Brit. J. Pharmacol. (1958), **13**, 52.

METABOLISM OF INJECTED [^{14}C]HISTAMINE IN THE KIDNEY OF THE DOG

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(RECEIVED SEPTEMBER 11, 1957)

In experiments on anaesthetized dogs, [^{14}C]histamine was given in a steady infusion into one of the renal arteries, while urine was collected from both kidneys separately. The kidney which received the intra-arterial injection of [^{14}C]histamine excreted several times more [^{14}C]-labelled methylhistamine, methylimidazoleacetic acid and imidazoleacetic acid than did the other kidney, indicating that histamine may be inactivated in the canine kidney not only by histaminase but also by the histamine methylating enzyme.

In a previous investigation (Lindell and Schayer, 1958), evidence was obtained that [^{14}C]histamine, given by vein, was taken up by the canine kidney and metabolized there not only by histaminase but also by the enzymes which lead to the formation of methylhistamine {4-(2-aminoethyl)-1-methylimidazole} and methylimidazoleacetic acid (1-methylimidazol-4-ylacetic acid (Schayer and Karjala, 1956). The work reported here is concerned with the fate of histamine injected into the renal artery of the dog.

METHODS

The dogs were anaesthetized with pentobarbitone sodium (30 mg./kg.) given intravenously. Under fluoroscopy, a catheter was guided into one of the renal arteries from a femoral artery (Lindell and Olin, 1957). [^{14}C]Histamine was dissolved in 0.9% saline containing 1 mg. glucose/ml. This solution was injected with a motor-driven syringe through the catheter in the renal artery, at a rate of approximately 1 ml./min. The concentration of [^{14}C]histamine in the solution was such that in the first experiment about 4 μg. histamine base was given/min. In the second experiment the amount was about 1 μg./min. These quantities had no observable effects on the blood pressure measured with a mercury manometer connected to a carotid artery. During the infusion of [^{14}C]histamine urine was collected from polythene tubes inserted into the ureters.

Assay of [^{14}C]Histamine and its Metabolites in Urine.—The [^{14}C]histamine, methylhistamine, methylimidazoleacetic acid and free imidazoleacetic acid were determined with the isotope dilution technique as described by Lindell and Schayer, 1957. The amounts are given in counts/min. above background (c./min.). The c./min. refer to the [^{14}C]-labelled compounds in the form of picrates; 1 μg. of [^{14}C]histamine in the form of the picrate gave 2,040 c./min. in the flow counter (background 19 to 22 c./min.), when non-isotopic histamine carrier corresponding to 40 mg. of histamine base had been used.

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RESULTS

The results of two experiments have been summarized in Table I. In the first experiment [^{14}C]histamine was injected into the right renal artery, at a rate of 4 μg./min. The urine collected from the ureters during the infusion was analysed for [^{14}C]histamine and its metabolites and the amounts of these compounds excreted/min. calculated. It may be seen in Table I that the right kidney which received the intra-arterial infusion of [^{14}C]histamine excreted 12 times more methylhistamine than did the left kidney, while the amount of methylimidazoleacetic acid appearing in the urine from the right kidney was nearly three times greater than that in the urine from the left kidney. The amount of free imidazoleacetic acid excreted/min. in the urine from the injected kidney was about 13 times greater than that in the urine from the other kidney. The sum of the differences between the kidneys in the amounts of [^{14}C]histamine and its metabolites excreted/min. was about 5,500 c./min., of which about 1,400 or 25% were in the form of histamine.

In the second experiment [^{14}C]histamine was injected into the right renal artery at a rate of 1 μg./min. As may be seen from the values of the renal excretion of [^{14}C]histamine and its metabolites, about 17 times more methylhistamine was excreted by the injected kidney than by the other kidney. For methylimidazoleacetic acid, the rela-

TABLE I

EXPERIMENTS ON ANAESTHETIZED DOGS

Urine was collected from each ureter, separately, while [^{14}C]histamine was infused into the right renal artery. In expt. 1, 4 μg./min. was given for 25 min. In expt. 2, 1 μg./min. was given for 20 min.

Expt. No.	Amounts of [^{14}C]Histamine or its Metabolites Excreted/min. During the Infusion of [^{14}C]Histamine (c./min.)				Wt. of Kidney (g.)	Volume of Urine (ml.)
	Histamine	Methylhistamine	Methylimidazole-acetic Acid	Imidazoleacetic Acid		
1. Male dog (8 kg.)						
Injected kidney	1,400	580	1,200	3,100	17	3
Control ,, ...	36	48	420	240	16	4·8
2. Male dog (26 kg.)						
Injected kidney	230	120	140	530	44	14
Control ,, ...	9	7	22	64	44	11

tion between the excretion on the injected side and on the other side was approximately as six is to one. The amount of free imidazoleacetic acid appearing/min. in the urine from the injected side was about eight times greater than that in the urine from the other side. The sum of the differences between the two kidneys in the amounts of [^{14}C]histamine and its metabolites excreted/min. was about 900 c./min., of which 220 or about 25% were in the form of histamine.

DISCUSSION

These results show that, as might be expected, much more [^{14}C]histamine was excreted in the urine from the kidney which received the intra-arterial injection of [^{14}C]histamine. However, metabolites of [^{14}C]histamine were also excreted in much greater amounts on the injected side. The excess of metabolites of [^{14}C]histamine on the injected side was so large that it must be assumed that a considerable amount of the metabolites had been formed in the kidney, which received the intra-arterial infusion. The volumes of the urines collected from each side were approximately equal. It should be mentioned that the catheter used for the intra-arterial injection did not influence the clearance of phenol red either on the catheterized side or on the opposite side (Lindell and Olin, 1957). Also it did not change the renal extraction and excretion of *p*-aminohippuric acid (Lindell, unpublished observation). The possibility that the [^{14}C]histamine was metabolized by the blood in the kidney on the catheterized side seems too unlikely to deserve serious consideration.

That the canine kidney can inactivate histamine is well known since the pioneer investigation of Best and McHenry (1930). Their results have been confirmed by, among others, Steggerda, Essex, and Mann (1935) and Valette, Huidobro, and Cohen (1955). The results in the present study indicate that of the [^{14}C]histamine removed from the blood by the kidney, part (25%) is excreted in the urine as histamine, part is oxidized to imidazoleacetic acid and part is methylated on the ring nitrogen atom remote from the side chain to form a methylhistamine, which seems to have very little biological activity (Lee and Jones, 1949). The excess of methylimidazoleacetic acid excreted on the injected side was probably due to oxidation in the kidney of some of the methylhistamine formed there. The results of the present investigation thus confirm those obtained in the earlier study on the renal removal of injected [^{14}C]histamine in dogs (Lindell and Schayer, 1958).

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