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CONVULSANT EFFECTS OF KAINIC ACID AND DIHYDROFOLATE ARE ANTAGONIZED BY SODIUM VALPROATE

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ABSTRACT Microinjection of dihydrofolic acid in rat caudate nucleus 10 min after kainic acid significantly enhanced the epileptic motor and ECoG discharges of the single compounds. Sodium valproate antagonized the motor and electrocortical epileptogenic disorders induced by previous intracaudate injections of kainic and dihydrofolic acids.

KEY WORDS sodium valproate; caudate nucleus; kainic acid; dihydrofolate; rats

Folic acid derivatives compete powerfully for kainic acid binding sites in rat brain and methyltetrahydrofolate may be an endogenous neuromodulator with both excitatory and neurotoxic properties[1]. The neurotoxic and convulsant properties of kainic acid[2] and folic acid derivatives[3,4] are well established. The purpose of the present study was to find whether convulsant effects after intrastriatal injections of kainic acid were potentiated by folic acid and whether such convulsant effects were prevented by sodium valproate, a drug known to increase brain GABA contents[5].

METHODS

Adult Wistar-Morini rats (292±SD 31 g) were anesthetized with chloral hydrate. Stereotaxic implantation of cannulae into the head of caudate nucleus was performed[6]. The volume of infusate was 1-2 μl for each intracaudate unilateral injection. Cortical electrodes were implanted[7].

Rats were tested at least 48 h after operative procedures. Drugs were dissolved in pyrogen-free saline, which was adjusted to pH 6.8-7. Control injections were done with same volume of distilled water used to dissolve kainic acid and folic acid and did not produce significant changes in overt behavior and electrocortical activity, which was recorded by an 8-channel OTE EEG machine. Behavioral effects were followed for 8 h after unilateral intracaudate injections. Locomotor activity was measured every 5 min by a LKB Animex types activity meter (Farad Sweden).

Kainic acid and dihydrofolic acid (Sigma, USA). Sodium valproate (Merck, USA).

RESULTS AND DISCUSSION

Dihydrofolate 50, 100 & 200 μg injected into the head of caudate nucleus of rats produced dose-dependent stereotyped movements, circling, motor abnormalities which were associated after the higher doses with high-voltage electrocortical spikes similar to those occurred in epilepsy (n = 10 rats for each dose). Immediately after the injection contralateral circling and an increase in locomotor activity lasted about 30 min; during this time no epileptogenic phenomena were recorded in the electrocortical activity which instead was desynchronized. Approximately 30-45 min after the injection myoclonic jerks of contralateral anterior limb or the head, neck and trunk were seen; these became in some occasions bilateral and emerged into some clonic generalized seizures.

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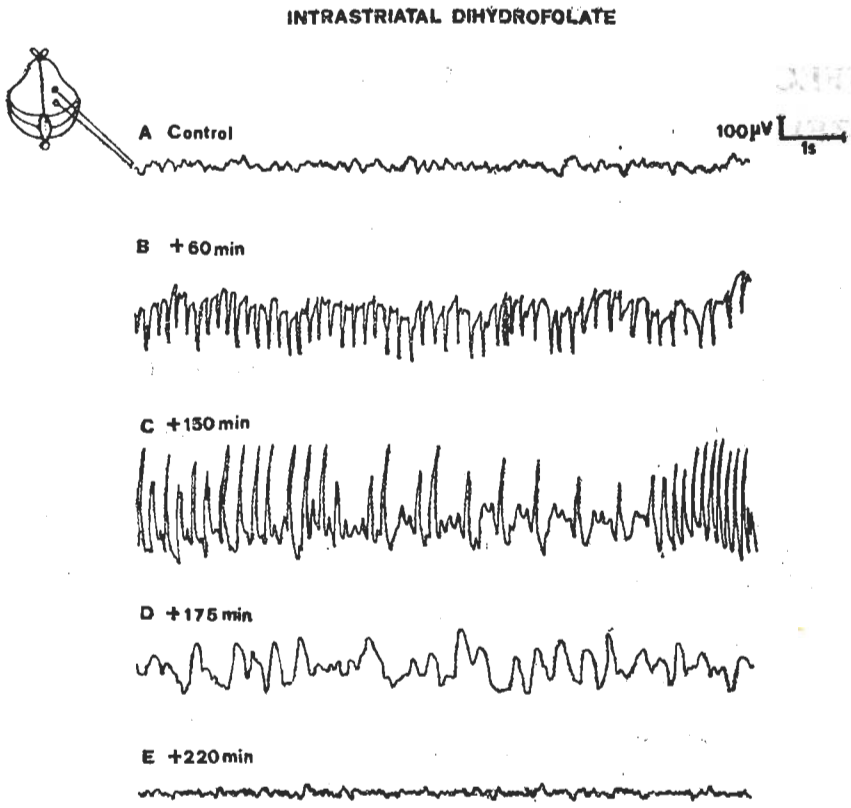

Fig 1. Electrocortical effects of dihydrofolic acid 100 μg after intrastriatal microinfusion in an adult rat. A) Control. B, C & D) Epileptogenic ECoG discharges 60, 150 & 175 min after dihydrofolic acid infusion. E) Return to control electrocortical activity after 220 min.

Electrocortical activity was characterized by periodic high voltage (300–400 μV) unilateral or bilateral spikes, high voltage slow-waves and spike wave complexes (Fig 1) concomitantly or independently from the motor phenomena. Both the intensity and duration of such electrocortical pattern appeared to be dose-dependent.

Similarly the injection of kainic acid into the caudate nucleus produced dose-dependent motor (Fig 2) and ECoG epileptic phenomena

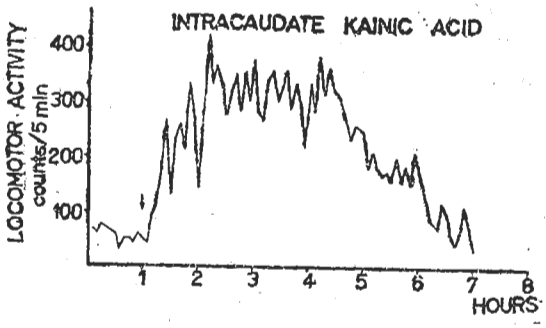

Fig 2. Increase of locomotor activity in an adult rat after intrastriatal injection of kainic acid 1.25 μg.

at doses of 1.25–5 μg (n = 10). But behavioral and electrocortical epileptogenic features were evident in only 30% of the rats receiving 1.25 μg. This dose was therefore chosen to ascertain whether there was a potentiation of the convulsant effects of dihydrofolate 50 μg which alone yielded epileptic phenomena in only 30% of the rats. Folic acid 50 μg injected 10 min after kainic acid 1.25 μg produced epileptic motor and ECoG discharges in 80% of the rats (n = 10); the intensity and duration of these effects were longer-lasting.

The epileptogenic properties of the association between kainic acid 1.25 μg and dihydrofolic acid 50 μg were antagonized (n = 6) by ip sodium valproate 200 mg/kg (Fig 3); such effects were evident 15 min after valproate and the electrocortical epileptogenic disorders (Fig 3 B, C) were substituted by a slow-wave electrocortical pattern (Fig 3 D).

The present experiments confirm that folic and kainic acids when applied directly into

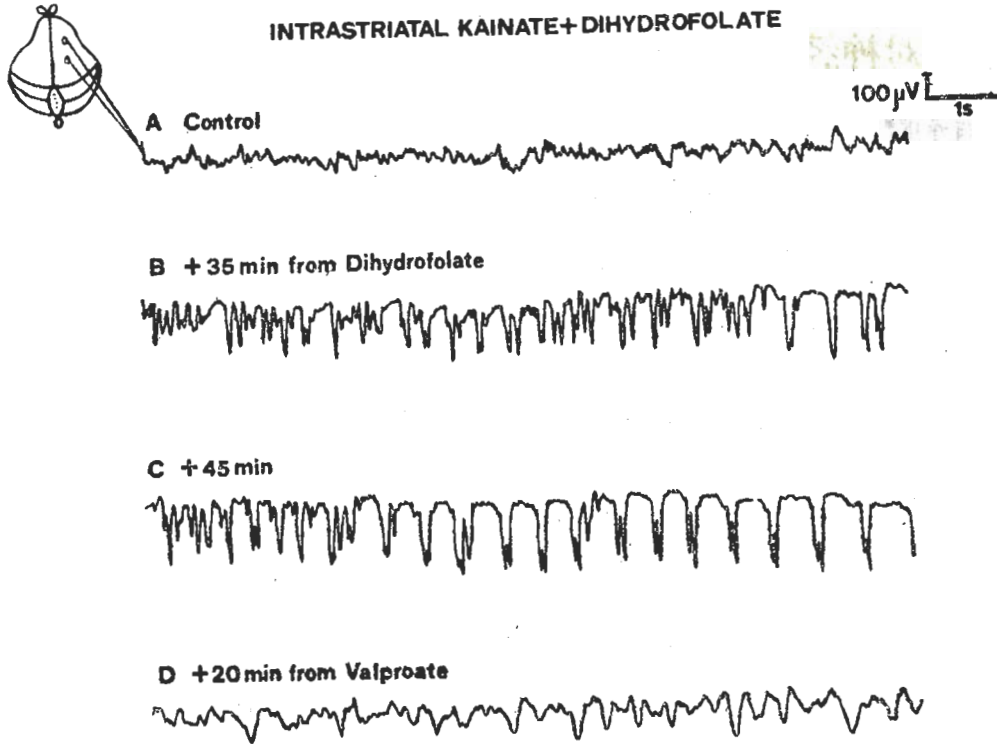

Fig 3. Antagonism by ip sodium valproate 200 mg/kg of epileptogenic electrocortical disorders induced by kainic and dihydrofolic acid.

the rat striatum produce sustained seizures[8].

It seems that convulsant properties of folates and kainic acid are due to stimulation of a common population of receptors different from glutamate receptors[9]. The present study clearly shows a potentiation of the neuroexcitant and neurotoxic effects of kainic and folic acid. The convulsant effects of these compounds are antagonized by drugs enhancing GABAergic mechanisms in the brain.

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