Histamine H₁ Receptor Antagonists Inhibit Autoregulation of Renal Blood Flow in the Dog

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SUMMARY. Histamine H₁ and H₂ receptors are present in the canine renal circulation. We have examined the effects of H₁ and H₂ receptor antagonists on autoregulation of renal blood flow in the dog. Renal arterial pressure was reduced in a step-wise fashion to 80 mm Hg by means of an adjustable aortic clamp positioned above the left renal artery. Infusion of H₂ antagonists, cimetidine or ranitidine, into the left renal artery at 10⁻⁵ mol/min had no effect on autoregulation of renal blood flow or on the reactive hyperemia that occurred when the aortic constriction was released. By contrast, intrarenal infusion of 10⁻⁵ mol/min chlorpheniramine, an H₁ receptor antagonist, reversibly attenuated reactive hyperemia and the ability of the kidney to autoregulate renal blood flow. Similar results were obtained with other, chemically dissimilar H₁ antagonists (terfenadine, diphenhydramine, and pyrilamine). The effects of chlorpheniramine on autoregulation of glomerular filtration rate also were evaluated. Before chlorpheniramine was infused (at 10⁻⁵ mol/min), the reduction of renal arterial pressure to 90 mm Hg had no effect on the glomerular filtration rate, whereas, during infusion of the H₁ antagonist, the glomerular filtration rate fell significantly when renal arterial pressure was reduced to 90 mm Hg. Infusion of histamine (1 μg/kg min) with increasing amounts of cimetidine, chlorpheniramine, diphenhydramine, or pyrilamine resulted in virtually identical dose-dependent decreases in histamine-induced renal vasodilation. However, even with 10⁻³ mol/min cimetidine or 10⁻⁵ mol/min chlorpheniramine, diphenhydramine, or pyrilamine, a significant histamine-induced renal vasodilation was observed. Thus, the amount of H₁ antagonist required to inhibit histamine activation of H₁ receptors is the same as needed to block autoregulation. Finally, renal vascular reactivity as estimated by acetylcholine-induced vasodilation was not substantially affected by chlorpheniramine or by pyrilamine. These observations provide evidence in support of a role for histamine as a chemical mediator of renal autoregulation. (Circ Res 54: 527-535, 1984)

AUTOREGULATION of renal blood flow is an established phenomenon. It is widely accepted that at least two mechanisms are involved, a myogenic event and a tubuloglomerular feedback process. One of the undefined components of autoregulation is the nature of the transducer which couples changes in renal perfusion pressure with changes in renal vascular resistance. As recently reviewed by Navar et al. (1980), current evidence does not support a major role for neural elements, the adrenergic system, or the prostaglandins. One substance that has not been widely studied as a potential mediator of renal autoregulatory events is histamine. We have recently demonstrated that both histamine H₁ and H₂ receptors are present in the canine kidney (Banks et al., 1978; Pawlik et al., 1980; Pollock et al., 1982). Selective activation of these two receptor populations with appropriate receptor agonists resulted in differential effects on renal hemodynamics. Thus, activation of H₁ receptors evoked a rapid increase in renal blood flow which achieved a plateau value within 30 seconds. In contrast, activation of H₂ receptors was accompanied by a slower increase in flow, requiring approximately 5 minutes before a steady state occurred.

The kidney contains few mast cells and only about 10⁻⁶ g histamine/g tissue (Reiman et al., 1981; Abboud et al., 1982). On the other hand, isolated glomeruli contain histidine decarboxylase (Heald and Hollis, 1976) and whole kidney homogenates have relatively large amounts of N-methyl transferase (Shaff and Beaven, 1979), localized predominately in tubular elements (Abboud, 1983) and diamine oxidase (Baylin et al., 1972), predominately found in glomeruli (Abboud, 1983). Moreover, the kidney appears to have the capacity to produce histidine (Fukuda and Kopple, 1979). Thus, the metabolic machinery of the kidney appears well-suited for both the synthesis and degradation of histamine.

Many factors are known to stimulate the synthesis of histamine. These include hormones such as thyroxine, glucocorticoids, and estrogen, as well as factors such as anoxia and catecholamines (for review, see Kahlson and Rosengren, 1968; Beaven, 1978).

In view of these considerations, we studied the effects of selective inhibition of H₁ and H₂ receptors on autoregulatory events associated with renal hemodynamics. Effects of histamine receptor antagonists on autoregulation of renal blood flow, glo-
Semple and deWardener (1959): ARI was calculated using the formulation of

\[ ARI = \frac{\frac{RBF_i - RBF_{so} \text{ mm Hg}}{RBP_i}}{\frac{RBP_i - 80 \text{ mm Hg}}{RBF_i}} \]

where \( i \) signifies the initial RBF and RAP values measured before RAP was reduced to 80 mm Hg.

**Methods**

Adult mongrel dogs of either sex (14–25 kg) were anesthetized with sodium pentobarbital (30 mg/kg) and intubated with a cuffed endotracheal tube. Saline was infused at a rate of 1 ml/kg per min for 15 minutes, then 0.25 ml/kg per min via a PE-100 catheter in the left femoral vein. The right femoral artery was also cannulated with a PE-100 catheter and the tip advanced to approximately the level of the left renal artery in order to determine renal arterial pressure (RAP). RAP was measured with a transducer (Physiograph, P-1000A) and recorded on a polygraph (Physiograph model 4). Although urine was not routinely collected in the current study, both ureters were cannulated with PE-100 tubing via an abdominal incision.

The left renal artery and a segment of the aorta above the renal artery were exposed through a flank incision. A length of postmortem thread was then positioned around the aorta approximately 1 cm above the junction of the vessel with the left renal artery. The ends of this thread were then passed through a 15-cm length of PE-260 tubing. Thus, a variable degree of tension could be applied to the aorta when desired. An electromagnetic flow probe (3.0 or 3.5 mm in diameter) was positioned on the left renal artery. The probe was connected to a blood flow amplifier (Narco Bio-Systems model RT400 with digital display meter model DD350), and renal blood flow (RBF) was recorded on the polygraph. A curved 25-gauge needle, connected to PE-50 tubing and a syringe infusion pump (Harvard Apparatus model 975), was inserted into the lumen of the renal artery. During control periods, we kept the needle patent by infusing saline at a rate of 0.188 ml/min. At desired times, histamine \( H_1 \) or \( H_2 \) receptor antagonists or histamine (Eli Lilly) were administered via this infusion system. The \( H_1 \) receptor antagonists used in the current study were chlorpheniramine maleate (Chemical Dynamics Corp), terfenadine (Merrell-Dow), diphenhydramine (Sigma), and pyrilamine maleate (Sigma). The \( H_2 \) receptor antagonists which we employed were cimetidine (Smith, Kline and French Labs) and ranitidine (Galxo, Ltd). Terfenadine was dissolved in ethanol (13 mg/ml) to which 5 ml of dog plasma and 14 ml saline were added. All other drugs were dissolved in saline.

**Autoregulation of Renal Blood Flow**

Renal arterial pressure was reduced in a step-wise fashion before, during, and after infusion of chlorpheniramine (10⁻⁵ mol/min) into the left renal artery (\( n = 3 \)). The \( H_1 \) antagonist was infused for 5–20 min; the infusion of the drug was terminated when the fractional decrease in RBF approximated the imposed fractional reduction in RAP. Similar experiments were performed with other \( H_1 \) antagonists (pyrilamine, 10⁻⁵ mol/min, \( n = 6 \); diphenhydramine, 10⁻⁵ mol/min, \( n = 6 \); terfenadine, 5 × 10⁻⁷ mol/min, \( n = 5 \)), with \( H_2 \) antagonists (cimetidine, 10⁻³ mol/min, \( n = 2 \); ranitidine, 10⁻⁵ mol/min, \( n = 3 \)), and with histamine (0.5–1.0 mg/kg per min, \( n = 9 \), 2 μg/kg per min, \( n = 6 \)). For each autoregulatory assessment, an autoregulatory index (ARI) was calculated using the formulation of Semple and deWardener (1959):

\[ ARI = \frac{RBF_i - RBF_{so} \text{ mm Hg}}{RBF_i} \times \frac{RBP_i - 80 \text{ mm Hg}}{RAP_i} \]

where RBFₚ is the maximum flow obtained after aortic constriction was released, and RAP is defined as follows:

\[ RH = \frac{(RBF_{pm}/RBF_i) \times 100}{RAP} \]

where RBF peak = maximum RBF value obtained after the aortic ligature was loosened and \( i \) represents the initial value.

**Autoregulation of Glomerular Filtration Rate**

Effects of chlorpheniramine on autoregulation of glomerular filtration rate (GFR) were evaluated in five dogs. The animals were surgically prepared as described above. An intravenous priming injection (5 ml) of a creatinine solution (3 g/100 ml saline) was followed by a constant infusion of 5 ml/hr. Approximately 1 hour after the rapid phase of volume expansion, two consecutive clearances were obtained. RAP then was reduced to 90 mm Hg, and after 5 minutes, two additional clearances were obtained. The aortic constriction was released and RBF was allowed to restabilize. An infusion of chlorpheniramine (10⁻⁵ mol/min) into the left renal artery was then begun, and after 5 minutes, a final clearance was obtained. The concentration of creatinine in urine and plasma was measured by the method of Folin and Wu (1919). The clearance of creatinine was taken to represent GFR.

**Effects of Receptor Antagonists on Histamine- and Acetylcholine-Induced Renal Vasodilation**

We evaluated the effects of graded doses of chlorpheniramine (\( n = 6 \)), pyrilamine (\( n = 3 \)), diphenhydramine (\( n = 3 \)), or cimetidine (\( n = 6 \)) on histamine-induced renal vasodilation. Dogs were surgically prepared as described above. When RBF had stabilized (30–45 minutes post-surgery), histamine (1 μg/kg per min) was infused into the left renal artery. After 5 minutes, the histamine infusion was stopped and RBF was allowed to restabilize. Histamine (1 μg/kg per min) + the antagonist (10⁻⁷ mol/min) then was infused into the renal artery for 5 minutes. This protocol was repeated with each receptor antagonist administered at 10⁻⁸ and 10⁻⁵ mol/min. Since terfenadine is a renal vasodilator (see Fig. 4), a similar series of experiments with progressive doses of terfenadine could not be performed. Consequently, the effects of terfenadine on histamine-induced renal vasodilation were evaluated in a different fashion. Terfenadine (5 × 10⁻⁷ mol/min) was infused into the renal artery of five dogs until a steady state was obtained (5 minutes). Terfenadine + histamine (1 μg/kg per min) was then infused for a second 5-minute time interval. The infusion solution was again changed, and terfenadine + histamine + cimetidine (10⁻³ mol/min) was infused for a third 5-minute interval (cimetidine was used to block the \( H_2 \) component).

Finally, we evaluated the effects of two \( H_1 \) receptor antagonists, chlorpheniramine and pyrilamine, on renal vascular reactivity to acetylcholine (ACH). After completion of several of the above experiments, ACH (10 μg/kg per min) was infused into the renal artery for 5 minutes.
before and again during infusion of chlorpheniramine ($10^{-5}$ mol/min, $n = 5$) or pyrilamine ($10^{-5}$ mol/min, $n = 5$).

Statistical analyses were based on Student's t-test for either pooled or paired data. Values were accepted as significantly different when the probability of no difference was less than 5%. Mean values ± 1 SEM are reported.

**Results**

**Autoregulation of Renal Blood Flow and Reactive Hyperemia**

The effects of each histamine H$_1$ receptor antagonist, chlorpheniramine, pyrilamine, diphenhydramine, and terfenadine, on autoregulation of renal blood flow are illustrated in Figures 1–4. In addition, the autoregulatory indices and the values for RH that were obtained before, during, and after infusion of these agents are summarized in Table 1. Several facts are apparent: (1) before infusion of the H$_1$ antagonists, step-wise reductions in renal perfusion pressure to 80 mm Hg had little effect on steady state values of renal blood flow—i.e., autoregulatory indices were approximately zero; (2) during infusion of each H$_1$ receptor antagonist, RBF decreased progressively as RAP was reduced with AR1 values approaching 1.0; (3) the effects of these agents on autoregulation were reversible; and (4) the antagonists decreased reactive hyperemia, an effect which was also reversible.

Infusion of the H$_2$ receptor antagonists, cimetidine ($n = 2$) or ranitidine ($n = 3$), into the renal artery at a dose of $10^{-5}$ mol/min had no effect on renal hemodynamics, either before or during reductions in RAP. During infusion of the H$_2$ receptor antagonists RBF averaged 2.4 ± 0.3 and 2.3 ± 0.3 ml/min
but often transient vasodilation, diphenhydramine and pyrilamine caused a slight vasoconstriction, and terfenadine was always associated with a pronounced renal vasodilation (the terfenadine vehicle had no effect on baseline hemodynamics or on autoregulatory events). To determine whether the effect of terfenadine on autoregulation of RBF was simply related to the drug-induced renal vasodilation, a similar study was performed in which a 40% increase in RBF was achieved by infusing histamine into the left renal artery (0.5–1.0 μg/kg per min). These data are summarized in Figure 4 and in Table 1. It is clear that autoregulation was not affected when histamine was infused in amounts sufficient to increase RBF 40%. In contrast, when histamine was infused at 2 μg/kg per min, a significant attenuation of RBF autoregulation could be demonstrated (Fig. 5, Table 1).

**Autoregulation of Glomerular Filtration Rate**

Effects of chlorpheniramine on autoregulation of GFR are shown in Table 2. Prior to infusion of the H₁ antagonist, there was no significant change in the GFR, or RBF, when RAP was reduced from control pressures to 90 mm Hg. In contrast, during infusion of chlorpheniramine, reduction of RAP to 90 mm Hg was associated with a significant decline in the GFR as well as RBF.

**Effects of Receptor Antagonists on Histamine- and Acetylcholine-Induced Renal Vasodilation**

Fractional increases in RBF produced by infusion of 1 μg/kg per min histamine are shown in Figure 6. Also shown are the subsequent effects on RBF of infusing histamine + progressively larger amounts of chlorpheniramine or cimetidine and the hemodynamic effects of infusing each receptor antagonist alone. Each histamine receptor antagonist caused a dose-dependent decrease in the histamine-induced renal vasodilation. Moreover, even during infusion of histamine with the highest dose of the antagonists.

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**TABLE 1**

<table>
<thead>
<tr>
<th>Autoregulatory Indices and Reactive Hyperemia Values</th>
<th>ARI</th>
<th>RH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Drug</td>
</tr>
<tr>
<td>Chlorpheniramine series (n = 6)</td>
<td>0.07 ± 0.04</td>
<td>0.73 ± 0.04*</td>
</tr>
<tr>
<td>Pyrilamine series (n = 6)</td>
<td>0.05 ± 0.07</td>
<td>0.82 ± 0.10*</td>
</tr>
<tr>
<td>Diphenhydramine series (n = 6)</td>
<td>0.10 ± 0.05</td>
<td>0.81 ± 0.12*</td>
</tr>
<tr>
<td>Terfenadine series (n = 5)</td>
<td>−0.11 ± 0.08</td>
<td>0.74 ± 0.09*</td>
</tr>
<tr>
<td>Histamine series (n = 9) low dose</td>
<td>0.08 ± 0.04</td>
<td>0.09 ± 0.06</td>
</tr>
<tr>
<td>Histamine series (n = 6) high dose</td>
<td>0.01 ± 0.01</td>
<td>0.67 ± 0.08*</td>
</tr>
</tbody>
</table>

* P < 0.05 compared to previous value.
† Only three values obtained.
‡ Only four values obtained.
Histamine Antagonists and Autoregulation

(10⁻⁵ mol/min) a significant vasodilation was observed (16 ± 5% in the chlorpheniramine series and 15 ± 3% in the cimetidine series). Similar experiments with diphenhydramine and pyrilamine are summarized in Table 3. As with chlorpheniramine, diphenhydramine and pyrilamine also caused dose-dependent decreases in histamine-induced renal vasodilation. The residual percentage increase in RBF observed during infusion of histamine + 10⁻⁵ mol/min chlorpheniramine, diphenhydramine or pyrilamine was similar for each antagonist.

Since terfenadine caused a marked increase in RBF, an experimental protocol involving dose-dependent decreases in histamine-induced renal vasodilation by this antagonist could not be performed. As indicated in Methods, we therefore evaluated effects of terfenadine and terfenadine + cimetidine on histamine-induced vasodilation. These results are summarized in Figure 7. As may be seen, histamine caused a significant vasodilation (P < 0.05) before and during infusion of terfenadine. However, the histamine-induced vasodilation during infusion of terfenadine was completely blocked by cimetidine.

Finally, the effects of two H₁ antagonists, chlorpheniramine and pyrilamine, on the renal vasodilation induced by acetylcholine (ACh) were studied, and the results are summarized in Figure 8. Infusion of chlorpheniramine (10⁻⁵ mol/min) during infusion of ACh (10 μg/kg per min) resulted in a small (−9 ± 2%) but significant (P < 0.05) decrease in RBF. On the other hand, pyrilamine (10⁻⁵ mol/min) had no effect on ACh-induced renal vasodilation.

Results of the current study demonstrate that the ability of the kidney to autoregulate renal blood flow and glomerular filtration rate is compromised during infusion of histamine H₁ receptor antagonists into the renal circulation. Two explanations for these results appear to apply: either histamine is a chemical modulator of renal autoregulation or the effects of the antagonists on autoregulation are nonspecific, i.e., non-histamine-related properties of H₁ antagonists account for the inhibition of renal autoregulation. With regard to the latter, it has been reported that some H₁ antagonists have chemical properties similar to those of cocaine (Johnson and Kahn, 1966) and to procaine (Halpern, 1942).

Although it is not possible, at the present time, to differentiate between the two possibilities, several facts indicate that the changes we observed in autoregulation and reactive hyperemia can be attributed to the H₁ receptor antagonist properties of the drugs. First, we obtained similar results with four different chemical classes of H₁ antagonists. Pyrilamine is an ethylenediamine, diphenhydramine is an ethanolamine, chlorpheniramine is an alkylamine, and terfenadine is a piperidine-type antihistamine (Cheng and Woodward, 1983). Second, we observed that these agents have different effects on baseline RBF, yet each compromises autoregulation. Pyrilamine and diphenhydramine are vasoconstrictor agents, whereas chlorpheniramine and terfenadine are vasodilators. Third, inhibitors of smooth muscle activity, such as procaine or papaverine, result in a marked and prolonged vasodilation (Thurau and Kramer, 1959; Waugh and Shanks, 1960). Fourth, Waugh and Shanks (1960) reported that procaine had no effect on pressure autoregulation when the concentration of the drug in the renal perfusate was 0.5 mg/100 ml (an exceedingly high concentration of 100 mg/100 ml perfusate was necessary to inhibit

### Table 2

Effects of Chlorpheniramine on Autoregulation of GFR

<table>
<thead>
<tr>
<th></th>
<th>Control RAP</th>
<th>Reduced RAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>No drug</td>
<td></td>
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</tr>
<tr>
<td>GFR (ml/min per g)</td>
<td>0.55 ± 0.11</td>
<td>0.57 ± 0.09</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>149 ± 7</td>
<td>90 ± 0*</td>
</tr>
<tr>
<td>RBF (ml/min per g)</td>
<td>3.44 ± 0.61</td>
<td>3.23 ± 0.64</td>
</tr>
<tr>
<td>Chlorpheniramine (10⁻⁴ mol/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR (ml/min per g)</td>
<td>0.54 ± 0.05</td>
<td>0.23 ± 0.08*</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>162 ± 5</td>
<td>90 ± 0*</td>
</tr>
<tr>
<td>RBF (ml/min per g)</td>
<td>2.86 ± 0.40†</td>
<td>1.96 ± 0.35*</td>
</tr>
</tbody>
</table>

*P < 0.05 compared with value from preceding period.
†Prior to infusion of chlorpheniramine, RBF was 3.14 ± 0.52 ml/min per g (P > 0.05).

Discussion

Results of the current study demonstrate that the ability of the kidney to autoregulate renal blood flow and glomerular filtration rate is compromised during infusion of histamine H₁ receptor antagonists into the renal circulation. Two explanations for these results appear to apply: either histamine is a chemical modulator of renal autoregulation or the effects of the antagonists on autoregulation are nonspecific, i.e., non-histamine-related properties of H₁ antagonists account for the inhibition of renal autoregulation. With regard to the latter, it has been reported that some H₁ antagonists have chemical properties similar to those of cocaine (Johnson and Kahn, 1966) and to procaine (Halpern, 1942).

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autoregulation). The concentration of H₃ antagonists in renal arterial blood of dogs in the current study would be 0.002–0.2 mg/100 ml (10⁻⁷ to 10⁻⁵ mol/min infused into an average RBF of 150 ml/min). Fifth, we found that the dose of the H₃ antagonists required to block histamine H₁-induced increases in RBF was similar to that required to attenuate autoregulation. It is of interest to note that terfenadine, which compromised autoregulation when infused at 5 × 10⁻⁷ mol/min, has also been reported to be about 10 times more effective than chlorpheniramine as an inhibitor of some H₁ mediated events (Miemegeers, Awouters and Janssen, 1983). Sixth, H₁ antagonist-induced changes in vascular reactivity can be excluded, since neither chlorpheniramine nor pyrilamine markedly affected acetylcholine-induced renal vasodilation. Finally, we noted that histamine H₂ receptor antagonists were ineffective in altering autoregulatory processes, indicating a specificity of the response for H₁ receptors.

The possibility that histamine mediates renal autoregulation and reactive hyperemia was not supported by the results of Scott et al. (1965). They reported that a decrease in renal arterial pressure was associated with the appearance of a vasodilator substance in renal venous blood; the release of the dilator substance was determined by perfusing a forelimb with renal venous blood from the experimental kidney. The fall in forelimb resistance when RAP was decreased was not prevented by diphenhydramine when administered in an amount sufficient to decrease the vasodilation associated with an infusion of histamine into the brachial artery. However, these investigators did not report (1) whether the response of forelimb blood flow to histamine was abolished or simply attenuated by diphenhydramine, (2) whether the decrease in forelimb resistance that occurred during perfusion with renal venous blood of autoregulating kidneys was also attenuated or completely unaltered by diphenhydramine, or (3) whether infusion of diphenhydramine alone significantly altered forelimb resistance. Along similar lines, the presence or absence of histamine in renal venous blood during autoregulatory events could have little bearing on localized, tissue concentrations of the amine. This possibility is supported by the results of Reilly and Schayer (1968), who demonstrated a significant endotoxin-induced synthesis of histamine within tissues such as lung and muscle without concomitant changes in blood histamine levels.

The dose-dependent reductions of histamine-in-

### Table 3

<table>
<thead>
<tr>
<th>Effects of Diphenhydramine (D) and Pyrilamine (PY) on Histamine (H)-Induced Renal Vasodilation</th>
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<tbody>
<tr>
<td><strong>No.</strong></td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>Diphenhydramine series</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>Pyrilamine series</td>
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<td>1</td>
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<td>3</td>
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duced renal vasodilation by each of the H₁ antagonists used in the current study and by cimetidine complement our previous conclusion that two histamine receptor populations are present in the canine renal circulation (Banks et al., 1978). Results of the current study also indicate that, except for terfenadine, a molar excess of the antagonists is required to inhibit each receptor population. This latter conclusion is based on the fact that the amount of histamine infused into a 20 kg dog was $2 \times 10^{-7}$ mol/min. If one assumes that these H₁ and H₂ receptor antagonists are relatively specific for each receptor population, the quantity of H₁ and H₂ receptors in the canine kidney are similar, since the residual histamine-induced vasodilation during infusion of histamine + $10^{-5}$ mol/min chlorpheniramine, diphenhydramine, or pyrilamine was identical to that obtained with histamine + $10^{-5}$ mol/min cimetidine.

An interesting facet of the current study relates to the finding that H₁ but not H₂ receptor antagonists attenuate each of the autoregulatory events we evaluated. These data point to a different spatial distribution of H₁ and H₂ receptors in the canine renal circulation. Such a spatial distribution would account for our proposed mechanism of an H₁ rather than an H₁ + H₂-mediated control of autoregulation. Additional indications of a difference in the spatial distribution of the two receptor populations have been reported previously (Banks et al., 1978). In that report, activation of H₂ receptors with the H₂ agonist, dimaprit, increased RBF and solute excretion but not GFR. That study also demonstrated that intrarenal infusion of the H₁ agonist, 2-(2-pyridyl) ethylamine (PEA), increased RBF but decreased urine flow rate, and tended to decrease the GFR (effects of PEA on GFR could not be resolved, since urine flow rate markedly decreased in several experiments). These data suggested that H₂ receptors were present in both pre- and postglomerular vessels, whereas H₁ receptors were predominantly postglomerular. However, it was subsequently demonstrated in the rat that histamine significantly increased glomerular capillary pressure (indicating that the amine caused preglomerular vasodilation) and that it also produced a decrease in the glomerular ultrafiltration coefficient (Ichikawa and Brenner, 1979). It is of interest to note that there is a predominance of H₁ receptors in the rat kidney (Ichikawa and Brenner, 1979). Since most investigators have reported that pressure-induced changes in renal vascular resistance occur in the afferent arteriole (for review, see Navar, 1978), it is necessary to propose that H₂ receptors are also located in this region in the dog. Furthermore, infusion of histamine directly into the canine renal artery results in a rapid activation of H₁ but a slower activation of H₂ receptors (Banks et al., 1978). It is possible, therefore, that H₁ components are located near the luminal surface of blood vessels. Since endothelial cells are known to synthesize histamine (Hollis and Rosen, 1972; Fujimoto, 1982), there may be a close spatial relationship between H₁ receptors (but not H₂ receptors) and the site of histamine synthesis.

Baer and Navar (1973) have reported that some agents, in particular, potent vasodilators such as acetylcholine and prostaglandin E₂, compromise autoregulation of RBF but not GFR. In the current study, the H₁ antagonist, chlorpheniramine, clearly
attenuated both autoregulatory events, suggesting that the antagonist blocks pressure-induced changes in afferent arteriolar resistance. Along these lines, it is also of interest to note that the attenuation of autoregulation by terfenadine was not related to the vasodilatory properties of the drug, per se, since a similar fractional increase in RBF induced by histamine had no effect on autoregulation. Baer and Navar (1973) also found that autoregulation was maintained during renal vasodilation with dopamine. In part, the variable effect of vasodilators on RBF autoregulation may be related to the dose of the vasodilator used. Thus, in current study, we observed no effects of a low dose of histamine (0.5-1.0 µg/kg per min) on autoregulation, whereas a higher dose (2 µg/kg per min) clearly attenuated the phenomenon.

Vasoconstrictors have been reported to compromise autoregulation (Folkow and Langston, 1963; Langard et al., 1981), to be without effect on autoregulation (Nahmod and Lanari, 1964), and even to reestablish autoregulation in atonic kidneys (Schmid et al., 1964). In the studies by Folkow and Langston (1963) and Langard et al. (1981), baseline RBF was reduced by 30-40%. In contrast, the doses of pyrilamine and diphenhydramine which markedly attenuated autoregulation in that current study, reduced baseline RBF by only 6% and 4%, respectively. Thus, it seems unlikely that effects of these H1 antagonists on autoregulation were due to changes in baseline renal hemodynamics.

In summary, the results of the current study clearly demonstrate that histamine H1 receptor antagonists abolish autoregulation of RBF and GFR, as well as reactive hyperemia. As discussed, our data suggest that these effects are related to the antagonism of H1 receptors. Nonetheless, further studies will be necessary to determine whether non-histamine-related events mediate the effects of these H1 antagonists on renal hemodynamics. Whichever mechanism prevails, it is clear that information will be gained concerning the biochemical process involved in renal autoregulation.

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