and abundance of microfilaments in these zones. The cell membranes were, however, closely apposed and no alterations were seen in junctions other than desmosomes. In the remaining material among the livers of 35 patients receiving no MTX, detached desmosomes were noted only in one (hyperlipoproteinemia). However, the association between mitochondria and microfilaments of structurally unaltered desmosomes has been readily observed in the MTX-treated (figures 2 and 3) as well as untreated groups. The findings indicate that detachment of desmosomal plaques is a rare junctional abnormality; that, however, is rather prevalent in the liver tissue of MTX-treated psoriatic subjects. Direct contact between mitochondria and filaments of separated desmosomes was considerably more frequent than in that of normal maculae adhaerentes of the human liver. The association of mitochondria with desmosomes is commonly noticeable in certain normal[5] and abnormal[6] tissues, suggesting that mitochondria actively participate in the formation and/or function of adhaerent junctions. Since fine structural evidence of mitochondrial injury is commonly found in the liver cells of MTX-treated subjects, it is reasonable to suppose that mitochondrial function is also impaired. MTX is known to interfere with nucleic acid metabolism[7]. In addition to nuclear DNA and RNA, the mitochondrial genetic material may also be a target of this toxic effect possibly resulting in quantitative and qualitative changes of the synthesis of mitochondrial nucleic acids and proteins. The relation of mitochondrial injury to the structural and possibly functional alterations of desmosomal attachments remains to be elucidated.

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A cannabinoid with cardiovascular activity but no overt behavioral effects[1]

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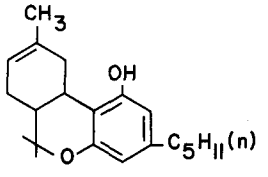
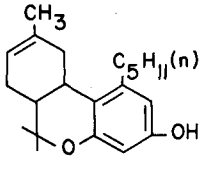
Summary. Abnormal-Δ^8-tetrahydrocannabinol (ABN-Δ^8-THC) failed to elicit central nervous system and cardiovascular effects in laboratory animals. Abnormal-cannabidiol (ABN-CBD) was also devoid of overt behavioral effects but produced marked hypotension with only slight bradycardia in anesthesized dogs.

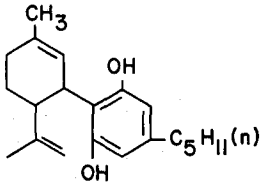
A number of naturally-occurring constituents of marihuana, including cannabidiol (CBD), Δ^8-tetrahydrocannabinol (Δ^8-THC) and Δ^9-tetrahydrocannabinol (Δ^9-THC) have been tested for their ability to produce cannabis-like pharmacological effects. The latter 2 compounds have been found to be the primary psychoactive compounds while CBD is much less active as a behavioral agent. Synthesis and testing of analogues of these naturally-occurring compounds has provided information regarding the structural requirements for cannabinoid activity. In a recent review of the literature, Mechoulam et al.[4] presented a summary of structure-activity relationships which showed the importance of a free phenolic group and an alkyl side chain for behavioral activity (figure). To determine whether the positions of these groups were relevant for pharmacological activity, ABN-Δ^8-THC and ABN-CBD were synthesized according to a recently reported procedure[5,6]. These novel analogs differed from the natural cannabinoids in that the phenolic hydroxyl group was transposed with the pentyl sidechain (figure). The purpose of the present study was to evaluate these abnormal compounds for cannabinoid activity.



Δ^8 - THC



ABNORMAL - Δ^8 - THC



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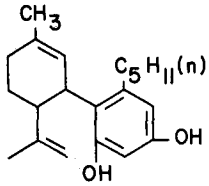

ABNORMAL CANNABIDIOL

Methods. The ability of these compounds to produce static ataxia (an effect unique to psychoactive cannabinoids) and other characteristic behavioral effects was examined in mongrel dogs of either sex (8–12 kg). The effects of cannabinoids on behavior, semiquantitated as previously described by Martin et al.[7], were observed for 30 min following i.v. administration. 3 observers independently rated the behavior of each dog, and the means of the maximum scores were recorded.

The effects of cannabinoids on spontaneous motor activity were assessed in Swiss-Webster mice (Dublin Farms, 20–25 g) after an i.p. injection of either vehicle or drug. 90 min after the injection mice were placed in photocell activity chambers (2 mice per chamber), and after a 10-min-orientation total counts were obtained for a 15-min-period. Uncorrelated sample means were compared statistically by applying Student's t-test. Cardiovascular

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experiments were conducted with pentobarbitol-anesthetized dogs of either sex (6–11 kg). Each animal received an i.v. injection (left femoral vein) of vehicle 30 min prior to the administration of a single dose of a cannabinoid. Blood pressure and heart rate were recorded 1, 3, 5, 15, 30, 45 and 60 min after drug administration. The vehicle for all cannabinoids was a mixture of Emulphor (EL-620, GAF Corporation), ethanol and saline[8]. 100 mg of drug was dissolved in 1 ml of a 1:1 mixture of Emulphor and ethanol. Proper dilutions were made with normal saline.

Results. Δ^8-THC produced classical cannabinoid behavioral effects (static ataxia, hyperreflexia, etc.) in the dogs at doses as low as 0.4 mg/kg. ABN-Δ^8-THC was tested at 2, 4 and 10 mg/kg and failed to elicit characteristic cannabinoid activity though the animals shied away each time they were approached by an investigator. When administered at doses of 0.1 mg/kg and 0.5 mg/kg, ABN-CBD produced no observable behavioral changes. CBD and ABN-CBD at doses of 2 or 10 mg/kg also failed to induce static ataxia and other manifestations of cannabinoid behavioral effects in dogs. CBD and ABN-CBD did cause some depression of activity at 2 mg/kg and produced profound sedation and apparent muscle relaxation associated with prostration at the higher dose. The vehicle produced no noticeable behavioral effects at any of the doses.

Δ^8-THC produced a reduction of spontaneous activity in mice at 2.5, 5 and 10 mg/kg. These results agree with data reported previously from our laboratory[7], as well as that from others[9]. Abnormal Δ^8-THC, CBD and ABN-CBD did not cause a significant reduction in spontaneous activity at doses of 2.5, 5, 10 or 20 mg/kg.

In the anesthetized dog, ABN-CBD produced marked hypotension that appeared to be dose-related and similar in magnitude to the hypotension produced by Δ^8-THC (table). The depressor activity of ABN-CBD was more rapid in onset than that of Δ^8-THC (peak effect at 1–3 min vs 10–20 min) and had a shorter duration (20–30 min as opposed to $>$ 60 min). At a dose of 0.5 mg/kg, the hypotensive effect of ABN-CBD was associated with an unaltered heart rate (table). The same dose of Δ^8-THC has been shown to produce similar hypotension associated with bradycardia[10]. This difference in the actions of ABN-CBD and Δ^8-THC on heart rate is also indicated in the table where it can be seen that 2.0 mg/kg of Δ^8-THC produced a significantly greater reduction in heart rate than an equal dose of ABN-CBD even though the hypotensive effects of the cannabinoids were similar. Neither ABN-Δ^8-THC nor CBD significantly altered blood pressure at a dose of 2 mg/kg even though CBD produced a slight but significant bradycardia (table).

Cardiovascular effects of cannabinoids in the anesthetized dog

Treatment	N	Dose (mg/kg)	Maximum percent change Mean arterial pressure*	Heart rate
Vehicle	4	–	0.5 ± 1.6	1.4 ± 3.0
ABN-CBD	4	0.5	−38.4 ± 13.4**	− 4.4 ± 7.5
Vehicle	12	–	− 8.4 ± 4.8 ***	3.4 ± 4.0
ABN-Δ^8-THC	3	2.0	−12.0 ± 4.0	− 7.4 ± 7.4
CBD	3	2.0	−12.8 ± 0.9	−12.6 ± 4.1
ABN-CBD	3	2.0	−64.2 ± 5.7	−19.4 ± 3.9
Δ^8-THC	3	2.0	−51.6 ± 2.8	−43.7 ± 4.1

The dogs were anesthetized with sodium pentobarbitol (30 mg/kg, i.v.). Arterial pressure was recorded from the left femoral artery, and heart rate was obtained from surface EKG recording using needle electrodes. The left femoral vein was cannulated to allow i.v. administration of drugs. Each animal received an i.v. injection of vehicle, equivalent to the amount contained in the corresponding drug doses, 30 min prior to the administration of a single dose of cannabinoid. In 43% of the animals, the initial injection of vehicle produced a profound decrease in mean arterial pressure, wheezing and urticaria that was apparently due to a mast-cell histamine release. This response subsided within 30 min and a second injection of vehicle at that time was devoid of activity. In these animals, the second injection of vehicle served as the control for subsequent injection of cannabinoid. *Mean arterial pressure = diastolic pressure + $^1/_3$ (systolic pressure–diastolic pressure). **Significantly different from vehicle (Student's t-test; $p < 0.001$). ***Values not included within the same bracket differ significantly from each other (Duncan's Multiple Range test; $p < 0.05$).

Cannabidiol (CBD), as previously reported[15], was found to be inactive in the behavioral testing procedures. This naturally-occurring cannabinoid did produce a slight decrease in heart rate but did not alter blood pressure. ABN-CBD also failed to produce classical cannabinoid behavioral effects. However, ABN-CBD was found to be as potent as Δ^8-THC in decreasing blood pressure. Thus, it would appear that the relative positions of the phenolic hydroxyl and pentyl side chain are less specific for cardiovascular activity than for CNS activity with the structural requirement varying depending on whether a compound is a congener of a tetrahydrocannabinol or cannabidiol.

Discussion. The dog static ataxia test has long been considered a relatively specific behavioral model for compounds having cannabis-like activity in man[11]. In addition to this activity, psychoactive cannabinoids have been demonstrated to suppress spontaneous motor activity in rodents[9] and produce bradycardia and hypotension in anesthetized dogs[12–14]. In the present study, the transposition of the hydroxyl and pentyl groups in the phenyl ring of Δ^8-THC resulted in a compound (ABN-Δ^8-THC) which was inactive in all 3 of the above paradigms. These data show that both the presence of these functional groups as well as their positions on the phenyl ring are requirements for cannabinoid activity.

The cardiovascular effects of cannabinoids have been attributed to central nervous system actions resulting in a reduction in peripheral sympathetic activity and enhancement of vagal tone[12, 13, 16]. While it may be possible that ABN-CBD is acting through a similar mechanism, its cardiovascular actions are different from Δ^8-THC in that its effects on heart rate are much less. The present study is the first to describe a cannabinoid with cardiovascular actions which lacks overt behavioral effects. ABN-CBD may be of interest as a potential hypotensive agent since it has only a slight effect on heart rate and appears not to cause behavioral changes.

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