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The role of histamine receptors in the release of renin

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1 The effect of intrarenal histamine, dimaprit (H_2-agonist) and 2-(2-pyridyl) ethylamine (H_1-agonist) on renin release was examined in anaesthetized dogs.

2 In dogs with intact kidneys, histamine and dimaprit administration resulted in renal vasodilatation, a two fold increase in urinary sodium excretion, and no change in renal renin release. 2(2-Pyridyl) ethylamine administration resulted in renal vasodilatation, a 25% decrease in urinary sodium excretion and a significant increase in renin release.

3 In dogs with non-filtering kidneys, dimaprit administration resulted in renal vasodilatation and a significant increase in renin release, while 2(2-pyridyl) ethylamine administration resulted in renal vasodilatation but no change in renin release.

4 Our data suggest that histamine is a potential participant in the release of renin through stimulation of H_2-receptors, but it is a weak agonist.

5 In addition, the direct effect of histamine analogues on renin release is modulated by their effects on electrolyte excretion probably by influencing the renal chemoreceptor release of renin mediated by the macula densa.

Introduction

There are several lines of evidence suggesting that histamine may play a role in the control of renal physiology. Infusion of L-histidine into the renal arteries of dogs has been shown to result in ipsilateral histamine synthesis demonstrating that the kidney has the rate limiting enzyme for histamine biosynthesis, histidine decarboxylase (Lindell & Schayer, 1958). A more direct demonstration of the presence of histidine decarboxylase has been reported in the glomeruli of the rat kidney (Heald & Hollis, 1976). Recently Torres, Northrup, Edwards, Shah & Dousa (1978) have demonstrated that histamine activates adenylate cyclase in the rat glomeruli, an effect blocked by H_2-receptor antagonists. In addition, the actual presence of H_2-receptors has been demonstrated in rat glomeruli by the use of [^{3}H]-cimetidine as a ligand (Chansel, Oudinet, Nivez & Ardaillou, 1982). In *in vivo* studies, infusion of histamine into the renal arteries of dogs resulted in renal vasodilatation, diuresis, natriuresis but no change in glomerular filtration rate (O'Brien & Williamson, 1971). Recently Banks, Fondacaro, Schwaiger & Jacobson (1978) have demonstrated that the renal vasculature contains both H_1- and H_2-receptors and that these receptors have different effects on renal function even though both receptors are involved in renal vasodilatation.

One aspect of renal physiology that has not been examined carefully is the possible role of histamine in the control of renin secretion. More specifically, we wanted to test the hypothesis that H_2-receptors are involved in renin release because of the possibility that renin secretion is a cyclic AMP-dependent process (Data & Whorton, 1982). We therefore first examined the effect of histamine on renal renin release, and then examined the contribution of H_1- and H_2-receptors on the effect by the use of specific receptor agonists in both filtering and non-filtering canine kidneys. We included the non-filtering kidney preparation to avoid any changes in the macula densa sodium chloride flux that could affect renin release during the infusion of histamine receptor agonists.

Methods

Animal preparation

A total of 31 mongrel dogs of either sex weighing between 15 to 30 kg were used in this study. The dogs were divided into three groups. In group 1($n = 12$) we determined the effect of intrarenal histamine diphosphate ($1\ \mu g\ kg^{-1}\ min^{-1}$) on renin secretion, renal blood flow, sodium and potassium excretion,

and glomerular filtration rate. In group 2 ($n = 11$) we determined the effect of intrarenal dimaprit (H_2-agonist), $5\,\mu g\,kg^{-1}\,min^{-1}$ and 2-(2-pyridyl) ethylamine (PEA, H_1-agonist), $100\,\mu g\,kg^{-1}\,min^{-1}$ on renin secretion, renal blood flow, sodium and potassium excretion, and glomerular filtration rate. In group 3 ($n = 8$) we determined the effect of intrarenal dimaprit, $5\,\mu g\,kg^{-1}\,min^{-1}$, and PEA, $100\,\mu g\,kg^{-1}\,min^{-1}$ on renin secretion and renal blood flow in dogs with a non-filtering kidney.

On the day of the experiment, all dogs were anaesthetized with sodium pentobarbitone (30 mg/kg i.v.) and supplemented as needed to maintain surgical anaesthesia. After endotrachial intubation, the dogs were placed on a Harvard apparatus respirator and ventilated with room air. The right femoral artery was cannulated for the continuous recording of blood pressure and heart rate. The right femoral vein was cannulated for the administration of inulin. The dogs in group 1 and 2 had the right and left kidney exposed through flank incisions. Both kidneys were denervated by cutting the renal nerves and swabbing the arteries with a 5% phenol solution. Both renal veins were cannulated for blood withdrawal. A Statham non-cannulating electromagnetic flow probe was placed around each renal artery and blood flow was monitored continuously with a Statham flowmeter. A 25 gauge needle was inserted into the left renal artery for the infusion of histamine or histamine analogues. The right and left ureters were cannulated for collection of urine for the determination of sodium, potassium, and inulin excretion rates. One hour was allowed for post surgical stabilization before the actual experiment was begun.

Forty-eight to 72 h before the experiment, the dogs in group 3 underwent aseptic surgery to produce a non-filtering right kidney as described by Blaine, Davis & Witty (1970). Through the right flank, the ureter was ligated and severed, and the renal artery was occluded for 2 h and then released. The incision was closed, 300,000 u of procaine penicillin was given intramuscularly and the dogs were allowed to recover. On the day of the experiment, the dogs in this group had the left kidney exposed and surgically removed. The dogs were instrumented as in groups 1 and 2 for infusion into the right renal artery and for measurement of right renal blood flow, plasma renin activity and arterial pressure.

Experimental design

In groups 1 and 2 after the completion of surgery, a saline solution containing sufficient inulin to maintain plasma levels at 150–200 μg/ml was infused (0.5 ml/min) into the femoral vein. One hour later, baseline values for arterial pressure, right and left renal blood flows, and arterial and right and left renal venous blood samples for plasma renin activity were obtained at zero time, immediately before the intrarenal infusion of histamine or histamine analogues. Urine samples were collected from both ureters for determining urinary electrolytes and inulin excretion rate for 10 min before beginning the infusion of histamine or analogues. A plasma sample was obtained for measurement of inulin concentration in the middle of the urine collection period.

In group 1, histamine $1\,\mu g\,kg^{-1}\,min^{-1}$ was infused intrarenally for 15 min. Urine was collected for 10 min starting 5 min after histamine infusion was began. Ten minutes after the start of the histamine infusion, plasma was obtained from both renal veins for plasma renin activity and femoral artery for plasma renin activity and inulin concentration.

Group 2 dogs had a similar protocol to group 1 dogs except that these dogs received 2 different infusions of histamine analogues separated by 60–75 min. Five dogs received an intrarenal dimaprit infusion for 15 min first and, after a 60–75 min recovery period, then received an intrarenal PEA infusion for 15 min with haemodynamic and biochemical monitoring as described for group 1 dogs. Six dogs received the PEA infusion first and, after a 60–75 min recovery period, then received the dimaprit infusion.

In group 3, the mean arterial pressure, renal blood flow and renin secretion were monitored in the same fashion as for the dogs followed by PEA infusion, and PEA was infused first in 4 dogs followed by dimaprit infusion. Again the infusions were continued for 15 min with plasma samples from the right renal vein and femoral artery obtained 10 min into the infusions.

After the experiments in group 3, 1 ml of 5% indigo carmine was injected into the renal artery and 15 min later the kidney was removed and examined grossly for the appearance of blue discoloration of the tubules and filtrates. The absence of colour indicated that the kidneys were non-filtering.

Blood samples collected from the femoral artery and renal veins were used for the determination of plasma renin activity; 5 ml of blood was collected into precooled collection vials containing 0.15 ml of 10% disodium edetate (EDTA). Plasma renin activity was determined by angiotensin I radioimmunoassay using a modification of the technique reported by Stockigt, Collins & Biglieri (1971). Net renin secretion was calculated by the following formula: (renal venous plasma renin activity − arterial plasma renin activity) renal plasma blood flow. Inulin was determined colorimetrically by reaction with anthrone in H_2SO_4 (Davidson & Sackner 1963) by a technique adapted for the Technicon Autoanalyzer (Earley & Friedler, 1965). Urine sodium and potassium concentration was determined by flame photometry.

Statistics

For the renal haemodynamic, renin secretion and renal functional data in groups 1 and 2 we used a paired Student's t test comparing changes in the infused kidney to the contralateral control kidney. For the renal haemodynamic, renin secretion, and renal functional data in group 3 dogs, as well as the mean arterial pressure changes in all the groups, we used Student's paired t test comparing the infused period to the control period. Results are expressed as mean ± s.e.mean. A P value of less than 0.05 was considered significant.

Drugs

Histamine diphosphate (Sigma Chemical Company, St. Louis, MO. U.S.A.), dimaprit, and 2-(2-pyridyl) ethylamine (PEA) (Smith, Kline & French Laboratories, Philadelphia, PA, U.S.A.) were dissolved in 0.9% w/v NaCl solution (saline) and infused intrarenally at a rate of 0.2 ml/min.

Results

In the filtering kidneys, histamine and dimaprit infusions were associated with ipsilateral renal vasodilation, natriuresis, kaliuresis but no change in renin release (Figure 1, Table 1). On the other hand, PEA infusion was associated with renal vasodilatation but a decreased excretion of sodium and a significant stimulation of renal renin release. The change in glomerular filtration rate (GFR) after PEA infusion was not statistically significant but there was clearly a trend towards a decrease in most of the dogs studied.

In contrast, in the non-filtering kidneys, a preparation where the macula densa mechanism of renin release is inactive, dimaprit administration resulted in a significant release of renin while PEA was inactive even though both histamine agonists caused renal vasodilatation without changes in systemic haemodynamics.

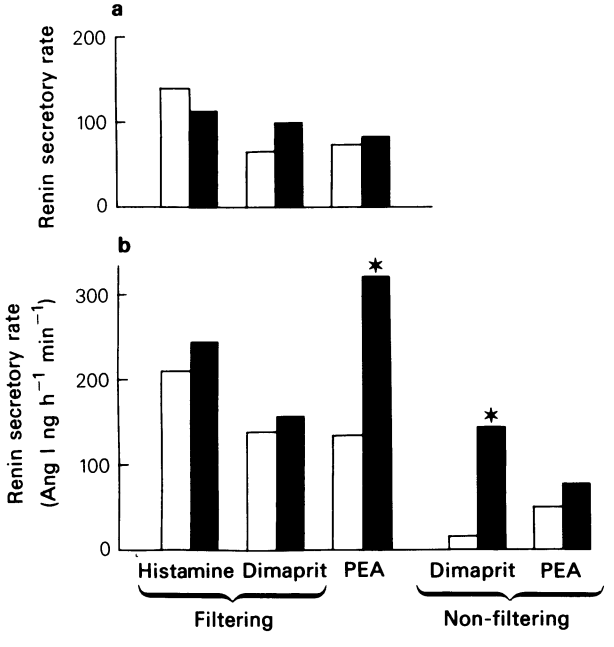

Figure 1 The effect of histamine, dimaprit and 2(2-pyridyl) ethylamine (PEA) on renin secretory rate in the filtering kidney is shown on the left side of the panel. Open columns: basal period; solid columns: infusion period. Both the infused (b) and control kidneys (a) are included. The effect of dimaprit and PEA on renin secretory rate in the non-filtering kidneys is shown on the right. The results are expressed as the mean of $n = 12$ for histamine, $n = 11$ for dimaprit and PEA for the filtering kidney, and $n = 8$ for the non-filtering kidney. Asterisk signifies that $P < 0.05$ using Student's paired t test.

Table 1 The effect of histamine and analogues on renal function and haemodynamics

	Renal blood flow (ml/min)		*MAP (mmHg)*	*GFR (ml/min)*		*Urinary Na^+ excr (μEq/min)*		*Urinary K^+ excr (μEq/min)*	
	I	*N–I*		*I*	*N–I*	*I*	*N–I*	*I*	*N–I*
Filtering kidneys									
Control	221±25	231±28	151±5	35±5	37±6	28±4	26±3	25±7	24±6
Histamine	267±30*	228±27	149±5	37±6	37±6	57±11*	26±5	50±17*	24±8
Control	194±22	221±30	155±4	32±3	34±4	55±19	46±14	29±5	27±7
Dimaprit	260±27*	224±30	154±6	33±3	33±4	110±29*	45±14	35±5*	26±7
Control	181±24	230±30	154±4	34±4	37±4	53±11	53±14	32±5	37±7
PEA	214±26*	229±29	153±3	30±4	36±4	40±10*	66±15	27±6*	39±7
Non-filtering kidneys									
	Renal blood flow		*MAP*						
Control	135±31		146±4						
Dimaprit	172±32*		146±7;						
Control	136±27		146±5						
PEA	172±27*		149±6						

MAP = mean arterial pressure; GFR = inulin clearance.

Discussion

Our data indicate that histamine could potentially be involved in the release of renin from the kidney. In addition, it is the H_2-receptor that is most probably responsible for the effect. Interestingly, in the filtering kidney neither histamine nor dimaprit (H_2-agonist) resulted in renin release but in these preparations the macula densa mechanism of renin release was intact. If the two fold increase in sodium excretion was secondary to a decreased proximal tubular sodium reabsorption, as has been proposed for renal vasodilator drugs, then the increased delivery of sodium chloride to the macula densa could have inhibited the direct stimulatory effect of these drugs on renin release. The fact that dimaprit stimulated renin release in the non-filtering kidney would support the inhibitory role of the macula densa on the stimulatory effect of dimaprit in the filtering kidney.

The effect of PEA on renin release was opposite to that observed for dimaprit. PEA stimulated renin release in the filtering kidney but was without an effect in the non-filtering kidney. Since PEA administration was associated with a significant antinatriuresis, the renin stimulatory effect was most probably indirect and via the macula densa. The antinatriuretic effect of PEA has been described previously (Banks *et al.*, 1978). The mechanism for this decreased urinary sodium excretion has not been characterized but is partly related to a reduced glomerular filtration rate.

Our data are compatible with the hypothesis that histamine could contribute to the stimulation of renin release from the kidneys. However, it is a relatively weak stimulator of renin release when compared to prostaglandins E_2, I_2, and isoprenaline. Prostaglandins E_2 and I_2 will stimulate renin release five to ten fold above basal levels when infused in the filtering kidney even though a marked natriuresis is observed with the renal vasodilatation (Gerber, Branch, Nies, Gerkens, Shand, Hollifield & Oates, 1978). It is possible that at higher infusion rates histamine and dimaprit would have stimulated renal renin release in the filtering kidney but at higher infusion rates there are changes in systemic vascular resistance which would have made accurate evaluation of the direct effect of histamine more difficult. Histamine H_2-receptor stimulation has been shown to be coupled to adenylate cyclase in many systems including the rat renal glomeruli and the mammalian brain (Torres, *et al.*, 1978; Nahorski, Rogers & Smith, 1974). Cyclic AMP analogues and compounds that stimulate adenylate cyclase have been shown to cause renin release (Data & Whorton, 1982). These facts are consistent with our findings that stimulation of the H_2-receptors can result in renin release when the inhibitory influence of the macula densa is excluded.

We can conclude from our data that histamine is a potential participant in the release of renin by the kidneys through stimulation of the H_2-receptor, but it is a weak agonist. In addition, we have demonstrated that the direct effect of histamine analogues on renin release is modulated by their effects on electrolyte excretion, probably by influencing the renal chemoreceptor release of renin mediated by the macula densa.

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