PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 160, 328-334 (1979)

Some Evidence for Interrelationship of Histamine and Prostaglandin on Renal Function (40444)

EWALD E. SELKURT, GREGORY M. HOCKEL[1] AND MYRON H. WEINBERGER[2]

Department of Physiology, Indiana University School of Medicine, Indianapolis, Indiana 46202

At least two well known substances produced by the kidney, prostaglandins, e.g., PGE_1 and PGE_2, and the renin-angiotensin mechanism have been found to have an interplay. Thus, PGE will stimulate renin release (RR) (1–4). Conversely, angiotensin II will promote increased synthesis and release of PG's (5, 6). In previous work done in this laboratory (7), histamine infused via the renal artery reproduced remarkably the renal effects of PGE, i.e., renal vasodilation, with constancy of GFR, thus, decrease in the filtration fraction (FF); increased electrolyte loss; polyuria, with dilute urine (U/P of osmolality decreases). The earlier findings (7) thus suggested the possibility that histamine might be acting in conjunction with the PG's, either by stimulating their release, or by acting at the receptor site in a similar manner.

In the present experiments, further evidence of the PG-like action of histamine was sought by examining its influence on renin release (RR). The hypothesis to be tested was to see if histamine could indeed increase RR, thus establishing another link in the chain of interrelationships of these substances.

Methods. Most of the details of methodology has been presented in the previous publication (7). Basically, these involved measurement of arterial blood pressure (MABP) and renal blood (and plasma) flow (RBF, RPF). The clearance of creatinine (C_{Cr}) was utilized to measure glomerular filtration rate (GFR).

The procedures of the present investigation followed those of the prior experiments, but we were primarily interested in the renin release mechanisms in the present investigation. The measurement of total direct blood flow of the left kidney, via a flank retroperitoneal approach, was done with an electromagnetic flow probe (Carolina Medical Electronics). The left ureter was catherized. Renal vein blood samples were removed through a small diameter polyethelene catheter introduced into the renal vein via the spermatic vein. Systemic arterial blood was taken from the femoral artery. Washed RBC's of each sample were returned in a volume of dextran equal to plasma removed (ca 5 ml). Mid-period blood samples of arterial and venous blood were drawn simultaneously.

Blood samples drawn for plasma renin activity (PRA) determination were delivered to EDTA-treated tubes packed in ice. Following immediate centrifugation at 4°, the plasma was removed to storage tubes and frozen for subsequent analysis. Plasma renin activity, PRA (ng/ml/3 hr), was determined using the radioimmunoassay technique developed by Haber et al (8). Renin release was calculated by the formula:

$$RR\ (ng/min) = DPF\ (PRA_{RV} - PRA_{Art})$$

DPF: total direct renal plasma flow, ml/min. PRA_{RV}: renal vein PRA in ng/ml. PRA_{Art}: systemic arterial PRA (ng/ml). The calculation yields total release per kidney.

A total of 29 male dogs ranging in weight from 17 to 24 kg (av. 18 kg) was utilized in the present experiments. Kidney weights at autopsy averaged ca 50 g. The animals were fasted on the day prior to the experiment, but had access to water. They were anesthetized with pentobarbital sodium (30 mg/kg/iv), for the necessary surgery. At least one hour was allowed before experimental measurements were made. Systemic vein infusate was continuously delivered by a constant infusion pump at the rate of 0.3 ml/min. This contained the substances for clearance analysis, e.g., creatinine.

[1] Present address: Department of Physiology and Biophysics, University of Mississippi School of Medicine, Jackson, Mississippi 39216.

[2] Department of Medicine, Indiana University School of Medicine.

0037-9727/79/030328-07$01.00/0

Histamine dihydrochloride was continuously infused into the renal artery via a 21 guage fish-hook needle, at a rate of 0.5 ml/min, with concentrations of histamine varying so as to deliver 7.5, 15, or 30 μg/min.

Protocols. Series A. Paired periods of 15-min duration each were alternated with paired 15-min control periods, with a 15-min equilibration period preceding the paired collections. When histamine was infused, it was begun 7.5 min prior to the paired experimental periods and continued through two 15-min periods. In this set, the dosages were randomly infused. A total of 14 observation periods was made in the histamine infused group.

Series B. In this series paired control periods of 15-min duration were followed by a 30-min discard period (no sample collections). Then followed 6 consecutive 15-min experimental periods (3–10) during which histamine was continuously infused, blood and urine samples were collected, and blood flow and arterial pressure recorded (total time, 80 min). This was followed by cessation of histamine infusion, with a 30-min equilibration (no collections) period. Finally a series of four observational (recovery) periods (11–14) followed. Figure 3 illustrates the experimental protocol. In a sub-group ($n = 6$) RO 20-5720 was injected in two doses of 3 mg/kg/iv. The first dose was given 27 min after start of histamine infusion (3 min prior to the first experimental period no. 3). The second injection was given at the start of period 7.

Statistical evaluation. Because the dogs were of heterogenous breeds and sizes, and since they were unconditioned prior to use with no antecedent control of dietary intake, some variation in renal blood flow was observed, as was true also of renin production rates and PRA values. Hence, to improve statistical sensitivity, the principle of each animal serving as its own control was employed (Fig. 2). [Paired *t* test, significance of small samples, in: Fisher, R. A.: Statistical Methods for Research Workers, Hofner Publishing Co., Inc., New York, 1954, pps. 121–122] Group *t* tests were used in Fig. 5.

We also used ANOVAR, a group by trials analysis of variance developed by D. J. Veldman, Department of Educational Psychology, Univ. of Texas, in conjunction with a Studentized range test (Table 15 A, p 568) in *Statistical Methods*, by G. W. Snedecor and W. G. Cochran, 6th Edit., Iowa State Univ. Press, 1967 (Figs. 4 and 5).

Results. Series A. In this group, step-function changes in histamine infusion rates were employed, with dosage given in a consecutive manner (e.g., 30 to 7.5 μg/min, 7.5 μg/min to 30), or with random permutations. In Fig. 1, an illustrative experiment is depicted in which the histamine dosage started at 30 μg/min, then was reduced to 15 and 7.5 μg/min. (In the figure, paired periods have been averaged.) RR correlated well with the histamine dosage in this experiment. Note that RBF increased in approximate proportion to the dose, but MABP and C_{Cr} were constant (typically, however, MABP decreased somewhat with continued infusion of histamine, as shown later).

In Fig. 2, the results of seven experiments are averaged. The bar graphs show RR during paired periods (0 histamine infusion) before and after paired periods in which varying doses of histamine were infused (7.5, 15, and 30 μg/min). The 30 μg/min dose produced a substantial average increment in RR of 3.6-fold over the control average.

Series B. A representative experiment showing the effects of long-term (2 hr) infusion appears in Fig. 3. MABP declined during the continuous infusion of 30 μg/min from 120 to 105 mm Hg, then was restored upon cessation of the infusion. Total renal blood flow increased from 270 to ca 375 ml/min, declining a trifle toward the end of the infusion period. C_{Cr} in this animal displayed an atypical increase (27 ml/min to a peak of 34.5). Constancy of this function is the general rule (7).

RR was substantially increased during the first hour of infusion, then declined to control values during the second hour.

Figure 4 shows that an average downward trend of RR is characteristic of the entire group (n = 8). This is explained by the underlying trend noted in the untreated animals, which showed a progressive decrement in RR with time.

The bottom panel of the figure depicts the changes in RR as the differences from the control trend (Δ *control* in the figure). With

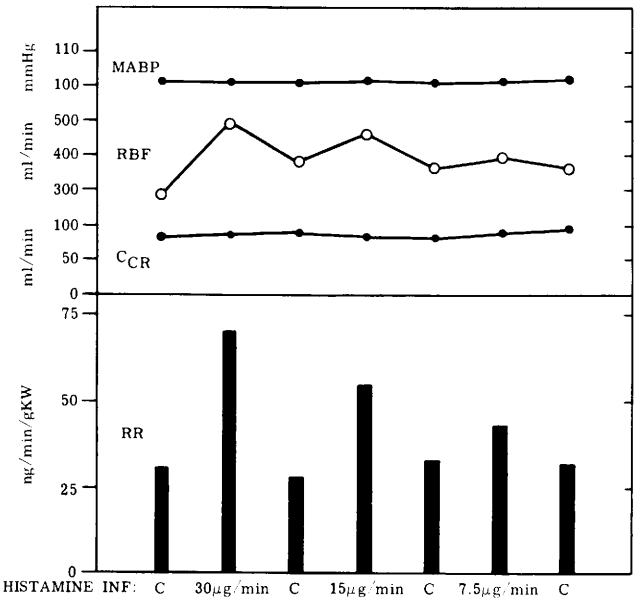

FIG. 1. Effect of graded doses of histamine on renin release (RR, per gm KW) in a representative experiment. Renal blood flow (RBF) and glomerular filtration rate (C_{Cr}) are for the whole kidney (left). Paired periods for each stage are averaged here. C is the average of intervening control paired periods. MABP: mean arterial blood pressure.

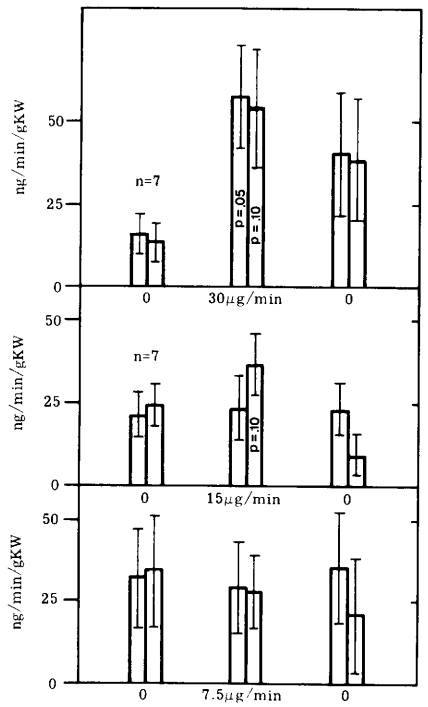

FIG. 2. Summary of all experiments, done as in Fig. 1. Alternative sequences of histamine infusion were also done, e.g., progressive increase in dosage, or random variation of dose. Means of individual paired consecutive periods, ± 1 SEM are shown.

this mathematical adjustment, the increments in RR produced by histamine infusion are reasonably constant and average 14 μg/min/g KW, an average of 76% increase over the control values.

The cyclo-oxygenase inhibitor RO 20-5720 appeared to block completely the increment in RR caused by histamine (Fig. 4). In fact, most values fell below control (bottom panel), suggesting an influence on endogenous production of PG's. Injection times for RO 20-5720 are indicated by the arrows.

Perhaps the best evidence for a stimulatory influence on the renin-producing cells of the JGA is revealed in Fig. 5, in which renal venous (RV) and systemic arterial renin concentration changes (PRA) resulting from continuous infusion of 30 μg/min of histamine are shown. Both arterial and RV PRA's increase significantly, the latter more markedly. The changes in the control series are not statistically significant from the initial values. Observe also that PRA values remained elevated after cessation of histamine infusion.

Discussion. It appears that histamine in adequate dosage constantly infused into renal artery results in a modest increment in RR by the kidneys of the anesthetized canine. The observed downward trend with time pre-

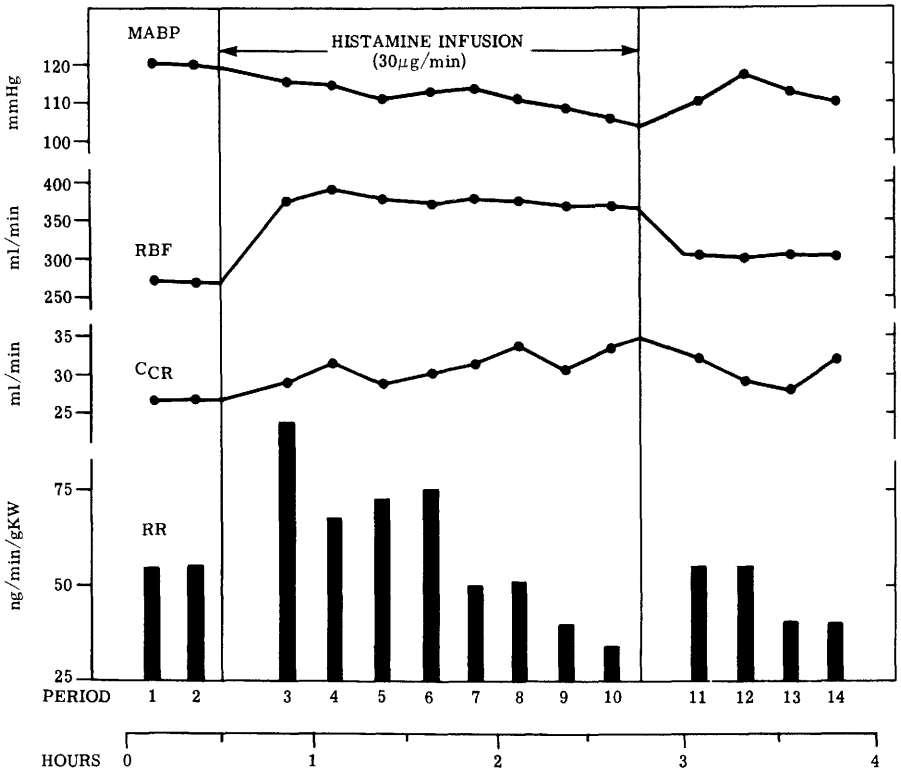

FIG. 3. Representative experiment, showing effects of continuous infusion of histamine, 30 μg/min.

sumably reflects an underlying trend manifested by the untreated group of animals. This could be a reflection of initially increased RR prompted by surgery and the induction of barbiturate anesthesia (9), from which the animal slowly recovers over the 4-hr period of observation.

The mechanism for the increment in RR resulting from histamine is not known, but some speculation can be made. The possibility involves the prostaglandins (especially of the E series), which are known to stimulate RR (1–4). Histamine has been shown to increase the release of prostaglandins (PGE, $PGF_{2\alpha}$) from guinea pig lung tissue (10). The effect of specific histamine inhibitor agents was to suppress PG release enhanced by histamine. If the histamine effect indeed involves the PG producing cells in a stimulatory manner, then a second order effect on renin production and release might be anticipated. The PG synthetase inhibitor, indomethacin, has been shown to suppress plasma renin activity in normal and hypertensive man (11). But workers in the field agree that this blocking agent is probably not specific in its action; thus, it may inhibit phosphodiesterase and allow cellular levels of c-AMP to rise (12). A study of PG production and release by the kidney, as prompted by histamine, needs to be done to test finally this possibility. However, the more specific inhibition of RR by RO 20-5720 strongly supports this as a probable mechanism (13). It is also possible that histamine may have a direct effect on the renin producing cells. This still leaves open the question of how the PG's influence RR. Not to be excluded are possible secondary effects on renal hemodynamics (baroreceptor activity, physical factors) and on tubular function: alterations of sodium and calcium load to the macula densa sensor (14–17).

Of interest is the observation that PRA values decremented slowly after cessation of histamine infusion (Fig. 5). The situation is complicated by several factors which might operate in a variable manner to prolong the effect: the half-life of renin, the duration of

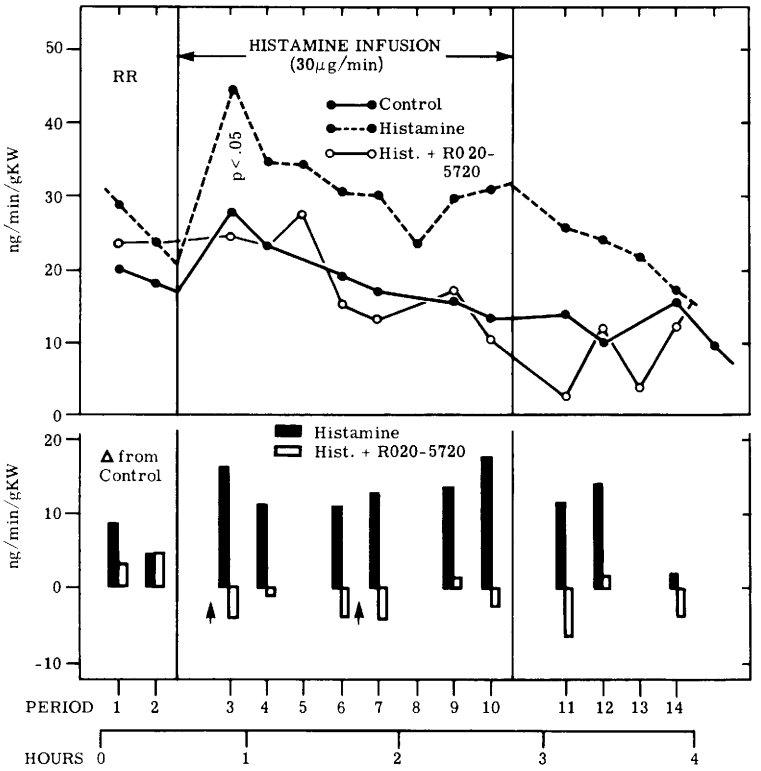

FIG. 4. Average trends of effect of continuous histamine infusion (30 μg/min) (n = 8), as compared with untreated control series (n = 8). Also shown are the effects of RO 20-5720, superimposed on histamine infusion (n = 6). Arrows show time of injection of RO 20 (3 mg/kg per injection). Paired t test analysis showed the renin release during the first period to be significantly higher than control ($P < .05$). Using ANOVAR, the group difference between the control and histamine infusion (average increments of experimental over paired control) gave a value for P of 0.15 (one in 7 occurring by chance). The P of the G × I value (group × interval) was 0.985, indicating a high degree of parallelism between the two groups. The RO 20-5720 treated animals also followed the control trend. On this basis, the differences from control for the histamine, and histamine + RO 20-5720 groups, were plotted in the lower panel of the figure, as: Δ from control (change from control). During histamine infusion the treated group averaged 14 ng/min/g KW higher than the control group's average of 19.6, an average increase of 76%. With histamine plus RO 20-5720 treatment, the values generally fell below control, suggesting inhibition of base-line endogenous synthesis and release of prostaglandins.

persistence of circulating histamine after cessation of infusion; and finally, if PG release is stimulated (e.g., PGE) which also stimulates RR, then the PG half-life needs also to be considered. In another investigation, we observed that the influence PGE_1 on RR persisted for over an hour after cessation of intra-arterial infusion (18).

Summary. Mild stimulation of the renin producing mechanism of the kidney results from intra-arterial infusion of histamine at a dosage which has minimal systemic effects. Both graded dosage, and continuous infusion were employed. The mechanism is believed to involve the PG system of the kidney, since RO 20-5720, a specific PG synthetase (cyclooxygenase) inhibitor minimized the histamine effect on renin release. The use of RO 20-5720 strengthens the possibility of such a mechanism, since it is more specific in its action than indomethacin and meclofenamate. The precise interrelationship between the PG and histamine action is not known at this time.

We are indebted to Dr. W. E. Scott, Hoffman-La Roche, Inc., Nutley, NJ, for the generous supply of RO 20-5720. The technical assistance of Mary Ann Neel and

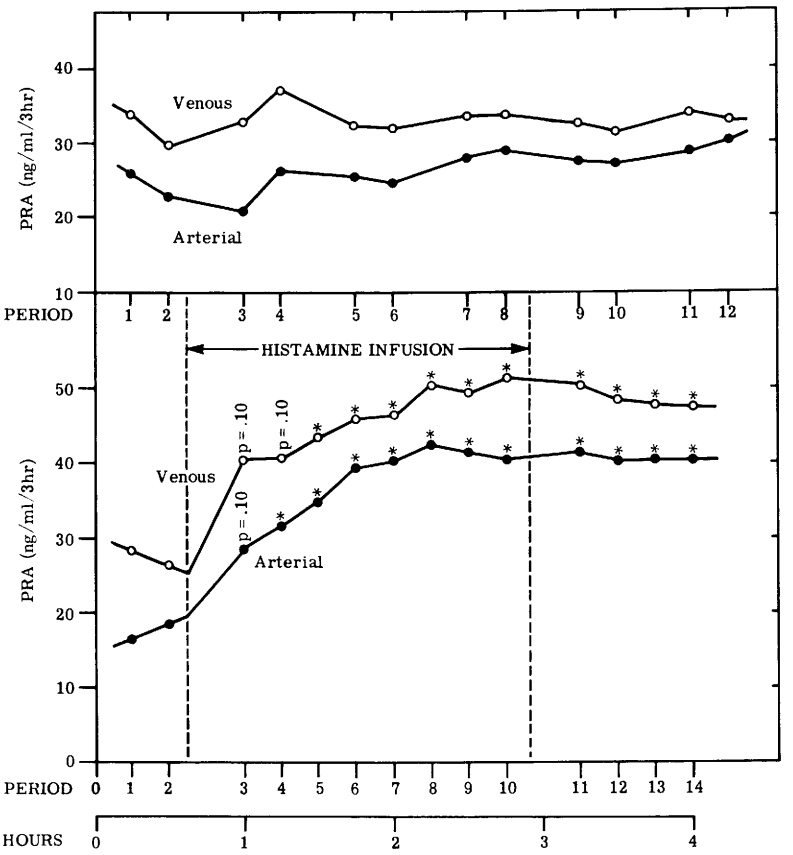

FIG. 5. The effect of continuous histamine infusion on plasma renin activity (PRA) of arterial and renal vein plasma (lower panel). Using the paired *t* test (average of each period compared to starting control values), the increases in both arterial and venous PRA values were significant ($P = < .05$) after the first two periods of infusion, and remained significantly elevated for at least an hour after stopping histamine infusion. As expected, the renal vein (RV) values were higher than the systemic arterial (Art_{PRA}). (* = $P < .05$) The control values did not change significantly from the initial values during 4½ hr of observation (upper panel). Using ANOVAR, the group average (G) PRA of arterial (38.3 ng/ml/3 hr) and RV (46.0) were not significantly different ($P < 0.22$) from the control group arterial (26.5 ng/ml/3 hr) and RV concentration (34.3). But the change with time per period (interval I) was highly significant ($P = < .0001$), and *P* value for G × I was .0014. The 6th through 12th intervals were different ($P < 0.05$) from control for both arterial and venous concentrations of renin.

Mary Ann Neill is greatly appreciated. Dr. Carl F. Rothe's advise on statistical treatment is acknowledged. The investigation was supported by National Science Foundation Grant PCM 76-04368. Technical assistance was also provided by the Specialized Center of Research in Hypertension (Grant No. HL-14159, Indiana University School of Medicine).

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Received October 12, 1978. P.S.E.B.M. 1979, Vol. 160.