaction. Data reduction included calculation of lymph-to-plasma ratio based on arterial blood plasma (L/P), lymph clearances (LC) and lymph concentration indices (LCI). Whole kidney fluid reabsorption rate was calculated as GFR minus urine flow; LC and LCI were calculated as:

$$LC = L/VP \times \dot{V}L \text{ and } LCI = (AP-L)/(AP-VP)$$ where:

L = Renal Lymph Concentration
VP = Renal Venous Plasma Concentration
$\dot{V}L$ = Renal Lymph Flow
AP = Arterial Plasma Concentration

LC may be defined as the ml of renal venous blood plasma completely cleared of a substance by its loss through a single hilar lymphatic vessel and LCI presents an arterial plasma-renal lymph concentration difference as a decimal percent of the overall arteriovenous concentration difference.

An analysis of variance (repeated measure design) was used for statistical comparisons using the "F test" with $P < 0.05$ considered "statistically significant". Independent comparisons within each data set were made using the "Least Significant Difference".

Results

Bradykinin infusion did not significantly later GFR, whole kidney fluid reabsorption rate (FRR) lymph flow or PAH extraction (EPAH). A significant ($P < 0.05$) increase in RBF was, however, observed (Table 1). When RBF was returned to control by mechanical restriction of the renal artery, GFR, FRR and lymph flow were decreased significantly ($P < 0.05$). Renal lymph composition relative to those of arterial and renal vein blood plasma is shown in Table 2. The protein L/P was unchanged during bradykinin infusion, but increased when RBF was returned to control. In contrast, the lymph clearance of protein (LC) was unchanged throughout. Renal lymph and plasma protein concentrations and lymph flows obtained in each experiment are shown in Table 3. The lymph concentration index (LCI) for PAH presents the arterio-lymph difference as a fractional percent of the arteriovenous plasma concentration difference. The decrease in LCI ($P < 0.05$) found during both

Table 1 Changes in renal fluid dynamics and function during bradykinin infusion

		Control	Bradykinin	Bradykinin (cont. RBF)
RBF (ml/min/g)	$\bar{x}$	4.14	5.96*	4.18
n = 7	S.E.	0.24	0.35	0.23
GFR (ml/min/M^2)	$\bar{x}$	42.7	37.9	19.9*
n = 5	S.E.	4.0	5.1	4.6
FRR** (ml/min)	$\bar{x}$	37.8	32.1	17.8*
n = 5	S.E.	4.3	5.5	4.5
Renal lymph flow	$\bar{x}$	24.3	26.7	16.1*
(μL/min) n = 7	S.E.	2.4	4.5	1.2
EPAH	$\bar{x}$	0.75	0.72	0.64
n = 5	S.E.	0.03	0.03	0.05

* Statistically significant ($P < 0.05$)
** Whole kidney fluid reabsorption rate

Table 2 Relative Changes in renal lymph composition during bradykinin infusion

		Control	Bradykinin	Bradykinin (cont. RBF)
L/P protein	$\bar{x}$	0.40	0.44	0.59*
n = 7	S.E.	0.04	0.03	0.05
LC** protein	$\bar{x}$	10.38	11.75	10.08
(μ L/min) n = 7	S.E.	1.72	2.17	1.03
LCI+ PAH (%)	$\bar{x}$	56.22	33.28*	39.42*
n = 5	S.E.	3.07	2.02	3.68

* Statistically signficant ($P < 0.05$) ** Lymphatic clearance + Lymph concentration index

Table 3 Renal lymph (L) protein concentrations/flow rates compared with corresponding arterial blood plasma (P) protein concentrations*

Exp. No.		Control	Bradykinin	Bradykinin (cont. RBF)
1	L	2.46/30	2.16/15	2.43/17
	P	5.08	4.96	4.44
2	L	1.97/23	2.43/18	3.34/12
	P	5.01	5.01	3.95
3	L	1.82/18	2.07/15	2.46/12
	P	5.18	4.85	4.62
4	L	2.52/25	2.37/44	2.70/19
	P	5.65	5.59	5.35
5	L	1.60/15	2.50/25	3.45/17
	P	8.40	8.32	8.15
6	L	3.08/26	2.74/30	3.54/20
	P	5.39	5.39	5.18
7	L	2.67/33	3.04/40	4.68/16
	P	6.68	6.62	6.38

* Protein concentrations are g/dl, and flows are μL/min

bradykinin infusion periods (Table 2), was independent of blood flow and GFR changes (Table 1). The relationships of LCI, shown as percent, to absolute arterial and renal venous blood PAH concentrations are summarized in Fig. 1. The control LCI for PAH is at about the midpoint between arterial (0%) and renal vein plasma (100%). In addition, this figure shows that renal lymph PAH concentration increased toward that of arterial plasma during both bradykinin infusion periods. The LCI values for these two periods were statistically identical even though the lymph PAH concentrations were different.

Discussion

It is well known that bradykinin is a very potent vasodilator in many peripheral vascular beds (5, 7, 8) including the kidney (4, 7). The mechanism of action of this agent in the kidney is, however, controversial. Both prostaglandins (9) and the renin-angiotensin system (10) may be involved in this response. Regardless of the mechanism of action, the high potency of bradykinin as a renal vasodilator is confirmed in the present research, since the renal blood flow increase obtained is similar to that produced by histamine infused at a much higher rate (2). On the basis of previous studies it would be predicted that the RBF increases produced by bradykinin would cause renal lymph flow increases of 40% to 50% without changes in protein L/P ratio (1, 2). Constancy of lymph flow during increased RBF signals a major difference between the renal response to bradykinin and

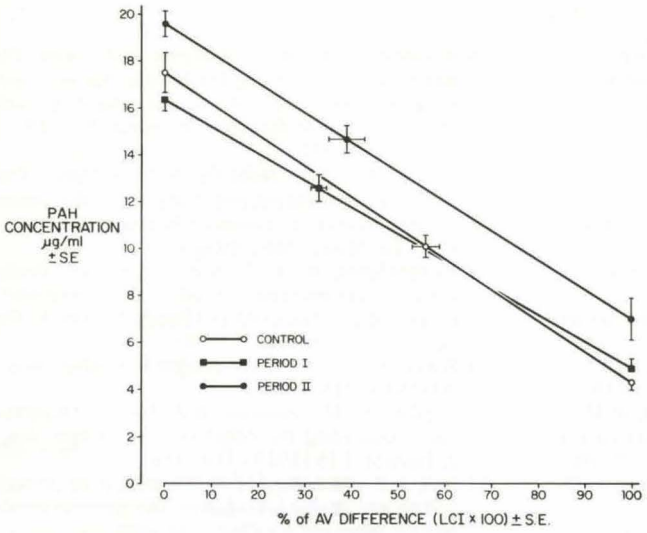

Fig. 1 LCI for PAH, shown as percent of overall arteriovenous concentration difference, is plated against PAH concentration. Means (n = 5) are shown for control, period I (bradykinin infusion) and period II (bradykinin infusion with RBF at control). Values for arterial and renal venous blood plasma are shown at 100 % and 0 %, respectively

that to other vasodilator substances, but the reason for this difference is not evident from the data presented. *Schwartz* and *Cotran* (4), however, report venular leakage of intravenously injected colloidal carbon in the peripelvic and periureteral fat in response to bradykinin. The hilar lymphatic vessels originate from plexuses around the arcuate vessels, and leave the kidney *via* peripelvic tissue (11). These findings suggest that bradykinin induced peripelvic edema may cause a passive increase in hilar lymphatic outflow resistance. If true, this hypothesis would also explain the decreased lymph flow during bradykinin infusion after returning RBF to control, but it does not account for the increased L/P ratio for protein observed during the latter period. The simultaneous decrease in GFR, fluid reabsorption rate and increase in protein L/P suggests that the lymph flow decrease may be due to abstraction from lymph of tubular reabsorbate (12), fluid lost from the glomeruli (13) or both. The constancy of lymph protein clearance reported in the present experiments in consistent with this conclusion and supports the suggestion that bradykinin fails to cause vascular leakage within the renal parenchyma (4).

This conclusion, however, does not account for the lack of lymph flow response to the bradykinin induced increase in RBF, and points out the need for further investigation on the nature of renal lymph formation. Even so, the data of the present research indicates that the permeability of the blood vessels from which renal lymph protein is derived is not significantly altered by bradykinin. The change in lymph PAH concentration relative to A–V difference suggests an alteration in the mechanism of renal lymph production that is independent of lymph flow, RBF and GFR. A similar response has been obtained during renal artery infusion of acetylcholine, and was attributed to alterations in medullary hemodynamics (1). Medullary interstitial fluid may find its way into hilar renal lymph even in the absence of demonstrable medullary lymphatic capillaries (14). Thus, these events may initiate or increase the formation of PAH rich lymph in the outer medulla (15). The data of the present study, however, neither confirms nor denies this hypothesis.

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