Effects of Δ^9-tetrahydrocannabinol on serum thyroxine concentrations in the rat

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Lomax (1970) previously investigated the effects of cannabis extract on the pituitary-thyroid axis by measuring the release of radiolabelled iodine (^{131}I) from rat thyroid gland. His findings showed that acute intraperitoneal administration of cannabis extract (containing 2·5 mg Δ^9-THC kg^{-1} plus other undetermined cannabis constituents) inhibited the release of ^{131}I from thyroid gland. Lomax further concluded that a site of drug action involved in this phenomenon lay somewhere in the central nevous system, since cannabis inhibition of iodine released from thyroid gland could be prevented by treatment with thyroid stimulating hormone (TSH) or electrolytic lesions in the caudal hypothalamus. The present study attempts to confirm and extend those findings by characterizing the nature of changes in circulating thyroxine concentrations following various schedules of THC treatment.

Total serum thyroxine concentrations of male Holtzman rats (250–350 g) were determined by use of Tetrasorb-125 diagnostic kits (Abbott Laboratories). The efficacy of this assay system was tested on three groups of rats following manipulations to stimulate conditions of euthyroidism, hypothyroidism, and hyperthyroidism (see Table 1). Blood samples were drawn (5–10 ml) by cardiac puncture. The data in Table 1 indicate the sensitivity of the assay technique is suitable to measure changes in circulating thyroxine concentrations in the rat.

Table 1. *Thyroxine, μg 100 ml serum of control rats, thiouracil-treated*, or rats receiving TSH 2 h before sampling.*

Treatment	n	Mean ± s.e.m.
Control	5	5·9 0·73
Thiouracil	6	2·5 0·14**
TSH (1 I.U.)	6	9·9 0·97***

* Received 1% thouracil in drinking water for one week.
** $P < 0.001$.
*** $P < 0.01$.

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The effects of THC on circulating thyroxine concentrations were investigated under both acute and chronic treatment schedules (Table 2). Rats with free access to food and water, and an 12–12 h light-dark cycles, received injections of THC or carrier vehicle alone (1% Tween 80, 10% propylene glycol, 0·9% NaCl) intraperitonially at 9.00 a.m. and 9.00 p.m., the onset of each light-dark phase. Blood samples were taken 6 h after the final 9.00 a.m. injection. TSH was administered 2·5 h before blood sampling.

Table 2. *Thyroxine, μg 100 ml serum of rats treated with injection vehicle, Δ^9-THC, or Δ^9-THC + 1 I.U. TSH.*

Treatment	n	Mean ± s.e.m.	
Single injections Δ^9-THC (10 mg kg^{-1})			
Vehicle	10	6·9 0·22	
Δ^9-THC	10	5·3 0·15	$P < 0.001$
Δ^9-THC + TSH	10	9·9 0·21	$P < 0.001$
Repeated injections Δ^9-THC (10 mg kg^{-1}) twice daily for 3 days			
Vehicle	10	7·9 0·19	
Vehicle + TSH	10	8·9 0·25	$P < 0.01$
Δ^9-THC	10	5·5 0·13	$P < 0.001$
Δ^9-THC + TSH	10	9·9 0·20	$P < 0.001$
Repeated injections Δ^9-THC (2·5 or 10 mg kg^{-1}) twice daily for 14 days			
Vehicle	5	6·5 0·6	
Δ^9-THC 2·5 mg kg^{-1}	5	7·5 0·4	N.S.
Δ^9-THC 10 mg kg^{-1}	8	6·1 0·5	N.S.

As the data in Table 2 indicate, acute administration of THC (single injections or repeated for 3 days) depress serum thyroxine concentrations. Single injections depress serum thyroxine after 6 h, indicating that THC may not be exerting an entirely central effect and may be acting at several levels to cause the rapid reduction. In either form of acute treatment, however, exogenous TSH can still elicit a significant elevation of serum thyroxine, indicating that THC acts on thyroid function indirectly, probably at the level of the hypothalamus or pituitary. When the vehicle + TSH treated rats were compared statistically with the THC + TSH treated rats, they were found to be different at the $P < 0.01$ level. This would indicate that THC had a potentiating effect on TSH. Under chronic THC treatment (twice daily for 14 days) an apparent tolerance to thyroid-depressant action develops. Tolerance development to hypothermic actions of THC (Haavick &

Table 3. *Thyroxine, μg 100 ml serum in rats treated with vehicle or Δ⁹-THC one week after adrenalectomy or sham operations.*

Treatment	n	Mean ± s.e.m.		
Vehicle	7	6·7	0·5	
Sham-operated vehicle	7	5·7	0·3	N.S.
Adrenalectomized Vehicle	9	6·0	0·3	N.S.
Sham-operated Δ⁹-THC (10 mg kg⁻¹)	8	4·7	0·2	$P < 0.01$
Adrenalectomized Δ⁹-THC (10 mg kg⁻¹)	9	4·8	0·2	$P < 0.01$

Hardman, 1973) and to depression of cellular respiration (Nazar, Harclerode & others, 1974) follow a similar pattern, suggesting a possible connection among these drug responses.

In an earlier study from this laboratory an interaction effect among THC, adrenal steroids, and ethanol was observed on tissue respiration rates (List, Bartram & others, 1975). With low concentrations of adrenal steroids THC depressed brain tissue respiration rate, whereas, in the presence of stress concentrations of adrenal steroids stimulated respiration rate. Administration of ethanol potentiated both actions of THC on tissue respiration rate.

A possible influence of adrenal steroids on THC-induced thyroid depression was examined in this study (Table 3). Adrenal function is known to influence thyroid function inversely, and THC has been demonstrated to stimluate adrenal cortical activity (Barry, Perhach & Kubena, 1970). To eliminate effects mediated on thyroid function by adrenal cortical activity, serum thyroxine concentrations following THC treatment were compared to adrenalectomized and non-adrenalectomized rats (Table 3).

Table 4. *Thyroxine μg/100 ml serum in rats treated with Δ⁹-THC, ethanol, or combined Δ⁹-THC and ethanol.*

Treatment	n	Mean ± s.e.m.		
Vehicle (2 ml kg⁻¹)	9	7·7	0·6	
Δ⁹-THC (10 mg kg⁻¹)	9	5·5	0·4	$P < 0.02$
Ethanol (2 g kg⁻¹)	10	4·8	0·6	$P < 0.01$
Δ⁹-THC + ethanol	9	6·0	0·5	N.S.

These data indicate that the presence of adrenal hormones is not required for depression of thyroid function by THC. The involvement of adrenal corticotrophic hormone (ACTH), however, still remains a possibility. Both THC treatment and adrenalectomy result in elevated concentrations of ACTH. Any involvement of ACTH, however, is at best permissive; adrenalectomy alone results in elevated concentrations of ACTH but not a depression of thyroxine concentrations (Table 3).

Because ethanol is known to interact with some actions of THC, serum thyroxine concentrations were also measured 2 h after administration of THC, ethanol, or a combination of THC and ethanol (Table 4). Each drug alone depresses serum thyroxine concentrations. The combined administration of both drugs results in a slight depression but not significantly different from vehicle controls.

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