REFERENCES

BANERJEE, A. K. & LEWIS, J. J. (1963). *J. Pharm. Pharmac.*, **15**, 409–410.
BANERJEE, A. K. & LEWIS, J. J. (1964). *Ibid.*, **16**, 439–440.
FERRARI, M. & CARPENEDO, F. (1968). *Archs int. Pharmacodyn. Thér.*, **174**, 223–232.
HATTINBERG, M., KUSCHINSKY, G. & RAHN, K. H. (1966). *Naunyn Schmiedeberg's Arch. Pharmak.* **253**, 438–443.
IMAI, S. & TAKEDA, K. (1967). *J. Pharmac. exp. Ther.*, **156**, 557–564.
KADLEC, O. & BAUER, V. (1971). *Experientia*, **27**, 815–816.
KADLEC, O. & ŠEFERNA, I. (1972). *Toxicon*, **10**, 465–472.
KARAKI, H., IKEDA, M. & URAKAWA, N. (1969). *Jap. J. Pharmac.*, **19**, 291–299.
LÜLLMANN, H. & SIEGFRIEDT, A. (1968). *Pflügers Arch.*, **300**, 108–119.
TASHIRO, N. & TOMITA, T. (1970). *Br. J. Pharmac.*, **39**, 608–618.

The effect of cannabidiol on maximal electroshock seizures in rats

The natural marihuana compounds, cannabidiol, cannabinol, Δ^9- and Δ^8-tetrahydrocannabinol, raise the threshold for hippocampal seizures obtained by electrical stimulation (Izquierdo, Orsingher & Berardi, 1973). Cannabidiol is the most potent of these compounds and apparently acts by a mechanism similar to that proposed for diphenylhydantoin (Nasello, Montini & Astrada, 1972), namely, an interference with hippocampal K^+ release upon afferent bombardment (Izquierdo & others, 1973). Hippocampal seizures are known to result from the extracellular accumulation of this released K^+ (Izquierdo & Nasello, 1970, 1972; Izquierdo, Nasello & Marichich, 1970; Izquierdo, 1972). Cannabidiol and diphenylhydantoin have several other common actions, such as inhibition of hippocampal facilitation and post-tetanic potentiation, of the RNA concentration increase caused by afferent stimulation, and of acquisition of avoidance conditioned responses (Izquierdo & Nasello, 1973). Like diphenylhydantoin (Swinyard, Brown & Goodman, 1952), cannabidiol has little effect against leptazol seizures in mice, where significant antagonism may only be observed with doses 40 to 100 times higher than those needed to inhibit hippocampal seizures (Carlini, Leite & others, 1973). Since diphenylhydantoin is known to be a potent antagonist of maximal electroshock seizures (Swinyard & others, 1952), we have examined the effect of cannabidiol on this test.

Adult female albino rats (160 to 250 g) were submitted to maximal electroshock convulsions by currents passed between both eyes as recommended by Swinyard & others (1952). Twelve animals received 0·2 ml per 100 g of 0·9% NaCl (i.p.) 1 h before electroshock; full-fledged convulsions were obtained in all rats, with a late hindlimb tonic extensor phase lasting 12·6 $\pm$ 1·1 s. Cannabidiol (1·5, 3, 6 and 12 mg kg^{-1}) was thinly suspended in the saline solution with a few drops of Tween 80 (Izquierdo & others, 1973; Izquierdo & Nasello, 1973; Carlini & others, 1973), and each dose was given to groups of 12 rats. The time of peak effect was investigated with a 3 mg kg^{-1} dose and was found to be 1 h. This time was then chosen to study the effect of the other doses. The results are in Fig. 1. At the two higher doses there was some protection against all components of the convulsion, and the ED50 for inhibition of the tonic extensor phase was 3 mg kg^{-1}. This is a lower dose than that of diphenylhydantoin and of other anticonvulsant agents (Swinyard & others, 1952), and close to that previously found in this laboratory to raise hippo-

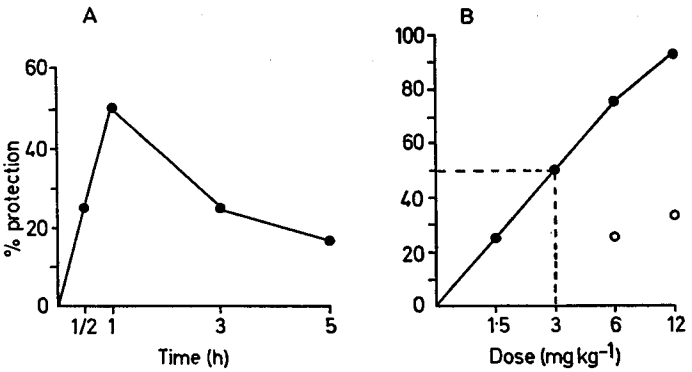

FIG. 1. A. % of rats showing no hindlimb tonic extension with maximal electroshock currents plotted against time of preadministration of 3 mg kg^{-1} of cannabidiol, i.p.

B. % of rats showing no hindlimb tonic extension (●) or no convulsion (○) with maximal electroshock currents plotted against dose of cannabidiol administered i.p. 1 h before.

campal seizure threshold by 100%, to block hippocampal K^+ release (Izquierdo & others, 1973), to inhibit hippocampal facilitation and post-tetanic potentiation, and to impair acquisition of a conditioned avoidance response (Izquierdo & Nasello, 1973). No alteration of stance and gait, and no sign of ataxia were observed over 5 h in rats treated with 12 mg kg^{-1} of cannabidiol and examined as recommended by Swinyard & others (1952).

Thus, cannabidiol appears to be a potent diphenylhydantoin-like anticonvulsant agent; it also seems to lack hallucinogenic and other neurotoxic properties typical of other marihuana compounds either in man or in laboratory animals (Korte & Sieper, 1965; Farnsworth, 1969; Izquierdo & Nasello, 1973; Carlini & others, 1973).

We thank Prof. R. Mechoulam, from Jerusalem, for his kind provision of cannabidiol. The experiments described here were performed at the Departamento de Farmacología, Universidad Nacional de Córdoba, Argentina, while one of us (I.I.) was its chairman and the other (M.T.) a visiting professor.

Departamento de Fisiologia,
Farmacologia e Biofisica,
Instituto de Biociencias, U.F.R.G.S.,
Porto Alegre, RS, Brazil.

IVAN IZQUIERDO
MARIO TANNHAUSER

July 4, 1973

REFERENCES

CARLINI, E. A., LEITE, J. R., TANNHAUSER, M. & BERARDI, A. C. (1973). *J. Pharm. Pharmac.*, in the press.

FARNSWORTH, N. R. (1969). *J. Am. Pharm. Ass.*, **NS9**, 410–415.

IZQUIERDO, I. (1972). *Behav. Biol.*, **7**, 669–698.

IZQUIERDO, I. & NASELLO, A. C. (1970). *Exptl Neurol.*, **27**, 399–409.

IZQUIERDO, I. & NASELLO, A. C. (1972). *Prog. Drug Res.*, **16**, 211–228.

IZQUIERDO, I. & NASELLO, A. C. (1973). *Psychopharmacologia (Berl.)*, in the press.

IZQUIERDO, I., NASELLO, A. G. & MARICHICH (1970). *Archs int. Pharmacodyn Thér.*, **187**, 218–228.

IZQUIERDO, I., ORSINGHER, O. A. & BERARDI, A. C. (1973). *Ibid.*, **28**, 95–102.

KORTE, F. & SIEPER, H. (1965). In *Hashish its: chemistry and pharmacology*, pp. 15–30. Editors: Wolstenholme, G. E. W. and Knight, J. London: Churchill.

NASELLO, A. G., MONTINI, E. E. & ASTRADA, C. A. (1972). *Pharmacol.*, **7**, 89–95.

SWINYARD, E. A., BROWN, W. C. & GOODMAN, L. S. (1952). *J. Pharmac. exp. Ther.*, **106**, 319–330.