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FURTHER OBSERVATIONS ON THE DIFFERENCE IN THE METABOLISM OF HISTAMINE IN MALE AND FEMALE RATS

BY

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In young rats a sex difference in the daily output of free histamine in the urine did not become apparent until after the 26th day of life, when males exhibited a lower excretion. Castration increased the urinary free histamine in male rats but had little or no effect in females. Testosterone depressed the urinary free histamine in castrated male and female rats, but did not change the excretion in intact females. When [^{14}C]-histamine was given by subcutaneous injection, the fraction of the dose appearing in the urine in the unchanged form followed closely the excretion of endogenous free histamine. Parallel changes were also seen in the amounts of [^{14}C]-histamine excreted after injection of [^{14}C]-(−)-histidine. Intact male rats methylated [^{14}C]-histamine given by injection and [^{14}C]-histamine formed in the body more efficiently than did castrated males and females. Testosterone increased the degree of methylation of injected [^{14}C]-histamine and of [^{14}C]-histamine formed in the body. It is suggested that androgenic hormones increase the rate of histamine methylation in the rat and that this effect provides a satisfactory explanation for the lower excretion of urinary histamine in male rats.

It has now been observed by several workers that the urinary excretion of free histamine is much lower in male than in female rats (Leitch, Debley & Haley, 1956; Gustafsson, Kahlson & Rosengren, 1957; Kim, 1959; Parratt & West, 1960; Marshall, 1961). The cause of the difference is not definitely known. There are, however, indications that male rats inactivate histamine differently. Thus both Gustafsson, Kahlson & Rosengren (1957) and Marshall (1961) found that male rats excreted more conjugated histamine.

A study of the catabolism of [^{14}C]-histamine injected into rats was made by Westling (1958), who found a distinct difference between the sexes. After subcutaneous injection only 1 to 2% of the [^{14}C]-histamine appeared unchanged in the urine of male rats, whereas female rats excreted 10 to 12% in the unchanged form. The difference between males and females persisted after treatment with aminoguanidine, and appeared therefore not to depend on the enzyme histaminase (diamine oxidase). Only a small percentage of the injected [^{14}C]-histamine was acetylated; the values were equally low in males and females. Male rats, however, excreted a larger proportion of methylated derivatives of [^{14}C]-histamine (methylhistamine and methylimidazoleacetic acid). This finding indicated that there was, in male rats, a larger activity of the histamine-methylating enzyme (Schayer, 1959). This could

explain the lower excretion of unchanged histamine in this sex. Kim (1959, 1961) and Netter, Cohn & Shore (1961) have confirmed that male as compared with female rats inactivate injected histamine more efficiently.

In the present study, experiments were performed to test the effect of castration and of testosterone on the urinary excretion of non-isotopic histamine in rats. The results of these experiments largely confirm the findings of Marshall (1961). Experiments on the effect of castration and testosterone on the catabolism of injected [^{14}C]-histamine and on the urinary excretion of [^{14}C]-histamine after injection of [^{14}C]-histidine are also reported.

METHODS

White, inbred Sprague-Dawley rats, reared in the department, were maintained on a diet which was essentially free from histamine (Kahlson, Rosengren & Westling, 1958). The rats were kept singly on a wire mesh in a glass beaker (if less than 6 weeks old) or in a metabolism cage. Urine was collected in the presence of enough HCl to keep the *p*H of the sample below 2.

Non-isotopic, free histamine was determined by bioassay on the guinea-pig ileum as described by Angervall, Bjurö & Westling (1961). The urinary excretion of free histamine (base) was expressed in μg/rat/24 hr.

During the period of urine collection some rats received a daily dose of aminoguanidine (20 mg/kg subcutaneously) to inhibit histaminase (Schayer, Wu & Smiley, 1954; Westling, 1958).

Adult rats were given 5 mg of testosterone propionate in oil as a single intramuscular injection. Smaller rats were given 2.5 to 3.5 mg/100 g.

Castration was performed at 2 to 4 weeks of age. Some rats were subjected to a sham operation.

[^{14}C]-Histamine was injected subcutaneously in a dose of 10 to 30 μg (approximately 0.1 μg/g rat). Urine was collected as described above and the content of [^{14}C]-histamine and its radioactive metabolites was measured by isotope dilution (Lindell & Schayer, 1958).

The urinary excretion of [^{14}C]-histamine after a subcutaneous injection of [^{14}C]-(−)-histidine (about 2 μg/g rat) was also measured by Schayer's technique (for references, see Bjurö, Westling & Wetterqvist, 1961).

[^{14}C]-Histamine and its radioactive metabolites were isolated with carrier amounts of the respective non-radioactive substances. The [^{14}C]-radioactivity was measured in a flow counter (background 18–22 counts per minute, c.p.m.) under rigidly standardized conditions. The samples were recrystallized repeatedly with different charcoal adsorbents until their radioactivity was constant.

When [^{14}C]-histamine or [^{14}C]-methylhistamine was extracted from the urine of animals given [^{14}C]-(−)-histidine, 50 mg of non-isotopic (−)-histidine was added together with a carrier amount of each of the respective amines. This "diluted" the [^{14}C]-(−)-histidine possibly present in the urine to about the same specific activity as the amine; contamination with highly radioactive [^{14}C]-(−)-histidine was thereby reduced.

[^{14}C]-(−)-Histidine (specific activity 63 μC/mg, 1 μg giving about 5.500 c.p.m. when converted to histamine and assayed under standard conditions) and [^{14}C]-histamine (specific activity 39 μC/mg, 1 μg giving 2.500 c.p.m. when assayed under standard conditions) were both labelled in the 2 position on the imidazole ring. They were purchased from the Radiochemical Centre, Amersham, England.

RESULTS

Development of sex difference in urinary free histamine (*Table* 1). It was found that male and female rats of less than 24 to 26 days had roughly the same daily

output of free histamine ; above this age males excreted less. The values for urinary free histamine in adult males were higher than those quoted in previous reports (Leitch, Debley & Haley, 1956 ; Westling, 1958), and the difference between the sexes was therefore not so pronounced. Nevertheless, the adult females excreted about 6 times more than the males.

TABLE 1

DEVELOPMENT OF SEX DIFFERENCE IN URINARY HISTAMINE AND THE EFFECT OF CASTRATION, PERFORMED AT 14 TO 28 DAYS OF AGE

Mean values for the urinary excretion of free histamine in μg/24 hr are given. Figures within parentheses denote number of animals

	Age in days						
Groups	21–23	24–26	27–29	30–33	34–38	≈90	≧120
Males (intact)	8 (4)	6 (9)	6 (11)	5 (3)	4 (12)	4 (6)	11 (5)
Males (castrated)	—	—	—	11 (3)	12 (9)	31 (3)	31 (4)
Females (intact)	10 (5)	11 (10)	13 (13)	11 (4)	15 (11)	37 (6)	70 (5)
Females (castrated)	—	—	—	10 (4)	10 (9)	26 (1)	48 (6)

An identical time course for the development of the difference between the sexes in urinary free histamine was described by Marshall (1961).

Effect of castration and of testosterone on urinary free histamine. The increased urinary output of free histamine in castrated male rats (Tables 1 and 2) confirms the findings of Kim (1959) and Marshall (1961), but not those of Leitch, Debley & Haley (1956). In the present series castrated females excreted slightly less histamine than intact or sham operated females. This is at variance with the observations of Marshall (1961), who found that castration increased the urinary histamine in female rats. The difference in results may be due to i.a. differences in age or, possibly, diet of the rats at the time of castration.

TABLE 2

URINARY EXCRETION OF FREE HISTAMINE IN ADULT MALE AND FEMALE RATS

Effect of castration, sham operation, aminoguanidine (20 mg/kg) and testosterone (5 mg/rat). The urinary excretion of free histamine (μg/24 hr) was measured in each rat for 3 days before and the 2nd and 4th day after the administration of testosterone. Mean values for the different groups are given. Figures within parentheses denote the number of animals (mostly litter-mates)

	Before testosterone				After testosterone			
	Intact or sham operated		Castrated		Intact or sham operated		Castrated	
Aminoguanidine:	−	+	−	+	−	+	−	+
Males	8·7 (6)	20 (3)	32 (8)	68 (4)	5·0 (2)	12 (1)	4·0 (3)	19 (3)
Females	57 (7)	106 (6)	43 (6)	88 (2)	54 (4)	96 (3)	6·0 (3)	21 (2)

Testosterone in a single dose of 5 mg uniformly depressed the urinary histamine in castrated male and female rats (Fig. 1, Table 2). Castration thus makes the female rat more sensitive to this action of testosterone ; an effect which may be due to the absence of ovarian hormones. In a few experiments in female rats of less than 35 days, testosterone depressed urinary histamine to the male level, just as it did in the castrated adult females, but over the age of 45 days testosterone

lost this effect, possibly because the ovaries start to secrete at this time. Table 2 shows that aminoguanidine raised the excretion of histamine in all groups of rats, before as well as after testosterone. However, differences between groups were not eliminated.

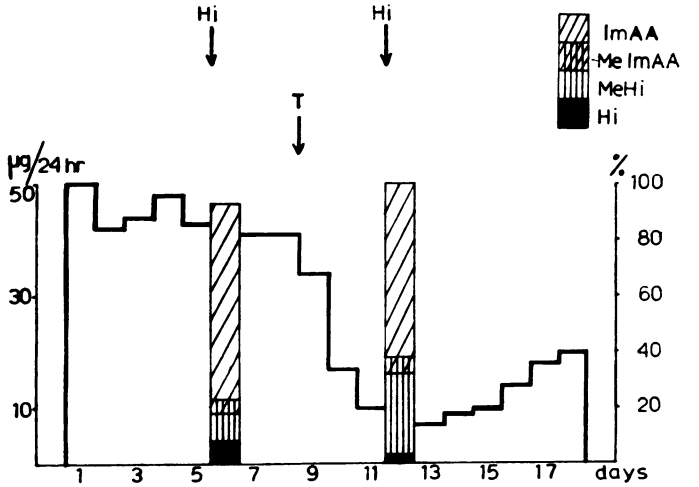

Fig. 1. Urinary excretion of free histamine (µg/24 hr, left ordinate) and urinary metabolites of [^{14}C]-histamine in % of injected amount (right ordinate). Castrated male rat. No aminoguanidine. At the arrows, Hi=subcutaneous injection of 20 µg [^{14}C]-histamine and T= intramuscular injection of 5 mg testosterone propionate. Hi=Histamine, MeHi=Methylhistamine, MeImAA=Methylimidazoleacetic acid, ImAA=Imidazoleacetic acid.

Catabolism of injected [^{14}*C*]*-histamine.* In some of the rats examined [^{14}C]-histamine was injected subcutaneously and the urinary excretion of unchanged [^{14}]-histamine measured. The results are given in Table 3. Male rats excreted much less unchanged [^{14}C]-histamine than did females; treatment with aminoguanidine did not eliminate the difference. Further, castrated males treated with aminoguanidine did not differ significantly from intact or castrated females in the

TABLE 3

% URINARY EXCRETION OF UNCHANGED [^{14}C]-HISTAMINE IN RATS

Unmetabolized histamine expressed as % of injected amount of [^{14}C]-histamine in male and female rats (mostly litter-mates). Effect of castration, sham operation, aminoguanidine (20 mg/kg) and testosterone. [^{14}C]-Histamine was injected subcutaneously twice, namely, 3 days before and 3 days after the intramuscular injection of 5 mg testosterone. Individual values are given. * Also shown in Table 4

	Before testosterone				After testosterone			
	Intact or sham operated		Castrated		Intact or sham operated		Castrated	
Aminoguanidine:	−	+	−	+	−	+	−	+
Males	5*	13*	8*	34*	3*	10*	2	6
	2	12	9	36			2	19*
	2			40*			3*	
Females	15*	46*	10	40*	10*	34*	2	8
	12	35	14*		22	36	2	19*
					20		4*	

percentage of unchanged [^{14}C]-histamine excreted. Without aminoguanidine the figures for castrated males were slightly lower than those for females (Table 3).

After injection of testosterone the catabolism of [^{14}C]-histamine became more efficient (Table 3), and this effect of testosterone was seen mainly in castrated rats, male or female (Fig. 1). In the intact male the already low excretion of unchanged [^{14}C]-histamine was further depressed. In the intact female testosterone was practically without effect.

When [^{14}C]-histamine was injected into male or female rats the proportion of the dose excreted as imidazoleacetic acid was similar in each sex (Table 4). The amounts of imidazoleacetic acid formed in animals treated with aminoguanidine were very low. Intact males, as compared with castrated males and females, excreted a higher proportion of the dose as ^{14}C-labelled methylhistamine and its oxidation product methylimidazoleacetic acid.

As the testosterone decreased the percentage of [^{14}C]-histamine excreted in unchanged form, the excretion of methylated histamine metabolites rose concomitantly. This increase was rather small in the non-castrated female (Table 4). Fig. 1 shows that the decrease in non-isotopic endogenous histamine following testosterone coincides with an increased excretion of methylated products of injected [^{14}C]-histamine.

It thus appears that the fraction of the injected [^{14}C]-histamine which is excreted unchanged is inversely related to the fraction that is methylated. This inverse relationship was independent of the sex of the rat, the effect of castration and of treatment with aminoguanidine and testosterone.

As in previous studies (Schayer & Cooper, 1956; Westling, 1958) we could not fully account for all of the injected histamine in terms of radioactive metabolites. Part of this discrepancy is due to the fact that only 90 to 95% of the ^{14}C injected is excreted. This percentage was, however, not measured in the present experiments. It appears to be the same in both sexes (Westling, 1958).

Urinary excretion of [^{14}C]*-histamine after injection of* [^{14}C]*-(−)-histidine.* A subcutaneous injection of [^{14}C]-(−)-histidine is followed by the appearance of [^{14}C]-histamine into the urine. The amount of [^{14}C]-histamine thus excreted depends on the rate of its formation from [^{14}C]-(−)-histidine and on the rate of its inactivation. It was decided to see whether the sexes differed or not in the amounts of [^{14}C]-histamine found in the urine after subcutaneous injection of [^{14}C]-(−)-histidine. The experiments were performed on 4 of the rats, the [^{14}C]-histamine catabolism of which had been studied previously without aminoguanidine (Table 4). The rats were allowed to "recover" from the effects of testosterone during four weeks. [^{14}C]-Histidine was then injected twice, before and after a new injection with testosterone, and urine collected as usual and assayed for non-isotopic, endogenous histamine. The [^{14}C]-histamine excretion was measured during 4 days after each injection of [^{14}C]-histidine.

The results are shown in Table 5 and Fig. 2. The intact male excreted smaller amounts of [^{14}C]-histamine than did the castrated male and the intact or castrated female. After testosterone, the values were reduced and the reduction was largest for the castrated animals.

TABLE 4

EXCRETORY PATTERN OF UNCHANGED [^{14}C]-HISTAMINE AND ITS RADIOACTIVE METABOLITES

Amounts excreted expressed as % of the amount of [^{14}C]-histamine injected subcutaneously. Eight rats were given [^{14}C]-histamine twice, namely, before and 3 days after the intramuscular injection of 5 mg testosterone; interval between [^{14}C]-histamine injections 6 days. Hi=Histamine. MeHi=Methylhistamine. MeImAA=Methylimidazoleacetic acid. ImAA=Imidazoleacetic acid

Rat no.	Sex	Operation	Amino-guanidine 20 mg/kg	Before testosterone						After testosterone					
				Hi	MeHi	MeImAA	MeHi + MeImAA	ImAA	Total	Hi	MeHi	MeImAA	MeHi + MeImAA	ImAA	Total
1	Male	—	No	5	24	4	28	62	95	3	31	7	38	55	96
2	Male	Castration	No	8	10	5	15	55	78	3	29	6	36	48	86
3	Female	—	No	15	9	8	16	60	92	10	10	8	18	59	87
4	Female	Castration	No	14	8	8	16	51	81	4	29	10	39	37	80
5	Male	—	Yes	13	45	17	62	5	80	10	52	18	70	4	84
6	Male	Castration	Yes	40	32	17	49	6	95	19	55	19	74	4	97
7	Female	—	Yes	46	23	14	37	5	88	34	30	17	47	4	85
8	Female	Castration	Yes	40	23	15	38	3	81	19	49	18	67	3	89

TABLE 5

EXCRETION OF [^{14}C]-HISTAMINE AND [^{14}C]-METHYLHISTAMINE AFTER INJECTION OF [^{14}C]-(−)-HISTIDINE

[^{14}C]-Histamine in the urine was measured for 4 days after the subcutaneous injection of about 2 μg/g of [^{14}C]-(−)-histidine. [^{14}C]-Methylhistamine was measured only during the 4th day after [^{14}C]-histidine. The amount of [^{14}C]-histidine injected to each rat contained about 500 c.p.m. of [^{14}C]-histamine as an impurity. The values given for [^{14}C]-histamine in the urine during the first day after the injection of [^{14}C]-histidine have been corrected for the impurity under the assumption that the percentage of the total amount given (namely, 550 c.p.m.) excreted was the same as the percentage of injected [^{14}C]-histamine excreted in unchanged form (in Table 4). The values during days 2 to 4 were not corrected for [^{14}C]-histamine present as impurity since this should be excreted almost completely within 24 hr. Rat numbers refer to the same rats as in Table 4

Rat no.	Sex	Operation		[^{14}C]-Histamine, c.p.m. per 24 hr				[^{14}C]-Methylhistamine c.p.m./24 hr
				Day 1	Day 2	Day 3	Day 4	Day 4
1	Male	—	Before testosterone	254	43	32	25	136
			After	182	24	34	31	271
2	Male	Castration	Before	781	101	78	80	102
			After	199	39	29	56	270
	Female	—	Before	514	106	56	61	26
			After	405	90	68	61	83
4	Female	Castration	Before	790	134	83	76	73
			After	211	34	31	25	191

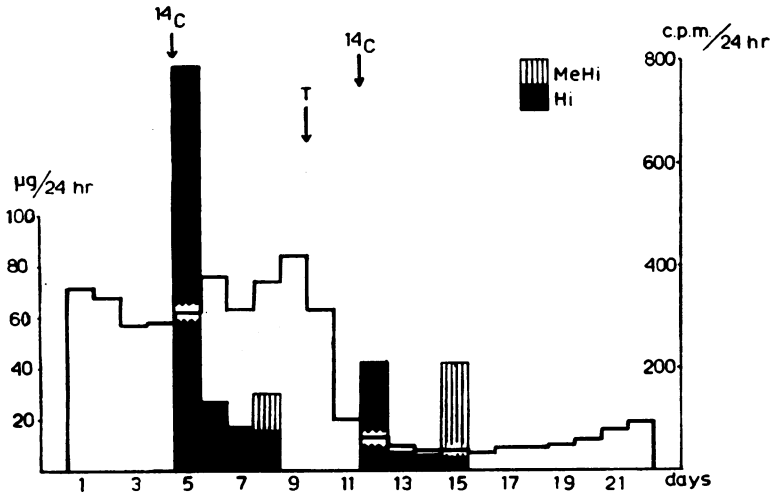

Fig. 2. Urinary excretion of free histamine (μg/24 hr, left ordinate) and urinary metabolites of [^{14}C]-histidine (c.p.m./24 hr, right ordinate). Castrated female rat. No aminoguanidine. [^{14}C]=subcutaneous injection of [^{14}C]-histidine. MeHi=Methylhistamine. Hi=Histamine. For further explanations see Fig. 1.

The 4 rats shown in Table 5 had earlier been given [^{14}C]-histamine injections. In these rats values were thus available for three "forms" of urinary histamine, that is, (1) non-isotopic, free endogenous histamine, (2) [^{14}C]-histamine excreted unmetabolized after injection of [^{14}C]-histamine, and (3) [^{14}C]-histamine excreted after [^{14}C]-(−)-histidine. The values for these three forms of urinary histamine

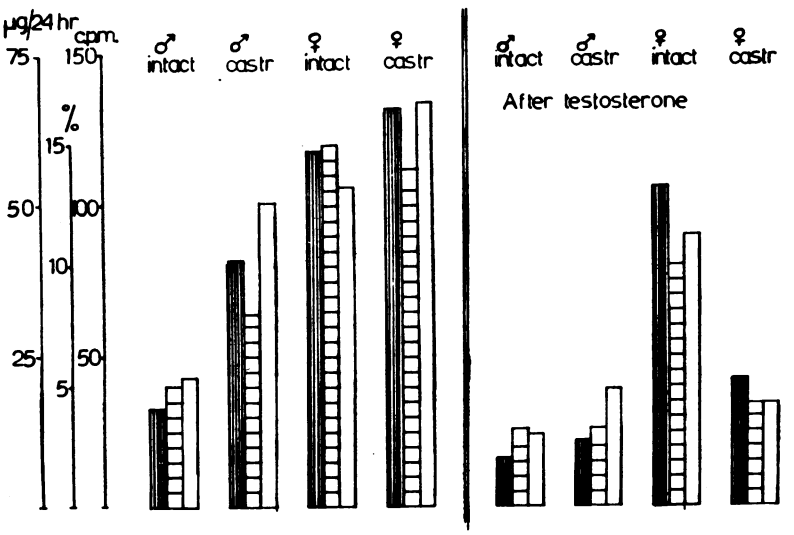

Fig. 3. Three forms of urinary histamine in intact and castrated male and female rats. Non-isotopic histamine (μg/24 hr), vertically striped bars. Per cent of unchanged [^{14}C]-histamine excreted during 24 hr after subcutaneous injection of [^{14}C]-histamine, horizontally striped bars. C.p.m. of [^{14}C]-histamine excreted during the 2nd day after subcutaneous injection of [^{14}C]-histidine, open bars.

before and after treatment with testosterone are shown in Fig. 3. The intact male excreted less of the three forms of urinary histamine than the castrated male, the figures of which are nearly as large as those for the females. Treatment with testosterone reduced the values for the castrated animals to the level of the intact male, whereas in the intact female the effect of testosterone was slight. There is a parallelism between the behaviour of the three forms of urinary histamine under the various experimental conditions, and this suggests that the variations studied are due to one and the same mechanism.

It may also be seen from Table 5 that the urinary excretion of ^{14}C-labelled methylhistamine was measured on the 4th day after each injection of [^{14}C]-(−)-histidine. The values for [^{14}C]-methylhistamine appear to vary inversely with those for [^{14}C]-histamine. An increased excretion of methylated histamine after testosterone may also be seen. The results strongly suggest that testosterone increases the rate of methylation of [^{14}C]-histamine that has been formed in the body from [^{14}C]-histidine, just as it does with injected [^{14}C]-histamine.

The sum, [^{14}C]-histamine + [^{14}C]-methylhistamine, increased after testosterone.

DISCUSSION

The results of Kim (1959), Marshall (1961) and those of the present study support the view that the lower urinary excretion of free histamine in male rats is dependent upon the presence of the testes and that testosterone can reduce the increased urinary histamine in castrated male rats. The sex difference in urinary histamine is not dependent upon the accessory sexual organs, since female rats can be made to show a " male " type of excretion of histamine by giving them testosterone after castration. The fact that testosterone does not alter the urinary output of free histamine in intact females suggests that ovarian hormones may antagonize the effect of testosterone on histamine metabolism.

The present experiments show that endogenous non-isotopic histamine, [^{14}C]-histamine excreted unmetabolized after injection of [^{14}C]-histamine and [^{14}C]-histamine excreted after an injection of [^{14}C]-histidine vary in parallel under different experimental conditions (sex of the rat, castration, treatment with testosterone or aminoguanidine). It seems therefore that the various treatments applied to the rats affect the urinary histamine by one and the same mechanism, namely, one which influences the rate of histamine catabolism.

The more efficient catabolism of histamine in the male rat was not caused by diamine oxidase (histaminase) since imidazoleacetic acid was excreted in equal amounts by the sexes. Gustafsson, Kahlson & Rosengren (1957) and Marshall (1961) found that male rats excreted more " conjugated " histamine than females, whereas Kim (1959, 1961) found no difference. The " conjugated " histamine may be acetylhistamine (Gustafsson, Kahlson & Rosengren, 1957), but Westling (1958) found no difference between the sexes in the degree of acetylation of injected [^{14}C]-histamine. The divergence in the results may be due to differences in the degree of enzymatic handling of exogenous and endogenous histamine. It is also possible that an unknown enzymatic pathway is responsible for the larger histamine-inactivating capacity of the male rat (Netter, Cohn & Shore, 1961). This possibility cannot be definitely

excluded since all of the injected ^{14}C cannot be fully accounted for in terms of known urinary metabolites (Westling, 1958); but the "missing" radioactivity is relatively small and equal in both sexes. In our opinion there is no need to assume that the more efficient catabolism of histamine in male rats is due to an unknown enzyme since variations in the degree of histamine methylation as seen in the present experiments appear to be a sufficient explanation.

It is believed that the results of the present experiments warrant the conclusion that the male rat is able to methylate histamine more efficiently than the female rat, and that this must be a major reason for the lower urinary free histamine in the male. The larger degree of methylation in the male need not necessarily be due to increased amounts of enzyme. Other factors may also play a role, for example, exposure of histamine to the enzyme and availability of co-factors. This may explain why Netter, Cohn & Shore (1961) found no sex difference in histamine methylation using homogenates from rat organs, whereas Aziz (1961) and Westling & Wetterqvist (1962) found that kidney slices from male rats have a larger histamine-inactivating capacity than slices from female rats.

The possibility must now be considered that the degree of histamine methylation is dependent upon the rate of production of the amine. It could be that the methylating enzyme has a limited capacity: progressively smaller fractions of histamine would then be methylated if the substrate concentration increased, and *vice versa*. If this explanation was valid, one would have to assume that testosterone diminished considerably the formation and release of histamine, and therefore a larger fraction could be methylated. The finding that the sum of [^{14}C]-histamine and [^{14}C]-methylhistamine after [^{14}C]-(−)-histidine injection actually increased after testosterone speaks against this explanation. Moreover, preliminary experiments indicate that the sex difference in histamine catabolism persists during the administration of large amounts of exogenous histamine (Westling & Wetterqvist, 1962).

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