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FORMATION OF HISTAMINE IN THE KIDNEY OF THE DOG

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In dogs [^{14}C]L-histidine was given in a steady infusion into one renal artery while urine was collected from both kidneys separately. The urine from the infused kidney contained considerably more [^{14}C]histamine than did the urine from the other kidney. The difference between the kidneys in the amounts of [^{14}C]histamine appearing in the urine was considered to be due to formation of histamine from histidine in the injected kidney. It is concluded that histamine formed in the kidney may contribute to the urinary histamine.

The source of the urinary histamine has not been definitely established. It has been proposed that the urinary histamine has been carried to the kidney in the plasma (Adam, Card, Riddell, Roberts, and Strong, 1954). On the other hand, evidence has been presented that L-histidine may be decarboxylated in the kidney of the rat and that the resulting histamine is excreted without having entered the circulation (Schayer, Wu, and Smiley, 1954).

The present study was undertaken to find out if histamine could be formed from histidine in the kidney of the living dog.

METHODS

The dogs were anaesthetized with pentobarbitone sodium (30 mg./kg.) given intravenously. Under fluoroscopy, a polythene catheter was guided into one of the renal arteries from a femoral artery (Lindell and Olin, 1957). 5 mg. of [^{14}C]L-histidine (activity 10 microcuries/mg.) was dissolved in a solution containing 0.9% NaCl and a small amount of HCl so that the *p*H was approximately 5. This solution was injected with a motor-driven syringe into the catheter in the renal artery at a rate of 25 to 30 μg. histidine/min. for 160 to 200 min. The [^{14}C]L-histidine solution which remained in the syringe at the end of the infusion was assayed for [^{14}C]histamine in the same way as the urine samples described below. It did not contain any measurable amount of [^{14}C]histamine. During the infusion of histidine, urine was collected from polythene tubes inserted into the ureters. The urine was collected in glass tubes containing 0.5 ml. 6 N-HCl. The volumes were measured and aliquots taken for the assays.

Assay of [^{14}C]Histamine, Methylhistamine {(4-(2-aminoethyl)-1-methylimidazole}, methylimidazoleacetic acid (1-methylimidazol-4-ylacetic acid) and imidazoleacetic acid.—The histamine samples were extracted as described by Schayer, Davis and Smiley (1955). The histamine dipicrates prepared were converted to pipsylhistamine before counting. All assays were performed as described by Lindell and Schayer (1958a).

Histamine showed constant radioactivity after the second recrystallization as the pipsyl derivative. The activity of the methylimidazoleacetic acid samples was not constant until after the sixth recrystallization as the picrates. The imidazoleacetic acid samples reached constant radioactivity after the ninth recrystallization as the pipsyl derivative.

RESULTS

The results of two experiments have been summarized in Table I. It may be seen that the urine from the injected kidney contained several times more [^{14}C]histamine than did the urine from the

TABLE I

ANALYSIS OF [^{14}C]HISTAMINE AND [^{14}C]METHYLHISTAMINE IN URINE FROM TWO EXPERIMENTS IN DOGS

In both experiments, 5,000 μg. of [^{14}C]L-histidine was given in a steady infusion into one renal artery while urine was collected from each kidney separately. Time of infusion in dog 1, 160 min., and in dog 2, 200 min. One μg. of the histamine formed from this histidine counted as the pipsyl derivative under standard conditions (40 mg. histamine base as carrier, in plates of 4 cm.[2] at infinite thickness in a flow counter), gives 580 c./min. above background.

	[^{14}C]Histamine in Urine Collected during Infusion (c./min.)	[^{14}C]Methylhistamine in Urine Collected during Infusion (c./min.)	Weight of Kidney (g.)	Volume of Urine Collected from the Ureter (ml.)
1. Male dog (9 kg.)				
Injected kidney	240	0	19	17
Control ,,	0	0	20	18
Difference ..	240	0		
2. Male dog (16 kg.)				
Injected kidney	380	0	40	18
Control ,,	90	0	38	16
Difference ..	290	0		

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other kidney. The difference may be interpreted as due to formation of histamine from histidine in the injected kidneys. In the first experiment, the value of 240 c./min. (difference between injected kidney and the kidney of the opposite side) is equal to about 0.4 μg. [^{14}C]histamine. In the second experiment, the difference is 290 c./min. or roughly 0.5 μg. [^{14}C]histamine. No methylhistamine could be detected in any of the urine samples.

[^{14}C]Methylimidazoleacetic acid and [^{14}C]imidazoleacetic acid were also determined in the urine samples. Their determination by the isotope dilution technique is, however, much more difficult than the determination of histamine and methylhistamine. This is so because of the presence of a huge excess of histidine and histidine metabolites, some of which are imidazolecarboxylic acids and have properties similar to methylimidazoleacetic acid and imidazoleacetic acid. For this reason a more rigorous establishment of purity is required before the values can be considered valid. The activity of the methylimidazoleacetic acid samples from these dog urine samples was about the same as the activity of the histamine samples. The imidazoleacetic acid samples, however, were about a hundred times more active than the histamine samples.

Discussion

Considerably more [^{14}C]histamine appeared in the urine from the infused kidney than in the urine from the other kidney. Since the histidine solution did not contain any measurable amounts of [^{14}C]histamine it seems likely that the excess [^{14}C]histamine in the urine from the infused kidney was formed in that kidney. In this connexion, it should be mentioned that the catheter used for the injections into the renal artery did not influence the clearance of phenol red neither on the catheterized side nor on opposite side (Lindell and Olin, 1957). Also it did not change the renal extraction and excretion of *p*-aminohippuric acid (Lindell, unpublished observation).

When [^{14}C]histamine was injected into dogs, [^{14}C]methylhistamine appeared in the urine in amounts which were of the same order of magnitude as the amounts of [^{14}C]histamine in the urine (Lindell and Schayer, 1958a and b). The absence of [^{14}C]methylhistamine in the urine samples from the present experiments might therefore indicate that very little [^{14}C]histamine reached the kidneys with the blood stream.

The amounts of [^{14}C]methylimidazoleacetic acid and imidazoleacetic acid appearing in the urine of dogs after injection of [^{14}C]histamine are usually of the same order of magnitude. In the present experiments where [^{14}C]L-histidine was injected the amounts of [^{14}C]imidazoleacetic acid in the urine were about a hundred times greater than the amounts of [^{14}C]methylimidazoleacetic acid. This suggests that in the dog imidazoleacetic acid can be formed from histidine by a pathway not involving histamine. Such a pathway has been reported to occur in rats (Wolf, Wu, and Heck, 1956).

In the present experiments, evidence was obtained that histamine was formed from histidine in the kidney of the dog. Since histidine occurs in the plasma of the dog (Wright, Russo, Skeggs, Patch and Beyer, 1947) it seems possible that some of the histamine that appears in the urine has been formed in the kidney.

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