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ANTI-EDEMA AND ANALGESIC PROPERTIES OF Δ^9-TETRAHYDROCANNABINOL (THC)

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ABSTRACT

SOFIA, R. D., S. D. NALEPA, J. J. HARAKAL AND H. B. VASSAR: Anti-edema and analgesic properties of Δ^9-tetrahydrocannabinol (THC). J. Pharmacol. Exp. Ther. **186:** 646–655, 1973.

Δ^9-Tetrahydrocannabinol (THC) is an orally effective anti-edema and analgesic agent. In the carrageenan edema test the potency of THC is 20 times that of aspirin and nearly twice that of hydrocortisone. The anti-edema activity of THC, at least in the carrageenan edema assay, appears to be mediated by stimulation of the pituitary-adrenal axis, since this activity was markedly attenuated in both adrenalectomized and hypophysectomized rats. However, the compound is devoid of corticosteroid-like activity since it did not prolong the survival time of adrenalectomized rats nor did it favorably influence the rate of change of body weight in these animals. Furthermore, THC is an effective inhibitor of developing adjuvant-induced arthritis and suppresses further development of the established disease. The analgesic activity for THC is substantially greater than that for aspirin. The compound has no antipyretic activity at a dose producing profound anti-edema effects.

Recently, it has been shown that Δ^9-tetrahydrocannabinol (THC), the major psychoactive constituent of marihuana (Hollister, 1971; Isbell *et al.*, 1967; Mechoulam, 1970), protected red blood cells against hypotonic hemolysis (Chari-Bitron, 1971). This appears to be a manifestation of several highly lipid-soluble drugs including tranquilizers, antihistamines, local anesthetics and nonsteroidal anti-inflammatory agents (Catanese *et al.*, 1969; Inglot and Wolna, 1968; Seeman, 1966; Seeman and Weinstein, 1966). In addition to demonstrating marked lipophilic characteristics (Agurell *et al.*, 1969; Wahlqvist *et al.*, 1970), marihuana extract and THC possess tranquilizing (Hollister, 1971), antihistaminic (Dewey *et al.*, 1970b) and local anesthetic activity (Loewe, 1946; Mikuriya, 1969) in experimental animals. Moreover, Burstein and Raz (1972) have shown that THC inhibits biosynthesis of prostaglandins *in vitro*, a property shared by such anti-inflammatory drugs as aspirin and indomethacin (Vane, 1971). Although it has not yet been directly established that THC displays anti-edema properties, stimulation of the pituitary-adrenal system has been reported for systemically administered THC in rats measured by a dose-related increase in plasma corticosterone levels (Kubena *et al.*, 1971) and a potent stimulation of adrenocorticotropin secretion as shown by depletion of adrenal ascorbic acid concentration (Dewey *et al.*, 1970c). Moreover, Nahas (1973) states that one of the many uses prescribed for extracts of *Cannabis* by ancient Muslims was to cure "inflammation." Therefore, the

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purpose of this investigation was to study the anti-edema and analgesic potential of THC in laboratory animals.

Materials and Methods

Animals. Nonfasted, Charles River male CD rats (Sprague-Dawley strain) and male CD mice (Swiss strain) were used in the following experiments only after an acclimation period of at least four days to the laboratory environment had elapsed.

Drugs. All drugs and their vehicles were administered by the oral route. An earlier report (Sofia *et al.*, 1971a) gives details on the preparation, solubility and storage of THC. The vehicle for THC administration to rats was undiluted propylene glycol while a 10% propylene glycol-1% Tween 80–0.9% saline solution was used for mice (Sofia *et al.*, 1971b). Hydrocortisone and aspirin were suspended in a 1% acacia solution in a concentration such that 0.5 ml/100 g of rat or 0.1 ml/10 g of mouse was given for each desired dose. THC was prepared for injection to permit a volume of 0.1 ml/10 g and 100 g b.wt. to mice and rats, respectively. Control rats received the appropriate volume of vehicle.

Anti-Edema Activity

Carrageenan edema test. The basic experimental procedure used has been described previously (Winter *et al.*, 1962). One hour after drug administration to rats (90–120 g), 0.05 ml of a 1% solution of calcium carrageenan in saline was injected s.c. into the plantar surface of the right hind paw. The volume of the injected foot to the level of the lateral malleolus was measured by water displacement immediately before oral drug administration and again three hours after carrageenan injection. The difference between the two measurements was called edema volume. Drug effectiveness was analyzed in the following manner. Mean paw volumes, pre- and postdrug, were statistically compared using the Student's *t* test. The percent inhibition of edema volume was obtained from the ratio of the predrug volume to the postdrug volume. In addition, the number of rats at each dose level whose edema volume was at least 25% less than that of the mean for the vehicle-treated controls was also tallied. An ED50 value (95% confidence limits) was then calculated based on this all-or-none representation of the data (Litchfield and Wilcoxon, 1949).

The carrageenan edema test was also performed on bilaterally adrenalectomized rats obtained from the supplier five days after surgery. In addition, hypophysectomized rats that had undergone surgery 10 days earlier were used.

Adjuvant-induced arthritis. An arthritic-like disease was induced in rats (140–160 g) by a subplantar injection of 0.1 ml of a 5 mg/ml suspension of *Mycobacterium tuberculosis* (Difco Laboratories, Detroit, Mich.) in heavy mineral oil into the right hind paw (Newbould, 1963). Control hind paw volumes (right and left) and body weight were recorded prior to *M. tuberculosis* injection and at subsequent intervals thereafter to observe the development of the arthritis. Paw volumes were measured by water displacement. All drugs and their respective vehicles were administered daily beginning either on the day of adjuvant injection (prophylactic treatment) and continued for 14 days or beginning on the 14th day after adjuvant injection (therapeutic treatment) and continued for 14 additional days. Final paw volumes were recorded one hour after the last oral dose.

Analgesic Activity

Acetic acid-induced abdominal constriction. This method has been described earlier (Koster *et al.*, 1959). Twelve mice per dose level were used. Thirty minutes after oral drug administration 0.25 ml of a 0.5% acetic acid solution was injected i.p. The number of abdominal constrictions per animal in each group was counted for a five-minute period starting 10 minutes after injection of acetic acid. Activity was assessed by noting the number of drug-treated animals showing a 50% or greater reduction in the average number of abdominal constrictions of the respective vehicle-treated control group (Blumberg *et al.*, 1965). ED50 values were calculated based on this all-or-none response (Litchfield and Wilcoxon, 1949).

Haffner's tail pinch. Twenty-four hours before drug administration mice were tested for their response to application of an artery clip to the root of the tail (Bianchi and Franceschini, 1954). The time it took each animal to respond, *i.e.*, biting at the clip, was recorded by stopwatch to the nearest 0.1 second. Those animals not responding within five seconds were not used. On the test day good responders were divided into groups of eight mice each and given either the test drug or its corresponding vehicle. Thirty minutes later the artery clip was reapplied and reaction times again were recorded. The number of mice in each group that displayed a 40% or greater increase in reaction time from their respective predrug control value was noted and ED50 values were determined (Litchfield and Wilcoxon, 1949).

Hot plate test. This method for measuring analgesic activity is based on the reaction time of mice to lick their forepaws and or jump after exposure to a copper surface hot plate heated and maintained at 54–56°C (Eddy and Leimbach, 1953).

A control reaction time (to the nearest 0.1 second) was obtained 24 hours before any test for drug effect. Only those mice with a control reaction time of 10 seconds or less were used. On the test day mice were divided into groups of eight mice each and given the test drug or its vehicle. Thirty minutes later each mouse was re-exposed to the hot plate surface and the reaction time was recorded. The data were handled identically as described above for Haffner's tail pinch test.

Randall-Selitto paw pressure test. Increased sensitivity to a painful stimulus can be achieved by the subplantar injection of 0.1 ml of a 20% brewer's yeast suspension in distilled water into the right hind paw of a rat (Randall and Selitto, 1957). This increased sensitivity is susceptible to modification by known analgesic drugs. One hour after yeast injection test drugs were administered orally to rats (90–120 g). The pain threshold was meaured one hour after drug injection by applying a steadily increasing pressure of 14 g sec to the surface of the inflamed paw *via* a Teflon cone which was continuously monitored (Analgesy-Meter, Ugo Basile, Milan, Italy). The end point or pain threshold was defined as the pressure (in grams) necessary to cause the animals to struggle and or vocalize. Mean pain thresholds were calculated for each vehicle and drug-treated group. Rats in the drug-treated group having an individual reaction threshold (grams) equal to or exceeding the control group mean threshold by 2 standard deviations of that mean (Swingle *et al.*, 1971) were counted as showing a significant analgesic effect.

TABLE 1

Effect of THC, aspirin and hydrocortisone on carrageenan-induced edema in the rat hind paw

Treatment Group[a]	Oral Dose	Edema Volume (Mean ± S.E.)	% Inhibition	ED50 (95% Confidence Limits)
	mg/kg	*ml*		*mg/kg*
Propylene glycol		0.74 ± 0.08		
THC	2.5	0.74 ± 0.05	0	
	3.75	0.57 ± 0.02	23[b]	
	5.0	0.46 ± 0.04	38[b]	4.1
	10.0	0.44 ± 0.05	40[b]	(3.3–5.2)
	20.0	0.32 ± 0.05	57[b]	
	100.0	0.21 ± 0.04	72[b]	
1% acacia vehicle		0.70 ± 0.08		
Aspirin	50.0	0.64 ± 0.06	8	
	100.0	0.46 ± 0.04	35[b]	80.0
	200.0	0.36 ± 0.06	48[b]	(50.8–157.2)
Hydrocortisone	5.0	0.64 ± 0.10	8	
	10.0	0.41 ± 0.08	41[b]	7.0
	20.0	0.18 ± 0.03	74[b]	(3.8–13.0)

[a] $N = 8$ rats per treatment group.
[b] $P \leq .05$ when compared with respective vehicle-treated control group.

and ED50 values were calculated (Litchfield and Wilcoxon, 1949).

Antipyretic Activity

Yeast-induced fever test. Rectal temperatures were determined using a Yellow Springs Telethermometer and thermistor probe inserted a constant depth of 3.5 cm. On the day before drug administration, rats (150–200 g) were injected with 1 ml/100 g b.wt. s.c. of a 15% suspension of brewer's yeast and 1% acacia to produce fever (Smith and Hambourger, 1935). Eighteen hours later temperatures were once again taken and the animals were dosed with appropriate vehicle or drug. This temperature recording was designated the 0 hour reading. Additional temperature measurements were made two and four hours after drug administration. The effect of each drug and its vehicle on the rectal temperature of non-pyretic rats was also determined.

Results

Anti-Edema Activity

Carrageenan edema test. THC, aspirin and hydrocortisone were shown to be effective inhibitors of carrageenan-induced rat paw edema (table 1). THC given orally in doses of 3.75 mg/kg or more induced a significant dose-dependent inhibition of paw swelling. In this test, the anti-edema effects of 10 mg/kg of THC (40% inhibition), 200 mg/kg of aspirin (48% inhibition) and 10 mg/kg of hydrocortisone (41% inhibition) were approximately equal. Relative to aspirin (potency = 1), the estimated potencies of THC and hydrocortisone were similar at about 20. A similar relationship is evident when the ED50 values of each drug are compared.

Anti-carrageenan activity of THC was compared in intact, adrenalectomized and hypophysectomized rats to determine if the anti-inflammatory effect was mediated through stimulation of the pituitary-adrenal axis. The results (table 2) show the anti-edema activity of THC was markedly affected by both bilateral adrenalectomy and hypophysectomy. Only small and non-significant inhibition (8–19%) of edema formation was observed after doses of THC ranging from 20 to 100 mg/kg to adrenalectomized rats. Moreover, a similar pattern of activity was demonstrated in hypophysectomized rats, except that a significant anti-edema effect (27% inhibition) occurred after the highest THC dose tested, 100 mg/kg.

Daily treatment with THC (20.0 mg kg) or aspirin (300.0 mg kg) did not prolong the survival time of untreated adrenalectomized rats maintained on regular tap water (table 3). In fact, daily treatment with these compounds decreased the time to 100% mortality by three or four days when compared with the untreated or vehicle-treated adrenalectomized control group. By contrast, daily treatment with hydrocortisone, 20.0 mg kg day p.o., enabled all adrenalectomized rats to survive. The same general overall results were obtained when the rate of change of body weight was observed in this same experiment. Body weight gradually decreased until death in all treatment groups except with 20.0 mg kg of hydrocortisone. Animals in the latter group gained weight equally with the untreated normal group until day 6 or 7, at which time a plateau was reached.

TABLE 2

Effect of THC on carrageenan-induced hind paw edema in intact, adrenalectomized and hypophysectomized rats

Condition of Rats	THC Oral Dose	Edema Volume[a] (Mean ± S.E.)	% Inhibition
	mg/kg	*ml*	
Intact	Vehicle	0.74 ± 0.07	
	20	0.32 ± 0.05	57[b]
	100	0.21 ± 0.04	72[b]
Adrenalectomized	Vehicle	1.07 ± 0.08	
	20	0.98 ± 0.06	8
	40	0.92 ± 0.11	14
	100	0.87 ± 0.14	19
Hypophysectomized	Vehicle	0.73 ± 0.06	
	20	0.74 ± 0.05	0
	40	0.72 ± 0.09	1
	100	0.53 ± 0.05	27[b]

[a] $N = 6$ rats per treatment group.

[b] $P \leq .05$ when compared with respective vehicle-treated control group.

Adjuvant-induced arthritis. On day 14 in the prophylactic test THC, aspirin and hydrocortisone were shown to be effective inhibitors of developing adjuvant-induced polyarthritis in rats (table 4). Edema formation in both injected and uninjected paws was significantly reduced by all three drugs in a dose-related manner. However, a higher dose of THC was required to significantly reduce the volume of the uninjected paw. Another manifestation of adjuvant disease is a reduction of body weight gain. All arthritic groups whether administered the test drug or respective vehicle significantly ($P < .05$) inhibited body weight gain when compared with the untreated, nonarthritic control group. However, daily administration of 10.0 and 20.0 mg/kg of THC markedly reduced body weight gain to a greater extent ($P < .01$) than did the propylene glycol-treated arthritic control group. Body weight gain for all aspirin and hydrocortisone-treated arthritic groups did not differ significantly from their control. However, none of these groups gained weight at the same rate as the nonarthritic control group.

Table 5 gives details on the therapeutic effects of THC, aspirin and hydrocortisone in established adjuvant-induced polyarthritis. The mean change in paw volume from day 14 to day 28 was strikingly similar for both vehicle-treated ar-

TABLE 3

Effect of daily oral administration of THC, aspirin, hydrocortisone or their respective vehicles on the survival time of adrenalectomized rats

Treatment Group[a]	Daily Oral Dose	Number of Rats Dead on Day									
		1	2	3	4	5	6	7	8	9	10
	mg/kg										
Untreated normal		0	0	0	0	0	0	0	0	0	0
Untreated adrenalectomized		0	0	0	2	2	3	3	6	10	
Propylene glycol		0	0	0	1	2	2	5	7	9	10
THC	20.0	0	0	3	9	9	10				
1% acacia		0	0	0	2	3	3	7	8	10	
Aspirin	300.0	0	1	6	9	9	10				
Hydrocortisone	20.0	0	0	0	0	0	0	0	0	0	0

[a] $N = 10$ rats per treatment group.

TABLE 4

Effect of prophylactic treatment with THC, aspirin and hydrocortisone on adjuvant-induced polyarthritis in rats

Treatment Group[a]	Daily Oral Dose	Hind Paw Edema Volume (Mean ± S.E.)		14 Day Body Weight Gain (Mean ± S.E.)
		Injected	Uninjected	
	mg/kg	*ml*		*g*
Nonarthritic controls		0.27 ± 0.04	0.31 ± 0.04	98.5 ± 8.1
Arthritic controls (propylene glycol)		2.26 ± 0.20[b]	1.27 ± 0.26[b]	69.0 ± 7.1[b]
THC-treated arthritics	5.0	2.04 ± 0.13	0.99 ± 0.18	55.3 ± 4.2
	10.0	1.75 ± 0.11[c]	0.77 ± 0.16	49.1 ± 5.7[c]
	20.0	1.64 ± 0.17[c]	0.49 ± 0.15[c]	48.6 ± 6.1[c]
Arthritic controls (1% acacia)		1.83 ± 0.14[b]	1.16 ± 0.23[b]	72.1 ± 8.3[b]
Aspirin-treated arthritics	150.0	1.58 ± 0.10	0.79 ± 0.14	60.0 ± 7.0
	300.0	1.37 ± 0.15[c]	0.48 ± 0.18[c]	76.0 ± 7.4
Hydrocortisone-treated arthritics	5.0	1.76 ± 0.10	0.79 ± 0.11	58.3 ± 6.0
	10.0	1.40 ± 0.14[c]	0.49 ± 0.10[c]	70.1 ± 9.3
	20.0	1.11 ± 0.12[c]	0.29 ± 0.03[c]	72.2 ± 3.4

[a] $N = 9$ rats per treatment group.
[b] $P \leq .05$ when compared with the nonarthritic control group.
[c] $P \leq .05$ when compared with each respective vehicle-treated arthritic control group.

TABLE 5

Effect of therapeutic treatment with THC, aspirin and hydrocortisone on adjuvant-induced arthritis in rats

Treatment Group[a]	Daily[b] Oral Dose	Hind Paw Edema Volume Change (Mean ± S.E.,[c]		14 Day Body Weight Gain, Day 14-Day 28 (Mean ± S.E.)
		Injected	Uninjected	
	mg/kg	*ml*		*g*
Nonarthritic controls		0.31 ± 0.04	0.31 ± 0.03	117.1 ± 7.3
Arthritic controls (propylene glycol)		1.64 ± 0.48[d]	0.32 ± 0.05	91.7 ± 7.8[d]
THC-treated arthritics	20.0	0.05 ± 0.02[e]	0.01 ± 0.02[e]	56.2 ± 6.4[e]
Arthritic controls (1% acacia)		1.41 ± 0.37[d]	0.40 ± 0.07	93.8 ± 7.6[d]
Aspirin-treated arthritics	300.00	0.71 ± 0.21	0.52 ± 0.08	70.2 ± 6.8[e]
Hydrocortisone-treated arthritics	20.0	0.20 ± 0.09[e]	0.16 ± 0.08[e]	115.3 ± 8.1

[a] $N = 9$ rats per treatment group.
[b] Oral dosing commenced on day 14 after injection of *M. tuberculosis*.
[c] Difference between paw volumes on day 28 and day 14.
[d] $P \leq .05$ when compared with the untreated control group.
[e] $P \leq .05$ when compared with respective vehicle-treated groups.

thritic groups. The data clearly point out the effectiveness of daily administration of 20.0 mg/kg of THC in this test system to inhibit the progression of the disease since there was virtually no change in the volume of each hind paw. Aspirin (300 mg/kg), on the other hand, caused a 50% reduction in paw volume change of the injected hind paw. Since there was greater variability among both the aspirin and 1% acacia-treated groups, these data were significant only at the 10% level. However, aspirin did not significantly affect the volume of the uninjected paw. Like THC, hydrocortisone had a profound therapeutic effect on adjuvant arthritis resulting in 84 and 60% reductions in the volume of the injected and uninjected hind paws, respectively.

Once again, as in the prophylactic experiment (table 4), THC administration was shown to significantly reduce body weight gain beyond that of its vehicle-treated arthritic control group. In addition, aspirin was also without effect in reversing the retardation of body weight gain produced in adjuvant arthritis. However, hydrocortisone-treated arthritic rats gained weight similarly to the nonarthritic control group.

Analgesic Activity

Acetic acid-induced abdominal constriction. THC was the most potent drug tested with an ED50 of 11.6 mg/kg (table 6). Next in potency were aspirin and hydrocortisone with ED50 values of 113.0 and >200.0 mg/kg, respectively. Hence, the potency of THC was 10 times that of aspirin and much greater than hydrocortisone.

Haffner's tail pinch. THC produced highly significant and dose-related analgesia in this test with an ED50 of 11.6 mg/kg (table 6). No analgesia was observed in mice treated with aspirin or hydrocortisone, 300.0 and 200.0 mg/kg, respectively.

Hot plate test. Table 6 reveals that only THC was effective in increasing mean reaction time to exposure to the painful stimulus, *i.e.*, heat. The response was dose-related resulting in an ED50 of 10.3 mg/kg.

Randall-Selitto test. Further evidence for the highly effective analgesic action of THC can be seen in table 6 when its ED50 value is compared with that obtained for aspirin, 0.9 and 230.0 mg/kg, respectively. Hydrocortisone was ineffective in this test system.

Table 7 shows the results of experiments in which pain thresholds of both the yeast-injected and uninjected left hind paws were determined. Both THC (0.5–16.0 mg/kg) and aspirin (125.0–500.0 mg/kg) significantly increased the pain threshold of the injected hind paw. Only after the two highest doses (8.0 and 16.0 mg/kg) of THC was the pain threshold of the contralateral uninjected hind paw significantly elevated. None of the doses of aspirin tested reliably increased the pain threshold in the uninjected paw, but a trend was observed in that direction.

Table 8 illustrates clearly the fact that the analgesic activity of either THC or aspirin is not due to an anti-inflammatory action of these compounds. When edema volume produced by intraplantar injection of yeast as outlined for the Randall-Selitto test was measured, neither THC nor aspirin significantly affected the response.

Antipyretic Activity

Yeast-induced fever. When administered an oral dose which did not affect rectal temperature in nonpyretic rats (20 mg/kg), THC failed to reduce rectal temperatures in fevered rats (table 9). On the other hand, aspirin at 100 mg/kg reduced fever at both two and four hours after administration. At the latter time interval rectal temperature had returned to control level (nonpyretic untreated control). This dose of aspirin did not alter rectal temperatures in nonpyretic rats.

Discussion

THC appears capable of inhibiting acute edema formation as demonstrated in the carrageenan edema test, an effect approximately equal to hydrocortisone, but 20 times greater

TABLE 6

Comparative analgesic effectiveness of THC, aspirin and hydrocortisone in mice and rats using four different models of experimentally induced pain

Test Compound[a]	ED50 (=95% Confidence Limits)			
	Acetic acid-induced abdominal constriction	Haffner's tail pinch	Hot plate	Randall-Selitto paw pressure
	mg/kg			
THC	11.6 (7.9–17.1)	11.6 (6.4–21.0)	10.3 (6.8–15.7)	0.9 (0.4–1.9)
Aspirin	113.0 (71.5–178.8)	>300.0	>300.0	230.0 (136.9–386.0)
Hydrocortisone	>200.0	>200.0	>200.0	>300.0

[a] $N = 8$ to 12 animals per dose (at least three doses of each compound were used to determine ED50 values).

TABLE 7

Effect of THC and aspirin on pain threshold of both injected and uninjected hind paws of rats using the Randall-Selitto paw pressure test

Treatment Group[a]	Oral Dose	Pain Threshold (Mean ± S.E.)			
		Injected paw		Uninjected paw	
		Pain threshold	% increase	Pain threshold	% increase
	mg/kg	*g*		*g*	
Propylene glycol		75.5 ± 3.7		109.0 ± 6.9	
THC	0.5	97.8 ± 5.6	30[b]	112.9 ± 8.9	3
	1.0	114.7 ± 10.1	52[b]	124.9 ± 12.5	14
	4.0	143.1 ± 14.3	90[b]	132.6 ± 19.2	22
	8.0	169.7 ± 15.3	125[b]	141.3 ± 10.0	30[b]
	16.0	204.3 ± 7.4	169[b]	188.6 ± 11.1	73[b]
1% acacia		70.9 ± 2.8		87.1 ± 3.8	
Aspirin	125.0	90.5 ± 7.4	28[b]	82.8 ± 4.5	−5
	250.0	93.0 ± 6.1	31[b]	93.8 ± 7.0	8
	500.0	101.9 ± 6.8	44[b]	100.3 ± 6.4	15

[a] $N = 8$ rats per treatment group.
[b] $P \leq .05$ when compared with respective vehicle-treated control group.

TABLE 8

Effect of THC, aspirin and hydrocortisone on yeast-induced edema in rats produced in the Randall-Selitto test

Treatment Group[a]	Oral Dose	Edema Volume (Mean ± S.E.)	% Change in Mean Edema Volume[b]
	mg/kg	*ml*	
Propylene glycol		1.35 ± 0.06	
THC	20.0	1.44 ± 0.06	+6.8
1% acacia		1.40 ± 0.06	
Aspirin	300.0	1.47 ± 0.06	+5.0

[a] $N = 6$ rats per treatment group.
[b] Based on a comparison between a drug-treated group and its respective control group.

than aspirin. However, this activity was shown to be mediated through adrenal activation since the anti-edema activity observed in intact rats was markedly attenuated in bilaterally adrenalectomized and in hypophysectomized rats. These data suggest a central rather than a peripheral activation of the pituitary-adrenal axis since removal of the hypophysis (adrenals intact) markedly altered the anti-carrageenan activity of THC. Since it has been shown that THC markedly increases plasma corticosterone levels (Kubena *et al.*, 1971) and decreases adrenal ascorbic acid concentration (Dewey *et al.*, 1970c), it is not surprising that the anti-edema activity of this compound is exerted through adrenal activation. Moreover, the proposed mechanism of central mediation is also corroborated by a diminution of the plasma corticosterone elevating activity in hypophysectomized rats after THC adminis-

TABLE 9

Effect of THC, aspirin and hydrocortisone on brewer's yeast-induced pyresis in rats

Rat Condition and Treatment Group[a]	Oral Dose	Postdrug Rectal Temperature (Mean ± S.E.)		
		0 hr	2 hr	4 hr
	mg/kg	*°C*		
Nonpyretic				
Untreated control		36.7 ± 0.1	36.5 ± 0.1	36.7 ± 0.1
Propylene glycol control		36.7 ± 0.2	36.6 ± 0.1	36.7 ± 0.1
THC	20.0	36.8 ± 0.2	36.9 ± 0.2	36.7 ± 0.1
1% acacia		36.8 ± 0.1	36.7 ± 0.1	36.8 ± 0.1
Aspirin	100.0	36.6 ± 0.1	36.6 ± 0.2	36.6 ± 0.1
Pyretic				
Yeast control		38.3 ± 0.2[b]	38.4 ± 0.2[b]	38.3 ± 0.1[b]
Propylene glycol control		38.1 ± 0.1	38.2 ± 0.1	38.2 ± 0.1
THC	20.0	38.2 ± 0.2	38.1 ± 0.1	38.1 ± 0.1
1% acacia		38.3 ± 0.1	38.2 ± 0.1	38.2 ± 0.2
Aspirin	100.0	38.2 ± 0.1	37.3 ± 0.1[c]	36.8 ± 0.1[c]

[a] $N = 7$ rats per group.
[b] $P < .001$ when compared with the nonpyretic untreated control group.
[c] $P < .001$ when compared with respective 0 hour rectal temperature.

tration (Kubena *et al.*, 1971). However, the inability of THC to maintain life in adrenalectomized rats shows that it is devoid of corticosteroid-like activity. On the contrary, it is quite possible that THC and aspirin act as stressors since both significantly decreased the time to death in adrenalectomized rats.

The prophylactic activity exhibited by THC in adjuvant-induced arthritis was intermediate in activity to that produced by hydrocortisone and aspirin. Not only was a dose of 20 mg/kg of THC beneficial in treating developing arthritis, it was also of therapeutic value since it completely retarded the progression of inflammation associated with the established disease. In contrast, 300 mg/kg of aspirin did not markedly affect the established arthritis. Unlike aspirin or hydrocortisone, THC markedly potentiated the reduction in body weight gain associated with both adjuvant test systems. Indirectly, it is possible the effect on body weight, at least in part, may have been responsible for the effectiveness observed in adjuvant-induced arthritis. However, it seems unlikely that the reduction of paw volume in the carrageenan edema test may be a consequence of weight loss or retardation of body weight gain since it is an acute experiment and completed over a span of four hours. When given acutely, it has been reported that THC decreases food consumption (Sofia and Barry, 1972). Furthermore, Manning *et al.* (1971) showed decreases in both food consumption and body weight gain after chronic administration of THC. Various stressors such as exposure to cold (Glenn and Gray, 1965) and malnutrition (Taylor *et al.*, 1967) have been shown to suppress the inflammatory process.

Another matter of concern is the specificity of the analgesic and anti-edema effects of THC. These activities cannot be explained by complete abolition of locomotor activity and general central nervous system depression. Although some degree of depression of spontaneous locomotor activity was apparent in the THC-treated animals (particularly doses of 5.0 mg/kg or greater), all animals demonstrated some spontaneous and evoked locomotor activity. These observations corroborate the findings of Kubena and Barry (1970), who found that spontaneous activity of rats was unaffected by acute administration of 4.0 mg/kg and significantly but not completely suppressed by 16.0 mg/kg of THC given i.p. Moreover, chronic administration of 50 mg/kg of THC for 119 consecutive days produced tolerance to several behavioral parameters such as disruption of conditional avoidance responding and spontaneous locomotor activity, with the latter significantly increasing following depression after the initial doses (Thompson *et al.*, 1971). Likewise, Manning *et al.* (1971) reported tolerance to many of the behavioral effects of THC developed rapidly in rats, *i.e.*, within 2 to 10 days after oral administration of 8.0 mg/kg daily.

THC showed marked analgesic activity in commonly used methods including chemical (acetic acid-induced abdominal constriction and Randall-Selitto test), mechanical (Haffner's tail pinch) and thermal (hot plate) stimuli. Aspirin and to a lesser extent hydrocortisone were effective against only the chemical stimuli. These data seem to suggest the analgesic activity of THC is exerted centrally rather than peripherally.

Both THC and aspirin displayed analgesic activity, with the former having an oral ED50 of 0.9 mg/kg and the latter 230.0 mg/kg to elevate pain threshold in the yeast-injected hind paw. However, only THC significantly increased pain threshold in the uninjected hind foot, a profile similar to that observed for morphine (Winter and Flataker, 1965). This latter effect occurred after 8.0 and 16.0 mg/kg of THC which was 16 to 32 times greater than the dose (0.5 mg/kg) necessary to produce an equal elevation of the pain threshold in the injected paw.

Neither THC nor aspirin when given therapeutically was able to reduce the already established yeast-induced edema produced as outlined for the Randall-Selitto test (table 8). These data suggest that the analgesic effectiveness of THC is independent of its anti-inflammatory action, *i.e.*, the increase in pain threshold is not related to a decreased paw volume and consequently decreased sensitivity to painful stimuli. Further evidence to support this comes from the results of the present investigation as well as from several experiments (Bicher and Mechoulam, 1968; Buxbaum *et al.*, 1969; Dewey *et al.*, 1970a, 1972) which demonstrated analgesic activity for THC in the abdominal constriction, hot plate and tail pinch procedures in which anti-inflammatory drugs like aspirin are ineffective.

THC was devoid of antipyretic activity at a dose (20.0 mg/kg) which produced profound anti-inflammatory activity. Moreover, the fever-

reducing ability already established for aspirin was corroborated in this study.

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