

EFFECT OF CIMETIDINE ON ADENOHYPHYSIS OF MALE ALBINO MICE UNDER CERTAIN EXPERIMENTAL CONDITION

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Abstract: Effect of 75 mg/kg of body weight of cimetidine administered intraperitoneally daily for 14 days to two groups of experimental animals (one of the experimental group was having intact testis and another group was bilaterally orchidectomized) was observed on cell population & cell volume of gonadotrophs and lactotrophs in pituitary gland, as it has not been studied earlier. In the experimental group of intact testis, there was significant reduction in the cell population of FSH cells in the cephalomedian area ($P < 0.001$) and in the lateral lobe ($P < 0.01$); the volume of both FSH and LH cells was also significantly reduced. In group 4 and group 5 there was significant increase in the population of lactotrophs and also in the volume of LH cells, FSH cells & lactotrophs. The change in the gonadotrophs in group 2 was due to increased production of testosterone from hypertrophied Leydig cells of testis rather than its direct effect on adenohiphysis; in group 4 and group 5 the changes were due to lack of testosterone as in those cases bilaterally orchidectomy already done.

Key words : cimetidine male albino mice adenohiphysis

INTRODUCTION

Cimetidine is a histamine H_2 - receptor antagonist when used chronically can be carcinogenic (1) through the formation of n-nitrosocimetidine (2). Recently an increase in the volume of Leydig cells and seminiferous epithelium of testis has been observed with 50 mg/kg cimetidine administered intraperitoneally (ip) for fourteen days (3). These changes were related to the increased secretion of testosterone. Since testicular steroidogenesis is influenced by pituitary gonadotrophins, an attempt therefore was made to find out the effect of cimetidine on adenohiphysis.

METHODS

Inbred 72 days old swiss strain male albino mice weighing 25-30 g were divided into five groups of ten each. Mouse food and water were given *ad libitum*.

Animals were divided as follows:-

Group 1- Control (saline, ip).

Group 2-Experimental (cimetidine 75 mg/kg, ip).

Group 3- Sham-operated (saline, ip).

Group 4- Bilaterally orchidectomized (saline, ip).

Group 5- Bilaterally orchidectomized (cimetidine 75 mg/kg, ip).

Bilaterally orchidectomy was done after exposing the testicular vessels and efferent ductules, which were ligated in the interval between testis and epididymis. The testis was removed after cutting proximal to ligature. Thus the epididymis was left back to the scrotum with its blood supply.

In sham-operated males, the testis and the epididymis were exposed, but returned into the scrotum without ligating or cutting the testicular vessels or the efferent ductules.

Group 2 and group 5 received 75 mg/kg of body weight of cimetidine daily ip for 14 day. To group 5, cimetidine was administered from the day of operation. To groups 1, 3 and 4, normal saline was administered similarly. Twentyfour hr after the last injection all the animals were sacrificed by swift cervical decapitation.

The pituitary gland was removed and fixed in formal sublimate for 24 hours and sections of 5 μ m thickness were cut parallel to the cranial surface of the hypophysis. Sections were stained by Brookes method for identification of lactotrophs and with PAS orange G technique for identification of LH and FSH gonadotrophs.

The stained sections were subjected to stereological study under amplival microscope (Carl-Zeiss) with a magnification \times 400. Hypophysial cells found with in one sq cm eye piece reticule were counted. A minimum two fields from the lateral lobe of each section for lactotrophs and gonadotrophs and an additional two fields for gonadotropha from the cephalomedian zone, since the gonadotrophs are said to be aggregated here (4) studied. The cell population and cell volume of different cell types were calculated (5, 6) by the following relation.

$$NV = \frac{NA}{D + t} \text{ where } NV \text{ is number per mm}^3, NA$$

is average number per mm², D is average diameter of cells in mm and t is thickness of section in mm. To calculate average diameter of cells, the formula used

$$\text{is } D = \frac{L + B}{2} \text{ where } D \text{ is average diameter, } L \text{ is average}$$

greatest diameter and B is average greatest diameter at right angles to 'L'. For determining the cellular diameter (7) the stage and ocular micrometer were used. A minimum of 50 cells of each type from each gland were studied with a magnification of X 1000.

b) Formula used for estimating cell volume:-

$$V = \frac{\pi}{6} LB^2, \text{ where } V \text{ is volume, } L \text{ is greater dia-}$$

meter and B is greatest diameter at right angles to 'L' above.

Statistical analysis unpaired student 't' test was used to determine differences in the cell population of different cells and cell volume between control and experimental groups.

RESULTS

Morphometric study of adenohypophysis revealed hypotrophy of gonadotrophs in group 2 and hypertrophy of gonadotrophs in group 4 & 5. These cells (gonadotrophs) were less stained due to less secretory granules in group 2 when compared with the same of group 1. Gonadotrophs of group 4 and group 5 have undergone hypertrophy as compared with the gonadotrophs of group 3. Cell population study revealed a significant reduction of both FSH and LH gonadotrophs in the lateral lobe and only FSH gonadotrophs in the cephalomedian zone in group 2 (Table I); the cell volume of both FSH and LH gonadotrophs were reduced significantly (Table I).

Cell volume of LH and FSH gonadotrophs along with the lactotrophs have been increased significantly in group 4 and group 5 as compared with that of group 3 (Table I). Cell population of lactotrophs also increases in group 4 and group 5 when compared with group 3 (Table I).

TABLE I : Showing the effects of cimetidine on lactotrophs and gonadotrophs (Values are expressed as $10^3 \pm$ S.E.M.).

Population of	Cells type	Group 1	Group 2	Group 3	Group 4	Group 5
In cephalomedian sex zono	LH	1.5 \times 10 ³ \pm 3803	1.1 \times 10 ³ \pm 3017**	1.6 \times 10 ³ \pm 4098	1.4 \times 10 ³ \pm 6703	1.4 \times 10 ³ \pm 5466
	FSH	9.7 \times 10 ⁴ \pm 2760	7.6 \times 10 ⁴ \pm 3899**	9.4 \times 10 ⁴ \pm 3542	8.9 \times 10 ⁴ \pm 3154	8.5 \times 10 ⁴ \pm 3571
Lateral lobe	LH	5.2 \times 10 ⁴ \pm 2436	4.1 \times 10 ⁴ \pm 3274	4.9 \times 10 ⁴ \pm 2808	4.3 \times 10 ⁴ \pm 3178	4.2 \times 10 ⁴ \pm 2159
	FSH	2.8 \times 10 ⁴ \pm 1984	1.9 \times 10 ⁴ \pm 975*	2.6 \times 10 ⁴ \pm 2702	2.6 \times 10 ⁴ \pm 1421	2.8 \times 10 ⁴ \pm 2458
Lactotrophs		4.1 \times 10 ⁴ \pm 3872	3.7 \times 10 ⁴ \pm 3940	3.6 \times 10 ⁴ \pm 4489	4.5 \times 10 ⁴ \pm 2429@	3.9 \times 10 ⁴ \pm 1655@
Volume of	Cells type					
	LH	383 \pm 14	198 \pm 12**	352 \pm 25	477 \pm 21@	469 \pm 18@
	FSH	598 \pm 27	376 \pm 21**	567 \pm 25	676 \pm 14@	661 \pm 27@
	Lactotrophs	237 \pm 11	241 \pm 13	227 \pm 16	307 \pm 25@	258 \pm 23

*P<0.01 : ** P<0.001 as compared with group 1.

@P< 0.05 as compared with group 3 and group 4.

@P<0.05 as compared with group 3.

DISCUSSION

The result of this study demonstrate the suppressive effect of cimetidine on gonadotrophs. Decreased secretory granules as indicated by low stained hypertrophied gonadotrophs and reduced cell population and cell volume indicated this effect. Studies have demonstrated that administration of testosterone suppresses the secretion of pituitary gonadotrophins (8,9). Recently it has been shown that cimetidine causes hypertrophy of Leydig cells and seminiferous epithelium of testis (3) and serum testosterone increases with the increase in the number & size of Leydig cells (10,11). Hence the observed suppressive of cimetidine on gonadotrophs of pituitary gland is due to increased production of testosterone from hypertrophied Leydig cells rather than it's direct effect on adenohypophysis.

Bilateral orchidectomy in mice causes significant hypertrophy & hyperplasia of gonadotrophs (both LH

and FSH cells) and lactotrophs which is due to lack of testosterone as there is total removal of testis. Administration of cimetidine to orchidectomized mice does not bring about any significant change in the gonadotrophs as observed in group 5. This is due to fact that the effect of cimetidine on pituitary gonadotrophs is mediated through the testis. Since the testes were removed "Cimetidine-testis-pituitary gland" cycle was broken.

It can be argued that administration of cimetidine to male albino mice can suppress the pituitary gonadotrophs through the secretion of testosterone from hypertrophied Leydig cells of testis.

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