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SUBACUTE CANNABINOID TREATMENT: ANTICONVULSANT ACTIVITY AND WITHDRAWAL EXCITABILITY IN MICE

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1 The effects of subacute treatment with cannabidiol, Δ^9-tetrahydrocannabinol (Δ^9-THC), phenytoin and phenobarbitone on anticonvulsant activity and on withdrawal excitability in mice were compared in three electrically induced seizure-threshold tests.

2 In the maximal electroshock-threshold test, subacute treatment did not alter the anticonvulsant activity of cannabidiol, phenytoin or phenobarbitone, but tolerance developed to Δ^9-THC.

3 In the 60 Hz electroshock-threshold test, the activity of Δ^9-THC and cannabidiol did not change, but tolerance developed to phenobarbitone, and there was an increase in sensitivity to phenytoin.

4 In the 6 Hz electroshock-threshold test, there was an increase in sensitivity to both Δ^9-THC and cannabidiol, there was tolerance to phenobarbitone, while the activity of phenytoin did not change.

5 Although tolerance developed in some of the seizure-threshold tests to Δ^9-THC and phenobarbitone, tolerance to cannabidiol and phenytoin did not develop in any of the tests.

6 Hyperexcitability followed withdrawal from only Δ^9-THC (6 Hz and 60 Hz electroshock-threshold tests) and phenobarbitone (maximal electroshock-threshold and 60 Hz electroshock-threshold tests).

7 The Δ^9-THC withdrawal hyperexcitability suggests that the use of marihauana may jeopardize the control of seizures in epileptics.

Introduction

Although the anticonvulsant activity of marihuana derivatives in laboratory animals has been extensively documented (Loewe & Goodman, 1947; Garriott, Forney, Hughes & Richards, 1968; Karler, Cely & Turkanis, 1973; 1974a, b, c, d; Karler & Turkanis, 1976a, b), the work of Fried & McIntyre (1973) and Karler *et al.* (1974a, c) has shown that tolerance develops to the anticonvulsant effects of Δ^9-tetrahydrocannabinol (Δ^9-THC) and suggests that the antiepileptic potential of the cannabinoids may be limited. A subsequent study in which the maximal electroshock test was used demonstrated that Δ^9-THC and cannabidiol tolerance in mice is indistinguishable from that of the well-established antiepileptic agents, phenytoin and phenobarbitone (Karler *et al.*, 1974c). Previously reported data from our laboratory indicated that cannabinoid tolerance is not due to changes in drug disposition but is associated rather with a central nervous system (CNS) adaptation (Karler *et al.*, 1974c; Karler & Turkanis, 1976a). However, a central mechanism raises the possibility that tolerance may not develop to all of the anticonvulsant effects of the cannabinoids. The goal of the present research, therefore, was to define the influence of subacute Δ^9-THC and cannabidiol treatment relative to phenytoin and phenobarbitone on a variety of antiseizure tests, including the maximal electroshock-threshold, the 6 Hz electroshock-threshold and the 60 Hz electroshock-threshold.

An additional aim was to assess the potential of cannabinoids for producing a withdrawal CNS hyperexcitability. The CNS excitatory properties of Δ^9-THC are well documented, e.g., in rats and mice (Karler *et al.*, 1974a; Turkanis, Chiu, Borys & Karler, 1977), in epileptic beagles (Feeney, Spiker & Weiss, 1976) and in a unique strain of rabbits (Martin & Consroe, 1976); but the cannabinoids are also central depressants (Hollister, 1971); the latter property suggests that abrupt withdrawal may increase CNS excitability (Wikler & Essig, 1970). If withdrawal from marihuana does, in fact, cause a rebound CNS hyperexcitability, then such a reaction may jeopardize seizure control in epileptics; therefore, marihuana use by epileptics may be contraindicated. In the present study, the withdrawal of both Δ^9-THC and cannabidiol was evaluated by means of electroshock thresh-

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olds because these threshold values, in the absence of spontaneous convulsions, yield quantitative measures of CNS excitability.

Methods

Experimental animals and design

The experiments were carried out on 4 to 5 week-old male, Charles River (ICR) mice. The doses employed were the intraperitoneal anticonvulsant dose$_{50}$ (ED_{50}) values as measured in the maximal electroshock test (Karler *et al.*, 1974a; Turkanis, Cely, Olsen & Karler, 1974): Δ^9-THC, 100 mg/kg daily; cannabidiol, 120 mg/kg daily; phenytoin 9 mg/kg daily; phenobarbitone, 12 mg/kg daily. The 3 or 4 day duration for the tolerance experiments was selected because at these specific times we have previously shown that daily treatments with ED_{50}s of the four drugs listed above completely abolished protection against maximal electroshock (Karler *et al.*, 1974c). In the withdrawal studies, a group of 75 to 100 mice was treated once daily for 3 consecutive days with cannabidiol, phenytoin or phenobarbitone, or for only 2 days with Δ^9-THC; in each drug study a control group of 75 to 100 mice received vehicle once daily. Twenty-four h after the last treatment, vehicle- and drug-treated groups of mice were subjected to a seizure test in order to determine their median-effective electroshock thresholds (Finney, 1971).

In each tolerance study, 3 groups of 75 to 100 mice were given daily doses of drug or vehicle for either 3 or 4 consecutive days: The control group received vehicle each day; the single-treatment group received drug only on the last treatment day and vehicle on the others; the subacute-treatment group received drug each day. The duration of the Δ^9-THC experiments was 3 days and of the others, 4 days. Following the last treatment, the mice were subjected to the same electroshock-threshold tests used in the excitability studies: peak-effect times, phenytoin and Δ^9-THC, 2 h; cannabidiol, 1 h; phenobarbitone, 3 h. Furthermore, mice, in both the withdrawal and tolerance experiments, were used in only one experiment in order to prevent any test or drug interaction.

Current- and voltage-effect curves have 3 to 6 points; each point represents the results obtained from 15 to 25 mice. Median-effective electroshock-threshold values and their 95% confidence limits were determined by probit analysis (Finney, 1971), and relative potency tests were carried out by the method of Litchfield & Wilcoxon (1949). Calculations were made by a Univac computer 1108; the experiments were conducted at room temperature, about 22°C.

Electroshock-threshold tests and equipment

Anticonvulsant activity was measured against electrically caused convulsions in the following laboratory procedures: maximal, 6 Hz and 60 Hz electroshock-threshold tests (Swinyard, 1969). Stimuli were applied by means of conventional corneal electrodes; the end-points were hind limb extension (a maximal seizure) for the maximal electroshock-threshold test, and front limb and jaw clonus (a minimal seizure) for the other two electroshock-threshold tests. A constant current stimulator (Wahlquist Instrument Co.) was used in the maximal and 60 Hz electroshock-threshold tests; the seizures were evoked with a 200 ms train of 60 Hz sinusoidal stimuli. In the 6 Hz electroshock-threshold test, a constant voltage stimulator (Wahlquist Instrument Co.) produced seizures by a 3 s train of 6 Hz, 200 ms, monophasic pulses.

Drug preparations and administration

Both drug and vehicle preparations were administered intraperitoneally. Sodium phenobarbitone was dissolved in isotonic sodium chloride solution. Our previously described technique (Turkanis *et al.*, 1974) was used to disperse the cannabinoids and phenytoin in isotonic saline solution with the use of Tween 80 (Sigma) and ultrasound (Branson Sonifer S75); the final drug preparations contained about 3% Tween and 97% saline solution.

Results

Tolerance studies

The general experimental design of the tolerance studies is graphically illustrated by the cannabidiol 6 Hz electroshock-threshold data in Figure 1. In each tolerance experiment, a stimulus (current or voltage)-effect relation, similar to those shown in Figure 1, was obtained for each of the three different treatment groups: a control, a single and a subacute treatment group. The median-effective electroshock thresholds and their 95% confidence limits were then determined (Finney, 1971) and compared statistically by a relative potency test (Litchfield & Wilcoxon, 1949). Tolerance or a decrease in sensitivity to the drug was seen when the median-effective electroshock threshold obtained with the subacute treatment group was significantly lower than the single treatment group's electroshock threshold; in contrast, a significant enhancement of the electroshock threshold indicated an increase in sensitivity to the drug.

Summaries of the tolerance experiments with each electroshock-threshold test are depicted in Tables 1A, 2A and 3A. The single-treatment data shown in these

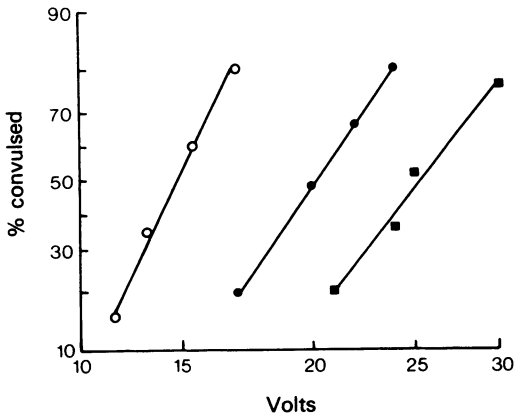

Figure 1 Influence of subacute cannabidiol treatment on 6 Hz electroshock threshold in mice. (○) Control group; (●) single-treatment group; (■) subacute-treatment group. Volts, log scale.

tables confirm our previous anticonvulsant findings for the cannabinoids (Karler *et al.*, 1974a; Turkanis *et al.*, 1974); that is, in the doses tested, both cannabidiol and Δ^9-THC elevate the 6 Hz and maximal electroshock thresholds, but in the 60 Hz test, cannabidiol is ineffective, while Δ^9-THC lowers the threshold. Subacute treatment altered the activity of the drugs in some of the tests, but the changes were various. In the 6 Hz electroshock-threshold experiments, both cannabidiol and Δ^9-THC caused a markedly greater electroshock-threshold increase in subacute than in single treatment tests (Table 1A). In contrast, phenobarbitone produced a statistically significant decrease in sensitivity, or tolerance, whereas the initial anticonvulsant activity of phenytoin was unaltered during 4 days of treatment.

The effects of subacute treatment in the 60 Hz electroshock-threshold test are shown in Table 2A and, like the 6 Hz electroshock-threshold data, are complex: single doses of Δ^9-THC lowered the 60 Hz electroshock threshold and there was no change in response to the drug with subacute treatment. Furthermore, cannabidiol exerted no significant activity with either dosage regimen, whereas phenytoin, which was inactive in single doses, raised the 60 Hz electroshock threshold significantly after multiple treatment. Thus, sensitivity to the anticonvulsant effects of phenytoin in this particular test developed only with multiple treatment. Lastly, phenobarbitone signifi-

Table 1 Six Hz electroshock-threshold test

(A) Influence of subacute anticonvulsant treatment on the sensitivity of mice

	Treatment		
Drug	*Control* (*V*)	*Single dose* (*V*)	*Subacute* (*V*)
Cannabidiol	15 (14–16)	20 (18–22)*†	26 (23–29)*†
Δ^9-THC	16 (14–18)	23 (20–27)*†	29 (26–33)*†
Phenytoin	15 (11–18)	22 (17–26)*	22 (18–26)*
Phenobarbitone	14 (13–16)	23 (20–26)*	19 (17–21)*†

(B) Influence of withdrawal from subacute anticonvulsant treatment on the CNS excitability of mice

Drug	*Control* (*V*)	*Treated* (*V*)
Cannabidiol	12 (11–13)	17 (15–19)*
Δ^9-THC	11 (10–12)	9.7 (9.1–10)*
Phenytoin	13 (12–14)	13 (11–14)
Phenobarbitone	17 (15–20)	17 (14–19)

Values are median-effective electroshock thresholds and their 95% confidence limits.
* Value is significantly different from control, as indicated by a relative potency test ($P \leq 0.05$).
† Value for the subacute group is significantly different from single-dose group, as indicated by a relative potency test ($P \leq 0.05$).

Table 2 Sixty Hz electroshock-threshold test

(A) Influence of subacute anticonvulsant treatment on the sensitivity of mice

	Treatment		
Drug	*Control* (*mA*)	*Single dose* (*mA*)	*Subacute* (*mA*)
Cannabidiol	5.4 (5.2–5.6)	5.6 (5.3–5.9)	5.0 (4.7–5.3)
Δ^9-THC	6.1 (5.4–6.7)	4.2 (3.7–4.7)*	4.2 (3.9–4.6)*
Phenytoin	5.4 (5.2–5.7)	5.5 (5.2–5.8)	6.8 (6.5–7.0)*†
Phenobarbitone	6.2 (5.7–6.6)	6.9 (6.5–7.3)*	6.3 (6.0–6.6)†

(B) Influence of withdrawal from subacute anticonvulsant treatment on the CNS excitability of mice

Drug	*Control* (*mA*)	*Treated* (*mA*)
Cannabidiol	6.2 (5.7–6.7)	5.9 (5.4–6.4)
Δ^9-THC	6.4 (6.2–6.6)	5.4 (5.0–5.7)*
Phenytoin	5.5 (5.2–5.7)	5.3 (4.9–5.6)
Phenobarbitone	5.7 (5.4–6.1)	4.8 (4.5–5.1)*

Values are median-effective electroshock thresholds and their 95% confidence limits.
* Value is significantly different from control, as indicated by a relative potency test ($P \leq 0.05$).
† Value for the subacute group is significantly different from single-dose group, as indicated by a relative potency test ($P \leq 0.05$).

cantly raised the 60 Hz electroshock threshold in single-dose studies, but in subacute treatment a decrease in sensitivity, or tolerance, was recorded.

With respect to the maximal electroshock threshold (Table 3A), in single doses all four drugs significantly elevated the median-effective electroshock-threshold values; however, tolerance occurred only to Δ^9-THC. In contrast, these four anticonvulsants exhibited marked tolerance in the maximal electroshock test itself (Karler *et al.*, 1974c); therefore, tolerance may develop to the anticonvulsant effect of a drug in the maximal electroshock test but not in the corresponding maximal electroshock-threshold test.

Withdrawal hyperexcitability studies

The design of the excitability experiments was similar to that of the tolerance studies, except that the various thresholds were measured 24 h after the last drug or vehicle treatment. This time was chosen because all 4 drugs have relatively short half-times in the mouse brain, and little or none of them would be present 24 h after withdrawal (Karler & Turkanis, 1976b; Karler & Turkanis, unpublished observations). From the stimulus-effect relations, median-effective electroshock thresholds were determined for both drug- and vehicle-treated mice and were compared statistically (Litchfield & Wilcoxon, 1949). A decrease in electroshock threshold, relative to control, indicated a drug-withdrawal increase in CNS excitability; on the other hand, an increase in electroshock threshold signified a withdrawal decrease in excitability.

The withdrawal-excitability data are summarized in Tables 1B, 2B and 3B. The results of the 6 Hz electroshock-threshold experiments shown in Table 1B indicate that in this test only the cannabinoids altered CNS excitability following abrupt drug withdrawal: cannabidiol treatment resulted in a decrease in CNS excitability, but Δ^9-THC produced the opposite effect, a rebound hyperexcitability. In the 60 Hz electroshock-threshold test (Table 2B), both Δ^9-THC and phenobarbitone caused a significant rebound hyperexcitability, but cannabidiol and phenytoin exerted no effect. However, only phenobarbitone caused a marked increase in CNS excitability in the maximal electroshock threshold (Table 3B).

In summary, the electroshock-threshold results show that, under the conditions of the present investigation, abrupt withdrawal from Δ^9-THC or phenobarbitone treatment can result in a rebound hyperexcitability; such withdrawal from cannabidiol or phenytoin treatment does not elicit the same response.

Table 3 Maximal electroshock-threshold test

(A) Influence of subacute anticonvulsant treatment on the sensitivity of mice

		Treatment	
Drug	*Control* (*mA*)	*Single dose* (*mA*)	*Subacute* (*mA*)
Cannabidiol	8.0 (7.0–9.0)	11 (9.8–12)*	11 (9.0–12)*
Δ^9-THC	8.9 (8.3–9.4)	11 (9.8–12)*	9.6 (8.9–10)†
Phenytoin	8.5 (7.8–9.2)	13 (11–14)*	13 (12–14)*
Phenobarbitone	8.5 (7.5–9.6)	13 (12–14)*	13 (11–14)*

(B) Influence of withdrawal from subacute anticonvulsant treatment on the CNS excitability of mice

Drug	*Control* (*mA*)	*Treated* (*mA*)
Cannabidiol	8.9 (8.3–9.6)	8.3 (7.9–8.8)
Δ^9-THC	8.3 (7.6–9.1)	8.2 (7.4–9.1)
Phenytoin	8.0 (7.3–8.6)	7.6 (7.0–8.3)
Phenobarbitone	8.5 (7.8–9.1)	6.9 (6.5–7.4)*

Values are median-effective electroshock thresholds and their 95% confidence limits.
* Value is significantly different from control, as indicated by a relative potency test ($P \leq 0.05$).
† Value for the subacute group is significantly different from single-dose group, as indicated by a relative potency test ($P \leq 0.05$).

Discussion

The present investigation is a continuation of our preclinical evaluation of the anticonvulsant properties of the cannabinoids relative to the well-established antiepileptics, phenytoin and phenobarbitone; specifically, it is an extension of our previously described studies of CNS excitatory properties and of tolerance development to the cannabinoids (Karler *et al.*, 1974a, c; Karler & Turkanis, 1976a; Turkanis *et al.*, 1977). In an earlier publication, we noted that subacute treatment with cannabidiol, Δ^9-THC, phenytoin or phenobarbitone produced marked tolerance in the maximal electroshock test (Karler *et al.*, 1974c). In contrast, the results of the present study illustrate that tolerance did not develop to most of the anticonvulsant effects as measured in three different seizure-threshold tests. In fact, tolerance was not exhibited to either cannabidiol or phenytoin in any of the experiments, but it did develop to Δ^9-THC in one test and to phenobarbitone in two tests (Tables 1A, 2A and 3A). Moreover, subacute treatment enhanced the activity of cannabidiol and Δ^9-THC in the 6 Hz electroshock threshold and was required for the development of the anticonvulsant effect of phenytoin in the 60 Hz electroshock-threshold test (Tables 1A and 2A). In summary, repeated treatment with cannabinoids

can result either in the development of tolerance, or in no change in activity, or even in enhanced activity, depending upon the drug and the test.

The observed enhancement of activity in subacute cannabinoid treatment in the 6 Hz electroshock-threshold test may possibly be related to the pharmacokinetics of these drugs in the brain because, under identical experimental conditions (Karler & Turkanis, 1976a; Karler & Turkanis, unpublished work), the cannabinoids and their metabolites accumulated in the brain. Such an explanation, however, cannot account for the diverse results obtained in the different anticonvulsant tests (Tables 1A, 2A and 3A).

The data described above suggest two conclusions regarding tolerance: first, because each drug did not exhibit tolerance in all the antiseizure tests, the mechanism responsible for the tolerance is unlikely to be associated with drug-disposition factors and, consequently, is probably due to a CNS adaptation. This conclusion is consistent with our earlier observations that, even though cross tolerance existed between the cannabinoids and phenytoin and phenobarbitone in the maximal electroshock test, cannabinoid-tolerant mice did not manifest a decreased hexobarbitone sleep time (Karler *et al.*, 1974c; Borys, Ingall & Karler, 1979). Furthermore, measurements of Δ^9-THC and its metabolites in the brain and plasma provided direct evidence that drug-disposition factors do not play a role in tolerance development (Karler & Turkanis, 1976a). Thus, the present study supports our previously published results indicating that a CNS-adaptive mechanism is responsible for cannabinoid-induced tolerance (Karler *et al.*, 1974c; Karler & Turkanis, 1976a).

The second conclusion that can be drawn from our data is that tolerance to cannabidiol did not develop in any of the specific anticonvulsant tests used (Tables 1A, 2A and 3A), despite the earlier description of the development of tolerance under identical conditions in the maximal electroshock test (Karler *et al.*, 1974c). The clinical significance of such observations in various seizure models is not clear; nevertheless, some investigators have interpreted the development of tolerance to the cannabinoids in the maximal electroshock test as an indication that these drugs have a seriously limited clinical potential (Feeney *et al.*, 1976). The validity of such a conclusion must be questioned because of the data presented above and because tolerance also develops rapidly in the maximal electroshock test to both phenobarbitone and phenytoin (Karler *et al.*, 1974c). However, there is no clinical evidence that tolerance develops to either of these antiepileptic drugs (Buchthal & Lennox-Buchthal, 1972a, b). The only conclusion that appears valid in view of the data is that tolerance in humans cannot be predicted on the basis of the results obtained from one antiseizure test in rodents.

In conclusion, the data presented support previous reports that Δ^9-THC, in contrast to cannabidiol, produces central excitatory effects (Karler *et al.*, 1974a; Turkanis *et al.*, 1974; 1977; Martin & Consroe, 1976). In the work described above, the CNS hyperexcitability induced by abrupt withdrawal from Δ^9-THC raises the possibility that the use of marihuana by epileptics can be detrimental to their seizure control, as is the case with ethanol (Victor, 1970). In support of such a possibility is the report of an epileptic who claimed that several hours after smoking marihuana he experienced grand mal seizures (Keeler & Reifler, 1967). The complexity of the influence of marihuana on seizure control, however, is illustrated by the report that smoking marihuana enhanced the antiepileptic activity of phenobarbitone and phenytoin in another patient (Consroe, Wood & Buchsbaum, 1975).

The data obtained on cannabidiol, on the other hand, add to its already impressive preclinical pharmacological profile as an anticonvulsant. The basic attractiveness of the drug as a potentially useful antiepileptic is its apparent lack of marihuana-like toxicity in humans (Hollister, 1971, 1973; Perez-Reyes, Timmons, Davis & Wall, 1973) as well as a chemical structure distinct from that common to most antiepileptics. The latter finding offers the hope that the mechanism of anticonvulsant activity differs from that of the conventional agents. In short, the cumulative data continue to support our previously drawn conclusion that cannabidiol exhibits clinical potential as an antiepileptic (Karler & Turkanis, 1976b), and, in this respect deserves further evaluation.

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