Psychopharmacologia (Berl.) 40, 285–295 (1975)

Comparative Analgesic Activity of Various Naturally Occurring Cannabinoids in Mice and Rats

R. Duane Sofia, Heidi B. Vassar, and Linda C. Knobloch

Wallace Laboratories, Department of Pharmacology and Toxicology
Cranbury, New Jersey

Received May 24, 1974; Final Version November 22, 1974

Abstract. The analgesic effectiveness of Δ^9-tetrahydrocannabinol (THC), a crude marihuana extract (CME), cannabinol (CBN), cannabidiol (CBD), morphine SO^4 and aspirin following oral administration was directly compared in mice using the acetic-induced writhing and hot plate tests and the Randall-Selitto paw pressure test in rats. THC and morphine were equipotent in all tests except that morphine was significantly more potent in elevating pain threshold in the uninflamed rat hind paw. In terms of THC content, CME was nearly equipotent in the hot plate and Randall-Selitto tests, but was 3 times more potent in the acetic acid writhing test. On the other hand, CBN, like aspirin, was only effective in reducing writhing frequency in mice (3 times more potent than aspirin) and raising pain threshold of the inflamed hind paw of the rat (equipotent with aspirin). CBD did not display a significantly analgesic effect in any of the test systems used. The results of this investigation seem to suggest that both THC and CME possess narcotic-like analgesic activity similar to morphine, while CBN appears to be a non-narcotic type analgesic like aspirin.

Key words: Δ^9-Tetrahydrocannabinol (THC) — Analgesic — Crude Marihuana Extract (CME) — Narcotic-Like — Cannabinol (CBN) — Non-Narcotic-Like — Cannabidiol (CBD).

A variety of pharmacological activities has been ascribed to *Cannabis* and its constituents following their administration to laboratory animals (Paton and Pertwee, 1973). However, one of the most pronounced effects of Δ^9-tetrahydrocannabinol[1] (THC), the major psychoactive constituent of marihuana (Burstein, 1973), is its analgesic activity, which has been demonstrated in the mouse, rat, rabbit and dog by several investigators (Bicher and Mechoulam, 1968; Scheckel *et al.*, 1968; Dewey *et al.*, 1972; Buxbaum, 1972; Sofia *et al.*, 1973; Chesher *et al.*, 1973; Kaymakcalan *et al.*, 1974).

Two other major components of *Cannabis*, which were shown to be "psycho-inactive" (Mechoulam, 1970), are cannabidiol (CBD) and cannabinol (CBN). Recently, however, many pharmacological properties of

[1] An alternative to this formal numbering for the same compound is the monoterpenoid numbering, Δ^1-tetrahydrocannabinol.

CBD and CBN have been revealed which are shared by THC. Layman and Milton (1971) have demonstrated an inhibitory effect of the "resting" release of acetylcholine *in vitro* from cholinergic nerve endings for CBD like that observed for THC. Raz *et al.* (1972) have found that *in vitro* both THC and CBD reversibly stabilized human erythrocytes against hypotonic hemolysis suggesting a possible anti-edema action. Results of *in vivo* experiments (Sofia *et al.*, 1973) verify an anti-edema action for THC, CBD and CBN in rats. Like THC (Sofia *et al.*, 1971) both CBD and CBN have been shown to exhibit significant anticonvulsant activity in mice and rats (Karler *et al.*, 1973; Izquierdo *et al.*, 1973). Finally, a reduction in spontaneous locomotor activity was observed following administration of CBN to mice (Welch *et al.*, 1971).

Therefore, because of this recent description of various activities for CBD and CBN, the purpose of the present investigation was to determine whether or not these agents possess significant narcotic or non-narcotic-like analgesic activity over a wide range of doses in mice and rats using chemical or thermal stimuli to induce pain and if so, how each compared to the THC effect. In addition to THC, CBD and CBN, a crude marihuana extract (CME) was also studied. For comparison, the narcotic and non-narcotic analgesic agents morphine SO_4 and aspirin, respectively, were included in this investigation.

Materials and Methods

Animals. Non-fasted, Charles River male CD rats (Sprague-Dawley strain) weighing 100 to 120 g and male CD mice (Swiss strain) weighing 18 to 26 g were used in the following experiments only after an acclimation period of at least 4 days to the laboratory environment had elapsed.

Drugs. All drugs and their vehicles were administered by the oral route. An earlier report by Sofia *et al.* (1971) gives details on the preparation, solubility and storage of THC. These same procedures apply to CME, CBN and CBD. Total cannabinoid content of CME was 21.1% with the individual content as follows: THC 16.0%, CBD 2.9% and CBN 2.2%. This analysis was carried out for the National Institute of Drug Abuse by the Research Triangle Institute. The only other component of CME that was assayed for was Δ^8-THC and none was detected. The vehicle for administration of each of these cannabinoids to rats was undiluted propylene glycol, while a 10% propylene—1% Tween 80—0.9% saline vehicle was used for mice (Sofia *et al.*, 1971, 1974). All cannabinoids were soluble in undiluted propylene glycol except CME, which was an evenly dispersed suspension. Likewise, each cannabinoid was administered to mice as a finely dispersed suspension. Each cannabinoid was prepared in such a concentration that 0.1 ml per 10 g and 100 g of body weight of mice and rats, respectively, was given for each desired dose. Morphine SO_4 (prepared as the salt) was dissolved, while aspirin was suspended in a 1% gum acacia vehicle and the desired dose of each was administered to mice in a volume of 0.1 ml per 10 g and rats, 0.5 ml per 100 g of body weight. Control animals received the appropriate volume of vehicle.

Acetic Acid-Induced Writhing (Chemical). This method basically is the one described earlier by Koster *et al.* (1959). Eight mice were used at each dose level.

30 min after oral drug administration 0.25 ml of a 0.5% acetic acid solution was given to each mouse intraperitoneally. The number of writhes (abdominal constrictions) per animal in each group was counted for a 5-min period beginning 10 min after injection of the acetic acid. Mean writhing frequency scores were calculated for each vehicle and drug-treated group and the percent change (from control) determined. In addition, activity was assessed by noting the number of drug-treated animals in each group that resulted in a 50% or greater reduction from the average number of writhes of the vehicle-treated group (Blumberg *et al.*, 1965). ED_{50} values were calculated based on this all-or-none response (Litchfield and Wilcoxon, 1949).

Hot Plate Test (Thermal). 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 sec) for each mouse was obtained 24 hrs before any test for drug effect. Only those mice with a control reaction time of 10.0 sec or less were used. On the test day, these mice were divided into groups of 8 each and given drug or vehicle orally. 30 min later each mouse was re-exposed to the hot plate surface and the reaction time determined with a cutoff of 20.0 sec. Mean pre-drug and post-drug reaction times and percent change were calculated. Thus, each mouse served as its own control. In addition, the number of mice in each drug group that displayed a 40%, or greater increase in reaction time from their pre-drug control value was noted and ED_{50} values determined (Litchfield and Wilcoxon, 1949).

Randall-Selitto Paw Pressure Test (Chemical). Increased sensitivity to a painful stimulus was achieved by subplantar injection of 0.1 ml of a 20% brewer's yeast suspension in distilled water into the right hind paw of the rat (Randall and Selitto, 1957). 1 hr after yeast injection test drugs or vehicle were administered orally. Pain threshold in both the injected (right) and uninjected (left) hind paws was measured 1 hr after drug administration or 2 hrs after yeast injection by applying a steadily increasing pressure of 14 g/sec to the surface of the inflamed then uninflamed paws via a teflon cone which was continuously monitored (Analgesy-Meter®, UgoBasile, Milan, Italy). The end point or pain threshold was defined as that pressure (in grams) necessary to cause the animals to struggle and/or vocalize. Mean pain thresholds and percent change were calculated for each drug-treated and vehicle-treated group. Those rats in each drug-treated group having an individual reaction threshold equal to or exceeding the control group mean threshold by 2 standard deviations of that mean (Swingle *et al.*, 1971) were designated as showing a significant analgesic effect, and ED_{50} values were calculated (Litchfield and Wilcoxon, 1949).

Results

Acetic Acid-Induced Writhing. The comparative effect of each cannabinoid, morphine and aspirin on writhing frequency in mice is depicted graphically in Fig. 1. From these data it is quite apparent that the slopes of the THC and morphine dose-response curves are comparable although the latter is somewhat shifted to the left. However, at doses of 5.0 and 10.0 mg/kg, the analgesic effectiveness of THC and morphine do not differ significantly from each other. Thus, in the acetic acid writhing test morphine is only slightly more potent than THC at best. Fig. 1 also reveals that CME and aspirin each produced dose-dependent reductions in writhing frequency, while the former was more potent on a mg/kg

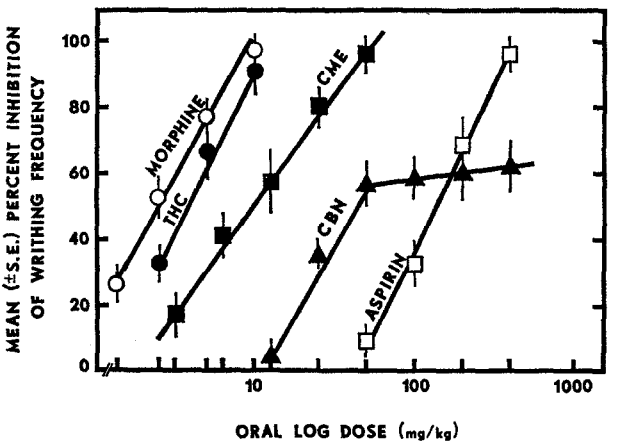

Fig. 1. Comparative analgesic activity of various cannabinoids, morphine and aspirin in the acetic acid-induced writhing test in mice

basis. Likewise, the inhibitory activity of CBN against acetic acid-induced writhing was linear and dose-related between oral doses of 12.5 and 50.0 mg/kg. However, even when the dose of CBN was increased to 400.0 mg/kg no greater inhibition of writhing frequency (approximately 60%) could be achieved, which is indicative of a threshold effect. On the other hand, a 90% or greater inhibition of the writhing syndrome was observed following 10.0 mg/kg of either THC or morphine, 50.0 mg/kg of CME and 400.0 mg/kg of aspirin. In addition, the lowest dose of each drug to produce a significant ($P < 0.05$) analgesic effect was: morphine 1.25 mg/kg, THC 2.5 mg/kg, CME 6.25 mg/kg, CBN 25.0 mg/kg and aspirin 100.0 mg/kg.

CBD did not significantly alter the writhing frequency after an oral dose as high as 400.0 mg/kg, which proved lethal to one of the eight mice dosed. Likewise, neither the vehicle for the cannabinoids nor that for morphine and aspirin were effective inhibitors of acetic acid-induced writhing.

Based on calculated ED_{50} values (Table 1) the order of analgesic potency in the mouse acetic acid writhing test is: morphine = THC > CME > CBN > aspirin > (CBD, inactive).

Hot Plate Test. THC, CME and morphine all exhibited dose-dependent analgesic activity in this test (Fig. 2). Although all these dose-response curves were parallel, indicating the magnitude of effect was similar for each substance, their mg/kg potency differed substantially. Fig. 2 reveals that the curve for morphine was shifted slightly to the left of that for THC. Although comparison of the slopes of each straight line of regression

Table 1. Comparative ED_{50} values for the analgesic effectiveness of THC, CME, CBN, CBD, morphine SO_4 and aspirin in mice and rats in three models of experimentally induced pain

Test compound	Oral ED_{50} ($\pm$ 95% Confidence limits), mg/kg[a]			
	Acetic acid-induced writhing (mice)	Hot plate test (mice)	Randall-Selitto paw pressure test (rats)	
			Injected paw	Uninjected paw
THC	4.2 (2.5—7.1)	7.7 (4.9—12.2)	4.0 (2.0—8.0)	32.0 (17.9—57.3)
CME	8.8 (4.1—18.9)	53.0 (28.2—99.6)	35.5 (22.2—56.8)	224.0 (148.0—338.0)
CBN	35.0 (19.1—64.5)	> 400.0*	148.0 (59.7—367.4)	> 320.0
CBD	> 400.0*	> 400.0**	> 320.0	> 320.0
Morphine SO_4	2.9 (1.2—3.8)	4.0 (2.1—10.1)	5.1 (2.4—10.7)	7.5 (3.8—15.0)
Aspirin	130.0 (82.3—205.5)	> 800.0	200.0 (111.0—360.0)	> 800.0

[a] These values were based on the all-or-non representation of the data as described in the "Materials and Methods" section of this paper.

* 1, ** 2 mice died within a 30-min interval following oral dosing.

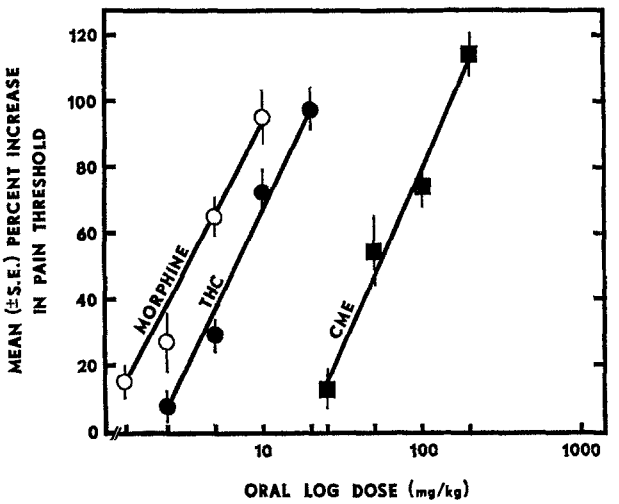

Fig. 2. Comparative analgesic activity of THC, CME and morphine in the hot plate test in mice

(Goldstein, 1964) revealed no statistically significant difference between the two drugs, a 2-factor analysis of variance resulted in an F value of 25.4 which was highly significant ($P < 0.001$). On the other hand, the CME curve was markedly shifted to the right of the THC dose-response curve. The dose of each drug producing approximately a 100% increase in pain threshold was 10.0, 20.0 and 150.0 mg/kg of morphine, THC and CME, respectively, while the lowest dose of the same drugs to produce significant analgesic activity was 2.5, 5.0 and 50.0 mg/kg.

Like the 2 vehicles, neither CBN, CBD nor aspirin were active in the hot plate test following oral doses as high as 400.0 mg/kg for each cannabinoid and 800.0 mg/kg for aspirin. At these high doses one mouse died 25 min following CBN administration, while 2 mice died approximately 15 min after CBD.

Table 1 reveals that the order of potency for those drugs active in the mouse hot plate test is quite similar to what resulted in the acetic acid writhing test, *i.e.*, morphine = THC > CME > (CBN, CBD or aspirin, all inactive).

Randall-Selitto Paw Pressure Test. Further evidence for the varying degree of analgesic effectiveness of each of these test substances can be seen in Fig. 3. Panels a and b of Fig. 3 reveal that both THC and CME, respectively, significantly increased pain threshold in both the injected (black bars) and uninjected rat hind paws (white bars) in a dose-related fashion. The magnitude of effect for this activity was quite similar for

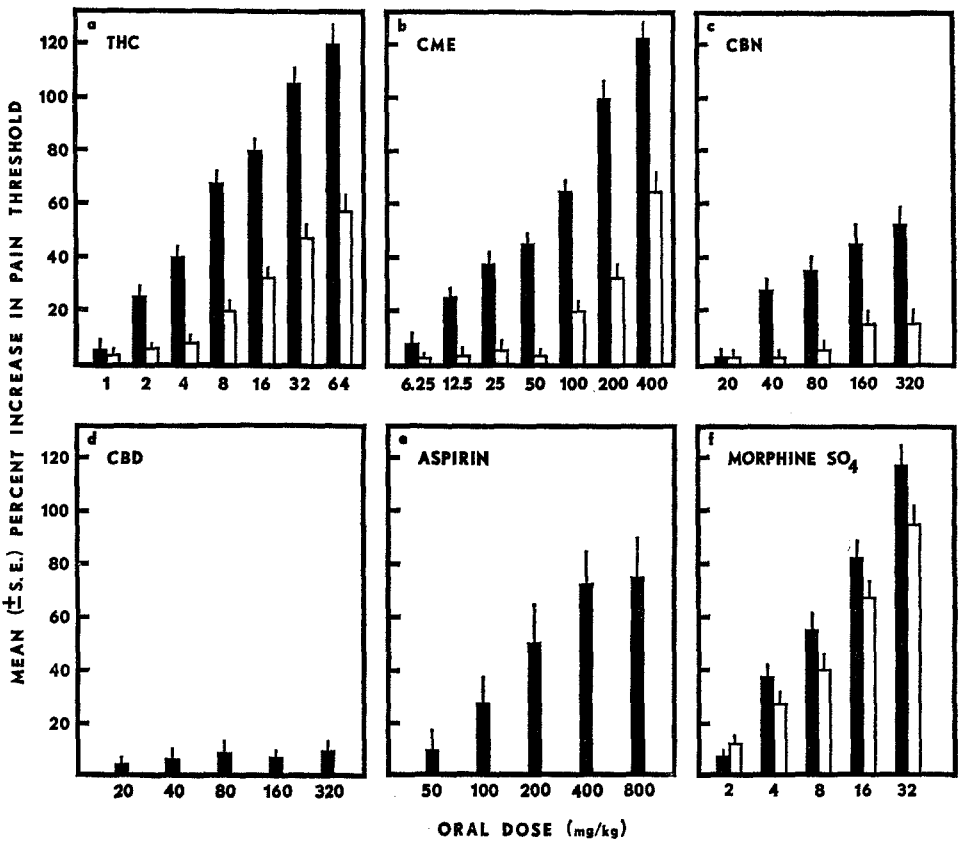

Fig. 3. Comparative analgesic activity of various cannabinoids, morphine and aspirin in the Randall-Selitto paw pressure test in rats. Black bars indicate pain threshold of the injected hind paw, while white bars denote the same measurement in the uninjected hind paw

each substance; however, on a mg/kg basis THC was significantly more potent. The lowest dose of each drug to significantly raise pain threshold in the injected paw was 2.0 and 12.5 mg/kg for THC and CME respectively, while in the uninjected paw these values were significantly greater, *i.e.*, 8.0 and 100.0 mg/kg. Hence, the analgesic effects of THC and CME were more pronounced on the injected paw in terms of mg/kg potency and magnitude of effect. The pattern of activity in the rat paw pressure test observed following oral administration of the narcotic analgesic morphine (panel *f*, Fig.3) was somewhat different from that of THC and CME. Indeed, morphine produced significant and dose-related analgesic activity in both the injected and contralateral uninjected rat hind paws;

however, the effect of morphine to raise pain threshold of either paw was nearly the same in both mg/kg potency and magnitude of effect. In fact, the only dose at which the degree of analgesia was significantly greater ($P < 0.05$) was 32.0 mg/kg in the injected paw. Moreover, the lowest oral dose of morphine required to produce a significant elevation in pain threshold of either paw was 4.0 mg/kg.

On the other hand, Fig. 3 reveals that the pattern of effect for both CBN (panel *c*) and aspirin (panel *e*) on pain threshold in the paw pressure test was similar. Each of these agents significantly increased the pain threshold of the uninjected paw. However, increasing the dose of CBN beyond 160.0 mg/kg and aspirin above 400.0 mg/kg did not elevate the magnitude of the analgesic activity. A significant effect ($P < 0.05$), however, was obtained following doses as low as 40.0 and 100.0 mg/kg for CBN and aspirin, respectively. None of the doses of CBN or aspirin used in this investigation significantly increased pain threshold in the uninjected paw. Although not shown in Fig. 3 (panel *e*), aspirin produced a slight but not significant hyperalgesic response in the uninjected paw following both the 400.0 and 800.0 mg/kg dose.

Finally, CBD (Fig. 3, panel *d*) had no reliable analgesic effect in the rat injected hind paw at oral doses as high as 320 mg/kg. Similar to aspirin and not shown in Fig. 3, CBD produced a slight hyperalgesic response in the uninjected hind paw following the highest dose studied.

In this model of experimentally-induced pain in the rat the order of potency to elevate pain threshold in the injected hind paw was as follows: morphine = THC > CME > CBN = aspirin > (CBD, inactive). Analgesic activity in the uninjected hind paw was observed according to the order of potency, morphine > THC > CME > (CBN = CBD = aspirin, all inactive).

Discussion

In the present experiments we have confirmed the analgesic activity of THC following oral administration to mice and rats (Bicher and Mechoulam, 1968; Dewey *et al.*, 1972; Buxbaum, 1972; Sofia *et al.*, 1973; Chesher *et al.*, 1973) using a variety of laboratory models. In addition, the magnitude of the effect of THC was dose-dependent in all tests as were those displayed by morphine. Similarly, the analgesic dose-response curves for THC were parallel to those for morphine and these two agents were equipotent in the acetic acid writhing test in mice (Fig. 1, Table 1) and decreasing sensitivity to painful stimuli in the yeast-inflamed hind paw of the rat (Fig. 3, Table 1). On the other hand, morphine was significantly more potent than THC in the hot plate test in mice (Fig. 2, Table 1) and raising pain threshold in the uninjected hind paw of rats (Fig. 3, Table 1). Unlike Buxbaum (1972) who reported non-parallelism

for the dose-response curves of THC and morphine, our results agree more closely to the data obtained by Bicher and Mechoulam (1968) and more recently Chesher *et al.* (1973).

CME also produced excellent dose-dependent analgesic activity in each of the three models of experimentally-induced pain (Fig. 1—3). Moreover, the slopes of each of these dose-response curves paralleled those of THC and morphine. CME had approximately 48, 15, 13 and 14% the potency of THC in the acetic acid-induced writhing test, the hot plate test and pain threshold in injected and uninjected hind paw in the Randall-Selitto test, respectively (Table 1). However, in terms of THC present (16%) in CME, this extract was approximately equipotent in the hot plate and Randall-Selitto tests, but was three times more potent in the acetic acid-induced writhing test. It seems highly unlikely that the small amount of CBN present in CME (2.2%) could account for this observation since a similar potency relationship would have been expected in the other tests. However, it is quite possible that this more potent effect of CME against acetic acid-induced writhing in mice might be due to constituents in the CME other than the cannabinoids (21.1%). Recently, Segelman *et al.* (1974) have shown that an aqueous extract of marihuana which was cannabinoid-free did possess pharmacological activity similar but less potent than THC.

Our investigation has shown CBN to be an effective analgesic in the acetic acid writhing test. However, this activity was dose-related only to a dose of 50.0 mg/kg (Fig. 1). Beyond this dose level, the magnitude of analgesia produced by CBN was not changed, suggesting a ceiling effect. However, CBN is approximately one-tenth as potent as morphine and THC, but four times more potent than aspirin in this test (Table 1). CBN like aspirin was only effective in elevating pain threshold of the injected hind paw in the Randall-Selitto test. Winter and Flataker (1965) have shown that the narcotic-like analgesics will significantly increase pain threshold in both hind paws, whereas the non-narcotic analgesics will be effective only in injected hind paws. In addition, in our hands CBN was ineffective against thermally-induced pain (hot plate test) at a dose which proved lethal. This finding is in contradiction to the effectiveness of CBN in the hot plate test reported by Chesher *et al.* (1973) who obtained an oral ED_{50} of 32.5 mg/kg. This difference in results might be due to the fact that 1) these investigators used an acetate salt of CBN and/or 2) they waited 60 min following oral dosing to test for activity. Irrespective of these differences, our data support the contention that CBN may be a non-narcotic type analgesic similar to aspirin since both are selectively effective against chemically-induced experimental pain.

Finally, CBD was devoid of significant analgesic activity in each of these models of pain even when the oral dose was increased to 400.0 mg/kg,

which proved fatal to some mice and 320.0 mg/kg in the rat. This observation corroborates the ineffectiveness of CBD in the hot plate test as reported by Karniol and Carlini (1973). However, these investigators only tested a single 20.0 mg/kg I.P. dose of this cannabinoid.

Acknowledgement. The authors wish to thank the Biomedical Research Branch, Division of Research, National Institute of Drug Abuse for the generous supply of THC, CME, CBN and CBD.

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Dr. R. Duane Sofia
Wallace Laboratories
Department of Pharmacology
and Toxicology
Cranbury, N.J. 08512
U.S.A.