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BRIEF COMMUNICATION

Effects of Dipropylacetic Acid on Late Components of the Photically Evoked Potential and Afterdischarge in Rat[1]

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SHEARER, D. E., D. E. FLEMING AND R. E. DUSTMAN. *Effects of dipropylacetic acid on late components of the photically evoked potential and afterdischarge in rat.* PHARMAC. BIOCHEM. BEHAV. 8(4) 501–504, 1978. – The effects of dipropylacetic acid (DPA) on primary, secondary and afterdischarge waves of the photically evoked potential were examined. It was observed that DPA selectively attenuated late wave components and afterdischarge. A thalamic locus of action for these effects is postulated.

Photically evoked potential Dipropylacetic acid Anticonvulsants Afterdischarge

THE EFFECTIVENESS of sodium di-n-propylacetate (dipropylacetic acid, DPA, sodium 2 propylpentanoate) as an anticonvulsant has been well documented [7–8, 12, 15–20] following the initial report of its usefulness by Meunier *et al.* [9]. DPA seems to be particularly effective in the control of typical absence seizures (both simple and complex) and atypical seizures to a lesser extent [17]. Cerebral concentration of γ-aminobutyric acid (GABA) is increased after the administration of DPA [6] and a positive relationship between these increases in cerebral GABA concentrations and protection from audiogenic seizures has been reported [16]. We have previously found DPA to be effective in the attenuation of rhythmical afterdischarge bursting recorded from the rat visual cortex following the presentation of a brief photic pulse [14]. This photically evoked afterdischarge bursting appears to be of thalamic origin [1–4] and has been demonstrated to qualify as a reasonably good model for the assessment of anticonvulsant agents, especially those useful in the treatment of petit mal epilepsy [13]. Although afterdischarge (AD) bursting has been shown to be affected by DPA, we have noted a paucity of research concerning the effects of this drug on the peak latencies and amplitudes of the wave components of the photically evoked potential (PEP). The dose level of DPA selected for this investigation has been reported to be effective in the control of experimentally induced seizures in the cat [18] and in the attenuation of AD bursting in the rat [14]. The purpose of this investigation was to examine the 3 regularly occurring positive–negative wave components of the PEP and AD bursting recorded from the waking albino rat following the administration of saline, DPA and a pentylenetetrazol (Metrazol) challenge.

METHOD

Animals

Eleven male Holtzman albino rats between the ages of 90 and 100 days at the start of the investigation were used. Each rat was anesthetized with pentobarbital sodium (45 mg/kg) and surgically prepared with indwelling, extradural stainless-steel screw 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 overlying the cerebellum and frontal sinus for reference and grounding, respectively. Seven days of postoperative recovery were allowed prior to the initiation of drug treatment sessions. All experimental procedures were carried out on waking animals having mydriatic pupils (1% ophthalmic atropine).

Apparatus

A Grass Model PS2C photostimulator was used to present 10 μsec light flashes into a reflecting hemicylinder. The hemicylinder was mounted 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 illumination of the reflecting surface was approximately 50 lux.

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

Procedure

The experiment was carried out in the following manner. The rats were acclimated to the hammock over several daily 15 min periods. When they were acclimated, single photic pulses were presented at a rate of 1 per 7 sec. Following 5 min of iterative stimulation, an evoked response to 25 consecutive electrocortical responses was summated by the CAT. Following recording of this baseline run, photic stimulation was interrupted and either 0.9% saline or 200 mg/kg DPA was administered and a 15 min period elapsed prior to the resumption of the iterative stimulation. PEPs were then summed from 2 blocks of 25 responses recorded at 15 and 30 min post saline or drug administration. Only the 30 min postinjection data will be reported. Irrespective of which substance had been given, when the second block of responses had been recorded, 10 mg/kg of Metrazol was injected as a challenge dose. Then after an additional 10 min of continued photic stimulation, a PEP was summed from 25 consecutive responses. Thus, 4 PEPs were obtained: 1 during the baseline period, 2 following either saline or DPA administration, and 1 following the Metrazol challenge. The DPA, saline and Metrazol were injected IP in equal volumes. Whether a rat received saline or DPA was determined on a random basis. Since each rat received both DPA and saline treatment during the course of the experiment, a minimum of 4 days elapsed between treatments.

Measurement and Statistical Analysis

PEPs from the right visual cortex were plotted. These responses typically included 3 positive–negative components labeled P1–N1, P2–N2 and P3–N3 which were followed by a rhythmic AD burst (see Fig. 1). The peak was determined for each positive or negative component and the peak-to-peak amplitude was determined for each component. In order to evaluate DPA and Metrazol induced changes of the AD activity, total excursion of the response was measured in centimeters (cm) from the third positive wave of the PEP to the end of each 1 sec plot with the use of a map reading wheel. The data were analyzed by t ratio statistics.

RESULTS

The mean peak latency and peak-to-peak amplitude values of the PEP wave components are presented in Table 1. It can be readily observed that peak latencies were unaffected by saline, DPA or Metrazol challenge administration. However, in comparison with saline administration, DPA resulted in a significant amplitude attenuation of a late wave, P3–N3, and AD excursion, $t(10) = 3.30$, $p<0.01$; and $t(10) = 2.55$, $p<0.05$, respectively. Concerning the effects of the Metrazol challenge on DPA, it can be seen that Metrazol failed to override the attenuating effects of DPA on P3–N3 amplitude and AD excursion, $t(10) = 6.60$, $p<0.001$; and $t(10) = 6.90$, $p<0.001$, respectively. On the other hand, with respect to saline, Metrazol challenge approached a significant augmentation of P3–N3, $t(10) = 2.15$, $p<0.06$, and did significantly potentiate AD excursion, $t(10) = 3.29$, $p<0.01$. Again, it should be noted that the administration of Metrazol failed to antagonize the effects of DPA on the late wave components of the PEP and its associated AD. A PEP with a following AD burst is presented in Fig. 1 for the examination of the PEP-AD relationship.

DISCUSSION

Preliminary experimentation has revealed that the suppression of AD bursting by DPA is not antagonized by Metrazol [14]; accordingly, the present study verifies these earlier findings and extends them to the late waves of the PEP complex. It is quite clear that of the various PEP

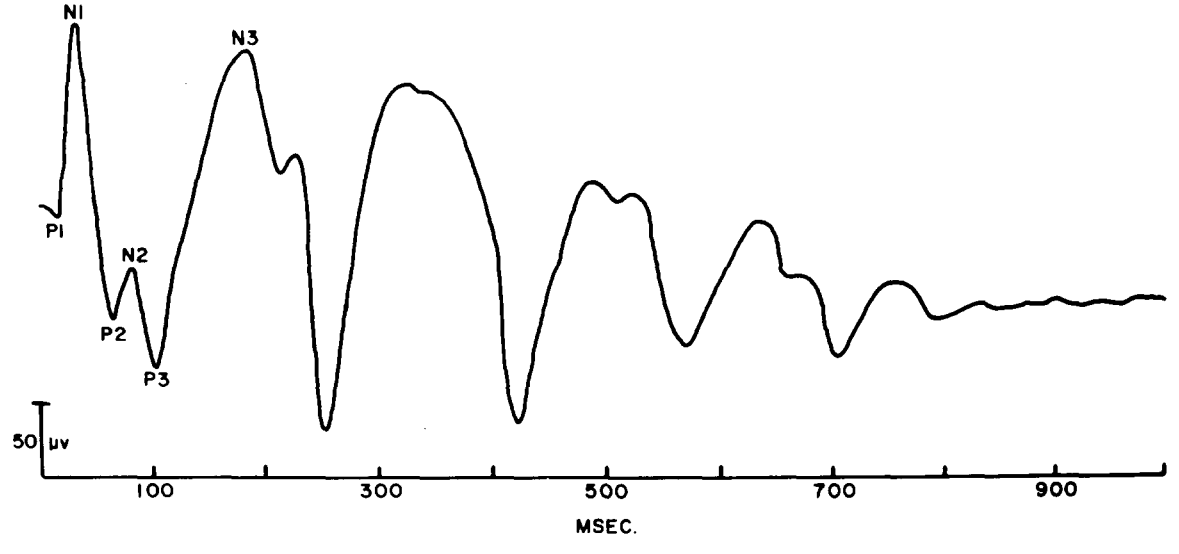

FIG. 1. A representative PEP recorded from the rat visual cortex with wave components labeled P1–N3 followed by AD bursting.

TABLE 1

COMPARATIVE EFFECTS OF SALINE, DPA AND METRAZOL CHALLENGE ON LATENCY AND AMPLITUDE OF EVOKED POTENTIAL WAVE COMPONENTS AND AFTERDISCHARGE

	30 Min Post Injection		Metrazol Challenge	
	Saline	DPA	Saline	DPA
Peak Latency (msec)				
P1	16.6	16.6	16.6	16.6
N1	27.7	27.7	27.7	27.7
P2	49.9	52.6	52.6	52.6
N2	83.1	83.1	88.6	85.9
P3	99.7	105.3	99.7	105.3
N3	174.5	177.3	177.3	182.8
Amplitude (μV)				
P1-N1	120.0	112.5	130.5	112.5
N1-P2	168.0	171.0	178.5	166.5
P2-N2	75.0	79.5	85.5	73.5
N2-P3	21.0	22.5	16.5	22.5
P3-N3	110.0	82.5†	130.5	81.0‡
AD (cm)	62.0	37.0*	90.0	41.0‡

*$p<0.05$.
†$p<0.01$.
‡$p<0.001$.

waves, only the late wave complex is affected by DPA. Moreover, it is equally clear that there exists a close correlation between the effects of DPA on the P3–N3 component and on AD bursting. Along these lines, it has been suggested by Fleming *et al.* [5] that the late negative wave of the PEP is the leading wave or precursor of AD bursting and that a common mechanism of thalamic origin is responsible for the occurrence of these neuroelectric events.

Bigler and his collaborators [1–4] have identified the lateral geniculate nucleus of the thalamus (LGN) as the site at which AD bursting (and presumedly the P3–N3 wave of the PEP) is produced. It appears that the Principal cells (P cells) of the LGN, as the result of a process of recurrent inhibition regulated by intrinsic thalamic circuits, discharge in regular bursts which are the generators for the 5–8 Hz AD bursting recorded from the surface of the visual cortex [2]. Ostensibly, the action of DPA is the suppression of mechanisms that are responsible for the iterative bursting of LGN P cells. Whether this suppression occurs directly at the level of the LGN or at some other thalamic site which modulates LGN activity (e.g., nucleus reticularis thalami [4]), is at the present time problematical. Nevertheless, DPA has a specific action, direct or indirect, on the proposed thalamic mechanism required for the production of the P3–N3 complex of the PEP and on AD bursting. While there is experimental support for an extrageniculate pathway which is apparently active in the generation of the late wave complex of the PEP [11], it is becoming apparent that the LGN must play a more important role in PEP late wave elaboration than previously considered. The interaction of geniculate and extrageniculate mechanisms in the production and modulation of PEPs remains to be elucidated; however, it appears that DPA could serve as a useful pharmacological tool for the separation of early and late wave components of the rat PEP.

It is of interest that DPA did not affect the early waves of the PEP complex. Since DPA administration results in an increase in GABA levels [6] and since GABA has been implicated as a retinal neurotransmitter [10] one could assume that DPA would modify retinal transmission and correspondingly affect the excitability of the visual pathways. However, because the early waves of the PEP were not affected by the DPA treatment, it seems unlikely the GABA-mediated pathways would have any specific influence on early PEP waves resulting from diffuse light stimulation of the retina. Thus, PEP parameters would be unchanged by DPA treatment. On the other hand, had patterned stimulation been used these GABA-mediated pathways may have had an effect on retinal transmission and accordingly DPA may have shown an effect on PEPs evoked by patterned stimulation.

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