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ANTIPYRETIC, ANALGESIC AND ANTI-INFLAMMATORY EFFECTS OF Δ^9-TETRAHYDROCANNABINOL IN THE RAT

Donald S. KOSERSKY[1], William L. DEWEY[2] and Louis S. HARRIS[2]
Department of Pharmacology, School of Medicine,
University of North Carolina, Chapel Hill, North Carolina 27514, U.S.A.

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The effects on body temperature produced by graded doses of Δ^9-tetrahydrocannabinol (Δ^9-THC) and phenylbutazone were compared in both normal and pyretic rats. Dose related hypothermic responses were produced by the oral administration of Δ^9-THC in normal animals. Moreover, Δ^9-THC significantly reduced elevated temperatures in yeast-induced pyretic rats to near normal levels at doses which exhibited little hypothermic activity in normal rats. The oral antipyretic potency of Δ^9-THC was approximately 2 times that of phenylbutazone. The comparative oral antinociceptive activity of Δ^9-THC and selected narcotic and non-narcotic analgesics was determined by the increase in response latency to pressure applied to normal and yeast-inflamed paws. Δ^9-THC administered orally was essentially inactive at dose levels below those producing pronounced central nervous system depression. The oral anti-inflammatory efficacy of Δ^9-THC was compared to phenylbutazone and acetylsalicylic acid. Δ^9-THC was ineffective in inhibiting carrageenin-induced edema of the rat paw following acute or chronic administration.

Δ^9-Tetrahydrocannabinol Antipyretic activity Analgesic activity Anti-inflammatory activity

1. Introduction

Prior to the introduction of numerous synthetic drugs into western medicine, various preparations derived from cannabis were frequently employed for therapeutic purposes. Among its numerous and diverse applications, cannabis was used principally for its analgesic and sedative properties. Although these same properties are incorporated into most clinically employed anti-inflammatory drugs, no reports evaluating the anti-inflammatory actions of cannabis derivatives have appeared in the current literature. The present studies were undertaken to investigate l-Δ^9-*trans*-tetrahydrocannabinol (Δ^9-THC), recognized as the major active component of cannabis, for possible anti-inflammatory and related pharmacologic activity. A preliminary account of the data has been presented (Kosersky, 1973).

2. Materials and methods

2.1. Yeast-induced pyrexia

The antipyretic efficacy of Δ^9-THC was determined by methods described by Smith and Hambourger (1935). Pyrexia was induced in male Sprague–Dawley rats weighing 200–250 g by the s.c. injection of a 20% dried brewer's yeast suspension in 0.9% NaCl (1 ml/100 g body weight). Rectal temperature measurements were made with a telethermometer attached to a thermistor probe inserted to a constant depth of 5.5 cm. Ambient laboratory temperature was maintained at 23 ± 0.1°C throughout the experiments. Rectal temperatures were recorded prior to yeast injection and 16 hr later. Animals not showing a minimal rise

[1] Present address: Department of Pharmacology, College of Pharmacy, Northeastern University, Boston, Massachusetts 02115. U.S.A.
[2] Present address: Department of Pharmacology, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia 23219, U.S.A.

of 1.0°C at this time were eliminated from the study. 12 or more animals per dose level were used. Graded doses of phenylbutazone and Δ^9-THC, suspended in 5% bovine serum albumin, were administered orally in a dosage volume of 10 ml/kg to both febrile and non-febrile groups of rats which had been food-deprived from the time of yeast injection. Following drug treatment rectal temperatures were recorded hourly for 3 hr. Control group animals received only the required dosage volume of albumin vehicle.

2.2. Yeast-induced rat paw hyperesthesia

The antinociceptive properties of Δ^9-THC were compared to selected analgesic reference compounds using an adaptation of the method of Randall and Selitto (1957) as modified by Gilfoil et al. (1963). Male Sprague–Dawley rats weighing 50–80 g were divided into groups of 6 animals each and deprived of food for 16 hr prior to testing. A 0.1 ml volume of a 10% aqueous suspension of brewer's yeast was injected into the subplantar region of each rat's right hind paw. 1 hr following yeast injection test drugs, suspended or dissolved in 5% bovine serum albumin, were administered orally to each animal in a dosage volume of 5 ml/kg. Reaction thresholds to pressure were measured 2 hr after drug administration. Each rat was held in a prone position so that its hind legs extended over the edge of a small platform. A rounded steel tip (1 mm) attached to the plunger of a 20 ml glass syringe was brought in contact with the plantar surface of the paw. Air pressure, supplied through an electrically activated solenoid valve, was regulated so that a constant pressure rise of 10 mm Hg/sec was maintained until the animal reacted vocally by a sharp 'squeak' or until the cut off pressure of 110 mm Hg was attained. The threshold pressure necessary to elicit vocalization was recorded by means of a Statham pressure transducer coupled to a Grass polygraph.

In a second series of experiments 0.05 ml of a 1% carrageenin suspension was substituted for yeast as the phlogistic agent. In this study graded doses of Δ^9-THC were injected p.o. once daily to groups of rats for 7 consecutive days. The final dose of Δ^9-THC was administered on day 7, 1 hr following carrageenin injection and the reaction threshold responses determined 2 hr later as described above.

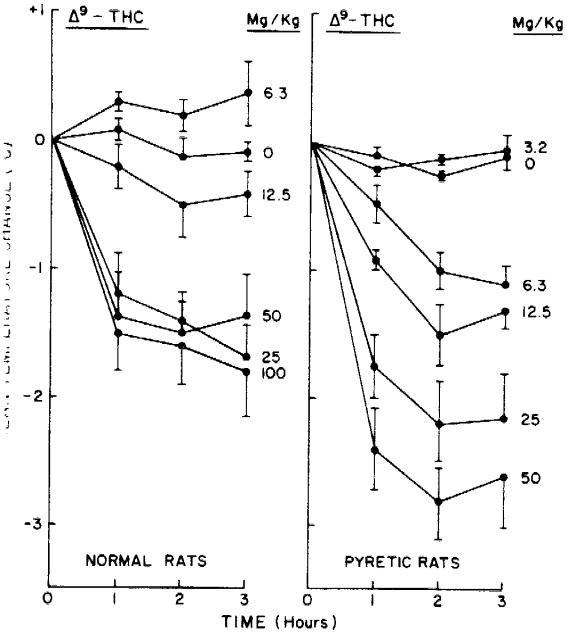
2.3. Carrageenin-induced edema

Male Sprague–Dawley rats weighing approximately 175 g were divided into experimental groups of 6 animals and deprived of food for 16 hr prior to use. Edema was induced by the subplantar injection into the right hind paw of 0.05 ml of a 1% carrageenin suspension in sterile 0.9% NaCl. The standard reference compounds phenylbutazone and acetylsalicylic acid as well as Δ^9-THC were suspended in 5% bovine serum albumin and administered by gastric intubation in a volume of 0.5 ml per 100 g body weight. Drugs were administered orally 1 hr preceding carrageenin injection. Control group animals received only the albumin vehicle. Paw volume determinations were made immediately following carrageenin injection and again 3 hr later according to methods described by Winter et al. (1963). Both injected and contralateral paw volumes were determined plethysmographically by immersing each paw into a cylinder containing mercury to an ink line across the lateral malleolus. The resulting change in pressure was measured with a Statham pressure transducer coupled to and recorded by a Grass polygraph. Volume displacement was calibrated by periodically introducing a graduated aluminum rod into the mercury-containing vessel. The

Table 1
Comparative oral antipyretic activity of Δ^9-tetrahydrocannabinol and phenylbutazone in the rat.

Drug treatment	Dose (mg/kg, p.o.)	n[a]	Body temperature change (°C) (mean ± S.E.M.)	
			Induced rise	2 hr after drug
Δ^9-Tetrahydrocannabinol	0	18	+1.2±0.15	−0.1±0.04
	3.2	18	+1.1±0.07	−0.2±0.04
	6.3	18	+1.0±0.11	−1.0±0.15[c]
	12.5	12	+1.0±0.08	−1.5±0.24[c]
	25	12	+1.3±0.03	−2.2±0.34[c]
	50	12	+1.1±0.13	−2.8±0.31[c]
Phenylbutazone	0	12	+1.2±0.06	−0.2±0.06
	12.5	12	+1.2±0.06	−0.4±0.10
	25	12	+1.0±0.10	−0.9±0.26[b]
	50	12	+1.1±0.13	−1.8±0.24[c]
	100	12	+1.0±0.11	−2.1±0.38[c]

[a] n, number of rats.
[b] $p<0.01$.
[c] $p<0.001$.



ig. 1. Changes in body temperature induced by oral admin-tration of Δ^9-tetrahydrocannabinol in normal and pyretic .ts. Each point represents the mean body temperature ıange (± S.E.M.) of groups of 12 or 18 animals.

'stem was equilibrated to atmospheric pressure im-ediately prior to each series of measurements.

In a second experiment graded doses of Δ^9-THC ere administered p.o. once daily to groups of rats)r 7 successive days. Carrageenin was injected on day 1 hr after the final Δ^9-THC treatment. Paw volumes ere measured immediately following and again 3 hr ter carrageenin injection in the same manner as out-ıed above.

Results

1. Yeast-induced pyrexia

The effects on body temperature produced by aded doses of phenylbutazone and Δ^9-THC were)mpared in both normal and pyretic rats. The rela-ve antipyretic efficacy for each compound was de-rmined 2 hr after oral administration during the me of peak drug effect (table 1). Significant changes ı body temperature (Student's *t*-test for unpaired observations) were produced by both agents, the oral antipyretic potency of Δ^9-THC being approximately 2 times that of phenylbutazone. Δ^9-THC also produced dose-related hypothermic response in normal (non-pyretic) rats. However, dose levels of Δ^9-THC (6.3–12.5 mg/kg) which produced only small and inconsistent changes in normal rats, significantly reduced the elevated body temperatures of pyretic rats to near normal levels (fig. 1).

3.2. Yeast-induced rat-paw hyperesthesia

The comparative oral antinociceptive efficacy of Δ^9-THC in increasing the threshold response latency to pressure applied to normal and yeast-inflamed paws is shown in table 2. All of the compounds tested significantly increased the threshold response when administered in adequate dosage. The order of potency for the clinically-used analgesic agents was found to be consistent with the results of other investigators (Takesue et al., 1969; Roszkowski et al., 1971; Greindl and Preat, 1971). As would be expected, relatively low doses of the centrally acting analgesics methadone and d-propoxyphene raised response thresholds in both normal and inflamed paws. On the other hand, phenylbutazone and acetylsalicylic acid, which probably act through peripheral mechanisms, effectively raised the reaction threshold in inflamed paws, but produced little effect in normal (non-inflamed) paws at the dose levels tested. In contrast to these effects, Δ^9-THC was essentially devoid of antinociceptive activity except at elevated doses which produced a marked catatonic-like state. At this dose level Δ^9-THC (100 mg/kg) significantly increased the threshold response in both normal and inflamed feet suggesting an antinociceptive mechanism different from the other compounds tested.

Similar results were obtained in the second experiment in which carrageenin was substituted for yeast as the phlogistic agent. After 7 daily oral injections Δ^9-THC significantly raised the threshold response in inflamed paws only at the highest dose level tested (100 mg/kg).

3.3. Carrageenin-induced edema

Table 3 summarizes the comparative anti-inflammatory activity produced by Δ^9-THC, phenylbuta-

Table 2
Comparative oral antinociceptive activity of Δ^9-tetrahydrocannabinol in the rat.

Drug treatment	Dose (mg/kg, p.o.)	Reaction threshold		p[a] (10 dF)
		Normal foot (mm Hg ± S.E.M.)	Inflamed foot (mm Hg ± S.E.M.)	
Δ^9-THC	0	79 ± 7.1	53 ± 5.9	–
	6.25	85 ± 7.7	56 ± 12.1	N.S.
	12.5	84 ± 5.4	68 ± 10.5	N.S.
	25	72 ± 6.2	50 ± 10.8	N.S.
	50	77 ± 7.6	56 ± 7.1	N.S.
	100	95 ± 4.9[b]	96 ± 7.2	< 0.01
Phenylbutazone	0	75 ± 7.6	33 ± 6.5	–
	100	78 ± 6.2	44 ± 6.9	N.S.
	200	68 ± 5.9	52 ± 7.4	< 0.05
	400	78 ± 5.7	63 ± 7.9	< 0.01
Acetylsalicylic acid	0	75 ± 7.6	33 ± 6.5	–
	100	72 ± 5.7	39 ± 8.7	N.S.
	200	73 ± 8.3	45 ± 11.1	N.S.
	400	79 ± 8.9	53 ± 7.1	< 0.05
d-Propoxyphene · HCl	0	76 ± 10.4	35 ± 8.9	–
	12.5	78 ± 5.9	49 ± 6.4	N.S.
	25	72 ± 9.8	71 ± 5.8	< 0.01
	50	102 ± 2.2[b]	89 ± 5.9	< 0.001
Methadone	0	76 ± 10.4	35 ± 8.9	–
	12.5	78 ± 5.9	69 ± 5.6	< 0.01
	25	97 ± 2.1[b]	79 ± 6.3	< 0.01
	50	105 ± 0.9[b]	96 ± 10.4	< 0.01
Δ^9-THC[c]	0	84 ± 6.8	58 ± 6.1	–
	25	85 ± 8.3	66 ± 5.7	N.S.
	50	78 ± 5.6	54 ± 8.7	N.S.
	100	91 ± 9.6	79 ± 7.6	< 0.05

[a] Compared with respective inflamed foot control group.
[b] Significantly different ($p < 0.05$) from respective normal foot control group.
[c] Animals treated once daily for 7 successive days prior to testing.

zone and acetylsalicylic acid in reducing carrageenin-induced edema of the rat paw. Effective dose-related anti-edema effects were elicited by both nonsteroidal reference compounds, the relative potency of phenylbutazone being approximately 2 times that of acetylsalicylic acid. Δ^9-THC, however, at all dose levels tested, was totally ineffective in reducing or preventing the edematous response. Moreover, Δ^9-THC failed to inhibit inflammatory edema induced in rats after repeated daily treatment (7 days) with the compound.

4. Discussion

The hypothermic response to cannabis and its d
rivatives has been noted in numerous reports and e
tends across several species including man (Mira
1965; Holtzman et al., 1969; Garattini, 1965; Wa
kow et al., 1970; Lomax and Campbell, 1971; Abel
al., 1972). The results presented in this paper furth
demonstrate that orally administered Δ^9-THC pro
uces dose-related hypothermic actions in the ra
However, the most important finding in the prese

Table 3
Inhibition of carrageenin-induced paw edema.

Treatment	Dose (mg/kg, p.o.)	Edema volume (ml ± S.E.M.)	Inhibition (%)	p (10 dF)
Δ^9-THC	0	0.84 ± 0.02	–	–
	25	0.86 ± 0.03	0	–
	50	0.89 ± 0.02	0	–
	100	0.84 ± 0.04	0	–
	200	0.79 ± 0.06	6	N.S.
Phenyl-butazone	0	0.84 ± 0.02	–	–
	25	0.68 ± 0.03	19	< 0.01
	50	0.63 ± 0.04	25	< 0.01
	100	0.48 ± 0.02	43	< 0.01
Acetyl-salicylic acid	0	0.84 ± 0.02	–	–
	50	0.71 ± 0.03	15	< 0.01
	100	0.64 ± 0.02	24	< 0.01
	200	0.44 ± 0.06	48	< 0.01
Δ^9-THC[a]	0	0.78 ± 0.05	–	–
	25	0.84 ± 0.06	0	–
	50	0.72 ± 0.03	8	N.S.
	100	0.76 ± 0.06	3	N.S.

[a] Animals treated once daily for 7 successive days prior to testing.

study is that Δ^9-THC is an effective antipyretic agent in rats with an acute oral potency exceeding that of phenylbutazone. Of further significance is the demonstration that Δ^9-THC effectively reduces the body temperature of febrile rats at dose levels which have little effect on normal body temperature (fig. 1, 6.3–12.5 mg/kg) and which produce no apparent behavioral effects. Although the antipyretic actions of phenylbutazone are generally considered to be mediated by central mechanisms similar to those of the salicylates, no direct evidence for a central site of antipyretic action for Δ^9-THC is provided in the present study. Accordingly, the antipyretic effects produced by relatively low doses of Δ^9-THC may be due in part to non-specific peripheral effects such as vasodilatation, as suggested by Beaconsfield et al. (1972). Cannabis has been utilized as a febrifuge in the folk medicine of Argentina (Manfred, 1947). In this regard, further investigations concerning the therapeutic usefulness of Δ^9-THC in the treatment of hyperpyrexia in man seem warranted.

Several reports have appeared in the literature pertaining to the analgesic activity produced by cannabis derivatives in laboratory animals. The results obtained in these studies, however, have been inconsistent and often contradictory. Our findings indicate that Δ^9-THC is essentially devoid of antinociceptive activity in the rat at dose levels below those which produce other pronounced central depressant effects.

Bicher and Mechoulam (1968) reported the analgesic effects produced by Δ^9-THC (20 mg/kg, i.p.) in mice as being comparable to those of morphine sulfate (10 mg/kg) in the writhing, hot plate and tail-flick tests. Buxbaum (1972) found Δ^9-THC to be equipotent to morphine when administered intraperitoneally to rats in both the hot plate and tail-flick tests. However, utilizing the same testing procedures Sofia and Barry (1972) determined Δ^9-THC to be $\frac{1}{2}-\frac{1}{3}$ as potent as morphine in mice and only $\frac{1}{8}$ as potent as morphine in rats.

In contrast to these reports Davies et al. (1946) were unable to produce analgesia in rats (tail-flick) by i.v. injection of hashish distillate and Scheckel et al. (1968) failed to produce analgesic effects in squirrel monkeys with doses of Δ^9-THC that produced pronounced behavioral aberrations. Moreover, Dewey et al. (1969) reported that Δ^9-THC administered i.v. or orally was essentially inactive in the hot plate and tail flick procedures in both mice and rats.

The wide divergence in the reported analgesic activity of Δ^9-THC may be due, in part, to differences in rates of absorption and metabolism in different animal species and strains. Accordingly, Ho et al. (1971) have demonstrated that tritiated Δ^9-THC injected i.p. in rats remains in the abdominal cavity with little absorption or distribution to other tissues. Nonspecific irritant effects may also account for the variability in the reported analgesic activity of Δ^9-THC when different routes of administration are employed. Of particular significance in this regard are the findings of Manning et al. (1971) and Sodetz (1972). These investigators have clearly demonstrated that Δ^9-THC, like other phenolic compounds, produces severe irritation and inflammation of the peritoneum in rats after i.p. injection. However, because of the relative water insolubility of Δ^9-THC this route of administration is favored by many investigators. The toxicological consequences of these irritant effects have important behavioral and pharmacological implications since responses to nociceptive stimuli are significantly modified by other stimuli simultaneously perceived

(Beecher, 1957). Noteworthy in this regard are the findings of Winter and Flataker (1965) concerning the effects produced by irritants in various analgesic testing procedures. The results of their experiments demonstrate that irritant or inflammatory substances injected i.p. into rats yield dose related analgesic-like effects which are similar, in all respects, to the centrally mediated antinociceptive effects produced by clinically proven analgesic compounds. Accordingly, the failure of Δ^9-THC to produce antinociceptive activity after oral or i.v. administration would suggest that the reported analgesia produced by Δ^9-THC following parenteral injection may be due to non-specific irritative actions of the compound.

Inflammatory edema induced by carrageenin provides a rapid and sensitive means for evaluating non-steroidal anti-inflammatory agents. Moreover, a high empirical correlation exists between the activity of drugs in this test and their anti-inflammatory activity in man (Kampmann and Frey, 1966). The results of the present investigation indicate a complete lack of activity for Δ^9-THC in this model of inflammation and do not lend support to a body of folk medicine reporting the use of cannabis as an effective anti-inflammatory agent (Mikuriya, 1969; Kabelik et al., 1960). It is important to note, however, that apart from Δ^9-THC cannabis contains numerous other active components which separately or in combination may produce significant anti-inflammatory activity.

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