MECHANISM OF ACTION OF CHRONICALLY ADMINISTERED CANNABIS EXTRACT ON THE FEMALE GENITAL TRACT OF GERBILS

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Summary: Daily administration of cannabis extract (2.5 mg/day for a period of 60 days) caused degenerative changes in the ovarian tissue. Luteinization was inhibited. Corpus-luteum degeneration was conspicuous. Distinct effects were produced upon the uterine biochemistry, consisting of decreased RNA, protein, sialic acid and glycogen concentration of the uterus. Vaginal RNA and protein contents were low. An anti-estrogenic action of cannabis extract in female gerbils is suggested.

Key words: Cannabis extract 
anti-estrogenicity
ovarian atrophy inhibition of RNA & protein synthesis

Cannabis is one of the oldest intoxicants in use. Δ⁹-Tetrahydro-cannabinol (Δ⁹-THC), has been shown to be the active component of marihuana (4 and 6). The Δ⁹-THC content of marihuana varies depending upon the source of the cannabis plant. Good quality marihuana contains about 1.5% of THC. Little attention has been paid to the examination of the action of this compound on the reproductive system of mammals.

In our previous studies we found that chronic administration of cannabis extract is anti-estrogenic in female mice and rats (2). The present study is a further confirmation of the results in the desert gerbils.

MATERIALS AND METHODS

As Δ⁹-tetrahydrocannabinol (Δ⁹-THC), the most potent naturally occurring cannabinol lacks specific effect on reproductive system, a total plant extract rather than THC or a purified active principle was preferred. Therefore, we extracted the authenticated samples of cannabis sativa harvested in Rajasthan (India), with 98% alcohol in a Soxhlet apparatus for 4 hours. The extract was evaporated to dryness and the residue weighed and redissolved in a mixture of alcohol, tween 80 and distilled water (10 : 1 : 89), to make concentration of 10 mg/ml.

Twenty young adult female gerbils with a regular oestrous cycle (4-6 days) were injected with cannabis extract intraperitoneally (2.5 mg/day for a period of 60 days). An equal number of controls received the vehicle alone. The animals were given standard rat feed (Hindustan Lever Private Ltd.) and water ad libitum. All animals were sacrificed 24 hour after administration of final dose of cannabis-extract and various organs were removed and weighed.
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RESULTS

Organ weights: Relative and absolute ovarian weight of cannabis extract treated
female gerbils was decreased markedly, indicating wide spread damage. The weights of
uterus, vagina and submaxillary glands were reduced (Table I). Adrenal and thyroid gland
weights did not change.

Histology: Cannabis extract administration for a period of 60 days resulted in wide
spread degenerative changes in the ovarian tissue. Primordial ova were reduced in number.
Atrias of large ovarian follicles was conspicuous. Luteinization was inhibited. Lutein
cells were vacuolated and undergoing cytolysis. Their nuclei were shrunken (mean nuclear
diameter of lutein cells, cannabis extract: 10.3±0.7 μ; control: 13.3±0.8 μ; P<0.01).
Histologically the corpus luteum showed signs of degeneration, luteal tissue showing infiltration
with fibroblasts. The average mean diameters of thirty corpora lutea was, cannabis treatment:
0.303 mm; vehicle treated control: 0.529 mm.

Uterus: In control female myometrium consists of 60% of the uterine volume. After
cannabis extract administration myometrial volume decreased in proportion to uterine
weight. Decrease in stromal connective tissue also paralleled the changes in uterine weight.
Uterine glands were regressed and without secretion. Stromal oedema was conspicuous.

Vagina: In cannabis extract treated gerbils, the vaginal epithelium appeared to
be atrophic. Cannabis extract administration interrupted the estrous cycle after 3 weeks.
Cells found in the vaginal smear during the cessation of cycling appeared to be that of
dioestrous.

Biochemical changes: Uterine glycogen and sialic acid contents were low after
cannabis extract administration (Table I). Total RNA and protein contents were decreased
significantly in uterus and vagina after cannabis extract administration, suggesting an
inhibition of synthesis. A slight depletion in the adrenal ascorbic acid concentration was
noticed (Table I).

DISCUSSION

When female gerbils with regular oestrous cycle were given a daily injection of cannabis
extract (2.5 mg/day for a period of 60 days), cyclic activity as judged by vaginal smears, ceased
after 3 weeks. Smears of the dioestrous type persisted as long as the medication was continued. The
vaginal cytology gave an appearance similar to that of late dioestrous type (1).
TABLE I: Changes in organ weights and in the concentration of RNA, protein, sialic acid, glycogen and adrenal ascorbic acid of female gerbils after Cannabis extract administration.*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Body Animals set g</th>
<th>Ovarian wt mg/100g body wt</th>
<th>Uterine wt mg/100g body wt</th>
<th>Thyroid wt mg/100g body wt</th>
<th>Adrenal wt mg/100g body wt</th>
<th>Submaxillary wt mg/100g body wt</th>
<th>RNA µg/mg tissue</th>
<th>Protein µg/mg tissue</th>
<th>Uterine sialic acid µg/mg tissue</th>
<th>Glycogen µg/mg tissue</th>
<th>Uterine Adrenal ascorbic acid µg/mg tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10</td>
<td>65±6</td>
<td>11.5±6</td>
<td>2.3±1</td>
<td>66.6±5</td>
<td>11.7±0.9</td>
<td>63.6±3.5</td>
<td>127±8</td>
<td>3.19±0.31</td>
<td>2.19±0.21</td>
<td>172±32</td>
</tr>
<tr>
<td>Cannabis Extract</td>
<td>10</td>
<td>65±6</td>
<td>11.5±6</td>
<td>2.3±1</td>
<td>66.6±5</td>
<td>11.7±0.9</td>
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</tr>
</tbody>
</table>

1P<0.02 compared with controls

*Biochemical estimations: means of six determinations.

2.5 mg Cannabis extract daily for a period of 60 days: total dose = 150 mg.
Suppressing the ovarian activity was reflected in large follicular atresia and degenerating corpora lutea. Furthermore, a reduction in the size of corpora lutea might have been due to interference by cannabis extract with ovulation.

The decreased concentration of uterine RNA, protein, glycogen and sialic acid indicate the possibility that cannabis extract inhibits estrogen production (3).

ACKNOWLEDGEMENTS

We are indebted to Professor A.S. Kapoor for providing facilities and encouragement. The investigation was supported by University Grants Commission (Grant No. 5672) New Delhi.

REFERENCES