Brit. J. Pharmacol. (1958), **13**, 44..

THE RENAL REMOVAL OF INJECTED [^{14}C]HISTAMINE FROM THE BLOOD IN DOGS

BY

S.-E. LINDELL AND R. W. SCHAYER*

From the Institute of Physiology, University of Lund, Lund, Sweden

(RECEIVED SEPTEMBER 11, 1957)

The amounts of [^{14}C]histamine in arterial blood, in renal venous blood and in urine during a steady intravenous infusion of [^{14}C]histamine were measured in five anaesthetized dogs. The extraction ratio for [^{14}C]histamine was 0.7 to 0.8, indicating that the histamine was efficiently taken up from the blood by the kidney. Only a small part (14 to 18%) of the [^{14}C]histamine removed from the blood by the kidney appeared in the urine as histamine. Evidence was obtained that [^{14}C]histamine was metabolized in the kidney not only by histaminase (diamine oxidase) but also by the histamine methylating enzyme.

The capacity of the canine kidney to inactivate histamine is well known since the investigations of Best and McHenry (1930). Some evidence has been obtained that only part of this capacity is due to the histaminase (diamine oxidase) of the kidney (Lindell, 1957a and b). The use of [^{14}C]histamine offered the possibility of studying the renal removal of injected histamine at blood concentrations of histamine sufficiently low to have little or no observable effects on the blood pressure. In the present study [^{14}C]histamine was given intravenously at a slow, steady rate and the amounts of [^{14}C]histamine in arterial blood, in renal venous blood and in urine were measured. The rôle of histamine-metabolizing enzymes in the renal removal of injected histamine was estimated in two ways. Firstly, from the effects of a potent histaminase inhibitor, aminoguanidine, on the renal extraction and excretion of [^{14}C]histamine. Secondly, from measurements of the amounts of known metabolites of [^{14}C]histamine in arterial blood, in renal venous blood and in urine.

METHODS

The dogs, which had been fasted overnight, were anaesthetized with pentobarbitone sodium as described by Lindell (1957a). The region of the renal vessels was exposed through an incision in the right hypochondrium. A polythene tube (PE 240, Clay Adams Comp. Inc., New York) with a suitably bent tip was inserted into a renal vein from a femoral vein under direct vision. If the left renal vein was used the ovarian vein was ligated. Polythene tubes (PE 100) were inserted into the ureters through the same incision on the right side and through a lower abdominal incision on the left side. Arterial blood was collected from a polythene tube in a femoral artery. Polythene tubes for the administration of pentobarbitone sodium, [^{14}C]histamine, *p*-aminohippuric acid (PAH), dextran [Macrodex (Pharmacia)], saline and aminoguanidine were introduced into suitable veins in the legs. The rectal temperature was maintained at approximately 38° as in the previous experiments (Lindell, 1957a). All injections were made with motor-driven syringes. During the operative procedure 50 to 100 ml. of 0.6% saline was given intravenously to increase the diuresis. The [^{14}C]histamine was dissolved in saline to which glucose was added (approximately 1 mg./ml.). The glucose helps to stabilize the histamine solution (Schayer, unpublished observation). The infusion of [^{14}C]histamine was at the rate of 0.3 to 0.9 μg./kg./min. and had little or no effect on the blood pressure recorded with a mercury manometer from the carotid artery. The [^{14}C]histamine was given for 20 to 30 min. before the start of the collection of urine. The urine collection periods were 15 to 40 min. and the volumes of urine collected in these periods were 2 to 10 ml. The arterial and renal venous blood samples were taken simultaneously. The blood flowed spontaneously from the catheter in the renal vein. The dogs were given 5 mg. heparin every hour. Blood losses were compensated for by a steady infusion of dextran. At the end of the infusion of histamine the kidneys were removed and weighed and in some experiments extracted for [^{14}C]histamine as described below.

Assay for [^{14}C]Histamine and its Metabolic Products in Blood.—The blood, usually 5 ml. for each sample, was taken into glass tubes containing 0.5 mg. heparin. The carrier [histamine, methylhistamine {4-(2-aminoethyl)-1-methylimidazole}, methylimidazoleacetic acid (1-methylimidazol-4-ylacetic acid) or imidazoleacetic

*Present address: Merck Institute for Therapeutic Research, Rahway, New Jersey, U.S.A.

acid] was added immediately. The sample was then thoroughly mixed and allowed to stand for at least 30 min.; 20% trichloroacetic acid (TCA) was added to give a final concentration of about 5%. After mixing, the sample was allowed to stand overnight. It was then filtered and the precipitate was washed repeatedly with 5% TCA. TCA was removed with ether before further extraction took place. The further treatment of the various samples was as follows.

[^{14}C]*Histamine.*—The histamine was extracted with butanol (Schayer, 1952). The dipicrate was prepared, converted to pipsylhistamine (Schayer and Cooper, 1956) and counted.

Methylhistamine.—This was extracted with chloroform (Rotschild and Schayer, unpublished observation) and the picrate prepared and counted.

Methylimidazoleacetic Acid.—After removal of TCA, the filtrate was passed through a Dowex 50 column in the acid form. The methylimidazoleacetic acid was eluted with ammonia solution. The volume of the eluate was reduced by evaporation and the picrate prepared and counted (Schayer and Cooper, 1956).

Free Imidazoleacetic Acid.—The picrate was prepared in the same way as with methylimidazoleacetic acid. It was then converted to imidazoleacetic acid hydrochloride by passage through a Dowex 1 column. Pipsylimidazoleacetic acid was prepared and counted.

Imidazoleacetic Acid Riboside.—This compound was estimated as the difference between total imidazoleacetic acid (the value obtained after hydrolysis as described by Schayer and Cooper, 1956) and free imidazoleacetic acid.

Determination of [^{14}C]*Histamine and its Metabolites in Urine.*—The urine was collected in glass tubes containing 0.5 ml. 6 N-HCl. The volume of urine used for each assay was usually 0.5 ml. to which carrier was added and the respective picrate prepared directly. The picrates were then treated as described above.

Estimation of the Amount of [^{14}C]*Histamine in the Kidney at the End of the Infusion of* [^{14}C]*Histamine.*—The kidneys from the dogs which had been given aminoguanidine were removed at the end of the infusion of histamine and packed in ice to obtain rapid cooling. They were then stored at −15°. At an early stage of thawing the renal tissue was cut with scissors, an aliquot was then put in a homogenizer together with 0.01 N-HCl and carrier added. After homogenization, TCA was added and the samples treated in the same way as the blood samples.

The samples were counted at infinite thickness in a flow counter, the background of which was 19 to 22 c./min. The counts of the blood samples ranged from 6 to 150 above background. The samples were recrystallized until constant radioactivity. At least 1,000 counts were taken after each recrystallization.

The concentrations of [^{14}C]histamine or metabolites in whole blood in the results are given in counts/min. above background/ml.(c./min./ml.). The concentration of [^{14}C] in histamine in whole blood when given in c./min./ml. may be converted to μg. histamine base/l. blood by multiplication by 0.5. The amounts of [^{14}C]histamine or metabolites in the urine are given in counts/min. above background (c./min.) excreted/min. To make the values for histamine and metabolites comparable, the counts obtained for pipsylhistamine and pipsylimidazoleacetic acid have been recalculated to the corresponding values in the form of picrates.

Measurement of Renal Blood Flow.—In two experiments the renal blood flow was estimated from the extraction and excretion of PAH with the use of the Fick principle. PAH (10 mg./kg.) was given as a priming dose which was followed by a continuous intravenous infusion of PAH at a rate of 5 to 6 mg./min. Arterial and renal venous blood samples for the determination of PAH were taken in the same way as the samples for assay of [^{14}C]histamine and its metabolites. The urine for PAH analysis was an aliquot from the urine sample used for assay of [^{14}C]histamine. The colorimetric determinations of PAH in whole blood and in urine were carried out at the Department of Clinical Physiology, Karolinska, Sjukhuset, Stockholm. In preliminary experiments, it was found that 85 to 90% of PAH added to whole blood was recovered. In the calculation of renal blood flow no correction has been made for this 10 to 15% loss.

The [^{14}C]histamine was obtained from the Radiochemical Centre, Amersham, England. The aminoguanidine was in the form of the sulphate (Eastman Organic Chemicals, Rochester, U.S.A.).

RESULTS

The first experiment was designed to show the renal extraction and excretion of [^{14}C]histamine during a steady intravenous infusion of [^{14}C]histamine (0.4 μg./kg./min.). The design and the results are summarized in Table I. Two arterial blood samples and two renal venous blood samples were taken in the middle of each urine collection period. Urine was collected in five periods spaced over nearly 4 hr. Three of these collections, I, III and V, took place during intravenous infusion of [^{14}C]histamine. The urine collections of periods II and IV took place 50 min. after interruption of the histamine infusions There was a good agreement between the duplicates in the assay of [^{14}C]histamine in blood. The extraction ratio ($\frac{A-V}{A}$, where A is the concentration of [^{14}C]histamine in arterial whole blood and V the concentration in renal venous blood) was 0.7 to 0.8 in periods I, III and V. The amount of [^{14}C]histamine excreted in these periods was nearly

TABLE I

Female dog, 9 kg. Catheter in right renal vein for collection of renal venous blood. Arterial blood taken from the right femoral artery. Urine collected from a catheter in the right ureter. Weight of the right kidney 24 g. The blood pressure was between 110 and 130 mm. Hg. during the experiment. The concentration of [^{14}C]histamine in whole blood is given in c./min./ml., which may be converted to μg. histamine base/l. blood by multiplication by 0·5. The counts above background obtained for the blood samples were about 5 times greater than those given in the Table, since the volumes of the samples were about 5 ml.

Time in Min.	Intravenous Infusion of [^{14}C]Histamine 0·4 μg./kg./min.	Period No.	Collection of Urine	Sampling of Blood	Conc. of [^{14}C]Histamine in Whole Blood (c./min./ml.)		Extraction Ratio	Amounts of [^{14}C]Histamine Excreted by the Kidney/min. (c./min.)
					Arterial	Renal Venous		
0								
20					5·1	1·1	0·8	
		I		←				72
				←	5·5	1·6	0·7	
40								
60								
80								
		II		←	0·7	—	—	0
100								
120								
				←	6·6	1·7	0·7	
		III		←	6·2	Lost	—	70
140								
160								
180								
		IV						1
200								
220								
				←	5·0	1·6	0·7	
		V		←	5·4	1·8	0·7	68
240								

the same, 68 to 72 c./min. being excreted/min. by the right kidney. Fifty minutes after the cessation of the infusion of [^{14}C]histamine, the urinary excretion of [^{14}C]histamine was 1 c./min. or less/min. The clearance value for [^{14}C]histamine calculated in the conventional way was about 0.5 ml. whole blood/min./g. of kidney in periods I, III and V.

The Effect of Aminoguanidine on the Renal Removal of [^{14}C]*Histamine.*—The results of the second experiment, which have been summarized in Table II, had in principle the same design as the first one. However, between periods III and IV aminoguanidine was given intravenously in a dose of 12 mg./kg. During periods I and II (Table II), the extraction ratio for [^{14}C]histamine was 0.7 to 0.8, being the same as in the preceding experiment. The amount of [^{14}C]histamine excreted/min. by the right kidney was 140 to 180 c./min. The clearance value was thus 0.6 to 0.7 ml. whole blood/min./g. of kidney. In period III 50 min. after the cessation of the infusion of [^{14}C]hist-

TABLE II

Female dog, 10 kg. The same experimental conditions obtained as in Table I. The blood pressure was 120 to 150 mm. Hg. Weight of right kidney 29 g.

Time in Min.	Intravenous Infusion of [^{14}C]Histamine 0·45 μg./kg./min.	Period No.	Collection of Urine	Sampling of Blood	Conc. of [^{14}C]Histamine in Whole Blood (c./min./ml.)		Extraction Ratio	Amounts of [^{14}C]Histamine Excreted by the Kidney/min. (c./min.)
					Arterial	Renal Venous		
0								
20		I		←	7·0	1·8	0·7	140
40		II		←	10	2·2	0·8	180
60								
80								
100		III		Aminoguanidine 12 mg. kg. (i.v.)				20
120								
140		IV		←	10	5·7	0·4	370
160		V		←	12	7·0	0·4	390
180								

amine, the amount excreted by the kidney/min. was 20 c./min. After the administration of aminoguanidine (periods IV and V), the extraction ratio fell to 0.4, while the amount of [^{14}C]histamine excreted by the kidney/min. increased to 370 and 390 c./min. The corresponding clearance values were 1.3 and 1.1 ml. whole blood/min./g. of kidney. The right kidney removed at the end of the infusion was extracted for [^{14}C]-histamine. The amount of [^{14}C]histamine found in the kidney was about 600 c./min.

To calculate the amount of [^{14}C]histamine removed from the blood by the kidney it was necessary to measure the blood flow through the kidney simultaneously with the estimations of [^{14}C]histamine in arterial and renal venous blood. In the third experiment in this series, PAH was given in a continuous intravenous infusion and the renal extraction and excretion of PAH were measured. From the values obtained, the blood flow through the kidney was calculated according to the Fick principle. The figures for renal blood flow, calculated in this way, were 150 to 210 ml./min. The results of this experiment have been summarized in Table III. It may be seen in the Table that the extraction ratio for [^{14}C]histamine in period I is 0.7 or the same as found in the two preceding experiments before the administration of aminoguanidine. After the injection of the histaminase inhibitor, the extraction ratio fell to 0.4 to 0.5 as in the previous experiment. The amount of [^{14}C]histamine removed by the kidney from the blood was calculated from the arterio-venous difference in the concentration of [^{14}C]-histamine and the figure for renal blood flow obtained in the PAH studies. In period I, approximately 14% of the [^{14}C]histamine removed from the blood by the kidney was excreted in the urine. After aminoguanidine, this % increased to 25 to 40. The clearance values, calculated in the conventional way, were, in period I, 0.6; in period II, 0.9; in period V, 0.5; and in period VI, 0.6 ml. whole blood/min./g. of kidney. The amount of [^{14}C]histamine found in the kidney removed at the end of period VI was 2,000 c./min. which may be compared with the 1,800 c./min. removed from the blood by the kidney/min. during the last urine collection period.

TABLE III

Female dog, 10 kg. Renal venous blood and urine were collected from the left kidney, otherwise the experimental conditions were as described in Table I. The blood pressure was 120 to 155 mm. Hg. Weight of left kidney 36 g.

Time in Min.	Intravenous Infusion PAH 10 mg./kg.	Period No.	Collection of Urine	Sampling of Blood	Conc. in Whole Blood of PAH (mg./100 ml.) [^{14}C]Histamine (c./min./ml.) Arterial Blood	Conc. in Whole Blood of PAH (mg./100 ml.) [^{14}C]Histamine (c./min./ml.) Renal Venous Blood	Amount of PAH Excreted by Kidney (mg./min.)	Blood Flow through the Kidney (ml./min.)	Amount of [^{14}C]Histamine Removed by the Kidney/min. (c./min.)	Amount of [^{14}C]Histamine Excreted by the Kidney/min. (c./min.)
0	PAH 6 mg. min.									
20		I		PAH	2·40	1·20	2·54	210		
40	[^{14}C]Histamine 0·5 µg./min.			←[^{14}C]Histamine	8·4	2·4			1,300	180
60										
80		II								8
100						Intravenous injection of aminoguanidine 12 mg. kg.				
120	[^{14}C]Histamine 0·5 µg./min.			PAH	3·0	1·20	2·63	150		
140		III		←[^{14}C]Histamine	13	6·0			1,100	410
160										
180										
200	[^{14}C]Histamine 0·3 µg./min.	IV								33
220		V		PAH	3·20	2·00	2·52	210		
240				←[^{14}C]Histamine	9·6	6·1			740	190
260	[^{14}C]Histamine 0·9 µg./min.	VI		PAH	4·95	3·20	2·86	160		
280				←[^{14}C]Histamine	22	11			1,800	450

The results obtained so far indicate: (1) That injected histamine may be relatively efficiently removed from the blood by the canine kidney, the extraction ratio being 0.7 to 0.8 (whole blood). (2) That only a small part (14%) of this removed histamine appears in the urine. (3) That the histaminase of the kidney is partly responsible for the renal removal of histamine, the evidence being that the extraction ratio decreased to 0.4 to 0.5 after the administration of a histaminase inhibitor. (4) That even after the injection of the inhibitor more histamine may be removed from the blood by the kidney than is excreted in the urine.

Since there was no evidence for the storage of any considerable amount of [^{14}C]histamine in the kidney, it seems not unlikely that some of the renal removal of histamine persisting after the administration of a histamine inhibitor is due to the action of a histamine metabolizing enzyme different from histaminase. This may be the methylating enzyme (Schayer and Karjala, 1956), which leads to the formation of methylhistamine

TABLE IV

Female dog, 13 kg. Urine and blood collected as described in Table I, but from the left kidney, which weighed 41 g. The blood pressure was 110 to 140 mm. Hg. The excretion of PAH was 2·33 mg./min. and the blood flow through the left kidney was 194 ml./min. (calculated according to the Fick principle). The amount of [^{14}C]histamine or its metabolites removed from the blood by the kidney/min. was calculated from the arterio-venous differences in the concentrations of these substances and from the figure for the blood flow through the kidney.

Time in Min.	Intravenous Infusions PAH 10 mg./kg.	Collection of Urine	Sampling of Blood	Conc. in Whole Blood PAH (mg./100 ml.) [^{14}C]Histamine and its Metabolites (c /min./ml.) Arterial	Renal Venous	Amount of [^{14}C]Histamine or Metabolite Removed from the Blood by the Kidney/min. (c./min.)	Amount of [^{14}C]Histamine or Metabolite Excreted by the Kidney/min. (c. min.)
0	PAH 5 mg./min.						
30	[^{14}C]Histamine 0·5 μg./kg./min.						
36			PAH	1·75	0·55		
			Histamine	15	4·4		
			Methylhistamine	8·2	3·8		
			Methylimidazoleacetic acid	21	16		
			Total imidazoleacetic acid	13	Lost		
			PAH	1·80	0·60		
			Histamine	12	3	1,900	340
			Methylhistamine	7·1	3·3	800	420
			Methylimidazoleacetic acid	24	18	1,100	1,900
			Total imidazoleacetic acid	14	14	0	1,000
49			Free ,, ,,	13	Lost	—	(1,000)
55							

and methylimidazoleacetic acid. In order to gain more information about this we have measured the amounts of [^{14}C]histamine, methylhistamine and methylimidazoleacetic acid in arterial blood, in renal venous blood and in urine during a steady intravenous infusion of [^{14}C]histamine. At the same time assays were also made for free imidazoleacetic acid and imidazoleacetic acid riboside, both products of the action of histaminase on [^{14}C]histamine (Tabor and Hayaishi, 1955; Karjala, Turnquest, and Schayer, 1956). Such an experiment which also included estimation of renal blood flow is illustrated in Table IV.

The concentration of PAH in the two samples of arterial blood taken with an interval of 7 min. was 1.75 and 1.80 mg./100 ml. The corresponding samples of renal venous blood contained 0.55 and 0.60 mg./ml. Thus the arterio-venous difference was 1.20 mg./100 ml. and, since the amount of PAH excreted/min. was 2.33 mg., the blood flow through the kidney calculated according to the Fick principle was 194 ml./min. The concentrations of [^{14}C]histamine and its metabolites in arterial and in renal venous blood are given in Table IV, which also shows the amounts of [^{14}C]histamine and its metabolites removed from the blood by the kidney as calculated from the arterio-venous differences and the figure for renal blood flow obtained from the PAH studies. For comparison the amounts of [^{14}C]histamine and metabolites appearing in the urine have also been included in the Table. The sum of the amounts of [^{14}C]histamine and its metabolites removed from the blood/min. equalled the sum of the amounts excreted in the same time. However, only 18% of the [^{14}C]histamine removed from the blood was found in the urine as histamine. Less methylhistamine was found in the urine than was removed from the blood, whereas the opposite was the case with the methylimidazoleacetic acid. It thus seems probable that some methylhistamine was oxidized to methylimidazoleacetic acid in the kidney. The sum of methylated [^{14}C]histamine derivatives appearing in the urine/min. was greater than the sum of the same derivatives removed from the blood in the same time. There is thus some evidence that methylation took place in the kidney. Little imidazoleacetic acid was removed from the blood and thus the greater part of the imidazoleacetic acid in the urine was probably formed in the kidney. The figures for free imidazoleacetic acid in arterial blood and in urine very nearly equalled those for total imidazoleacetic acid, indicating that the dog did

TABLE V

Male dog, 9 kg. Urine and blood samples collected as described in Table I. Weight of right kidney 22 g. The blood pressure was 100 to 130 mm. Hg.

Time in Min.	Intravenous Infusion of [^{14}C]Histamine 0·5 μg./kg./min.	Collection of Urine	Sampling of Blood	Conc. in Whole Blood of [^{14}C]Histamine and its Metabolites (c./min./ml.)		Arterio-venous Difference in the Concentration of [^{14}C]Histamine and its Metabolites (c./min./ml.)	Extraction Ratio	Amount of [^{14}C]Histamine or Metabolite Excreted by the Kidney/min. (c./min.)
				Arterial	Renal Venous			
0	┐							
	┆							
20	┆	┐						
	┆	┆						
32	┆	┆	┐ Histamine	9·8	1·8	8·0	0·8	150
	┆	┆	Methylhistamine	2·2	1·2	1·0	0·5	150
	┆	┆	Methylimidazoleacetic acid	17	13	4	0·2	870
	┆	┆	Free imidazoleacetic acid	3·5	3·1	0·4	0·1	260
44	┆	┆	┘					
	┆	┆						
56	┘	┘						

not form imidazoleacetic acid riboside. This is in agreement with the results obtained by Schayer (1956).

The sum of the arterio-venous differences for [^{14}C]histamine and its metabolites in Table IV is about 19 c./min./ml. blood and the sum of the same compounds appearing in the urine/min. is about 3,700 c./min. If these values are used in an estimation of the renal blood flow according to the Fick principle the value obtained is 195 ml./min. The blood flow as calculated from the PAH values was as mentioned above 194 ml./min.

Another experiment comprising of estimations of [^{14}C]histamine and its metabolites in arterial blood, in renal venous blood and in urine during a steady infusion of [^{14}C]histamine is summarized in Table V. As PAH was not given to this dog, the blood flow through the kidney was not calculated. The extraction ratio for [^{14}C]histamine was 0.8. From the estimates for the arterio-venous differences in the concentration of [^{14}C]histamine and its metabolites it may be seen that the methylated [^{14}C]histamine derivatives comprise 40% of the [^{14}C]-labelled compounds removed from the blood, whereas in the urine the methylhistamine and the methylimidazoleacetic acid comprised 70% of the [^{14}C]-labelled substances. This may be taken to indicate that methylation had taken place in the kidney. As judged from the values for imidazoleacetic acid, assayed in the free form only, the greater part of this acid appearing in the urine was formed in the kidney.

DISCUSSION

In the present study the renal extraction and excretion of [^{14}C]histamine during a steady intravenous infusion of [^{14}C]histamine were measured in five dogs. At a concentration of 5 to 15 c./min./ml. arterial blood of [^{14}C]histamine in these experiments, the extraction ratio was 0.7 to 0.8 in dogs which had not been given a histaminase inhibitor. This high extraction ratio could be explained on the assumption that histamine is secreted by the tubular cells in the kidney. Lindahl and Sperber (1956) showed that histamine is excreted by the tubular cells in the kidney of the hen, and a mechanism for the tubular secretion of organic bases has been demonstrated in the dog kidney too (Beyer, Russo, Gass, Wilhoyte, and Pitt, 1950). The relatively small amounts of [^{14}C]histamine appearing in the urine do not, however, lend support to the view that the histamine was secreted to any greater extent by the tubular cells of the kidney. In the two experiments

presented in Tables III and IV, only 14 to 18% of the [^{14}C]histamine removed from the blood by the kidney was excreted in the urine. The clearance values for [^{14}C]histamine calculated in the conventional way are 0.5 to 0.7 ml. whole blood/min./g. of kidney in dogs which had not been given aminoguanidine. The results of the present study indicate that the histamine was taken up from the blood by the tubular cells of the kidney but was not, or only to a small extent, secreted by these cells so that it appeared as histamine in the urine. Emmelin (1951) showed that in cats large quantities of histamine could be taken up from the blood by the kidney and kept there for some time. In our experiments with dogs, where comparatively small doses of histamine were used, there was no evidence for the storage in the kidney of any greater part of the [^{14}C]histamine that had been removed from the blood by the kidney. Evidence was, however, obtained that the histamine was metabolized in the kidney. The canine kidney is richly supplied with histaminase and it seems likely that this enzyme is responsible for the metabolism of some of the histamine in the kidney. This view is supported by the observation here and in previous studies that histaminase inhibitors decrease the capacity of the kidney to remove injected histamine from the blood. Additional evidence for the metabolism of histamine by the renal histaminase was obtained from the experiments presented in Tables IV and V, which indicated that the greater part of the imidazoleacetic acid appearing in the urine during an intravenous infusion of [^{14}C]histamine was formed in the kidney. In this as well as in previous investigations (Lindell and Westling, 1956; Lindell, 1957a and b), it was found that the kidney retained a considerable capacity to remove injected histamine from the blood even after the administration of histaminase inhibitors. The effects of the dose of aminoguanidine used here (12 mg./kg.) on the renal removal of injected histamine were not materially increased by the administration of other histaminase inhibitors (Lindell, 1957a). The methylation of histamine (Schayer and Karjala, 1956) is not inhibited by aminoguanidine and it seems possible that some of the renal removal of injected histamine from the blood is connected with the action of the methylating enzyme. The studies of the amounts of methylhistamine and methylimidazoleacetic acid in arterial blood, in renal venous blood and in urine during an intravenous infusion of [^{14}C]histamine indicated that methylation may take place in the canine kidney and also that methylhistamine may be oxidized in the kidney to methylimidazoleacetic acid.

It should perhaps be pointed out that with a substance such as histamine, which seems to be rapidly metabolized in the kidney, the term clearance may be misleading. The experiment presented in Table IV may serve to illustrate this. The clearance value for [^{14}C]histamine in this experiment calculated in the conventional way would be about 25 ml. whole blood/min. The amount of [^{14}C]histamine removed from the blood by the kidney/min. was 1,900 c./min. as calculated from the mean of the arterio-venous differences in the concentration of [^{14}C]histamine (9.8 c./min.) and the value for renal blood flow, based on the PAH studies (194 ml. blood/min.). Since the mean concentration of [^{14}C]histamine in arterial blood was 14 c./min./ml., it might also be said that 140 ml. blood had been cleared of [^{14}C]histamine by the kidney in one minute.

References

Best, C., and McHenry, E. W. (1930). *J. Physiol.*, **70**, 349.

Beyer, K. H., Russo, H. F., Gass, S. R., Wilhoyte, Katherine M., and Pitt, Alice A. (1950). *Amer. J. Physiol.*, **160**, 311.

Emmelin, N. (1951). *Acta physiol. scand.*, **22**, 379.

Karjala, S. A., Turnquest, B., and Schayer, R. W. (1956). *J. biol. Chem.*, **219**, 9.

Lindahl, Kerstin M., and Sperber, I. (1956). *Acta physiol. scand.*, **36**, 13.

Lindell, S.-E. (1957a). Ibid., **41**, 168.

—— (1957b). Ibid., **41**, 255.

—— and Westling, H. (1956). Ibid., **37**, 307.

Schayer, R. W. (1952). *J. biol. Chem.*, **199**, 245.

—— (1956). *Brit. J. Pharmacol.*, **11**, 472.

—— and Cooper, J. A. D. (1956). *J. appl. Physiol.*, **9**, 481.

—— and Karjala, S. A. (1956). *J. biol. Chem.*, **221**, 307.

Tabor, H., and Hayaishi, O. (1955). *J. Amer. chem. Soc.*, **77**, 505.