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SHORT COMMUNICATION

Influence of Phenytoin and Valproate on Thalamocortical Evoked Potentials and Their Paired-pulse Potentiation

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Summary

The action of phenytoin and valproate on thalamocortical responses was studied in adult rats. Single responses were not influenced by either drug. Paired-pulse potentiation of the initial components (first positive and first negative) observed with intervals from 50 to 200 ms under control conditions was abolished by phenytoin (60 mg/kg i.p.) but only moderately influenced by valproate (400 mg/kg i.p.). Paired-pulse potentiation of thalamocortical phenomena cannot be put into connection with the generation of the spike-and-wave rhythm.

Key words

Thalamocortical responses – Potentiation – Rat – Phenytoin – Valproate

Abundant information is available on the mechanisms of action of antiepileptic drugs among which phenytoin is the most frequently studied (for review see Woodbury 1980, 1982, Macdonald and McLean 1986, de Lorenzo 1989, Rogawski and Porter 1990). Contemporary studies at the membrane and molecular level are provided in different parts of the brain and the question if there is a structure responsible for the anticonvulsant action of antiepileptics or if they act diffusely throughout the central nervous system is often neglected. Therefore, we started a series of studies of the action of phenytoin on different brain systems; the present experiments were focused on the thalamocortical system. Valproate was used for comparison as a drug exhibiting its action through the ubiquitous GABAergic system (Chapman *et al.* 1982, Johnston and Slater 1982, Johnston 1984, Fariello and Smith 1989).

Experiments were performed on adult male albino rats of the Wistar strain. Surgical preparation (trephine openings over sensorimotor cortical areas of both hemispheres, tracheostomy and insertion of a tracheal cannula) was done under ether anaesthesia, then all wounds and future pressure points were carefully anaesthetized with benzocaine. Ether anaesthesia was discontinued and the rats were immobilized by d-tubocurarine (0.2 ml/kg i.p.). Electrolytically sharpened stainless steel wires isolated up to their tips with an optical varnish (diameter of the tips between 50 and 80 μm) serving for stimulation were introduced stereotaxically into the right thalamic ventrobasal complex at coordinates AP 2; L 2.5; H 6.5 mm (Fifková and Maršala 1960 – under the name of ventral dorsomedial nc.). Silver ball recording electrodes were placed on the right, i.e. ipsilateral sensorimotor cortical area (AP 0; L 2.5 mm). An indifferent electrode was localized on the nasal bone.

Stimulation with 0.3-ms rectangular pulses always started with an estimation of the threshold voltage; a twofold threshold value was used throughout the experiment. Then single pulses were applied, followed by paired pulses with intervals of 20, 50, 70, 100, 125, 160, 200, 250, 300, 350, 400, 500, 750 and 1000 ms between the pulses. The pairs were applied with at least 5-s intervals. Sixteen responses were always averaged by means of an ANOPS-101 analyzer and recorded on an XY plotter. Then either phenytoin (Epanutin^{R} Parke and Davis, 60 mg/kg i.p.) or valproate (Gerot Pharmazeutica, 400 mg/kg i.p.) were administered and 15 min later the whole stimulation

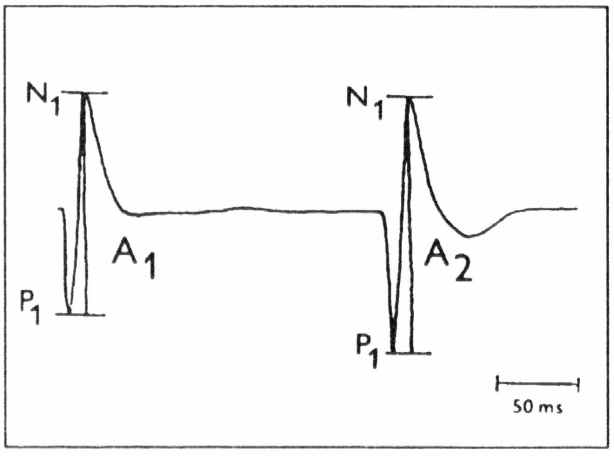

Fig. 1
Schematic representation of the paired cortical interhemispheric responses and amplitudes of the P_1 and N_1 components.

series was repeated. During the pause, benzocaine local anaesthesia was renewed. An additional series was performed with valproate treatment studying in detail short intervals: 10, 20, 30, 40, 50, 60, 70, 80, 90 and 100 ms were used. The experimental schedule was identical with that used for longer intervals in all other points.

Amplitude and latency of the first two components of the cortical response – positive and negative (P_1N_1) – was measured (Fig. 1). Amplitude of the second response was compared with that of the first one in the pair and expressed as percentage. Statistical comparison of the pre- and postdrug values was done by means of the paired t-test. Only the animals with histologically confirmed localization of stimulation electrodes in thalamic ventrobasal complex were taken into consideration.

Phenytoin effects were studied in eight rats (Fig. 2). It left the latencies of thalamocortical responses as well as the amplitude of single responses unchanged. Paired-pulse potentiation expressed with interpulse intervals from 50 to 200 ms under control conditions was abolished by phenytoin. On the contrary, a tendency to depression of the second response was observed; the level of statistical significance (in comparison with the appropriate first reponse in the pair) was reached only with the longest intervals (500 ms and more). The solvent used for phenytoin (a mixture of water, propyleneglycol and ethanol), which is the same as for clonazepam, was studied in previous series of experiments (Kubová and Mareš 1992) and it did not change the excitability cycle of thalamocortical responses.

Valproate was examined in other nine rats (Fig. 3). It did not change the latencies of responses and amplitude of the single response as well. Paired-pulse potentiation was not abolished, its magnitude decreased reaching the level of statistical significance only exceptionally. An additional series of 12 rats where short intervals were studied in detail could not again demonstrate statistically significant changes.

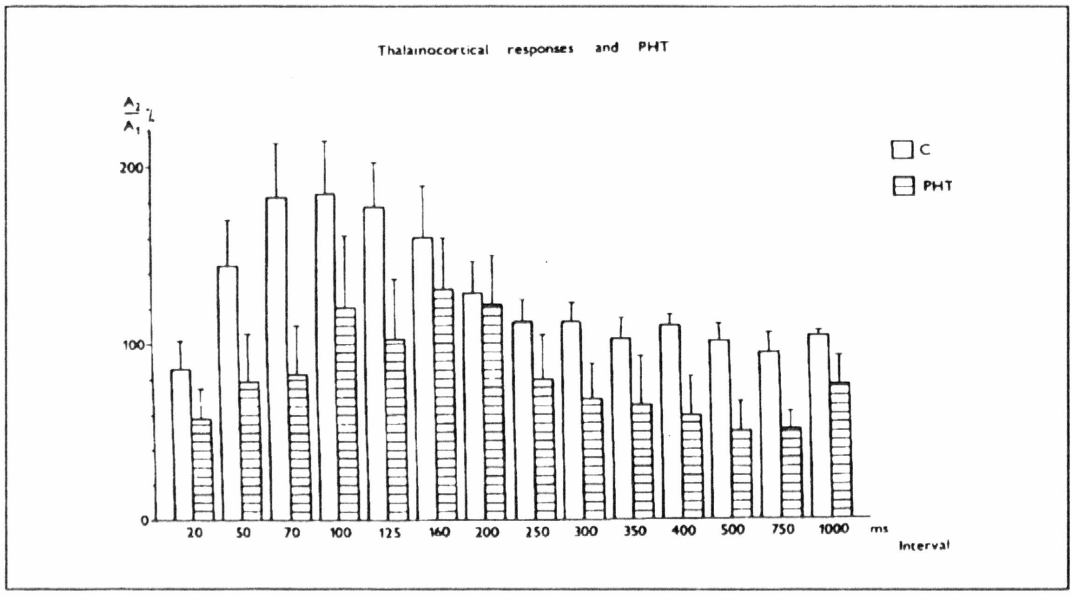

Fig. 2
Excitability cycles of cortical evoked potentials before (white columns) and after phenytoin in a dose of 60 mg/kg i.p. (hatched columns). Means and S.E.M. are given for each interval. Abscissa - intervals between the first and the second stimulus in seconds; ordinate – relative amplitude of the second response (the first response was always taken as 100 %).

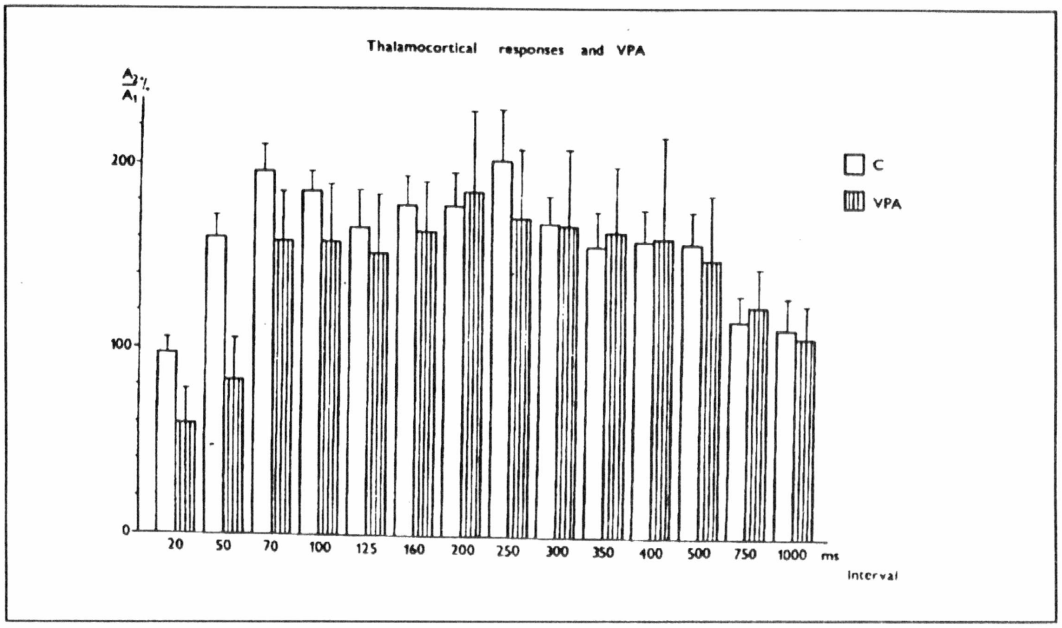

Fig. 3
Excitability cycles of cortical evoked potentials before (white columns) and after valproate in a dose of 400 mg/kg i.p. (hatched columns). Details as in Fig. 2.

The abolition of the paired-pulse potentiation of the thalamocortical response by phenytoin demonstrated for the early components of the response in agreement with the data of Englander *et al.* (1977) might be due to the diminished cortical excitability. The data demonstrating an increase in thresholds for eliciting cortical epileptic afterdischarges after phenytoin pretreatment (Aston and Domino 1961, Blum 1964) speak in favour of this explanation. On the contrary, paired-pulse potentiation of the cortical interhemispheric responses could not be suppressed by phenytoin (Mareš *et al.* – submitted). The same discrepancy in the behaviour of the early components of two types of evoked potentials in the same cortical area was demonstrated with clonazepam (Kubová and Mareš 1992). This anticonvulsant drug again suppressed paired-pulse potentiation of thalamocortical responses leaving intact the same phenomenon in interhemispheric responses. Similarity in the shape of the early components of the thalamocortical and interhemispheric responses does not mean identity. The two subsets of neurones receiving thalamic and callosal afferents (Killackey 1983, Macchi and Bentivoglio 1986) probably respond differently to antiepileptic drugs.

Phenytoin exhibited an action on the simplest potentiation phenomenon in the thalamocortical system, probably at the cortical level. This mechanism may take part in the suppressant action of phenytoin on the spread of epileptic activity (Woodbury 1980, 1982). On the other side, the action of PHT at the thalamic level cannot be excluded. The weak effect of valproate was surprising. The specific suppression of potentiation with intervals of about 300 ms described by Nowack *et al.* (1979) was not found in our experiments. Valproate was found to be efficient against spike-and-wave afterdischarges induced by rhythmic thalamic stimulation under identical experimental conditions (Mareš *et al.* 1984) as well as against the spike-and-wave rhythm induced by small doses of pentylenetetrazol (Mareš and Velíšek 1986). The frequency of these rhythms in rats is rather higher than 3 Hz (4-5 Hz – Zouhar *et al.* 1980, Mareš *et al.* 1982) so that an effect on the intervals of 200-250 ms might have been expected. The failure of such a finding signifies that the paired-pulse potentiation of thalamocortical responses has probably nothing to do with the generation of the spike-and-wave rhythm.

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