Anticonvulsant drugs and folic acid on the development of epileptic kindling in rats

D. GOFF, A.A. MILLER & R.A. WEBSTER

Pharmacology Laboratory, Wellcome Research Laboratories, Beckenham, Kent BR3 3BS, and Department of Pharmacology, University College, London WC1E 6BT

Electrical stimulation of discrete brain areas provides a relatively simple experimental method for reproducing the ictal components (EEG changes accompanying seizures) of focal epilepsy (Ajmone Marsan, 1972). The progressive increase in this response to repeated stimulation over a period of time is termed kindling (Goddard, McIntyre & Leech, 1969). We have investigated the effects of various drugs on both the acute and long term responses to repeated stimulation over a period of weeks.

Rats (Wistar, male, 250–300 g) were implanted with epidural electrodes over the frontal and parietal cortex and in some cases with an intraventricular cannula (Goff, Miller, Smith, Smith & Wheatley, 1975). Electrical stimulation (100 Hz, 1 ms pulses for 1 s duration) sufficient to elicit EEG after-discharge and behavioural clonus was applied through the frontal leads once weekly on 12 occasions. Drugs were administered before each treatment period trial (Figure 1).

The response (clonus duration) of the control rats was significantly ($P \leqslant 0.05$) increased after 9 trials (kindling). Phenobarbitone, diazepam, and ethanolamine o-sulphate (a GABA-T inhibitor, at a dose which significantly elevated brain GABA concentrations) significantly ($P \leqslant 0.05$) prevented the onset of kindling without reducing the clonus response. Folic acid, at a sub-convulsive dose, consistently prolonged clonus with a significant increase ($P = 0.03$) at week 10, and following the cessation of treatment 3 rats showed epileptic EEG activity which persisted for at least 10 weeks. This was abolished, but returned after diazepam (20 mg/kg p.o.) and phenytoin (40 mg/kg p.o.) treatment.

The kindling model reveals the ability of some anticonvulsant drugs to limit the progressive intensification of seizures. Elevated brain folate concentrations enhanced kindling in agreement with the known proconvulsant action of folic acid (Miller & Webster, 1975). The ability of folic acid when administered in combination with electrical stimulation, to induce spontaneous epileptic EEG may provide a useful model of focal epilepsy.

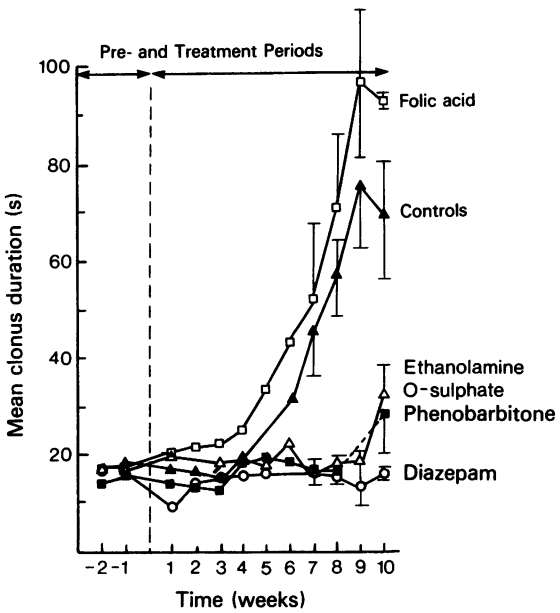

Figure 1 Effect of drugs on duration of clonus induced by electrical stimulation of the frontal cortex of rats at weekly intervals. Phenobarbitone sodium (■) 6 mg/kg and diazepam (○) 31.2 mg/kg were both given p.o. 2 h before testing at 2 × ED_{50} values in the leptazol hind limb extension test. Ethanolamine O-sulphate (△) at 160 μg anf folic acid (□) at 10 μg were given intraventricularly (i.c.v.) 24 h and 15 min before test respectively. Mean values (n = 4) are plotted. Controls (▲) (n = 6) received either saline p.o. or artificial C.S.F. i.c.v. Vertical bars indicate s.e. of mean.

References

AJMONE MARSAN, C. (1972). Focal Electrical Stimulation. In: *Experimental Models of Epilepsy—A Manual for the Laboratory Worker*. eds. Purpura, D.P., Penry, J.K., Tower, D.B., Woodbury, D.M. & Walter, R.D. pp. 148–172, Raven Press, New York.

GODDARD, G.V., McINTYRE, D.C. & LEECH, C.K. (1969). A permanent change in brain function resulting from daily electrical stimulation. *Expl. Neurol.*, **25**, 295–330.

GOFF, D., MILLER, A.A., SMITH, R.E., SMITH, S.J. & WHEATLEY, P.L. (1975). Combined EEG recording and intraventricular administration of drugs in the conscious rat. *Br. J. Pharmac.*, **55**, 312P–313P.

MILLER, A.A. & WEBSTER, R.A. (1975). Proconvulsant action of folic acid. *Br. J. Pharmac.*, **55**, 265P–266P.