THE EFFECTS OF HISTAMINE ON RENAL FUNCTION IN 
HYPERTENSIVE AND NORMOTENSIVE SUBJECTS

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(Received for publication June 16, 1948)

Little is known of the effects of histamine upon
the renal circulation. According to Dale and
Laidlaw (1), the rate of urine flow after the injec-
tion of histamine follows roughly the arterial blood
pressure; their renal plethysmographic studies
showed a decrease in the volume of the kidney,
possibly due to active arteriolar constriction.
These observations have generally been confirmed
by other investigators (2-4), who found a reduced
blood flow in laboratory animals and an oliguria
in human beings. Following administration of
histamine to human subjects, Bjering (5) noted
a fall in the clearances of urea and creatinine
which he ascribed to changes in renal circulation.

The favorable effect of antihistaminic drugs
upon experimental nephritis in rabbits and on
albuminuria and hematuria in certain cases of human
glomerular nephritis suggests that histamine-like
substances may cause the glomerular vasodilatation
and increased permeability observed in the latter
disease (6, 7). Some human subjects manifesting
arterial hypertension of the "neurogenic" type (8)
show a definite hypersensitivity to histamine and
respond to the intracutaneous injection of a small
dose with a so-called "diencephalic blush" (9).
Because of these observations bearing on the in-
fluence of histamine upon renal and vascular dis-
ease, an attempt was made to investigate further
the effect of histamine upon renal function. We
describe below the influence of a subcutaneous in-
jection of histamine upon renal function as meas-
ured by the clearance technique.

1 This investigation was supported by a grant-in-aid
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SUBJECTS AND METHODS

Experiments were performed upon five patients with
essential hypertension without ascertainable antecedent
renal disease, and upon five normotensive patients.

Mannitol and para-aminohippurate (PAH) were meas-
ured in blood and urine during five or six consecutive
periods of 10 to 20 minutes duration. After a priming
dose had been administered, the blood levels of mannitol
and PAH were maintained approximately constant by
intravenous administration of a 0.9% sodium chloride
solution containing these substances, at a rate of 4 cc.
per minute. Urine was collected by catherization, and
the bladder was rinsed with 0.9% sodium chloride solu-
tion at the end of each period. The analytical procedures
used were essentially those employed by Goldring and
Chasis (10). Among factors considered in performing
the plasma and urine mannitol blanks were non-ferment-
able reducing substances contributed by plasma or urine,
or "Factor 1," reducing substances contributed by the
yeast suspension, or "Factor 2," and adsorption or de-
struction of mannitol by the yeast suspension, or "Factor
3." In performing the plasma blank, all three factors
were corrected for, save in the case of the three subjects,
L. C., I. H., and M. L., when compensation was made
only for Factor 1. In performing the urine blank, Factors
2 and 3 were corrected for, save in the case of the same
three subjects, when compensation was made only for
Factor 2. Data on the technique employed for these
blank determinations will be presented elsewhere (11).

The renal plasma clearances of mannitol and PAH
were calculated using the formula "UV/P," where "U"
and "P" are respectively concentration of the substance
in urine and plasma, and "V" the volume of urine ex-
creted per minute expressed in cubic centimeters (12).
The value of P at the exact midpoint of each period was
calculated by interpolation between the values observed
during each period. The "filtration fraction" was calcu-
lated as the ratio of the mannitol clearance to the PAH
clearance.

The afferent and efferent arteriolar resistances (R_4
and R_8) were computed from our data according to Lam-
4 The mannitol and PAH solutions administered were
generously contributed by Sharpe and Dohme Company;
the starch-free baker's yeast used in the mannitol analyses
was given by Anheuser-Busch, Inc.
5 Miss Ellabeth Houghton, Mrs. Mattie Heady and
Mrs. Harriet Weil rendered technical assistance in per-
forming and reporting the investigations.

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TABLE I
Renal clearances of mannitol and para-aminophenylurea (PAH) in five hypertensive subjects before and after histamine injection

<table>
<thead>
<tr>
<th>Subject</th>
<th>Period</th>
<th>Histamine dose</th>
<th>Urine flow</th>
<th>Plasma levels</th>
<th>Urine levels</th>
<th>Plasma clearances</th>
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<th>RA‡</th>
<th>RA§</th>
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<td>.232</td>
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<td>5.58</td>
<td>83.2</td>
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<tr>
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<tr>
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<td>0.88</td>
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<td>2.70</td>
<td>0.95</td>
<td>.0389</td>
<td>37.7</td>
<td>6.48</td>
<td>106.3</td>
<td>449</td>
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<td>165/110</td>
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</table>

* Filt. frac. = filtration fraction = mannitol clearance

† Blood pressure = arterial blood pressure.

‡ RA = afferent arteriolar resistance in mm. of mercury per cc. renal plasma flow per minute.

§ RE = efferent arteriolar resistance in mm. of mercury per cc. renal plasma flow per minute.

port’s formulae (13). In these computations we arbitrarily assumed a hematocrit of 0.43, a plasma protein concentration of 7.0 grams per 100 cc., and a ratio of albumin to globulin of 2.2. The injection of histamine did not influence the hematocrit values in the two experiments in which the measurement was made.

In addition to the 10 clearance experiments, the renal extraction of PAH and mannitol before and after subcutaneous administration of 0.5 mgm. of histamine was determined in three subjects by catheterization of the right renal vein, using the technique devised by Courmand and Ranges (14) for the heart and developed by Warren, Brannon and Merrill (15) for the renal vein. The blood pressure was measured in the arm by the auscultatory technique.

The dose of histamine was chosen so as to elicit a moderate general reaction with flushing of the face and headache. Lachrymation, palpitation, and tachycardia occurred in some patients; the blood pressure fell regularly only in hypertensive subjects. Usually 0.3 to 0.5 mgm. of histamine, calculated as the pure base, was administered, depending on body weight; in one case (F. W.) a marked reaction was produced by 0.15 mgm., and in another (L. C.) the administration of a total of 0.7 mgm. in two doses resulted in almost no reaction and no striking changes in renal clearances. The histamine clearance as usually calculated (UV/P) and the clearance computed from the calculated renal blood flow and the observed renal extraction of mannitol (23). However, we assume that for our purposes the clearance methods permit a useful approximation of kidney function.
was administered subcutaneously as the acid phosphate in a solution containing 1 mgm. of the pure base in 1 cc. Renal clearance measurements were made for two or three control periods before injecting histamine.

**RESULTS**

The most constant changes in renal clearances after the injection of histamine were a decrease, as indicated by the PAH clearance (16), in the plasma flow and an associated increase in the filtration fraction. The filtration rate, as measured by the mannitol clearance (17), was not consistently altered (Tables I, II). These characteristic features are summarized in Table III. In Figure 1 are presented schematically the mean values observed in both the hypertensive and non-hypertensive groups. In the normotensive subjects, there appeared to be no correlation between the reduction in renal plasma flow and the systemic blood pressure, the latter showing a very variable behavior. The frequent elevation in the filtration fraction in both groups of subjects indicates that active arteriolar constriction occurred. It has been generally assumed that spasm of the efferent arterioles accounts for this elevation of the filtered portion of plasma passing through the kidney (18).

Whereas four out of five hypertensive individuals showed a definite rise in the filtration fraction, such an elevation was evident in only two normotensive subjects; in two others it was questionable, occurring slowly possibly because of spontaneous changes in arteriolar tone unrelated to the injection of histamine (18). In one hypertensive subject and one normotensive subject

<table>
<thead>
<tr>
<th>Subject</th>
<th>Period</th>
<th>Histamine dose</th>
<th>Urine flow</th>
<th>Plasma levels</th>
<th>Urine levels</th>
<th>Plasma clearances</th>
<th>Filt. frac.</th>
<th>Blood pressure</th>
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<td>59.8 7.77</td>
<td>113 774</td>
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<tr>
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<td></td>
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<td>PAH</td>
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<td>.154</td>
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<tr>
<td></td>
<td>0.4</td>
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<td>Mannitol</td>
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<td>50.2 9.56</td>
<td>57† 330†</td>
<td>.174</td>
<td>90/55</td>
<td>.0112</td>
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<td>0.3</td>
<td>21 years</td>
<td>2.29†</td>
<td>Mannitol</td>
<td>1.21 .0388</td>
<td>54.1 9.64</td>
<td>102† 569†</td>
<td>.179</td>
<td>90/55</td>
<td>.0060</td>
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<tr>
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<td>1.73</td>
<td>PAH</td>
<td>1.22 .0426</td>
<td>52.7 8.45</td>
<td>74 343</td>
<td>.217</td>
<td>.0079</td>
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<tr>
<td></td>
<td>5</td>
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<td>1.60</td>
<td>Mannitol</td>
<td>1.19 .0386</td>
<td>57.8 9.30</td>
<td>78 383</td>
<td>.202</td>
<td>100/55</td>
<td>.0153</td>
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</tbody>
</table>

*See Table I footnotes for abbreviations.
†Residual urine in the bladder after the first period may account for these differences.
there were no changes in filtration fraction. The average curves (Figure 1) indicate that the mean increase in filtration fraction was about the same in both series, amounting to 12% in the normotensive group and 14% in the hypertensive patients. Two normotensive individuals appeared to be very sensitive to the injected amine.

The calculated efferent arteriolar resistance was increased in four and unchanged in one hypertensive subject. It was also increased in four (in three only slightly) and unchanged in one normotensive individual. The afferent arteriolar resistance was decreased in three and unchanged in two hypertensive patients; in normotensive subjects, changes were roughly parallel to those in the efferent resistance.

As will be seen in Table IV, the renal extraction percentage of mannitol and PAH was not consistently influenced by the injection of histamine. The data on subject F. C. presented in Tables II and IV were obtained during the same experiment.

Qualitative (heat) tests on the urine of nine of the ten patients revealed no proteinuria occurring during the clearance period immediately following the injection of histamine. The tenth patient (I. H.) exhibited traces of urinary protein antecedent to the injection of histamine; the injection caused no immediate increase in proteinuria.

**Table III**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Plasma flow</th>
<th>Filtration rate</th>
<th>Filtration fraction</th>
<th>Blood pressure</th>
<th>R_A</th>
<th>R_E</th>
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<td>I. H.</td>
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<td>i.</td>
<td>d.</td>
<td>d.</td>
<td>i.</td>
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<td>s.d.</td>
<td>i.</td>
<td>i.</td>
<td>d.</td>
<td>d.</td>
<td>i.</td>
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<td>d.</td>
<td>d.</td>
<td>i.</td>
<td>d.</td>
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<tr>
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<td>s.i.</td>
<td>i.</td>
<td>d.</td>
<td>u.</td>
<td>i.</td>
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<tr>
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<td>d.</td>
<td>u.</td>
<td>d.</td>
<td>u.</td>
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<tr>
<td>Normotensive</td>
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<td></td>
<td></td>
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<td>d.</td>
<td>d.</td>
<td>u.</td>
<td>u.</td>
<td>s.i.</td>
<td>s.i.</td>
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<tr>
<td>M. C.</td>
<td>u.</td>
<td>u.</td>
<td>u.</td>
<td>i.</td>
<td>u.</td>
<td>u.*</td>
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<tr>
<td>J. R.</td>
<td>d.</td>
<td>d.</td>
<td>u.</td>
<td>u.</td>
<td>s.i.</td>
<td>s.i.</td>
</tr>
<tr>
<td>F. C.</td>
<td>d.</td>
<td>s.d.</td>
<td>i.</td>
<td>s.i.</td>
<td>i.</td>
<td>i.</td>
</tr>
<tr>
<td>C. F.</td>
<td>d.</td>
<td>s.d.</td>
<td>i.</td>
<td>s.i.</td>
<td>s.i.</td>
<td>s.i.</td>
</tr>
</tbody>
</table>

* Actually slightly increased but probably not significantly.
  i. = increased. d. = decreased. s.i. = slightly increased.
  s.d. = slightly decreased. u. = unchanged.

**FIG. 1.** Schematic Presentation of Averages for Renal Clearances and Filtration Fraction (FF)

Broken line presents data on five hypertensive subjects (Table I); solid line on five normotensive subjects (Table II). Histamine injected at start of third period. Clearances of para-aminohippurate (PAH) and mannitol (M) expressed as cc. plasma per minute.

**DISCUSSION**

From these observations it would appear that the reduction in renal plasma flow following the subcutaneous administration of histamine was often due to efferent arteriolar constriction. In some cases (M. S., J. R.), in whom there was observed no change in filtration fraction, it seems likely that constriction of the afferent arteriole took place. The fall in systemic blood pressure may have played a part in reducing renal plasma flow in patient L. C.

It is known that histamine may produce vasoconstriction of arterioles, but constriction alone, wherever it might take place in the kidney, would hardly account for the absolute increase in the mannitol clearance simultaneous with a fall in systemic blood pressure observed in two hypertensive patients (I. H. and M. L.). With efferent arteriolar constriction, if relaxation of afferent arteriolar tone or increased permeability of glomeru-
lar endothelium did not occur, one would expect little change in or a reduction of the filtration rate. The occurrence of afferent arteriolar relaxation seems to be supported by the experiment on patient I. H. presented in Table I. In the third period there was no change in the mannitol clearance, but blood flow was significantly reduced. This finding can be related to efferent arteriolar constriction. After the second injection of histamine at the start of the fourth period, however, there was a sudden increase in both PAH and mannitol clearances, the former reaching its previous level, the latter rising markedly above it. As the filtration fraction remained practically unchanged concurrent with these increases, relaxation of afferent arterioles can be considered as probably responsible for this phenomenon. Further evidence in favor of this view is found in the values for efferent and afferent arteriolar resistance; the former increased during the third period, the latter decreased during the fourth. Change in permeability of glomerular endothelium could not of itself account for the observed increase in the PAH clearance.

As regards possible increased glomerular permeability, it is of interest that the slight proteinuria observed in this patient before histamine was administered did not increase.

A significant increase in the filtration rate without simultaneous reduction of renal blood flow was also evident in subject M. L. (Figure 2). Here again two interpretations are possible—afferent arteriolar spasm plus afferent relaxation, or increased endothelial permeability. The first possibility seems to be enhanced by the behavior of efferent and afferent resistance, since the former increased from 0.0084 mm. of mercury per cc. of plasma per minute to 0.0109 and the latter decreased from 0.0825 to 0.0542. It is worthy of emphasis that this absolute increase in the filtration rate did not occur in any of our normotensive subjects, suggesting that the glomerulus of the hypertensive kidney may react in a characteristic manner.

We therefore interpret our data bearing on the state of the afferent glomerular artery as indicating that in some subjects the administration of histamine produces constriction, and in others either no effect on, or relaxation of, this vessel. Relaxation was observed only within the hypertensive group of subjects.

There was no consistently pronounced effect of the injection of histamine upon the urine volume. Changes in the reabsorption of water seemed to occur spontaneously, more or less independently of the filtration rate. Data obtained from analysis
It is uncertain whether the observed effects upon renal physiology were due to histamine alone, or whether the action of epinephrine was involved. It is conceivable that in our experiments the administration of histamine, itself possibly inactive upon the kidney, induced a response due to adrenaline; such an effect of histamine may occur in patients with pheochromocytoma (20, 21). There is little doubt that the effects of histamine upon renal arteriolar tone are similar in some respects to those of epinephrine.

The reaction of the efferent arteriole to histamine must be emphasized, as it is elicited in this case by a so-called "hypotensive" amine. It appears that various drugs are capable of inducing an elevation in filtration fraction similar to that found persistently in hypertensive subjects.  

The possibility that histamine may play a part in the pathogenesis of glomerular nephritis has already been referred to. If the action of histamine is involved in the etiology of the disease, on the basis of our observations it might be expected that the filtration fraction would be found to be higher than normal. Earle et al. (22), however, observed an abnormally low filtration fraction in glomerular nephritis. The two patients studied by those authors who were in initial stages of their disease had manifested symptoms for three and five weeks. At this stage alterations of the capillaries may have reduced the "filtering bed." Studies performed during the very first days of the disease would provide a more acceptable basis for evaluating the possible role of histamine in its pathogenesis.

**SUMMARY**

1. The effect of a subcutaneous injection of histamine upon renal function was investigated in five hypertensive and five normotensive subjects.

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8 In an additional patient with hypertension studied after this work had been completed, a large dose of histamine (0.5 mgm.) produced a dramatic reaction with pallor and palpitation. The filtration fraction decreased from 0.256 to 0.100 consequent to a fall in mannitol and an elevation in PAH clearance. These findings suggested efferent arteriolar relaxation, or, as the urine flow was markedly reduced, a back diffusion of mannitol through the tubular walls. Blood pressure was not measured. Although this picture was observed only in one instance, it indicates how the effects of the same drug may vary with the susceptibility of the patient.
with the aid of measurements of the mannitol and para-aminohippurate clearances.

2. Four of five hypertensive subjects responded with an increase in the filtration fraction and efferent arteriolar resistance, probably caused by a constriction of efferent glomerular arterioles. In two of the four patients, this constriction was accompanied either by relaxation of the afferent glomerular arteriole (decreased afferent resistance), or, less likely, by increased glomerular permeability. In the fifth subject there occurred a proportional reduction of renal blood flow and filtration rate in spite of decreased afferent resistance, probably related to a fall in blood pressure.

3. In four of five normotensive patients, there were observed manifestations of efferent and afferent arteriolar constriction. One normotensive subject showed no change in renal clearance following administration of histamine.

4. Significant changes in the urine volume were not regularly observed.

5. The renal extraction of para-aminohippurate did not change after administration of histamine in three subjects.

BIBLIOGRAPHY


