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THE METABOLISM OF HISTAMINE IN VARIOUS SPECIES

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This laboratory has demonstrated that in all mammalian species tested—rats (Schayer, 1953), mice, guinea-pigs (Schayer and Karjala, 1956), and man (Schayer and Cooper, 1956)—there are two major histamine-metabolizing enzymes. One is diamine oxidase; it leads to the production of imidazole-4-acetic acid and l-ribosylimidazole-4(5)-acetic acid (Karjala, Turnquest, and Schayer, 1956). The second enzyme methylates histamine on the ring nitrogen remote from the side chain. It leads to the formation of l-methyl-4-(β-aminoethyl)imidazole and l-methylimadazole-4-acetic acid. These four metabolites will be referred to as ImAA, ImAA-riboside, 1,4-methylhistamine, and 1,4-methyl ImAA respectively.

In this paper are reported quantitative analyses for histamine metabolites in the urine of various species after feeding or injecting ^{14}C histamine. An experiment to identify the precursor of bound histamine in the cat is also reported.

TABLE I

QUANTITATIVE ANALYSIS FOR HISTAMINE METABOLITES IN THE URINE OF VARIOUS SPECIES AFTER FEEDING OR INJECTING ^{14}C HISTAMINE

	Histamine Metabolites, % of Total ^{14}C in Urine					
	Histamine	1,4-Methyl Histamine	1,4-Methyl ImAA	ImAA Free	ImAA Riboside	Acetylhistamine
Rabbits, 2.0 and 2.1 kg. 60 μg. ^{14}C histamine each, subcutaneously, combined urine† ..	—*	—	41	Trace	40	0·5
Cat, 2·5 kg. male, 50 μg. ^{14}C histamine subcutaneously ..	9	—	72	—	—	0
Cat, 0·6 kg. female, fed 100 μg. ^{14}C histamine	0·3	0·6	77	5	4	—
Mice, four, average wt. 21 g. female, each fed 14 μg. ^{14}C histamine	—	—	8	18	47	—
Man, 85 kg. male, Subject H.K. fed 100 μg. ^{14}C histamine ..	0	—	64	—	—	—
Dog, 22 kg. mongrel, male, 120 μg. ^{14}C histamine subcutaneously	0	7	61	21	0 to 1‡	—
Dog, 9 kg. mongrel, male, 60 μg. ^{14}C histamine subcutaneously	0	9	66	—	—	—

* A line indicates that the assay was not performed.

† Most urine samples were collected for a period of 6 hours following the administration of ^{14}C histamine; the only exception was the 22 kg. dog whose urine was collected for 27 hours.

‡ The value obtained for total ImAA was 22%. Since the value obtained for free ImAA was 21% there is no evidence for the presence of conjugated ImAA.

METHODS

The determination of urinary metabolites of histamine by isotope dilution has been described (Schayer and Karjala, 1956; Schayer and Cooper, 1956). ^{14}C histamine in cat tissues was determined by addition of carrier followed by the usual extraction procedure (Schayer, 1952). The carrier histamine was converted to the dibenzenesulphonyl derivative (Schayer, 1956) and counted in a Packard Tri-Carb Liquid Scintillation Spectrometer (background 10–11 counts/min.).

RESULTS

Various species were given ^{14}C histamine by feeding or by subcutaneous injection. Urine was collected in vessels containing hydrochloric acid and toluene. Complete analysis for all known metabolites were not done on all samples; in some cases only those assays were performed which were required to show the major pathway of histamine metabolism. The experimental conditions and results of assays are summarized in Table I.

DISCUSSION

From the data of Table I the following inferences can be made:

In the rabbit histamine is metabolized by oxidation and by methylation to approximately the same extent.

The mouse, which methylates most injected histamine (Schayer and Karjala, 1956), metabolizes most intestinal histamine by oxidation, not by methylation.

In cats and man,* on the contrary, methylation is the principal route of metabolism for both fed

* The percentage of total ingested ^{14}C in the urine of the human subject H. K. at various time intervals was: 0-6 hr., 40%; 6-12 hr., 14%; 12-24 hr., 7%; 24-48 hr., 5%. Total recovery in 48 hr. was 66%.

and injected histamine. In man, no fed histamine could be detected unchanged in the urine.

In the dog, methylation is the main means of inactivation of injected histamine. Dogs are the only animals tested in which none of the injected histamine could be detected unchanged in the urine. Furthermore, dogs do not appear to conjugate appreciable quantities of ImAA with ribose.

To test the recent suggestion by Waton (1956) that intestinal histamine might be a source of bound histamine in carnivores, the cat which had been fed ^{14}C histamine was killed 8 days after the feeding and various tissues assayed for ^{14}C histamine content. This cat had received 4.6 microcuries of radioactive histamine. Results in counts per minute were: intestine (60 g.) 2, skin (70 g.) 1, stomach (64 g.) 2, and lung (64 g.) 3. These counts are too low to indicate the presence of ^{14}C histamine.

On the other hand, another cat (a litter mate of the first cat) 8 days after injection with ^{14}C L-histidine had definitely detectable quantities of ^{14}C histamine in its tissues. The values in counts per minute were: intestine (sample lost), skin (48 g.) 73, stomach (39 g.) 71, and lung (46 g.) 29. This cat received 20 microcuries of ^{14}C L-histidine; however, it should be emphasized that only a minute fraction of injected L-histidine is converted to histamine. These results suggest that in cats, as in other species (Schayer, 1952; Schayer and Smiley, 1954), the precursor of bound histamine is L-histidine and not exogenous histamine.

Summary

Quantitative analyses for histamine metabolites in the urine of various species are reported. An experiment is described which identifies L-histidine as the precursor of bound histamine in the cat.

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