Interaction of Δ^9-tetrahydrocannabinol and cannabidiol with phenobarbitone in protecting mice from electrically induced convulsions

In a previous study (Chesher & Jackson, 1974) we reported that the protection against electrically-induced seizures afforded mice by phenytoin, was potentiated significantly by Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). In contrast, these cannabinoids failed to alter the effect of phenobarbitone on the convulsive threshold to leptazol induced seizures. Although THC itself showed a weak anticonvulsant activity against electrically induced seizures, it failed to affect the convulsive threshold to leptazol. These findings suggested that the interaction between the cannabinoids and phenytoin possibly involved activity in the central nervous system rather than a metabolic interaction. This hypothesis is supported by the results of the present study which reports the potentiation by the cannabinoids of the effect of phenobarbitone on electrically-induced seizures.

Random bred male mice (QS strain, 18–30 g) were used and allowed free access to food and water up to the time of the experiment. Maximum electroshock seizures (MES) were induced using a current of 50 mA, 50 Hz and 0·3 s duration applied by corneal electrodes moistened with 0·9% saline (Swinyard, 1949; Swinyard, Brown & Goodman, 1952). Two endpoints were recorded; the abolition of the hind limb extensor component of the seizure was taken to represent protection and, in those animals where hind limb extension occurred, its duration was recorded by means of a stop-watch. Cannabinoids were prepared in a suspension in propylene glycol and Lissapol-Dispersol (Whittle, 1964) as described previously (Chesher, Dahl & others, 1973) and administered by gavage (1 ml 100 g^{-1} body wt) 1 h before phenobarbitone (i.p.) and 2 h before MES. The data were analysed by probit analysis.

The results (Table 1) show that THC (50 mg kg^{-1}) significantly potentiated the protection afforded mice by phenobarbitone when determined both by protection from seizures and by the shortening of the duration of hind limb extension. CBD (50 mg kg^{-1}) was much less active and whilst it significantly reduced the ED50 of phenobarbitone when assessed as protection from convulsions, it produced no significant change when effectiveness was assessed by the duration of hind limb extension.

Table 1. *The effect of phenobarbitone and phenobarbitone plus THC and/or CBD on electrically-induced seizures in mice.* The data are expressed as the ED50 values for phenobarbitone calculated by probit analysis, using either the dose required to protect 50% of animals against convulsions or that required to reduce the mean extensor time by half. The mean duration of the hind limb extensor phase of control animals, dosed vehicle only, was 14·4 s ± 0·2 (s.e.m.) n = 162. The doses of phenobarbitone used were between 9·3 and 40 mg kg^{-1} depending upon pre-treatment, but in each case at least 4 dose levels were used. For each part at least 20 animals were used.

Treatment	ED50 value (mg kg^{-1}) ± s.e.m. Protection from convulsions	Extensor time
Phenobarbitone	29·7 ± 0·5	23·3 ± 0·1
" + THC (50)	15·9 ± 0·7	13·4 ± 0·7
" + CBD (50)	25·8 ± 0·6	22·7 ± 0·6
" THC + CBD (25+25)	16·1 ± 0·7	12·8 ± 0·8
" THC + CBD (50+50)	12·5 ± 0·8	8·3 ± 1·0

The greatest potentiation was observed when both THC and CBD were administered together, before phenobarbitone, and so resembles the intereaction reported earlier between the cannabinoids and phenytoin (Chesher & Jackson, 1974). Despite the much lower activity of CBD, the combination of 25 mg kg^{-1} each of CBD and THC produced a reduction in the ED50 of phenobarbitone which was not significantly different (using both end-points) from that produced by THC 50 mg kg^{-1}. Nevertheless, the degree of potentiation produced by the combination of THC and CBD was rather lower with phenobarbitone than had previously been reported for the same combination of cannabinoids with phenytoin (Chesher & Jackson, 1974).

This drug interaction is unlikely to be explained by a cannabinoid-induced inhibition of phenobarbitone metabolism and is possibly an effect upon the central nervous system. CBD and THC themselves possess extremely weak anticonvulsant activity against electrically induced seizures and are without effect on leptazol seizures (Chesher & Jackson, 1974). Furthermore, in this same study, THC and CBD failed to potentiate the phenobarbitone protection against leptazol seizures. If the drug interaction were of a metabolic nature, a potentiation might be expected under this test solution, as CBN, CBD and THC have been shown to interfere with the metabolism of pentobarbitone (Siemens, Kalant & others, 1974). CBD is the most potent of the cannabinoids in potentiation of barbiturate anaesthesia in mice (Chesher, Jackson & Starmer, 1974) and under *in vitro* conditions, for the inhibition of metabolism of pentobarbitone and phenazone by liver microsomes (Siemens & others, 1974; Paton & Pertwee, 1972). In the present study, however, THC was considerably more active than CBD in its potentiation of the activity of phenobarbitone. This finding is similar to that observed for the potentiation of phenytoin by CBD and THC and suggests that the activity of the cannabinoids on this parameter is occurring in the central nervous system. This would seem to be further supported by the potentiation of ether anaesthesia in mice by THC (Malor, Jackson & Chesher, 1975).

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