Mechanisms of Action of Histamine and Histamine Antagonists on the Glomerular Microcirculation in the Rat

IEKUNI ICHIKAWA AND BARRY M. BRENNER

SUMMARY We made direct measurements of preglomerular, glomerular, and postglomerular pressures and flows before and during intra-aortic infusion of a mildly vasodepressor dose of histamine in 20 Munich-Wistar rats. As with whole kidney GFR, single nephron (SN) GFR remained unchanged during histamine infusion, despite significant mean increases in total renal and glomerular plasma flow (Qa) rates, as well as in mean glomerular capillary hydraulic pressure (Poc). These hemodynamic changes were accompanied by proportionately greater reductions in afferent than in efferent arteriolar resistances. A decline in the glomerular capillary ultrafiltration coefficient, Kr, served to offset the increases in Qa and Poc, thus accounting for the near-constancy of SNFGR and GFR. Infusion of diphenhydramine, but not metiamide, largely prevented these histamine-induced changes in the glomerular microcirculation, indicating that, in the Munich-Wistar rat, the action of histamine on the glomerulus is channeled largely through an H1-receptor system. Fractional clearances of uncharged dextrans with molecular radii of 20-42 Å, measured in a separate group of five rats, were unaffected by histamine infusion. Using a hydrodynamic theory describing transport of macromolecules through an isoporous membrane, we showed that histamine did not affect glomerular pore size but did produce a major reduction in the ratio of pore area:pore length, a measure of pore density. Taken in conjunction with the finding of a histamine-induced decline in Kr, the results with dextrans suggest that the fall in Kr is due largely to a functional reduction in total filtration surface area.

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HISTAMINE causes local edema in skin and skeletal muscle by increasing net fluid filtration and transcapillary passage of circulating macromolecules (Gregg et al., 1972; Haddy et al., 1972; Rippe and Gregg, 1978). Although histamine also behaves as a potent vasodilator of the renal circulation, an accompanying increment in glomerular filtration rate has been found to be either small or absent (O'Brien and Williamson, 1971; Selkurt, 1977; Banks et al., 1978). Moreover, in rats receiving high doses of histamine, Schwartz and Cotran (1972) failed to detect alterations in the transglomerular passage of macromolecules, including carbon particles. To characterize more fully the renal microcirculatory actions of histamine, we measured preglomerular, glomerular, and postglomerular pressures and flows before and during histamine infusion in Munich-Wistar rats. Fractional clearances of uncharged dextrans also were measured, thus permitting an evaluation of the effects of histamine on the transglomerular passage of macromolecules. Finally, experiments were performed using H1- and H2-receptor antagonists in order to evaluate the nature and specificity of histamine receptors in the renal cortical microcirculation of these rats.

METHODS

General

Studies were performed on 25 Munich-Wistar rats that weighed 188-302 g and that were allowed free access to water and a standard rat pellet diet. Immediately after the induction of anesthesia with Inactin (100 mg/kg, ip), the left femoral artery was catheterized, followed by a baseline collection of ~70 μl of arterial blood. This arterial catheter was used for subsequent blood sampling and estimation of AP. AP was monitored with an electronic transducer (model P23Db, Statham Instruments Division, Gould Inc.) connected to a direct-writing recorder (model 7744A, Hewlett-Packard Co.). Polyethylene catheters were also inserted into the right and left jugular and left femoral veins for infusions of inulin, isoncotic rat plasma, and histamine antagonists (see below). Intravenous infusions of homologous rat plasma (obtained at the time of micropuncture study by exsanguination of a littermate) and 7.5% inulin solution in 0.9% NaCl were begun, and the latter continued throughout the duration of each experiment at a rate of 1.2 ml/hour. After tracheostomy, rats were prepared for the micropuncture study as described previously (Ichikawa...
et al., 1978). To permit intra-aortic infusion of histamine, a 27-gauge needle was placed into the abdominal aorta just above the origin of the left renal artery, and infusion of isotonic saline was started at the rate of 0.6 ml/hour. Throughout the period of surgical preparation and experimental study, each rat received a continuous infusion of isoncotic rat plasma to maintain circulating plasma volume at conscious (or euvoletic) levels. The details of the protocol employed are given elsewhere (Ichikawa et al., 1978).

In all experiments, micropuncture measurements were carried out as follows. Exactly timed (1- to 2-minute) samples of tubule fluid were collected from surface proximal convolutions of two or three nephrons for determination of flow rate and inulin concentration. These measurements permit calculation of single nephron glomerular filtration rate (SNGFR). Coincident with these tubule fluid collections, two or three samples of femoral arterial blood were obtained in each period for determination of hematocrit (Hct) and plasma concentrations of protein and inulin. Whole blood, obtained on the morning of study from a littermate, was infused after each blood collection to replace (volume-for-volume) blood withdrawn for analytical purposes. In addition, two or three samples of urine from the experimental kidney were collected for determination of flow rate, inulin concentration, and calculation of whole kidney glomerular filtration rate (GFR). For these urine collections, indwelling ureteral polyethylene catheters (PE-10) were used. Time-averaged pressures were measured in surface glomerular capillaries (PC), proximal tubules (PT), and third-order peritubular capillaries (PC), using a continuous-recording, servo-null micropipette transducer system (model 3, Instrumentation for Physiology and Medicine). Micropipettes with outer tip diameters of 2–3 μm and containing 2.0 M NaCl were used. Hydraulic output from the servo system was coupled electronically to a second channel of the Hewlett-Packard recorder by means of a pressure transducer.

Colloid osmotic pressures (π) of plasma entering and leaving glomerular capillaries were estimated from values for protein concentration (C) in femoral arterial (CA) and surface efferent arteriolar (CE) blood plasmas, using the equation described previously (Deen et al., 1973). Values for CA and thus πa, for femoral arterial plasma are taken as representative of values of C and r for the afferent end of the glomerular capillary network. These estimates of pre- and postglomerular plasma protein concentration permit calculation of single nephron filtration fraction (SNFF) and ultrafiltration coefficient (KT), as well as resistances of single afferent (RA) and efferent (RE) arterioles, total arteriolar resistance (RTA = RA + RE), and initial glomerular capillary plasma flow rate (QA).

In six rats (four in group 1, two in group 3; groups are defined below), left renal arterial blood flow was measured continuously throughout each experiment with a small-diameter flow probe (model EP401.5, 1.5 mm in circumference) connected to an electromagnetic flowmeter (model 501, Carolina Medical Electronics, Inc.). This flowmeter system was calibrated in vivo (Arendshorst et al., 1975).

Experimental Groups

We initially studied the effects of histamine in 13 euvoletic rats (groups 1 and 2) to determine its actions on renal and glomerular hemodynamics. Ninety to 120 minutes after beginning the surgical preparation in these rats, collections of tubule fluid,
urine, and efferent arteriolar and femoral arterial bloods, and measurements of AP, \( P_{OC} \), and \( F_{r} \) were begun and completed in the subsequent 45-minute interval. At the end of this first study period, an infusion of histamine (Sigma Chemical Co.) was started at the rate of \( 1.5 \times 10^{-5} \) M/hour per kg body weight via the aortic needle and continued for the duration of each experiment. Measurements of the various determinants of SNGFR then were repeated. Further, immediately after completion of this second study period, diphenhydramine (Benadryl, Parke Davis Co.) (seven rats; group 1) or metiamide (Smith, Kline and French Lab.) (six rats; group 2) was given as a continuous iv infusion at rates of \( 3.3 \times 10^{-5} \) M/hour per kg body weight or \( 1.2 \times 10^{-3} \) M/hour per kg body weight, respectively. Following a 45-minute equilibration period from the start of diphenhydramine or metiamide infusion and while histamine infusion was continued, all of the above-described measurements and collections were repeated in the subsequent 45 minutes (third study period).

In a separate group of seven rats (group 3), we studied the effects of diphenhydramine pretreatment of rats given histamine. In these euolemic rats, the first study period was carried out in identical fashion to that employed in groups 1 and 2. Subsequently, diphenhydramine was given intravenously at the rate of \( 3.3 \times 10^{-5} \) M/hour per kg body weight, i.e., identical to the dose employed in the third study period of group 1. Following a 45-minute equilibration period, measurements and collections of the quantities specified above were repeated in the subsequent 45-minute interval. After this second study period, an intra-aortic infusion of histamine was begun at the rate of \( 1.5 \times 10^{-5} \) M/hour per kg body weight, and the diphenhydramine infusion was also continued. Pertinent measurements and collections then were completed in the subsequent 45-minute interval (third study period).

Dextran Clearance Studies

In a separate group of five rats, after surgical preparation as if for routine micropuncture, an isotonic saline solution (0.4 ml) containing tritiated dextrans of broad molecular size distribution (concentration \(<300 \text{ mg/100 ml}, \text{ specific activity } = 25 \mu\text{Ci/ml} \) was infused intravenously, followed by a constant infusion of the same solution at 1.2 ml/hour. Approximately 2–3 minutes after completion of the priming injection, we began the continuous collection of blood from the femoral artery at a constant rate (1.2 ml/hour), using a withdrawal pump (model 941, Harvard Apparatus Co.). Urine also was collected during this continuous femoral arterial blood withdrawal. After completion of these collections in the first study period, rats were infused with histamine (second study period) and, subsequently, histamine and diphenhydramine (third study period), employing dosages and time courses identical to those used in group 1 rats. During these second and third study periods, dextran clearance measurements were repeated in the same manner as described above.

Analytical and Calculations

Details of the experimental procedures employed in the present study for collecting, processing and analyzing blood, urine, and tubule fluid are given elsewhere (Chang et al., 1975a; Bohrer et al., 1977a; Ichikawa et al., 1978). Details of the equations used for calculation of SNGFR, \( \pi_{A} \) and \( \pi_{K} \), SNFF, \( Q_{A} \), and \( K_{f} \) are also given elsewhere (Ichikawa et al., 1978). With a theory based on macromolecular transport through an isoporous membrane, the effective pore radius (\( r_{o} \)) and the ratio of pore surface area-to-pore length were calculated as discussed in detail elsewhere (Chang et al., 1975b).

Statistical analyses were performed by the paired and unpaired \( t \)-test, where appropriate. Statistical significance is defined as \( P < 0.05 \).

Results

Effects of Histamine Infusion

Figure 1 summarized several whole kidney functions measured before and during histamine infusion in six euolemic rats from groups 1 and 2. Along with slight, but uniform, reductions in AP (on average from 111 ± 2 mm Hg to 103 ± 2 (mean...
TABLE 1

Single Nephron Functions Measured in Euvolemic Rats (n = 13) before and during Histamine Infusion

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Histamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>(mm Hg)</td>
<td>(g/dl)</td>
<td>(mm Hg)</td>
</tr>
<tr>
<td>AP</td>
<td>P&lt;sub&gt;c&lt;/sub&gt;</td>
<td>P&lt;sub&gt;r&lt;/sub&gt;</td>
</tr>
<tr>
<td>Control</td>
<td>111</td>
<td>48.5</td>
</tr>
<tr>
<td></td>
<td>±2</td>
<td>±0.7</td>
</tr>
<tr>
<td>Histamine</td>
<td>103</td>
<td>54.5</td>
</tr>
<tr>
<td></td>
<td>±2</td>
<td>±0.8</td>
</tr>
</tbody>
</table>

P value: <0.001 <0.001 >0.10 <0.001 >0.10 <0.001 >0.10 <0.001 <0.001 <0.001 >0.50 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001

Values are expressed as means ± SE.
* Mean value for minimum K<sub>r</sub>
Figure 2 Summary of changes in single nephron function in response to intra-aortic infusion of histamine alone and histamine + iv infusion of diphenhydramine (H1-blocker) in euvoilemic rats (group 1). In Figures 2-4, open circles and filled circles denote mean minimum and unique values of Kf, respectively. Average by ~30%, ~10%, and ~20%, but the changes were statistically significant only for R_A (P < 0.01) and R_TA (P < 0.025).

Thus, despite continued infusion of histamine, addition of the H1-receptor antagonist resulted in return of P_OC, ΔP, Q_A, Kf, R_A, R_E, and R_TA to or toward pre-histamine levels.

Effects of H1-Receptor Antagonist in Histamine-Treated Rats (Group 2)

Data regarding the effects of metiamide, a specific H2-receptor antagonist, in six rats given histamine (group 2) are summarized in Figure 3. Whereas metiamide led to a significant increase in ΔP, on average to pre-histamine levels, this H2-blocker failed to change Q_A or SNGFR significantly in the third study period. Likewise, whole kidney GFR remained essentially unchanged (1.4 ± 0.1 ml/min before and 1.3 ± 0.1 ml/min during metiamide). SNFF also remained essentially unchanged (Fig. 3), as did P_OC and P_T. Thus, as shown in Figure 3, the mean value for ΔP was also unchanged, averaging 40.2 ± 0.7 before and 39.3 ± 0.9 mm Hg during metiamide (P > 0.1). As with π_A (Fig. 3), values for π_E also remained essentially unaltered. Therefore, the ratio of π_E/ΔP remained significantly less than unity. Unique values for Kf calculated during metiamide infusion were not significantly different from values prior to metiamide, as shown in Figure 3. As also shown in Figure 3, metiamide led to slight increases in R_A and R_E (and R_TA), but the changes were statistically significant only for R_TA (P < 0.05).

Effects of H2-Receptor Antagonist Infusion followed by Addition of Histamine (Group 3)

With diphenhydramine infusion alone, ΔP remained essentially unaltered. As with whole kidney

Figure 3 Summary of changes in single nephron function in response to intra-aortic infusion of histamine alone and histamine + iv infusion of metiamide (H2-blocker) in euvoilemic rats (group 2).
GFR (from 1.2 ± 0.1 to 1.2 ± 0.1 ml/min, P > 0.20), SNGFR also remained unaltered with diphenhydramine, as shown in Figure 4. Likewise, diphenhydramine failed to change any of the determinants of SNGFR shown in Figure 4. Thus, QA (from 137 ± 15 to 138 ± 19 nl/min), SNFF, PGC (from 49.0 ± 0.5 to 48.6 ± 0.6 mm Hg), PT (from 13.7 ± 0.6 to 14.0 ± 0.8 mm Hg), and ΔP (from 35.3 ± 0.6 to 34.6 ± 0.6 mm Hg) remained at preinfusion levels, in contrast to the significant changes observed in histamine-pretreated group 1 rats given histamine alone. As with QA, values for WE also failed to change with diphenhydramine. The ratio of WE/ΔP therefore remained essentially equal to unity (0.99 ± 0.01, P > 0.10). Calculated minimum values for Kf averaged 0.110 ± 0.010 nl/(s-mm Hg), not significantly different from the mean value obtained prior to addition of histamine (P > 0.50). Thus, the persistence of filtration pressure equilibrium and the high Kf values are in marked contrast to the filtration disequilibrium and the large reduction in Kf seen in rats in groups 1 and 2 given histamine alone. Also, in contrast to the significant declines in RA, RE, and RTA induced by histamine in groups 1 and 2, simultaneous infusions of diphenhydramine and histamine failed to affect these indices significantly in group 3 rats.

Dextran Clearance Studies

Mean values for fractional dextran clearances [(U/P)D/(U/P)IN] with molecular radii of 20–42 Å obtained in three consecutive study periods in five euolemic rats are given in Table 2. As can be seen for the control (first study) period, fractional clearances of dextrans decreased progressively with increases in molecular size, approaching zero at 42 Å. These results are similar to those reported previously for hydropenic rats (Chang et al., 1975a). During infusion of histamine, fractional clearances of dextrans remained essentially unchanged over the wide range of effective radii shown in Table 2. Treatment with diphenhydramine also failed to alter dextran clearances to any significant extent.

In view of the evidence already reported (Bohrer et al., 1977a) that fractional dextran clearances for the whole kidney provide a reliable measure of dextran permeation across capillaries of a single superficial glomerulus, it was possible to calculate both effective pore radius and the ratio of pore surface area:pore length for each study period, using a model described elsewhere (Chang et al., 1975b). Mean values for (U/P)D/(U/P)IN ratios for each effective dextran radius from these five rats, together with mean values for Kf, ΔP, QA, and Cα obtained in group 1 rats, were used as input quantities. Mean values are given in Figure 5 for control period (open circles), during histamine infusion (filled circles), and histamine + diphenhydramine...
Table 2 Fractional Dextran Clearance during Control Period, Histamine Infusion, and Histamine + Diphenhydramine Infusion

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Histamine</th>
<th>Histamine + $H_1$-blocker*</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 Å</td>
<td>0.95±0.02</td>
<td>0.94±0.03</td>
<td>0.90±0.05</td>
</tr>
<tr>
<td>22 Å</td>
<td>0.92±0.02</td>
<td>0.89±0.03</td>
<td>0.86±0.06</td>
</tr>
<tr>
<td>24 Å</td>
<td>0.86±0.02</td>
<td>0.83±0.03</td>
<td>0.82±0.06</td>
</tr>
<tr>
<td>26 Å</td>
<td>0.77±0.02</td>
<td>0.74±0.03</td>
<td>0.75±0.08</td>
</tr>
<tr>
<td>28 Å</td>
<td>0.66±0.02</td>
<td>0.64±0.03</td>
<td>0.64±0.07</td>
</tr>
<tr>
<td>30 Å</td>
<td>0.55±0.03</td>
<td>0.52±0.03</td>
<td>0.60±0.06</td>
</tr>
<tr>
<td>32 Å</td>
<td>0.55±0.03</td>
<td>0.41±0.02</td>
<td>0.43±0.06</td>
</tr>
<tr>
<td>34 Å</td>
<td>0.43±0.03</td>
<td>0.31±0.02</td>
<td>0.33±0.04</td>
</tr>
<tr>
<td>36 Å</td>
<td>0.33±0.03</td>
<td>0.22±0.02</td>
<td>0.23±0.03</td>
</tr>
<tr>
<td>38 Å</td>
<td>0.23±0.03</td>
<td>0.14±0.01</td>
<td>0.15±0.01</td>
</tr>
<tr>
<td>40 Å</td>
<td>0.15±0.03</td>
<td>0.086±0.005</td>
<td>0.091±0.01</td>
</tr>
<tr>
<td>42 Å</td>
<td>0.092±0.009</td>
<td>0.086±0.005</td>
<td>0.091±0.006</td>
</tr>
</tbody>
</table>

Values are expressed as means ± 1 SE. $P > 0.01$ among the three study periods for the entire range of dextran molecular radii examined.

* Diphenhydramine.

Infusion of histamine resulted in a significant rise in both total renal and individual glomerular plasma flow rates. Despite these increases in RPF and QA, total kidney GFR and SNGFR remained essentially constant. These differing effects of histamine on RPF and GFR have been observed previously by other investigators (O'Brien and Williamson, 1971; Selkurt, 1977; Banks et al., 1978). For example, in a recent series of experiments in dogs (Banks et al., 1978), only a small (12%) mean increase in GFR was detected despite a marked (67%) rise in RPF during intrarenal arterial infusion of histamine.

In view of these significant increases in RPF, near-constancy of GFR requires a histamine-related adjustment in one or more of the remaining determinants of GFR so as to offset the effects of this rise in RPF. The Munich-Wistar rat, which possesses surface glomeruli accessible to micropuncture, enabled us to assess these determinants at the level of individual glomeruli. Given the observed increase in QA, the postulate (Banks et al., 1978) that postglomerular resistance declines with histamine necessitates the conclusion that $\Delta P$ also declines with histamine. However, direct measurements of $P_G$ and $P_T$ revealed that $\Delta P$ actually increased with histamine, due solely to a rise in $P_G$, since $P_T$ remained essentially constant. Moreover, these histamine-induced increases in QA and $P_G$ were consequences not of predominant reductions in efferent, but rather afferent, arteriolar resistance.
In view of the rise in $\Delta P$ observed with histamine, which would have been expected to increase SNGFR, and the near-constant value for $\sigma_A$, the only remaining possible explanation for the failure of SNGFR to increase is that histamine induced a fall in $K_f$. Indeed, as shown in Table 1, $K_f$ decreased on average by more than 50% during histamine infusion. Thus, whereas histamine behaves as a potent vasodilator of the renal circulation, just as in many other vascular beds (Chand and Eyre, 1975; Tucker et al., 1975; Wahl and Kuschinsky, 1979), this substance results in marked reductions in glomerular $K_f$, thus accounting for the failure of GFR and SNGFR to increase.

The glomerular $K_f$ value is the product of total glomerular capillary surface area and capillary hydraulic permeability. A reduction in either or both of these terms could account for the observed histamine-induced fall in $K_f$. To gain additional insight into the determinants of glomerular wall permeability, we measured fractional clearances of uncharged dextran macromolecules. Fractional dextran clearances were found to be essentially unchanged, on the average, in response to histamine infusion for dextrans with effective radii ranging from 20 to 42 Å. In view of the pronounced fall in $K_f$, this finding of relative constancy of fractional dextran clearances argues against a change in effective pore radius of the glomerular wall (Fig. 5), since a reduction in pore size is predicted from theory to lead to a dramatic decline in fractional dextran clearances. Instead, as shown in Figure 5, our findings demonstrated a marked fall in the ratio of pore area:pore length, a result which is consistent with the possibility that the histamine-induced fall in $K_f$ is due primarily to a net reduction in filtration surface area, rather than to a decrease in hydraulic permeability per se, but other mechanisms are also possible, including an increase in pore length (Bohrer et al., 1977b). As to the mechanism involved, it is noteworthy that, since glomerular mesangial cells contain an abundance of contractile myofilaments, the $K_f$-lowering effect of histamine may be mediated, directly or indirectly, by mesangial cell contraction, which thereby serves to reduce the glomerular capillary surface area for ultrafiltration.

This $K_f$-lowering effect of histamine on the glomerular microcirculation is in marked contrast to its effects in other tissues, where histamine is well known to increase net fluid filtration in various capillary beds, including skin, skeletal muscle, and intestine (Grega et al., 1972; Haddy et al., 1972; Fox and Wayland, 1976; Rippe and Grega, 1978). Moreover, these histamine-induced increases in net fluid filtration have recently been observed to be accompanied by increases in capillary filtration coefficients (Carter et al., 1974; Rippe and Grega, 1978; Wahl and Kuschinsky, 1979). Such increases in filtration coefficients are believed to be a consequence of histamine-induced formation of interen-

dotheial gaps in postcapillary venules (Haddy et al., 1976). Further, gap formations generally are considered to be caused by active contraction of adjacent margins of venular endothelial cells, presumably mediated by intracellular actomyosin filaments (Majno et al., 1969; Rippe, 1978). It remains possible, therefore, that the apparent functional disparity between histamine’s effects on capillary filtration coefficients in glomeruli vs. other tissues might be due solely to structural differences in the types of capillaries involved, with glomerular visceral epithelial cells precluding the formation of gaps in these capillaries, whereas, in peripheral capillaries, no such epithelial cell layer exists to exert this restraining function. Obviously, additional studies involving structure-function correlations are required to resolve this interesting issue.

At least two distinct histamine receptors (H$_1$ and H$_2$) are known to exist in mammalian tissues (Chand and Eyre, 1975; Torres et al., 1978). In the dog, both receptors have been demonstrated in the renal circulation. We therefore studied the effects of specific H$_1$- and H$_2$-receptor antagonists in histamine-treated rats in the present study. As shown in Figure 2, despite continuous infusion of histamine, the presence of diphenhydramine, a specific H$_2$-receptor antagonist, returned $Q_A$ and $\Delta P$ essentially to levels measured prior to histamine infusion. These changes were associated with return of both $R_A$ and $R_E$ (and thus $R_{TA}$) to pre-histamine levels as well. Likewise, the histamine-induced changes in $K_f$ were reversed completely with diphenhydramine. By contrast, metiamide, a specific H$_2$-receptor antagonist, failed to alter the histamine-induced changes in $Q_A$, $\Delta P$, $K_f$, $R_A$, or $R_E$ to any significant extent. Collectively, these results suggest that, for this strain of rats, at least, the functional role of histamine on the glomerular microcirculation is channeled largely through an H$_1$-receptor system.* In keeping with this conclusion, Banks et al. (1978) observed a significant reduction in GFR with infusion of an H$_1$-receptor agonist in dogs, but not with an H$_2$-receptor agonist, whereas increases in RPF were observed in both cases.

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* Since values for $R_{TA}$ increased slightly, but significantly, during metiamide infusion in histamine-treated rats (Fig. 3), and since both $R_A$ and $R_E$ tended to decrease (although not significantly) with histamine in diphenhydramine-treated rats (Fig. 4), the possibility remains that the H$_2$-receptor system may play a minor role in the renal vasodilatory response to histamine.
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