Cannabidiol and *Cannabis sativa* extract protect mice and rats against convulsive agents

Anecdotal reports concerning anti-epileptic properties of *Cannabis sativa* extracts have been known since the last century (O'Shaughnessy, 1838; Shaw, 1843; Reynolds, 1890). Synhexyl has been reported to be of value in treatment of human epilepsy (Davis & Ramsey, 1949) and to be able to protect animals against leptazol convulsions (Loewe & Goodman, 1947). (−)-Δ^1-*trans*-tetrahydrocannabinol (Δ^1-THC) has been shown to be effective in protecting mice and baboons against leptazol and photostimulation challenges (Garriott, Forney & others, 1968; Sofia, Solomon & Barry, 1971; Killam & Killam, 1972). These data suggest that cannabinoid compounds might have an anti-epileptic value, a possibility which is strengthened by the findings with synhexyl and Δ^1-THC. However, any eventual application of this potential therapeutic property would obviously be hindered by the hallucinogenic effects of the drugs. We reasoned that if the anticonvulsant activity was in part due to the chemical moiety common to the cannabinoids then there was a possibility that a compound might be found without the hallucinogenic effects but active as an anticonvulsant. Cannabidiol (CBD) is a likely candidate. It is devoid of hallucinogenic effect (Farnsworth, 1969), strongly potentiates barbiturate sleeping-time (Paton & Pertwee, 1972) and is able to antagonize several excitatory effects of Δ^1-THC (Karniol & Carlini, submitted for publication).

As a first attempt to test this hypothesis a joint work, carried out between our laboratory and the Department of Pharmacology, University of Cordoba, Argentine, has shown that CBD decreased the susceptibility of rat dorsal hippocampus to seizure discharges caused by afferent stimulation (Izquierdo, Orsingher & Berardi, 1973). In this test CBD was more active than Δ^1-THC, mysoline and diphenylhydantoin. We now report that CBD and a *Cannabis sativa* extract were able, respectively, to protect mice against the leptazol-induced convulsions and deaths and to block audiogenic convulsions in rats in abstinence from previous barbitone sodium administration.

Three month old male mice were injected with control solution (a 0·7% mixture of Tween-80-saline i.p.) or 10–200 mg kg^{-1} (i.p.) of CBD (generously given by Prof. R. Mechoulam). Sixty min later the animals received 60 or 80 mg kg^{-1} (s.c.) leptazol and the number of convulsions and deaths occurring were recorded (Table 1). 200 mg kg^{-1} significantly protected the mice from the convulsant and lethal effects of leptazol.

Twenty Wistar male rats, 3 month old, were induced to drink a solution of barbitone sodium as the only liquid at an initial concentration of 1 mg ml^{-1} increasing up to 4 mg ml^{-1} over 38 days. The daily intake in the last days of the experiment being 300–400 mg kg^{-1}. The barbiturate was then withheld and 48 h later half of the animals were treated (i.p.) with a control solution and the other half with 20 mg kg^{-1} of a *Cannabis sativa* extract prepared according to Carlini & Kraemer (1965). Thirty min later the animals were subjected to a bell giving 95–105 decibels for 1 min. A scale of 0 to 4 grades, as recommended by Schreiber & Schlensinger (1972) was used to assess the effects of pretreatment and the marihuana-treated group were significantly protected from audiogenic seizures since 6 animals on the control solution but only one on the extract showed wild running + clonic-tonic convulsions ($P \leqslant 0{\cdot}02$). Of the other animals, 4 controls and 7 treated rats showed no response and 2 treated rats responded with wild running. It is interesting also that cannabis-treated rats showed an aggressive behaviour which was similar to that observed in morphine-abstinent rats treated with marihuana (Carlini & Gonzalez, 1972). Other drugs failed to afford protection towards convulsions in such rats (Crossland & Turnbull, 1972) and in dogs (Essig, 1967).

Table 1. *Protection by cannabidiol of leptazol-induced convulsions and death in mice.*

Drug	Pretreatment Dosage (mg kg^{-1})	Leptazol (mg kg^{-1})	Convulsions[a]	Deaths[a]
Control soln	1·0 ml kg^{-1}	80	10/10	8/10
CBD	10	80	10/10	6/10
Control soln	1·0 ml kg^{-1}	80	10/10	8/10
CBD	50	80	10/10	5/10
Control soln	1·0 ml kg^{-1}	80	10/10	10/10
CBD	200	80	3/10*	2/10*
Control soln	1·0 ml kg^{-1}	60	8/10	6/10
CBD	200	60	3/10*	2/10**

[a] Number of animals showing the effect/number of animals tested

* Differs significantly from control group ($P \leqslant 0{\cdot}03$; Fisher test); ** $P \leqslant 0{\cdot}07$

In a pilot study with normal healthy volunteers CBD (10 and 20 mg) was given by mouth daily during 21 days. The drug did not induce any subjective symptoms and hallucinations, and there was no signs of hepatic, kidney or cardio-circulatory disturbances (Mincis, Pfeferman & others, 1973). It is our opinion that the absence of hallucinogenic and toxic effects in man and the anticonvulsant action in animals make a trial of CBD worthwhile for the treatment of epilepsy.

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Note added in proof. Using another sample of CBD (also provided by Prof. Mechoulam) we have observed that 25 mg kg^{-1} protected barbiturate-abstinent rats from audiogenic seizures. Thus, only one of 10 treated rats responded with wild running whereas 6 of 10 control rats showed wild running + clonic-tonic convulsions.

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