Anticonvulsant Action of Cannabis in the Rat: Role of Brain Monoamines

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Abstract. The role of brain monoamines in the anticonvulsant action of Cannabis indica resin (CI), against maximal electroshock-induced seizures in albino rats, was investigated by using pharmacologic agents that influence brain monoamine activity. Delta-9-tetrahydrocannabinol content of cannabis resin was estimated to be 17%. The anticonvulsant action of CI (200 mg/kg, i.p.) was significantly inhibited after pretreatment with drugs that reduce brain serotonin activity but not by drugs that reduce brain catecholamine activity. Similarly, the anticonvulsant action of a subanticonvulsant dose (50 mg/kg, i.p.) of CI was potentiated by serotonin precursors but not by catecholamine precursors. Potentiation of the anticonvulsant action of CI by nialamide or by imipramine was inhibited after pretreatment with 5,6-dihydroxytryptamine. The results suggest that the anticonvulsant action of CI in the rat is serotonin- and not catecholamine-mediated.

Key words: Cannabis indica — Anticonvulsant action — Brain monoamines

Cannabis has been used as an anticonvulsant drug in the ancient Hindu system of medicine (Shreshthireniria, 1953; Singh, 1974). The anticonvulsant action of cannabis and its various constituents, against maximal electroshock-induced seizures, has been reported by a number of workers (Loewe and Goodman, 1947; Garriott et al., 1968; Izquierdo and Tannhauser, 1973; Karler et al., 1973, 1974a, b; Singh and Das, 1975), but the mechanism of this anticonvulsant action is not clear.

There is ample evidence that suggest the involvement of brain monoamines in electroshock-induced convulsions (Chen et al., 1954; Rudzik and Mennear, 1965; Azzaro et al., 1972; Wenger et al., 1973). Reserpine-induced facilitation of electroshock-induced convulsions (Chen et al., 1954) and the antagonism of this facilitating effect by monoamine oxidase inhibitors (Chen and Bohnier, 1959; Prockop et al., 1959; Rowe et al., 1959), as well as the anticonvulsant effect of monoamine oxidase inhibitors (Prockop et al., 1959) and imipramine (Bhattacharya et al., 1976a), provide unequivocal evidence for a correlation between brain monoamines and the sensitivity to electroshock-induced convulsions.

Cannabis and its constituents are known to affect the brain concentration and turnover of serotonin, noradrenaline (NA), and dopamine (DA) in a number of species, including the rat (Schildkraut and Efron, 1971; Jonsson and Fuxe, 1972; Kilbey et al., 1973; Maitre et al., 1974; Ueki and Fujiwara, 1975; Poddar et al., 1976). In view of the well-documented effect of cannabis on brain monoamine activity and the equally well-accepted involvement of the latter in electroshock-induced convulsions, it was considered worthwhile to investigate the role of brain monoamines in the anticonvulsant action of cannabis against electroshock-induced seizures.

Materials and Methods

Wistar strain albino rats (100 – 200 g) of both sexes were used. Food was withdrawn 18 h prior to and water just before experimentation. Supramaximal electroshock (150 mA, 0.2 s) was given through corneal electrodes using a Techno convulsiometer. The hind-limb extensor response was taken as the end point (Toman et al., 1946) and all the rats used were screened for positive extensor response.

Cannabis resin was extracted from the flowering tops of Cannabis indica with petroleum ether (60 – 80°C) and was suspended in 1% Tween-80 for experimentation. Delta-9-tetrahydrocannabinol (THC) content of the resin was biologically assayed by the 4-point
assay method, using pure THC as standard and taking the hypothermic activity in albino rats as the assay parameter. The THC content of the resin was estimated to be 17%. Cannabis resin (CI) was used at two dose levels, based on earlier studies (Singh and Das, 1975). The first (200 mg/kg, i.p.) produced 100% anticonvulsant action (ED\textsubscript{100}), while the second dose (50 mg/kg, i.p.) had no anticonvulsant action (ED\textsubscript{0}). CI was administered 1 h before testing for anticonvulsant activity.

The following drugs, with dose and pretreatment time given in parentheses, were used to investigate cannabis action: reserpine (5 mg/kg, 18 h), 5,6-dihydroxytryptamine (75 \mu g/rat, 72 h), 6-hydroxydopamine (250 \mu g/rat, 7 days), p-chlorophenylalanine (100 mg/kg, once daily for 3 days), 3-methyl-tyrosine (250 mg/kg, 4 h), 3-nethylldopa (400 mg/kg, 4 h), diethylthiocarbamate (300 mg/kg, 4 h), methysergide (2.5 mg/kg, 1 h), cyproheptadine (5 mg/kg, 30 min), propranolol (1 mg/kg, 1 h), phenoxybenzamine (5 mg/kg, 2 h), phenotamine (1 mg/kg, 30 min), haloperidol (2 mg/kg, 30 min), 5-hydroxytryptophan (75 mg/kg, 1 h), l-dopa (400 mg/kg, 1 h), nialamide (50 mg/kg, 2 h), imipramine (5 mg/kg, 30 min), and apomorphine (0.5 mg/kg, 15 min). All drugs were administered i.p., suspended in 1% Tween-80, except 5,6-dihydroxytryptamine (DHT) and 6-hydroxydopamine (6-HD), which were administered intraventricularly, dissolved in artificial cerebrospinal fluid.

Since rapid tolerance develops to the anticonvulsant action of cannabis (Karler and Turkanis, 1976), different rats were used in each experimental group. Statistical analysis was done by the \( \chi^2 \) test.

### Results

None of the pharmacologic agents used to evaluate the mechanism of cannabis action had any effect per se on the experimental parameter used (Table 1).

The anticonvulsant (ED\textsubscript{100}) action of CI was completely inhibited by reserpine and DHT, but was not significantly affected by 6-HD. The serotonin-synthesis inhibitor, p-chlorophenylalanine (PCPA), also totally anulled CI effect. The catecholamine synthesis inhibitors, \( \alpha \)-methyl-p-tyrosine (MPT), \( \alpha \)-methylldopa (MD), and diethylthiocarbamate (DDC), failed to affect the anticonvulsant action of CI. The serotonin-receptor antagonists, methysergide and cyproheptadine, significantly inhibited CI effect, whereas the adrenocorticot antagonists propranolol, phenoxybenzamine, and phenotamine, as well as the specific DA-receptor antagonist haloperidol, had either insignificant or no effect on the anticonvulsant action of CI (Table 2).

Reserpine-induced inhibition of the anticonvulsant effect of CI was significantly reversed by the serotonin precursor 5-hydroxytryptophan (5-HTP), but not by l-dopa, administered alone or in DDC-pretreated rats (Table 3).

The sub-anticonvulsant (ED\textsubscript{0}) dose (50 mg/kg, i.p.) of CI was significantly potentiated by 5-HTP, nialamide, and imipramine, but not by l-dopa either alone or in DDC-pretreated rats. Apomorphine, a DA-receptor agonist, also failed to potentiate CI effect. Nialamide- and imipramine-induced potentiation of the anticonvulsant action of CI was not seen in DHT-pretreated rats (Table 4).

### Discussion

In the present study, we attempted to elucidate the importance of individual monoamines in the anticonvulsant action of cannabis.