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BRIEF COMMUNICATION

Suppression of Photically Evoked After-Discharge Bursting Following Administration of Anticonvulsants in Waking Rats

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SHEARER, D. E., D. E. FLEMING, E. D. BIGLER AND C. E. WILSON. *Suppression of photically evoked after-discharge bursting following administration of anticonvulsants in waking rats.* PHARMAC. BIOCHEM. BEHAV. 2(6) 839–842, 1974. – Tridione, depakine and dilantin were examined with respect to their effect on the occurrence of photically evoked after-discharge (AD) bursting. It was observed that each of these anticonvulsants reliably suppressed AD bursting although tridione and depakine were significantly more effective than was dilantin. These results were attributed to the locus of action of the anticonvulsants and suggest the usefulness of AD as an index of the effectiveness of thalamically active drugs.

Photically evoked after-discharge Visually evoked response Anticonvulsants Metrazol Drug interactions

FOLLOWING the initial investigations of the rhythmical after-discharge evoked from the visual cortex of waking rats by iterative photic stimulation [8,10] our laboratories have further analyzed the visually evoked after-discharge (AD) in detail under varied conditions [3–6, 11]. Wilson and Creel [19] reported in a preliminary study that the thalamically active anticonvulsant, trimethadione (tridione), suppressed the AD of albino rats that had been augmented following the administration of pentylenetetrazol (metrazol). Kästner *et al.* [7] reported that tridione reduced spindle activity facilitated by metrazol in the EEG of freely moving rats. Along these same lines Wenzel *et al.* [17] reported that another anticonvulsant, ethosuximide, also suppressed metrazol induced spindle activity in the visual cortex of freely moving rats. Apparently these results lend support to the notion that tridione, ethosuximide, and other anticonvulsant agents effective in controlling petit mal epilepsy share a common thalamic site of action. Current thought also places the generation of AD bursting at this same level [14].

A natural outgrowth of this and previous avenues of research has prompted us to evaluate further the effects of the following three anticonvulsants: tridione, diphenylhydantoin (dilantin), dipropylacetate (depakine) and their combination with metrazol on photically evoked after-discharge bursting in waking albino rats.

METHOD

Animals

Ten male Holtzman albino rats between the ages of 90–100 days at the start of the investigation were anesthetized with pentobarbital sodium (45 mg/kg) and surgically prepared with indwelling extradural stainless steel electrodes implanted over the right and left visual cortices at points 7 mm posterior to the bregma and 3 mm lateral to the midline. Electrodes were also placed in the calvarium over the cerebellum and frontal sinus for reference and

grounding, respectively. Seven days of recovery were allowed prior to initiation of the drug treatment sessions. All experimental procedures were carried out on waking animals with mydriatic pupils.

Apparatus

A Grass Model PS2C photostimulator was used to present 10 μsec light pulses to a reflecting hemicylinder. The hemicylinder was placed in front of a hammock in which an animal was held under light restraint. With the photostimulator lamp placed 70 cm behind and slightly above the hemicylinder, the illimination of the reflecting surface was approximately 5 ft-c.

Brain responses were amplified with Grass 7P5A preamplifiers and Model 7 Polygraph amplifiers (bandwith, 0.3 Hz–3 kHz; time constant, 0.24 sec) and recorded conventionally on magnetic tape. Visually evoked responses (VERs) and ADs were summated with a Model 400B Computer of Average Transients (CAT) over a 1 sec epoch. Visually evoked responses and associated ADs were plotted on 25 × 38 cm graph paper by a X-Y plotter for parametric quantification.

Procedure

Each rat was administered the following drugs: dilantin (50 mg/kg), depakine (200 mg/kg), tridione (100 mg/kg), metrazol (10 mg/kg) and 0.9% saline. The drugs were injected in equal volume amounts intraperitoneally according to an individualized random schedule. The effective dose level of the drugs used had been previously determined.

A minimum of 5 days elapsed between drug treatments. The experiments were carried out in the following manner: A rat was acclimated to the hammock for 15 min. Single photic pulses were then presented at a rate of 1/7 sec. Blocks of 25 consecutive responses each were summed by the CAT starting at 0, 5 and 15 min following initiation of the iterative stimulation. When the third block of responses had been recorded, photic stimulation was interrupted, a drug injected, and a 15 min period elapsed before the iterative stimulation was resumed. Three blocks of 25 responses each again were recorded (0, 5, 15 min). Irrespective of which drug had been administered, when the third block of responses had been recorded, 10 mg/kg of metrazol were immediately injected, and following 7 min of continued photic stimulation, another block of 25 responses was recorded. The entire procedure yielded a series of 3 predrug and 3 postdrug plots and a plot indicating the response to the drug-metrazol interaction.

Measurement and Statistical Analysis

VERs from the right visual cortex were plotted for each set of 25 photic pulses. These responses typically included 3 positive–negative components followed by a rhythmic AD (see Fig. 1). In order to gain an indication of anticonvulsant and metrazol induced changes of the AD activity, total excursion (TE) of the AD tracing was measured from the third positive wave of the VER to the end of each 1 sec plot with a map reading wheel. The data were analyzed by analysis of variance techniques.

RESULTS

The effects of the various anticonvulsant drugs and saline control on the elicitation of AD bursting are displayed in Table 1 and Fig. 1.

Newman-Keuls tests based on a reliable analysis of variance ($F = 7.59$, $df = 3/27$, $p<0.001$) indicated that tridione and depakine differed reliably from saline control measures although dilantin did not. Tridione had the greatest suppressive effect on AD bursting while dilantin had the least effect. These results are also presented in Table 1.

The injection of metrazol following the drug treatments resulted in an increase in AD TE with the saline ($t = 2.60$, $df = 9$, $p<0.05$), dilantin ($t = 3.03$, $df = 9$, $p<0.02$), and the tridione ($t = 4.05$, $df = 9$, $p<0.01$) treatments. Metrazol did not override the effects of depakine on AD TE.

An examination of the parameters of the various VER components revealed the drug treatments to be generally ineffective in modifying either peak latencies or peak-to-peak amplitudes of the wave complexes. However, the peak-to-peak amplitude of one wave complex (P_3N_3) was

TABLE 1

MEAN (± STANDARD ERROR OF THE MEAN) TOTAL EXCURSION (IN cm) OF AFTER-DISCHARGE BURSTING FOR PREINJECTION, POSTINJECTION, AND DRUG-METRAZOL INTERACTIONS CONDITIONS

	Total Excursion			
	(A)	(B)	(C)	(D)
	Preinjection	Postinjection	Drug Metrazol Interaction	Difference Between B–C
Saline	115.6 ± 12.3	105.5 ± 13.3	133.3 ± 13.6	27.8 ± 10.7*
Dilantin	104.4 ± 20.3	88.0 ± 10.5	98.9 ± 10.3	10.9 ± 3.6*
Tridione	120.1 ± 13.2	58.4 ± 6.0	83.5 ± 9.0	25.1 ± 6.2*
Depakine	118.6 ± 16.1	81.1 ± 11.7	80.0 ± 9.6	1.1 ± 8.9

*Difference statistically significant (see text)

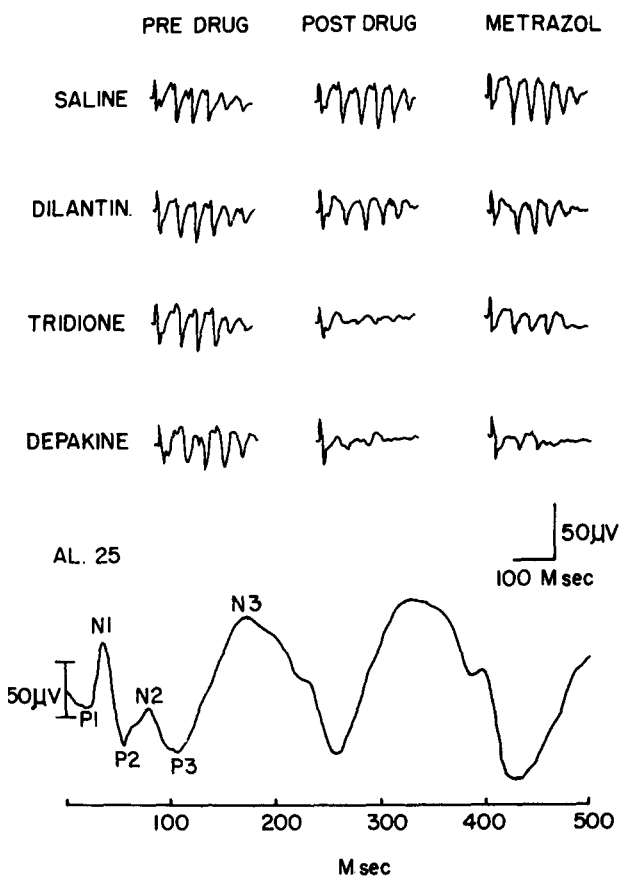

FIG. 1. Illustration of pre-injection, post-injection and drug-metrazol interaction after-discharge bursting as affected by the various drug treatments. The lower half of the figure displays a typical rat VER. Following the third negative wave (N_3) after-discharge bursting may be seen.

reliably suppressed by tridione ($t = 6.42$, $df = 9$, $p < 0.01$). A VER with a following AD burst is presented in Fig. 1 for the examination of the VER-AD relationship.

DISCUSSION

Evidently, the mechanism for photically evoked AD production resides in the lateral geniculate nucleus of the thalamus and involves recurrent inhibitory pathways [9,14]. According to Anderson and Andersson [1] recurrent inhibition is a common principle underlying rhythmic discharges produced by the several thalamic nuclei; however, whether rhythmic discharging is an intrinsic property of these nuclei or a property imposed by an intrathalamic driving mechanism is in question [12, 13, 15].

It is quite clear that the anticonvulsant drugs used in the present study suppressed AD bursting by presumably interacting with the thalamic pacing mechanism or the cortical elaboration of the rhythmic bursts. It has been noted by Woodbury [20] that dilantin is much more effective in modulating shifts in cortical excitability than in the regulation of diencephalic excitability. On the other hand, tridione is extremely effective in reducing excitability increases induced by stimulation of thalamic nuclei. Furthermore, thalamic nuclei seem to be particularly sensitive to tridione. Consistent with this observation, tridione is much more effective in controlling petit mal epilepsy than is dilantin. Along these lines, depakine also has been shown to be effective in the treatment of petit mal epilepsy [16].

Woodbury [20] has indicated the existence of a specific antagonism between tridione and metrazol. In the present investigation the measurement of AD TE revealed that metrazol injection enhanced TE following saline, dilantin, and tridione treatments. It may be of significance that depakine treatments were resistive to metrazol-induced facilitation. Esplin and Zablocka-Esplin [2] reported that metrazol functions to increase excitatory polysynaptic activity, increases repetitive firing of nerve fibers and shortens refractory periods and synaptic recovery time. Because metrazol potentiates the occurrence of AD bursts [6,18] it seems likely that metrazol facilitates the "rebound excitation" discussed by Anderson and Andersson [1] following a period of inhibition. On the contrary, tridione presumably suppresses "rebound excitation" as may depakine. However, the effects of tridione are antagonized by metrazol; apparently this is not the case with depakine.

As both tridione and depakine effectively suppressed AD bursting as compared to dilantin and that AD is presumably mediated by thalamic mechanisms it seems apparent that AD bursting could be utilized as a means of screening the relative effectiveness of thalamically active anticonvulsant drugs.

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