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Suppression of Prolactin Secretion by Acute Administration of Δ^9-THC in Rats[1] (38370)

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In animals, Marihuana constituents have been reported to interfere with endocrine functions.

Acute administration of delta- 9- tetrahydrocannabinol (Δ^9- THC = Δ^1THC) stimulates ACTH secretion (1), but depresses thyroid function (2). It has been subsequently shown (3) that Δ^9-THC inhibits the release of "iodine" from the thyroid, and that this inhibition can be overcome by thyroid stimulating hormone. This inhibition was interpreted as depression of the secretion of thyroid releasing hormone (TRH).

On the other hand, TRH is capable of releasing prolactin in both animals (4, 5) and humans (6). It is therefore, of interest to study the effect of Δ^9-THC on prolactin secretion. In this study we report the suppression of prolactin release in male rats by acute administration of Δ^9-THC, and its inability to counteract prolactin release induced by perphenazine treatment (7, 8).

Materials and Methods. Adult male rats of the Hebrew University Sabra strain, weighing 140–160 g were used. They were housed five in a cage and were exposed to artificial lighting for 12 hr daily, receiving purina chow and water *ad libitum*.

Delta-9-tetrahydrocannabinol (Δ^9- THC = Δ^1THC) was prepared and kindly furnished by Dr. R. Mechoulam. Stock solution of Δ^9-THC (20 mg/ml) in propylene glycol was prepared and kept at −12°. Prior to use, the stock solution was suspended in 1% Tween-80 in saline resulting in a working solution so that similar volume calculated per animal body weight, was injected. Perphenazine (Trilafon, Schering) was dissolved in 0.03 *N* HCl 5 mg/ml. Control animals received the solvent only.

All materials were injected ip, and animals were killed by cervical dislocation. Blood samples were collected from the descending aorta within a period not exceeding 20 sec and left for 10–20 min at room temperature for clotting. Serum was separated by centrifuging (1700*g*, 20 min at 20°). One mg of sodium azide was added to each ml serum which was then stored at −20° until assayed 1–7 days later.

Radioimmunoassays (RIA) of serum prolactin were performed as reported earlier (9), using the NIAMD RIA Kit for rat prolactin with the following changes: (a) ^{125}I-Na (Amersham, England) was used for radioiodination; (b) A "short" assay was adapted: first incubation was performed at 37° for 24 hr, then optimal amount of goat, antirabbit gamma globulin (second Antibody) was added to all tubes followed by a second incubation at 4° for an additional 24 hr. Significance of the results was calculated by the unpaired Student's *t* test.

Results. Figure 1 shows the dose response effect of Δ^9THC on serum prolactin in male rats, 30 min after ip administration of the drug. While doses of 0.5 and 1 mg/kg showed no significant effect on serum prolactin, doses of 2, 5 and 10 mg/kg significantly lowered serum prolactin by 37, 65, and 47%, respectively.

The dose of 5 mg/kg was selected for further studies of time-related effects of the drug.

Figure 2 shows that the effect of Δ^9-THC in lowering serum prolactin starts within 15 min and terminates after 4 hr. The maximal effect was obtained after 30 min, where a dose of 5 mg/kg Δ^9-THC lowered serum prolactin to 37% of the levels found in control animals which received the solvent only.

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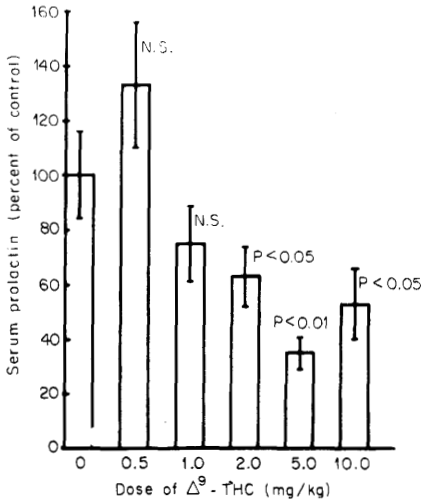

FIG. 1. Effect of ip administration of various doses (0.5–10 mg/kg B.W.) of delta-9-tetrahydrocannabinol (Δ⁹-THC) on serum prolactin of eight-animal groups of adult male rats, assayed 30 min after injection. Serum levels of each group is compared to control levels of prolactin and expressed as percent change.

Bars indicate SE of the mean; N.S. = not significant.

Figure 3 shows the effect of Δ⁹-THC (5 mg/kg), perphenazine (5 mg/kg) and a combination of both drugs on serum prolactin levels 1 hr after ip administration of the drugs. Δ⁹-THC lowered serum prolactin to 40% and perphenazine increased serum prolactin to 350%. The concurrent administration of Δ⁹-THC and perphenazine did not significantly alter the increase (350%) in serum prolactin achieved by perphenazine.

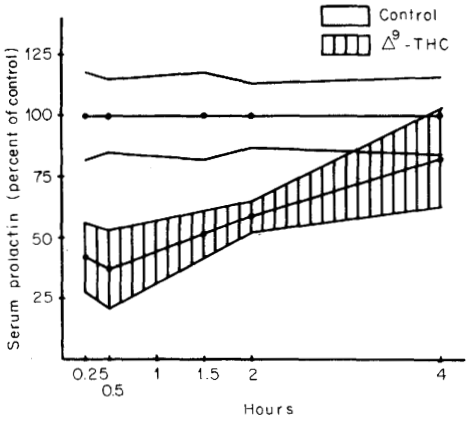

FIG. 2. Acute effect of a single dose of 5 mg/kg Δ⁹-THC on serum prolactin levels, and their 95% confidence limits, of adult male rats, assayed 0.25, 0.5, 1.5, 2, and 4 hr after ip administration of the drug. Serum levels of prolactin of treated animals are expressed as percent change of control rats received solvent solution only.

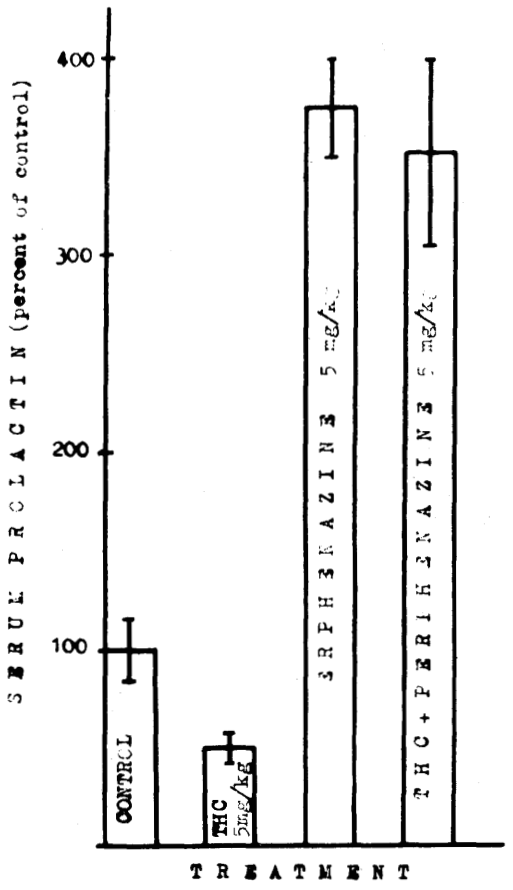

FIG. 3. Effects of 5 mg/kg Δ⁹-THC and 5 mg/kg perphenazine (sole and combined treatment) on prolactin serum levels of eight-animal groups of adult male rats, 60 min after ip administration of the drugs. Values are expressed as percent change of control animals which received only solvent solutions.

Bars indicate SE of the mean.

Discussion. While many drugs are known to increase prolactin secretion (10), only a few are capable of lowering serum prolactin levels. These include so far L-Dopa (11) and certain ergot alkaloids (12).

L-Dopa is believed to exhibit its effect of lowering serum prolactin via increase of dopamine in the CNS which in turn stimulates the production and secretion of the hypothalamic prolactin inhibiting factor (PIF) (13). Ergocryptine, however, is believed to lower serum prolactin mainly via a direct effect on pituitary cells secreting prolactin and indirectly via increase of PIF (12).

The pathway by which Δ^9-THC lowers prolactin secretion is unknown as yet. Theoretically, the following possibilities exist:
(a) Activation of dopaminergic stimulation of the hypothalamus.
(b) Lowering of TRH.
(c) Direct effect on pituitary cells secreting prolactin.
(d) Any combination of the above possibilities.
(e) Influencing other kinds of mechanisms controlling prolactin secretion, *e.g.*, other catecholaminergic or serotoninergic pathways.

Perphenazine, a well-known dopaminergic blocker, is believed to exert its prolactin releasing activity via decreasing endogenous dopaminergic stimulation on PIF. It was also found that the prolactin releasing effect of perphenazine can be counteracted by dopamine (14).

Since Δ^9-THC was unable to lower the prolactin release induced by perphenazine (Fig. 3), it is not likely that the Δ^9-THC induced suppression of prolactin secretion is effective via activation of the dopaminergic pathway. The fact that Δ^9-THC suppresses TRH which in turn is capable of inducing prolactin release, even in the minimal doses needed to release TSH (15), indicates that Δ^9-THC decreases prolactin release most likely via suppressing TRH. This might be a novel mechanism for suppressing prolactin release. This and other pathways are currently under further study in this laboratory.

Summary. The effect of acute administration of Δ^9-THC, an active principle of marihuana, on serum prolactin was studied in normal, adult, unanesthesized male rats. Animals were ip injected with doses ranging between 0.5 and 10 mg/kg and killed after periods of 15–240 min. Serum prolactin was measured by a radioimmunoassay. Delta-9-THC (5 mg/kg) significantly lowered serum prolactin to 37% of control values within 30 min. This effect, however, was terminated after 4 hr.

As reported earlier, perphenazine treatment resulted in a profound increase (350%) in serum prolactin. This effect, however, was not counteracted by addition of Δ^9-THC. The mechanism by which Δ^9-THC suppresses prolactin release is yet unknown.

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