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Changes in Tissue Histamine During the Estrous Cycle, Pregnancy and Pseudopregnancy in the Golden Hamster (42095)

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Abstract. The histamine content of reproductive tissues and skeletal muscle was determined in the golden hamster during the estrous cycle, pregnancy, and pseudopregnancy. Histidine decarboxylase activity was measured in uterine implantation sites and intersites from Day 4 to Day 10 of pregnancy. Histidine decarboxylase was also measured in mesometria and placentas on selected days of gestation. During the estrous cycle, uterine and skeletal muscle histamine levels were highest on Day 2 and lowest on Day 4 of the cycle. The ovarian histamine content did not change significantly among the different stages of the cycle. While the histamine content of uterine implantation sites of attachment was high on Days 4 and measurable on Days 5 and 6 of pregnancy, the levels were below the limits of detection by Day 7. On the other hand, the highest levels of histamine were in the uterine interimplantation sites on Days 8 and 9. The ovarian levels of histamine were highest on Day 13 of pregnancy. Histamine in skeletal muscle did not change significantly during pregnancy. The histidine decarboxylase activity in the implantation sites began rising on Day 9 and increased dramatically on Day 10. Placental histidine decarboxylase activity was very high on Days 13 and 15. Overall, we observed changes in uterine and skeletal muscle histamine during the estrous cycle that may be explainable in light of previously reported changes in mast cell numbers and circulating estrogens. During pregnancy, histamine levels of implantation sites and implantation intersites varied, as did the histamine content of ovarian tissue. Histidine decarboxylase activity rises in the uterus and placental tissue after the formation of the placenta.

Histamine (HA) is a biogenic amine found in most mammalian tissues. HA's biosynthetic pathway involves a one-step decarboxylation of its amino acid precursor, histidine, by histidine decarboxylase (HDC) (1). While the amine has recently been of interest to researchers because of its action as a neurotransmitter, its functions in relation to vasodilation and gastric acid secretion are well established (2, 3). Roles for HA in implantation and parturition have been postulated. However, despite lively debate over HA's involvement in reproductive processes, there is no general agreement about its reproductive function(s). Furthermore, there is little information available about the levels of HA present in female reproductive tissues of either pregnant or nonpregnant animals.

The controversy over the participation of HA in implantation began in the 1950s when Shelesnyak (4) first reported that HA induces decidualization and Spaziani and Szego (5) demonstrated that estrogen causes the release of HA. DeFeo (6) argued against Shelesnyak's contention that HA is prominently involved in the implantation process, but Nalbandov (7) revived the hypothesis that the amine is required for nidation to occur. In light of newer evidence, including the existence of multiple pools of HA and the existence of two distinct types of HA receptors, Dey and Johnson (8) recommended a reappraisal of the action of HA in implantation. Kahlson and Rosengren (9) asserted the view that HA may also be important in relation to the initiation of parturition.

The hamster is an especially useful animal model in which to study the role of HA in reproductive processes because, like the human, the hamster cannot delay implantation.

The objective of this study was to measure HA levels in reproductive tissues during the estrous cycle, pregnancy, and pseudopregnancy to provide baseline information for planning future studies of HA's functions in reproduction. The HDC activity of selected tissues was also determined at various stages of pregnancy.

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Materials and Methods. *Animals.* The hamsters used for these studies were from the reversed light colony (light from 10:00 PM–10:00 AM) maintained by Dr. Margaret Orsini at the University of Wisconsin, since 1956. All animals were of known age and reproductive history, were more than 80 days of age, and their body weights were over 80 g. All were checked daily for the stage of the cycle according to the procedures described by Orsini (10). Only animals showing regular cycles were used. In this report, the day of the prominent postestrous discharge is designated Day 1; hence, the 4-day cycle, pregnancy, and pseudopregnancy are parallel. All pregnancies were timed from the time of ovulation, 5:00 PM in this colony (i.e., equivalent to 0 hr of Day 1). Pseudopregnancy was induced by copulations with a vasectomized male and, like pregnancy, was timed from ovulation.

Tissue collection and preparation for analysis. The hamsters were anesthetized with Nembutal (ip injection of 8.5 mg Nembutal/100 g body wt) and killed by decapitation at comparable hours of the day. Uterine tissue, ovaries, and skeletal muscle were removed immediately and subsequently analyzed for HA content. All tissues collected were trimmed, weighed, and frozen at −80°C.

For Days 4, 5, 6, 7, 8, and 9, determinations of the HA content of both uterine implantation sites and intersites were made. On Days 4 and 5, we measured HA in the implantation sites and intersites of the animals after injecting Pontamine sky blue (0.25 ml of a 1% solution) and separating the uterus into blue areas, i.e., implantation sites, and nonblue areas, i.e., intersites. As the conceptual sites increase in size by midpregnancy, there is little, if any, interimplantation site remaining. Therefore, we did not evaluate the HA level in the intersites after Day 10. The mesometria were cut free at the mesometrial–uterine juncture and just above the main uterine artery. Placentas were excised from the uterus.

For the pseudopregnant animals, pseudopregnancy was confirmed by the presence of functional corpora lutea, external vaginal phenomena, and zona-free ova (11). One set of pseudopregnant animals was subjected to decidualization by injection of 0.1 ml air into one uterine horn on Day 4 during the sensitive period. The animals were killed on Day 7, the peak of decidual development. The deciduomata (DCR) were peeled away from the uterus, then both DCR and nondecidualized control horns were analyzed separately for HA.

HA assay. The procedure used to measure HA is a radioenzymatic assay that has been previously described in detail by Hegstrand and Hine (12).

HDC assay. This procedure has been described by Hegstrand and Seybold (13). In brief, the production of [^{3}H]HA from L-[^{3}H]histidine was quantitated as a measure of HDC activity. The reaction was performed in a 40-μl vol in 400-μl polyethylene tubes containing 2 μmole potassium phosphate buffer, pH 7.2; 4 nmole α-methyldopa; 4 nmole impromidine; 0.4 nmole pyridoxal phosphate; 15–40 pmole L-[^{3}H]histidine (0.2–1.0 μCi); and enzyme. Blanks contained homogenizing buffer in place of enzyme. The reaction was incubated at 45°C for 30 min for placentas and 120 min for uterine implantation sites, intersites, and mesometria at 45°C. Termination was with 10 μl of 10 μg HA and 20 nmole of NaOH in 50% ethanol. The extraction of [^{3}H]HA was with 100–200 μl of H_2O-saturated *n*-butanol. After a 5-min centrifugation in a Beckman Microfuge B, 50 or 100 μl of the butanol extract were spotted onto Whatman LK5D TLC plates. The plates were developed and radioactivity quantified by scintillation spectrophotometry as in the HA assay (12).

Because of the small variations in the amount of subsaturating L-[^{3}H]histidine used in this assay and because the activity is linear in that range, all reported activities are at 0.4 μ*M* L-histidine.

Protein determinations. Protein was determined by the method of Bradford (14) using bovine γ-globulin as standard. The protein content of uterine tissues including implantation sites, intersites, and DCRs was comparable for a given wet weight of tissue. Since HA levels are generally expressed per wet weight and HDC activity per milligram protein, our data are reported in the same manner.

Statistical analyses. Data are presented as the means ± the standard error of the mean

($x \pm$ SEM) except where indicated. Comparisons between two groups were made using Student's t test. Differences among several group means were evaluated using one-way analysis of variance (ANOVA). The Neuman–Keuls procedure was utilized for all post hoc testing (15).

Results. *Estrous cycle.* HA levels in reproductive tissues and skeletal muscle of hamsters in each day of the estrous cycle are presented in Table I. Using ANOVA, a significant difference in uterine HA was observed among the days of the estrous cycle [$F(3,20) = 3.71$; $P < 0.05$]. The Neuman–Keuls procedure showed a difference between uterine HA on Days 2 and 4 ($P < 0.05$), with the highest mean uterine HA level on Day 2. The skeletal muscle followed the same temporal pattern observed in the uterus, with a peak on Day 2 followed by a low on Day 4. Likewise, these differences in tissue HA were statistically significant [$F(3,20) = 11.44$; $P < 0.01$]. The HA content of skeletal muscle was higher on Day 1 than on Day 4 ($P < 0.01$). Skeletal muscle HA was also higher ($P < 0.01$) on Day 2 as compared with both Days 3 and 4. For the ovaries, there were no significant variations in mean HA content among the days of the cycle.

Plotting the data (Fig. 1) for uterus and skeletal muscle along with Brandon and Evans' (16) data on the number of uterine mast cells present on each day of the estrous cycle illustrates that the variations in HA levels measured for each respective day parallels the changes in uterine mast cells. The mast cells are most abundant on Day 2, the day on which the quantity of uterine and skeletal muscle HA peaks.

TABLE I. HISTAMINE LEVELS IN UTERI, OVARIES, AND SKELETAL MUSCLE FROM HAMSTERS AT VARIOUS STAGES OF THE ESTROUS CYCLE

Day	n	Uterus (μg/g tissue)	Ovary (ng/g tissue)	Skeletal muscle (μg/g tissue)
1	6	9.2 ± 1.5	37 ± 35	11.5 ± 0.6[b]
2	6	12.8 ± 1.5[a]	38 ± 16	13.88 ± 1.3[b]
3	5	8.0 ± 1.1	35 ± 16	9.5 ± 0.7
4	7	6.8 ± 1.2	17 ± 7	7.5 ± 0.6

[a] Uterine HA levels differ between Days 2 and 4; $P < 0.05$.

[b] For skeletal muscle HA, Day 1 was higher than Day 4 ($P < 0.01$) and Day 2 was significantly higher than Days 3 and 4 at the $P < 0.01$ level.

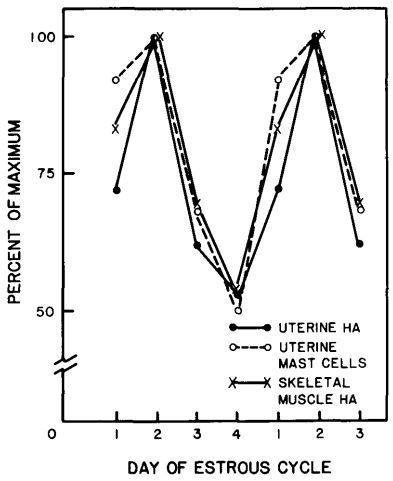

FIG. 1. Uterine and skeletal HA levels and uterine mast cell numbers expressed as percentage of the maximum value on each day of the estrous cycle. The maximum values and significant changes in uterine and skeletal muscle HA levels are shown in Table I.

Pregnancy. The HA levels and HDC activity in uterine implantation sites and intersites on Days 4–6 of pregnancy are shown in Table II. There is a significant difference ($F(2,11) = 7.21$, $P < 0.01$) in the HA content of the implantation sites in the peri-implantation period with the HA levels on Day 4 higher than on Days 5 or 6 ($P < 0.01$). After Day 6, the HA content of the implantation sites was below 0.2 ng/g tissue, which is the

TABLE II. HISTAMINE LEVELS AND HISTIDINE DECARBOXYLASE ACTIVITY IN UTERINE IMPLANTATION SITES AND INTERIMPLANTATION SITES DURING THE PERIIMPLANTATION PERIOD OF PREGNANCY[a]

Tissue	Day of pregnancy	HA content (μg/g)	HDC activity (fmole/hr/mg protein)
Sites	4	15.66 ± 1.89[b]	11 ± 3
	5	6.01 ± 1.36	11 ± 1
	6	3.52 ± 0.36	9 ± 1
Intersites	4	13.04 ± 2.09	10 ± 3
	5	7.26 ± 3.32	9 ± 0.2
	6	14.90 ± 2.76	7 ± 1

[a] Values are expressed as the means ± SEM with an n of four to six animals.

[b] $P < 0.01$, differences between Days 4 and 5 and between Days 4 and 6.

lower limit of our HA assay. There were no differences in HDC activity in either the uterine implantation sites or the interimplantation sites during Days 4–6 of gestation. The HA levels of the interimplantation sites were variable in the peri-implantation period.

The HA content of the interimplantation sites was determined for several other days and is plotted in Fig. 2 as a percentage of the maximum value. The variability in the HA levels of the interimplantation sites persists but it is clear that when comparing all days on which determinations of HA in the interimplantation sites there is a significant difference among the days ($F(6,26) = 11.85$, $P < 0.01$). The HA levels of interimplantation sites on Day 8 were significantly higher ($P < 0.01$) than any other day for which HA values were determined. This marked difference is illustrated in Fig. 2.

Ovarian levels of HA also varied significantly during pregnancy ($F(7,25) = 7.30$, $P < 0.01$). The data on ovarian HA are also plotted in Fig. 2. The mean levels of ovarian HA on Day 13 (40 ± 14 ng/g) were significantly higher ($P < 0.01$) than those on Days 4 (9 ± 2 ng/g) and 5 (6 ± 1 ng/g). However, by Day 15, the ovarian HA level had dropped by about 50% of the peak level observed on Day 13.

During pregnancy, there were no significant changes in skeletal muscle HA content determined by ANOVA. The average HA content for all 8 days for which skeletal muscle HA was assayed was 11.6 ± 0.8 μg/g.

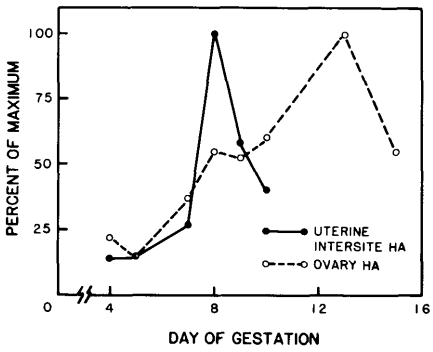

FIG. 2. Uterine interimplantation site and ovarian HA levels expressed as a percentage of the maximum value on selected days of gestation. The maximum values and significant changes in interimplantation sites and ovarian HA content are 31.1 ± 4 μg/g tissue and 40 ± 14 ng/g tissue, respectively.

TABLE III. HISTIDINE DECARBOXYLASE ACTIVITY IN UTERINE IMPLANTATION SITES FROM HAMSTER AT VARIOUS DAYS OF PREGNANCY[a]

Days of gestation	HDC activity (fmole/hr/mg protein)
7	7 ± 1
8	3 ± 1
9	27 ± 1
10	462 ± 16

[a] Values are the means ± SEM from two to four animals.

HDC activity was measured from uterine implantation sites and interimplantation sites on Days 7–10 of gestation. For each of those 4 days, there were less than measurable amounts of HDC activity present in the interimplantation sites. As shown in Table III, the HDC activity in the implantation sites began rising at Day 9 and increased dramatically on Day 10. Placentas from Days 13 and 15 had similar amounts of activity (83,400 ± 7000 fmole/hr/mg protein; $n = 8$) which was about 200-fold greater than that observed for the Day 10 uterine implantation site. HA levels for these placentas averaged 45 ng/g.

Data on uterine mesometrial HDC activity and HA content for Days 7, 10, and 13 are presented in Table IV. HDC activity was two to three times greater on Day 10 than on Days 7 and 13. To establish whether this is a real and consistent difference, more animals need to be studied. The levels of HA were very high, averaging 18,000 ng/g tissue with no pronounced differences among the different days of gestation. There was a very

TABLE IV. HISTIDINE DECARBOXYLASE AND HISTAMINE LEVELS IN MESOMETRIUM FROM HAMSTERS ON VARIOUS DAYS OF GESTATION[a]

Day	HDC activity (fmole/hr/mg protein)	HA level (ng/g tissue)
7	78	22,000
10	203	17,000
13	80	15,000

[a] Values are the average from two animals which varied less than 20%.

dramatic difference in the ratios of HDC activity (fmole/hr/mg protein) to HA (ng/g tissue) between placenta and mesometrium. These ratios are 1900 and 0.0067, respectively.

Pseudopregnancy. The data on tissue HA levels and HDC activity on Day 7 of pseudopregnancy are presented in Table V. The HA content and HDC activity of the uteri and DCRs (the maternal portion of the pregnant uterus) were analyzed separately. The HA content of the DCR tissue was less than 0.2 ng/g tissue which is the lower limit of our HA assay. Similarly, the HDC activity in the DCR tissue was very low and consequently is an approximation rather than an accurate determination. On the other hand, both the HA content and HDC activity in the uterine tissues were well within the useful regions of our assays and were both greater than in DCR tissues, $P < 0.01$ and $P < 0.05$, respectively. In addition, we examined the HA content of uteri with DCRs in four animals on Day 5, 6.0 ± 2.0 μg/g, and in two animals on Day 7, 3.4 μg of pseudopregnancy. These values were not significantly different.

Discussion. The uterine, ovarian, and skeletal tissue HA values essentially followed the same trends over the 4 days of the estrous cycle with highest levels of HA measured on the first 2 days of the cycle and lower levels thereafter. The differences that existed in tissue HA among the days of the estrous cycle may be explained in relation to mast cells or sex steroids. For uterine tissue, changes in the mast cell population may largely account for the variation in uterine levels of this amine. There are at least two reports in the literature of the number of uterine mast cells present on each day of the hamster estrous cycle. Harvey (17) was the first to publish data on endometrial mast cells which were found to be higher on Day 1 and lower on the remaining days of the cycle. In contrast, Brandon and Evans (16) noted a peak in the mast cell number on Day 2 and the lowest number of uterine mast cells on Day 4. There is no apparent explanation for the discrepancy in uterine mast cell number changes found by the different investigators. The changes we observed in uterine HA levels during the estrous cycle paralleled the variations in mast cell numbers reported by Brandon and Evans (16) which is consistent with a mast cell localization of a substantial portion of the HA in hamster uterine tissue. However, it is unlikely that mast cells serve as the only source of HA in uterine tissue. The W/W^v strain of mice are mast-cell-deficient, yet there is measurable HA present in the uterus (18).

TABLE V. HISTAMINE LEVELS AND HISTIDINE DECARBOXYLASE ACTIVITY IN UTERINE TISSUE FROM PSEUDOPREGNANT HAMSTERS[a]

Tissue	HA content (μg/g)	HDC activity (fmole/hr/mg protein)
DCR	N.D.[b]	6 ± 1[c]
Uterus without	5.7 ± 1.6	19 ± 4

[a] Values are the means ± SEM with an n of 4.
[b] Not detectable.
[c] $P < 0.05$ two-tailed Student's t test.

Alterations in tissue HA during the estrous cycle may be because HA levels are affected by variations in progesterone, estrone, or estradiol. Saidapur and Greenwald (19) measured peripheral blood and ovarian levels of sex steroids in the cyclic hamster observing positive correlation between blood and ovarian levels of sex steroids. They found progesterone to be the dominant circulating sex hormone on the first 2 days of the cycle and they documented that there is an inverse relationship between progesterone and estradiol for the first 3 days of the cycle. Estradiol levels tripled between Days 1 and 3 and achieved a peak on the afternoon of Day 4. Thus, the higher levels of tissue HA that we observed on the first 2 days of the cycle were associated with low estrogen and high progesterone levels. Since estrogen has been shown to promote the release of HA, it is possible that the lower levels of HA measured on Day 4 may be the result of the release of this amine. While there is little published information on the relationship of peripheral tissue HA to steroid hormones, Scheinmann *et al.* (20) measured tissue HA in castrated male and female mice and found significant changes in tissue HA in skeletal muscle and other tissues only in the female, suggesting a possible interaction between tissue HA levels and female sex steroids. Evidence of a differ-

ent sort also links HA to the sex hormones; HA has been suggested to be involved in gonadotrophin release (21).

Changes in tissue HA levels were observed during gestation as well as in the estrous cycle. The HA content of uterine implantation sites was highest on Day 4 of pregnancy, the day on which implantation begins in the hamster. However, the levels plummet during the next few days. These findings can also be related to existing information on the mast cell numbers in the peri-implantation period. Brandon and Bibby (22) and Harvey (17) also evaluated the mast cell population in pregnancy. Brandon and Bibby (22) observed in the rat that there was an increase in mast cells in the preattachment phase around the time that blastocyst attachment was initiated but mast cell number decreased during the attachment phase of pregnancy. Harvey (17) found mast cell numbers to be quite variable during early gestation but to drop on Day 4 between 79 and 91 hr postovulation. The timing of our sample collection on Day 4 may account for the high values of HA in uterine implantation sites measured for that day. In any event, it is clear that with so many alterations in the mast cells during early pregnancy, it would be advisable to analyze uterine tissue and evaluate mast cell populations of tissues collected at the same day and time. This is probably particularly important on Days 4 and 5 since between 80 and 91 hr the uterus shows the "blue response" at the site of initial attachment, and by 115 hr the blastocyst is beginning to embed (23).

For the later stages of pregnancy, our measurements of tissue HA confirmed some of the earlier work of Rosengren (24), Kahlson *et al.* (25), and Kahlson *et al.* (26), who reported data on HA and HDC in the hamster. Rosengren (24) injected [^{14}C]histidine subcutaneously and measured [^{14}C]HA and [^{14}C]telemethylhistamine excreted. They observed that on the 11th day of pregnancy the excretion of HA in the urine began to rise and continued to increase until near the time of parturition when the levels declined to nonpregnant levels. Kahlson *et al.* (25) noted that the amount of HA excreted was positively associated with the number of young. Rosengren (24) identified the placenta as the source of HDC since the HA forming capacity in the placenta (HDC activity), like the urinary metabolites, surges in the latter stages of pregnancy but declines at parturition. She hypothesized that HA may be involved in the mechanism(s) controlling contractility of the uterus. There are no published data on HA receptors in the hamster uterus; however, in the rat uterus, HA relaxes the smooth muscle via H2 receptors (27). In contrast, the guinea pig has both H1 and H2 receptors in the uterus, and a contractile effect is produced by HA indicating there are species differences.

The uterine wall of the nonpregnant and early pregnant hamsters has little HDC activity to measure (24) whereas uterine implantation sites by Day 10 have a marked amount of HDC activity. By the latter part of the 9th day of gestation, the allantois vascularizes the plate formed by the union of the chorion and trager and circulation begins in the chorioallantoic placenta (28). Early placental formation undoubtedly accounts for the marked rise in HDC activity observed in the uterine implantation sites on Day 10. In fact, hamster placenta has been reported to have more HDC activity than any other organ measured for HDC in any species (24). Our findings in Table III substantiate earlier findings of Rosengren (24) who found uterine wall HDC activity increased with pregnancy, and was especially concentrated in the hamster placenta.

The exceedingly large ratio of 1900 for HDC activity (fmole/hr/mg protein) to the HA level (ng/g tissue) is consistent with either a very high turnover rate for HA and/or HA being transported for use elsewhere in the mother or fetuses. HA has been implicated to play a role in rapidly growing tissues (29). For the purpose of comparison, we examined uterine mesometria for HDC activity and HA content. This tissue is rich in mast cells which have low HDC activity but high HA levels. The ratio we obtained of 0.0067 for these two parameters bears out the observation of others that HA turns over very slowly in mast cells (30). Further studies must be undertaken to establish whether HDC activity and HA levels do change in the uterine mesometrium with gestational

day and what the physiological significance of such a change might be.

This study of HA levels and HDC activity during the estrous cycle and gestation supplies information about the levels of this amine and its biosynthetic enzyme under various physiological conditions but also raises many questions that merit further study. There were changes in HA in reproductive tissue and skeletal muscle during the estrous cycle that could be explained by variations in mast cell numbers and circulating sex steroids. During the estrous cycle, it would be optimal to simultaneously assess mast cells and circulating steroids when HA levels are determined to confirm a relationship of amine levels with the other two variables. The same is true for early pregnancy, especially in the peri-implantation period when we observed high levels of HA in the uterine implantation sites. The information presented here is valuable because it demonstrates that there are sometimes marked changes in tissue HA and HDC levels as gestation progresses. These studies have provided new information about the dynamics of HA levels and HDC activity. These results support the need to determine the cellular source of this amine and its role in implantation, placentation, and parturition in the hamster and other species.

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