Anti-epileptic properties of sodium valproate in rat amygdaloid kindling

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Kindling is a term which has been applied to the progressive induction of epileptiform seizures by repeated low intensity stimulation of discrete brain regions, most notably the amygdala (Goddard, McIntyre & Leech, 1969; Racine, 1972). In this study we present an electrographical and behavioural assessment of the effectiveness of the anti-convulsant, sodium valproate (Epilim) in this model of experimental epilepsy.

Bipolar electrodes were implanted chronically into the basolateral amygdala of male Sprague–Dawley rats (280–300 g); one group received daily stimulation for 2 s (biphasic d.c. pulses, 100 μA; 1 ms duration; 62.5 Hz—standard stimulation) until they displayed reproducible generalised clonic convulsions comprising forelimb clonus, rearing and loss of posture (mean number of days = 11). Amygdaloid EEG was recorded differentially between the electrode terminals. The effect of sodium valproate on this fully kindled epilepsy was investigated in dose groups of 8 rats. Control convulsions and after-discharges (ADs) were triggered on three successive days; on the fourth day one of the following—sodium valproate, 200, 400, 600 mg/kg or drug vehicle (dist, H_2O)—was administered orally and 60 min and 24 h later a further standard stimulation was given. Valproate, 400 and 600 mg/kg significantly decreased in a dose-related manner both the duration of AD ($P < 0.01$) and the incidence of forelimb clonus and full convulsions at 60 min but not at 24 h, post-treatment.

A further experiment examined the influence of valproate on epileptogenic threshold. AD threshold currents were determined in 6 kindled rats (mean current, 63 ± 8.2 μA peak to peak). Valproate (400 mg/kg, p.o., 1 h before stimulation) elevated the AD threshold by 10–20% in 5 animals.

To study the effect of valproate on kindling development, groups of 6 rats, previously unstimulated, were dosed orally once daily on 14 consecutive days with one of the following: sodium valproate, 100, 200, 400 and 600 mg/kg or dist. H_2O, 1 h before delivery of standard kindling stimulation. Following cessation of drug treatment rats were stimulated daily until they all showed full convulsions. Valproate (200, 400 and 600 mg/kg) significantly retarded AD development during the treatment period ($P < 0.01$) in a dose-dependent manner; and no convulsions occurred in the two top dose-groups. At both these doses there was a post-treatment dissociation of AD activity from convulsive behaviour: ADs attained full maturity within 3 days post-treatment, but the mean total number of days to full seizure was 30 in both groups, compared with 11 days in the control group.

These findings demonstrate that sodium valproate has an anti-epileptic action on the kindled epileptic focus which correlates well with the observed anticonvulsant effect. Valproate also has a pronounced prophylactic effect on kindled seizure development.

References

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PGE_2 mediated negative feedback of noradrenaline overflow in the central nervous system

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Evidence for a prostaglandin E_2 (PGE_2) mediated negative feedback control of noradrenaline (NA) release is plentiful in the peripheral nervous system (see Hedqvist, 1977). Less data are available for the central nervous system. Previously, using rat brain synaptosomes, no effect of PGE_2, $PGF_{2\alpha}$ or indomethacin on the spontaneous or K^+ evoked overflow of [^{3}H]-NA was evident (Hillier, Roberts & Templeton, 1979). This work has now been extended to study the effects of PGs, indomethacin, and the endoperoxide analogue U44619 ((15S)-hydroxy-11α, 9α-(epoxymethano) prosta-5Z, 13E-dienoic acid) on rat brain cortex slices (0.2 mm × 0.2 mm) preloaded with [^{3}H]-NA. Spontaneous efflux of [^{3}H]-NA from slices was similar to synaptosomes, but the Ca^{2+} dependent