

## MITOMYCIN C INDUCED INHIBITION OF ADRENAL STEROIDOGENESIS IN FEMALE RATS

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**Abstract :** Mitomycin C (MC), an antibiotic which depresses DNA synthesis causes suppression of enzyme  $\Delta^5$  3  $\beta$ -hydroxysteroid dehydrogenase ( $\Delta^5$  3  $\beta$  OHD) and glucose-6 phosphate dehydrogenase (G-6 PD) in the rat adrenal tissue. The treatment resulted in a fall in DNA content together with an accumulation of cholesterol and ascorbic acid in the gland. The results suggest a diminution in adrenal steroid biogenesis similar to gonadal inhibition previously reported.

**Key words :** antitumor mitomycin C

adrenals

DNA synthesis

### INTRODUCTION

Matsumoto and Lark (1) have suggested that mitomycin C (MC) blocks DNA synthesis by cross linkage with complementary DNA strands. Deb et al (2) have reported that the antitumor antibiotic causes a fall in the nuclear area of Leydig cells along with suppression of testicular steroidogenesis. The same drug is also reported to cause a diminution in ovarian steroid biogenesis, as evidenced by several experimental evidences (3).

Although the effect of MC on gonadal physiology has been reported, the effect of this drug on adrenal steroidogenesis are lacking. In this communication histochemical and biochemical studies on the effect of the antibiotic on adrenal function has been reported.

### METHODS

Sixty adult 4-day cyclic female rats of Wistar strain were selected from a group purchased from local animal dealer. They were maintained on standard laboratory diet and water *ad libitum* and kept for a few days prior to experimentation. The animals were randomly divided into two groups of 30 animals each. One of the groups were injected intraperitoneally with

a solution of MC in distilled water at a dose level of 30  $\mu$ g/100 gm body weight daily for 12 days. The control group received equal amount for solvent only. The animals were decapitated 24 hours after the last treatment. Proper care was taken to see that the rats do not have unnecessary pain during sacrifice. Six animals from each group were selected for histochemical localization. Preparation of sections for the histochemical demonstration of  $\Delta^5$  3  $\beta$  OHD and G-6-PD were carried out exactly in a similar way as described in a previous communication from this laboratory (4). The ascorbic acid and cholesterol content of the gland were estimated biochemically in a similar way as described in the same publication (4). DNA content of adrenal was estimated according to the modified method of Abalain (5).

The results of all biochemical experiments were analysed using ANOVA by multiple comparison using 2 tailed 't' test.

### RESULTS

A marked fall in histochemical localization of enzymes G-6-PD and  $\Delta^5$  3  $\beta$  OHD were observed following MC treatment compared to control. The activity which was similar among the animals of the same group were found to be absent when the sections

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were incubated in substrate free media. The biochemical results indicated a fall in the DNA content of adrenals together with an increased concentration of both cholesterol and ascorbic acid (Table I).

TABLE I: Effect of Mitomycin C on DNA, Cholesterol and Ascorbic acid content of Adrenals in Cyclic female rats (Values are Mean  $\pm$  S.E. Figs. in parenthesis indicate number of test animals).

	DNA content mg/100 mg tissue	Cholesterol mg/gm tissue	Ascorbic acid mg/gm tissue
Control (8)	182.21 $\pm$ 3.90	52.64 $\pm$ 0.50	2.60 $\pm$ 0.08
Mitomycin C (8)	156.86 $\pm$ 2.11*	60.56 $\pm$ 0.60*	3.94 $\pm$ 0.21*

P < 0.01

## DISCUSSION

In the present investigation, a fall in the DNA content of adrenals has been noted. It seems that the effect of MC on adrenal steroidogenic activity is mediated through inhibition of DNA synthesis in the organ and thereby affecting the synthesis of the corresponding messenger RNA for the apoproteins of the enzymes resulting in decrease in the synthesis of the two enzymes studied in the present investigation, namely G-6-PD and  $\Delta^5$  3  $\beta$  OHD. G-6-PD generates NADPH for steroid hydroxylation (6) has been

demonstrated histochemically in the adrenals (7)  $\Delta^5$  3  $\beta$  OHD present in the organ is the key enzyme directly involved in steroidogenesis (8).

The role of ascorbic acid (9) and cholesterol (10) as a precursor molecule in the synthesis of steroid hormone has been well established. Thus the accumulation of this lipid along with ascorbic acid in the adrenals in MC treated rats is suggestive of its impaired utilization in the synthesis of corticosteroids. Sayers and his coworkers (11) have also noted that injection of ACTH in rats and guinea pig lowered both cholesterol and ascorbic acid in adrenals.

All such evidences indicate that both gonadal and adrenal steroidogenesis are inhibited after administration of the antitumor antibiotic. The effect of MC on adrenal steroidogenic activity appear to be direct, because it has also been reported to cause suppressed testicular steroidogenesis in immature rats (12). On basis of above discussion, it may be suggested that MC inhibits adrenal steroidogenesis through the inhibition of DNA synthesis in mature female rats by suppressing activities of enzymes having key role in the process.

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