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Dissociation Between Behavioral and Electrocortical Manifestations of Electroshock Convulsions During the Action of an Anticonvulsive Drug[1]

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DE-LA-CRUZ, F. AND M. RUSSEK. *Dissociation between behavioral and electrocortical manifestations of electroshock convulsions during the action of an anticonvulsive drug.* PHARMAC. BIOCHEM. BEHAV. 16(1) 177–180, 1982.—It was shown that 5-OH-5-ethyl-5-phenyl-butiramide (formerly called 5-ethyl-5-phenyl-2-pyrrolidinone) significantly reduces convulsions induced by electroshock in rats, and by drugs in mice. We are reporting a dissociation between the effects of this drug on the behavioral manifestations of electroshock and on the electrocortical afterdischarges. At 50 mg/kg, the drug reduced greatly the duration of the tonic phase of muscular convulsions, but had little or no effect on their total duration or on the electrocortical afterdischarges. At 100–150 mg/kg, the effect on the tonic phase was only slightly larger, but the total duration of behavioral convulsions and the intensity of electrocortical afterdischarges were substantially reduced, while the duration of the latter was either slightly reduced or increased. Only 200 mg/kg, which had clear depressant effects, produced a complete disappearance of all manifestations of electroshock convulsions. It can be concluded that this drug acts more strongly on subcortical structures that transmit cortical convulsions to the muscles, than on the cortical mechanisms that generate electrocortical afterdischarges.

Electroshock convulsions Anticonvulsants Electrocortical afterdischarges

CARVAJAL [2,4] produced a new drug which, according to the synthesis procedure should correspond to the formula 5-ethyl-5-phenyl-2-pyrrolidinone. Later it was shown by nuclear magnetic resonance and X-ray crystallography [3,4] that the pyrrolidinone ring did not form so the actual formula was 5-OH-5-phenyl-5-ethyl-butiramide (synonym to 4-OH-4-phenyl-hexanamide). This substance has a mild inhibitory action on the gamma-aminobutyric/alpha-ketoglutaric transaminase *in vitro*, but it does not increase the cerebral levels of gamma-aminobutyric acid significantly [2]. Nevertheless, it has a powerful action against electroshock-induced muscular convulsions in rats and protects mice against convulsions and death induced by thiosemicarbazide and penthylenetetrazol [2]. It also showed a potent clinical anticonvulsive action in patients having *grand mal* seizures [1].

In this study, no observations were made on the electrocortical afterdischarges that accompany the muscular convulsions. The present communication reports the effects of this drug on the cortical and peripheral manifestations of electroshock convulsions.

METHOD

Cortical screw electrodes were chronically implanted in male Wistar rats, 200–240 g (approximately 6–8 months), 2 mm rostral to the bregma, 2 mm from the midline on each side. The same electrodes were used to stimulate and record. Electromyogram electrodes were implanted in the neck muscles. At least three days were allowed for post-operative recovery. The experiments were performed in a padded box to preclude injury to the rats during the convulsions. The parameters of electroshock were: rectangular pulses of 2 msec duration and 10–20 V at a frequency of 25/sec, for 5 sec, applied every 15 min. With this stimulus, maximal convulsions of a fairly constant duration (15–25 sec) were obtained for at least 3 hours. 5-OH-5-ethyl-5-phenyl-butiramide (HEPB) was administered intraperitoneally after 3 or 4 control convulsions, at doses of 50, 100, 150 and 200 mg/kg dissolved in water at a concentration of 10 mg/ml. IP saline injections of the maximum volume used in the drug injections were administered as a control and no effect on the duration of the convulsions was observed.

[1]5-OH-5-ethyl-5-phenyl-butiramide. We thank Dr. Guillermo Carvajal for providing the substance for this study.

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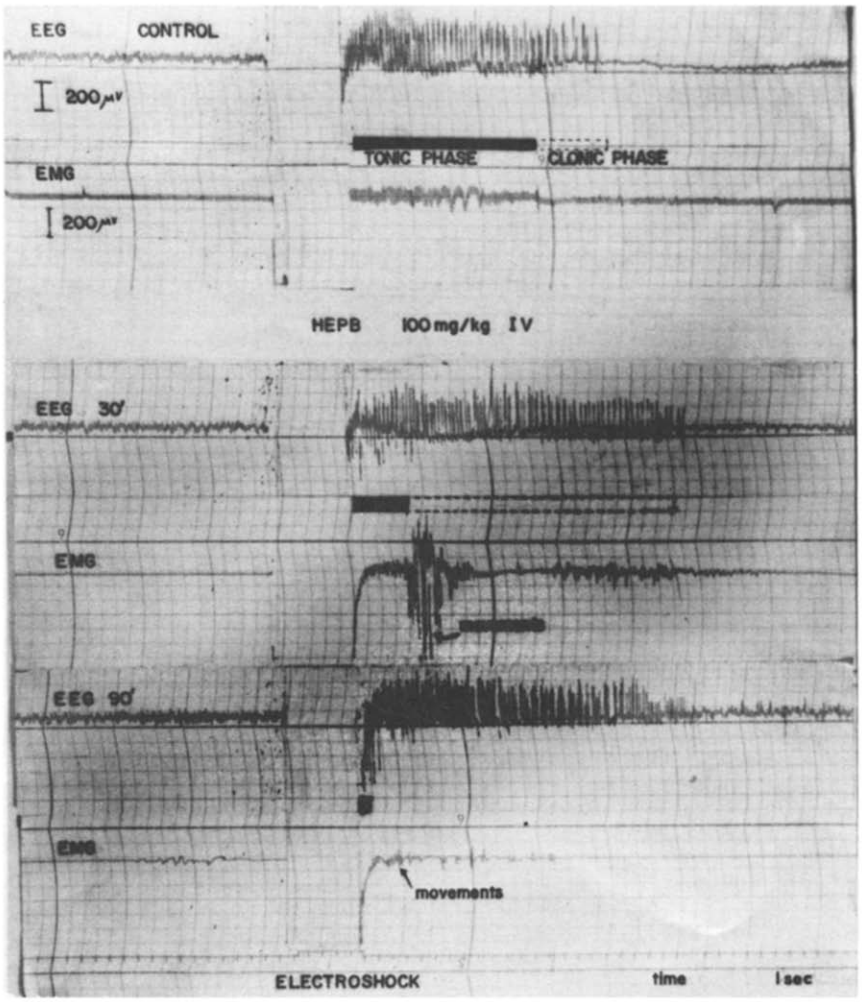

FIG. 1. Electroencephalographic (EEG) and electromyographic (EMG) recordings, and muscular convulsions (dark bars) before and at two time intervals after the injection of 100 mg/kg of 5-OH-5-ethyl-5-phenyl-butiramide (HEPB).

Electromyogram and electroencephalogram were recorded by a Narco Physiograph Mark IV. Simultaneously, the tonic and clonic phases of the convulsions were observed visually and measured chronometrically.

RESULTS AND DISCUSSION

The behavioral muscular convulsion consisted of a tonic phase that started with maximal extension of limbs and body (the rats lying on their backs or sideways) that was gradually transformed into a flexion of the limbs. This phase was abruptly interrupted by clonic contractions of the four limbs at a frequency of about 1/sec, constituting the clonic phase which ended in a complete relaxation of all muscles (post epileptic depression), accompanied by tachypnea.

There is a clear dissociation between the effects of the drug on the tonic and clonic phases of the muscular convulsion, on the one side, and the electrocortical afterdischarges, on the other. Even when no muscular convulsion can be observed, either visually or electromyographically, an afterdischarge of the same duration as the control may be present (Fig. 1).

The average effect of the lowest dose (50 mg/kg) is to shorten the tonic phase without affecting the total length, that is, the tonic contractions are transformed into clonic (Fig. 2). The changes in the electrocortical afterdischarges at this dose were negligible. At larger doses (100 and 150 mg/kg), both the tonic and clonic phases of the muscular convulsion are substantially reduced, but the electrocortical discharge may have the same duration as before the injection. However, its intensity judged by the product of maximum frequency times maximum amplitude, is clearly reduced. At 200 mg/kg, all cortical and peripheral manifestations of the convulsion are suppressed, but the rats seemed depressed and moved little between convulsions. They usually died after three or four stimulations, even though no convulsions were elicited.

These data suggest that the drug potentiates a central inhibitory mechanism acting both at the cortical level and at subcortical structures that play a role in the spreading of the convulsive activity from cortex to muscles. Low doses would act mostly on subcortical structures, blocking the transmission of the electrocortical discharge to the muscles, while higher doses will also affect the intensity of the cortical

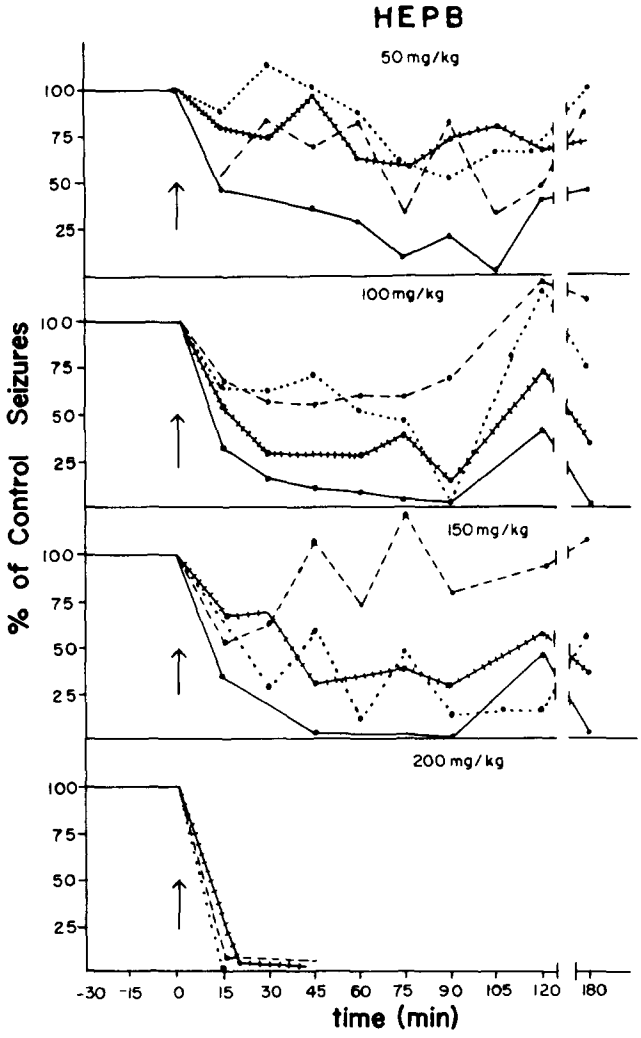

FIG. 2. Effect of different doses of 5-OH-5-ethyl-5-phenyl-butiramide (HEPB) on the convulsions elicited by electroshock in the rat. Ordinates: percent of control. Abscissa: time in minutes. Solid line: duration of tonic phase measured chronometrically. Broken line: duration of electrocortical discharge. Line of points: duration of muscular convulsion measured by electromyogram. Striped solid line: intensity of electrocortical discharge determined as maximal amplitude multiplied by maximal frequency. Convulsions were elicited every 15 minutes before and after the intraperitoneal injection of the drug (marked by the arrow). The 100% control was the average of the three convulsions preceding the injection. The curves represent average of 4 rats.

afterdischarges. Only doses that kill the animal suppress completely the cortical convulsive activity during the period before death. It is known that stimulus subthreshold for muscular convulsions may elicit electrocortical afterdischarges [5]. Thus, we could say that this drug increases the threshold for peripheral convulsions, transforming threshold stimuli into subthreshold ones.

It has been reported that hydantoines block the propagation of an afterdischarge without suppressing the convulsive activity in the primary epileptogenic focus [6], which may be a similar phenomenon to the one described in the present communication.

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