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# EFFECT OF HISTAMINE ON REPRODUCTION IN FEMALE MICE

BY

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Histamine fed to laying chickens causes an abrupt cessation of egg production (Shifrine, Adler & Burkhalter, 1963). Experiments were thus designed to determine whether ingested histamine has an effect on the reproductive system of mice.

In this paper we describe the effect of histamine fed to mice on ovulation and the oestrous cycle, pregnancy, the size of the adrenal "X" zone and medulla, food and water consumption, and the output of urine and faeces.

## METHODS

Five experiments were conducted on 126 virgin and 10 pregnant Swiss White Mice (Webster Strain C3) using groups of five to fifteen in each experiment. The mice were housed in metal cages or plastic metabolic cages. They were maintained in the experimental environment for at least 3 days and given pulverized mouse feed. The experimental diets were pulverized commercial mouse rations mixed with histamine diphosphate to give 0.1 or 0.25% histamine as free base. A record was kept of the daily food and water consumed, and the output of urine and faeces. The mice were weighed daily and at necropsy.

In pregnancy studies the pregnant mice were allowed to litter and were then immediately bred and held in metabolic cages to observe date of parturition and thus to assess date of conception. Vaginal smears were taken daily for 10 days from virgin females 60 days old and fed 0.1 and 0.25% histamine, and from control mice. The smears were stained with Giemsa and cells were examined to assess the stage of the oestrous cycle and the occurrence of ovulation (Snell, 1941). The latter was also determined by the character of maturing ovarian follicles, corpora haemorrhagica, and corpora lutea on gross and microscopic examination after mice were fed 0.1 or 0.25% histamine for periods ranging from 7 to 31 days.

In all instances only the right adrenal gland was removed for sectioning. For histopathological studies, tissues were fixed in 10% neutral formalin and stained with haematoxylin and eosin. After staining, the adrenal "X" zone and medulla were measured with a microscopic ocular reticle at $\times 110$. In each case only adrenal sections which were cut clearly across the centre of the gland, and only in areas representative of the whole gland, were chosen for measurements. This greatly reduced the number of adrenal glands used for tabulation.

Ratios reported are of "X" zone relative to the total adrenal cortex, and medulla as a percentage of the total width of gland.

## RESULTS

Mice kept in plastic metabolic cages and fed 0.1 or 0.25% histamine were initially observed to behave in a more agitated manner than the controls. This included constant movement about the cage, increased nose scratching and more wastage of food and water.

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Feeding 0.1 and 0.25% of histamine reduced the size of the " X " zone from 42.3% of the total cortex in control mice, to 32.9% in mice fed 0.1% histamine for 7 to 24 days; and to 33.8% in mice fed 0.25% histamine for 7 to 31 days (Table 1). The reductions were significant at the 5% level.

TABLE 1

PERCENTAGE OF CORTICAL WIDTH OCCUPIED BY " X " ZONE IN VIRGIN FEMALE MICE FED HISTAMINE

Values are means and standard deviations. Each group of histamine-fed mice gave results which differed significantly from the control ($P<0.05$)

| Histamine fed (%) | No. of adrenals examined | " X " zone as % of cortex |
|---|---|---|
| 0 (control) | 23 | 42·3 |
| 0·1 | 17 | 32·9±7·4 |
| 0·25 | 19 | 33·8±3·3 |

The width of the medulla compared with the total width of the adrenal gland was not altered in the two experiments so recorded, in which 0.1 and 0.25% histamine was fed to virgin female mice. Medulla measurements from control mice were 39% of total adrenal width compared with 40% for mice fed 0.1% histamine and 40% for mice fed 0.25% histamine.

No effect was noted on the oestrous cycle of twenty-one virgin female mice by the vaginal smear technique. Nor was any effect observed on ovulation in three other experiments on 105 mice.

No effect was observed on the duration of pregnancy of five mice fed 0.1% histamine from 4 days after fertilization to parturition. The size of litters and weights of newborn mice were the same as those of the control animals.

Food and water consumption and excretion of urine and faeces of virgin or pregnant females fed 0.1% histamine were not significantly different from an equal number of controls. The final weights of virgin and pregnant female mice fed 0.1 or 0.25% histamine were no different from the controls.

## DISCUSSION

The decrease in size of the " X " zone of the adrenal gland of mice is believed to be due to the influence of androgenic hormone (Jones, 1957) secreted by the testes in males and by the adrenal cortex or ovary in pregnant females (Vinson & Jones, 1963). The reduction in size of the " X " zone in these experiments could be due to stimulation of the zona fasciculata to produce corticosteroids (or their intermediates), some of which have androgenic activity (Moon, 1961). Such adrenal gland stimulation could be effected by the small amounts of histamine absorbed from the nasal mucosa, mouth, or digestive tract and act in a similar manner to the " stress " reaction (Fortier, Yrarrazaval and Selye, 1951; Ohno, 1962). Involution of the " X " zone appeared less acute than that observed in stressed, starved or formalin-injected mice (Ohno, 1962) but some lipid accumulation, oedema and increased vascularity were noted.

The lack of apparent effect on ovulation, oestrous cycle and pregnancy indicates that, unlike the laying chicken whose ovulation is stopped by 0.25% histamine, the mouse can

tolerate such doses when given orally. It is possible that most of the histamine fed is metabolized before absorption, so that concentrations in the circulation are insufficient to interfere with the reproductive cycle.

Schayer (1956) fed 100 $\mu$g of [$^{14}$C]-histamine to four mice and collected their urine. Within 6 hr, 73% of the dose given appeared in the urine as histamine metabolites.

Whether this rate of metabolism will remain the same under continuous feeding, as reported here, is a matter of conjecture. Apparently there is sufficient concentration in the circulation to exert an effect on the " X " zone; whether this is a direct effect or induced through the hormonal system requires further study.

SUMMARY

1. Feeding of 0.1 or 0.25% histamine to 126 virgin and 10 pregnant Swiss White Mice (Webster Strain C3) for periods of 7 to 31 days decreased the size of their adrenal " X " zone.

2. There was no significant effect on the size of the medulla, in relation to the total width of the adrenal gland, or on ovulation, oestrous cycle or pregnancy.

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