PROPERTIES OF MAXIMAL SEIZURES, AND THEIR ALTERATION BY ANTICONVULSANT DRUGS AND OTHER AGENTS

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INTRODUCTION

Despite the high incidence of convulsive disorders and widespread use of shock therapy in the major psychoses, relatively few investigations have dealt with the physiological properties of experimental seizures (1, 2, 3, 10, 12, 14, 16, 17). Convulsive threshold has received considerable attention, particularly in the testing of anticonvulsant drugs (11, 13, 15, 18, 21, and others), but threshold is only one of many properties which might be examined in any excitable system. Furthermore, measurements of threshold are of but limited value in the detection of antiepileptic potency (5, 6, 7, 8, 19, 20). For example, diphenylhydantoin, which has been found superior to phenobarbital in the treatment of psychomotor epilepsy and of comparable value in grand mal, is relatively ineffective in raising the threshold either for metrazol or electroshock seizures in laboratory animals.

Therefore we have undertaken a series of studies on other properties of experimental seizures (7, 8, 19, 20, 23). Several new techniques for the testing of anticonvulsant drugs have already evolved from these studies (7, 8, 20, 22). The technique which to date has shown the best correlation with clinical antiepileptic efficacy is based upon the ability of certain drugs to alter the character of major seizures produced by supramaximal electroshock stimulation. The present report deals with some elementary properties of maximal seizures in normal animals, and with the effects of anticonvulsant drugs upon these properties.

METHODS

Seizures were produced in cats, albino rabbits, and Sprague-Dawley rats by an Offner clinical electroshock apparatus delivering from 0 to 700 milliamperes (mA.) of 60 cycle alternating current with stimulus duration of 0.05 to 10.0 sec. For small current values an external attenuator was added. Current during stimulation was checked with an external peak AC milliammeter. For shocks of longer duration a variable transformer was used. Shocks were usually delivered through Spiegel corneal electrodes (18). In some rabbits the stimulating electrodes were insulated steel screws aseptically implanted over the visual and motor areas of one cerebral hemisphere. In these animals similar electrodes over the opposite hemisphere were used for recording of EEG seizure discharges, the visual and motor areas being compared with an "indifferent" electrode in the nasal bone; the EEG was recorded with a Rahm E2X60 twin-channel thermal-writing electroencephalograph.
with time constant of 0.2 sec. and flat frequency-response characteristic up to 40 cycles per sec.

For determinations of seizure threshold, shocks of 0.2 sec. duration were given at intervals of 5 or more minutes with successive increments of 10 per cent in current until a "minimal" seizure occurred. This "minimal" seizure, which was shown in rabbits to be the least overt activity accompanied by EEG seizure discharges, consisted of 10 or more seconds of facial clonus without loss of righting reflexes. At least several hours were permitted for recovery following each seizure, except in those cases where the recovery period itself was investigated. "Submaximal" seizures of increasing severity were produced by successive small increments of current above threshold. The "submaximal" seizures consisted either of generalized clonus, or contained a preliminary tonic phase with flexion at limb joints. In either case postural reactions were lost during the seizure. When further increments of current failed to alter the pattern or duration of seizures, they were considered to be "maximal" seizures. They usually consisted of a short flexor and long extensor tonic component with little or no terminal clonus. All strengths or current above that required to produce them in normal animals were considered "supramaximal." In most animals the "supramaximal" level began not more than 20 per cent above threshold. When it was necessary to produce unequivocal "maximal" seizures for studies of recovery or drug action, the stimulating current was arbitrarily set at least 200 per cent above the normal seizure threshold.

In evaluating the effect of antiepileptic drugs the following simplified procedure was used ("supramaximal electroshock method"). In each determination a series of animals was treated with a range of doses up to the toxic level. After a suitable interval for optimal drug action, the neurological status of each animal was examined. Immediately afterward corneal electrodes were applied and a supramaximal shock delivered. Animals were observed for presence or absence of an extensor tonic component in the hindlegs during the seizure. The protective dose of the anticonvulsant agent was taken to be that required to abolish this extensor tonic component. The toxic dose was taken to be that causing minimal signs of central impairment. A protective index was calculated for each agent by dividing the toxic dose by the protective dose. Antiepileptic agents studied by this method included sodium diphenylhydantoin (dilantin), sodium phenobarbital, 3,5,5-trimethyl-oxazolidine-2,4-dione (tridione), dimethyl-N-methyl-barbituric acid (AN 22), diethyl-N-methyl-barbituric acid (AN 23), benzimidazole, sodium bromide, and 1(+) glutamic acid. Other details of technique will be found under Results.

RESULTS

Evidence indicating that tonic extensor seizures are maximal. Tonic extensor seizures were elicited in most rabbits by shocks not more than 20 per cent above threshold for minimal seizures. The only consistent trend noted with increasing current was a decreased latency. Thus in six animals the average latent period before development of flexor tone was reduced from six sec. at 75 mA. to two sec. at 300 mA. The total duration of seizure was correspondingly reduced with increasing strength of current. In 108 seizures elicited in 50 albino rabbits stimulated for 0.2 sec. with 300 mA. (or approximately six times the threshold current for minimal seizures), the following components of the convulsion were relatively invariable in character, sequence and duration: (a) Latent period. Approximately two seconds. (b) Flexor component of tonic phase. Extreme tonic flexion at all limb joints with slight superimposed tremor, lasting approximately three seconds. (c) Extensor component of tonic phase. Extreme extension at all limb joints with

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1 Generously supplied by Dr. Oliver Kamm of Parke, Davis and Co.
2 Generously supplied by Dr. R. K. Richards of the Abbott Laboratories.
little or no tremor, followed by abrupt relaxation; average duration 14 seconds. The average elapsed time from stimulation to end of the tonic phase was 19 seconds (range 15 to 25 sec., SD ± 2 sec.). (d) Clonic phase (frequently absent). One or more extensor thrusts, followed by complete relaxation; average duration two seconds. (e) Period of post-seizure depression. Inability to exhibit contact placing reactions and to maintain a second maximal seizure; average duration four minutes.

In two out of 52 albino rabbits, and in four out of seven colored rabbits, it was impossible to produce the extensor tonic component, even though the current was increased to 500 mA. Such animals were avoided in assays of anticonvulsant drugs.

In rats and cats the seizure pattern was identical with that in rabbits except for the time scale. In 50 control rats, tested with supramaximal shocks of 150 mA. and 0.2 sec. duration, or approximately five times the threshold, the average elapsed time to the end of tonic seizures was 14 seconds (range, 12 to 17 sec., SD ± 1 sec.). In two additional rats, flexor tonic seizures only were elicitable. Twenty-four cats were tested with 400 mA. for 0.2 sec., or approximately five times threshold. The mean duration to the end of the extensor tonic component was 15 sec. (range, 10 to 20 sec., SD ± 3). In four additional cats, only flexor tonic seizures were exhibited.

The following procedures failed to increase the duration or severity of tonic extensor seizures in rabbits and rats: variation in electroshock current from 20 per cent above threshold to 10 times threshold; variation in shock duration from 0.2 to over 30 sec.; stimulation by additional supramaximal shocks at various times during the course of a seizure; reduction in electroshock threshold by metrazol or by cellular hydration. It would therefore appear that the brain is maximally active during a tonic extensor seizure, and the discharge once initiated is independent of the stimulus.

Modification of maximal seizures by repetition. Thresholds were reetermined in rabbits at various intervals following maximal seizures. They were found to average 200 per cent of normal at 4 minutes, and 118 per cent at 60 minutes, so that the period of increased threshold considerably outlasted any overt neurological signs of post-seizure depression. Maximal seizures could be elicited again as early as four minutes after a previous seizure (i.e., when the threshold had fallen to 200 per cent of normal). However, continued repetition of seizures resulted in a progressive slowing of recovery and a modification of the various components of seizures in the following order: (a) The first effects were an increased duration of flexor tonic component, a reduced duration of the hindleg extensor tonic component, a decrease in total tonic phase, an increase in duration of the clonic phase, and an increase in total seizure duration. If the tonic flexor component persisted beyond approximately 10 sec., no tonic extension developed. The tonic flexor component itself did not persist beyond 15 sec. (b) With further elicitation of seizures the tonic flexor component was shortened until it also
disappeared. The seizure was now completely clonic, often severe, and frequently longer in duration than that of the unmodified maximal seizure. (c) With still further elicitation of seizures, the clonic type of convulsion became shorter and milder and sometimes was abolished completely. (d) Following a mild clonic seizure or a complete failure to respond, the next shock in such a series often produced a severe submaximal convulsion. Thereafter the responses tended to alternate between mild and severe.

The progressive effects of repeated supramaximal electroshock are illustrated in Figure 1. The time course of recovery of seizure threshold following maximal convulsions was studied in normal rats and found to be similar to that in rabbits. The results are illustrated in Figure 2. The recovery period was also investigated in rats in which cellular hydration produced by extracellular electrolyte depletion (20) had reduced the seizure threshold by more than 50 per cent. In spite of the difference in threshold, the time course of recovery was identical in both normal and hydrated animals, indicating the relative independence of the excitation and recovery processes.

As might be expected, thresholds in both rats and rabbits were found to be greater after maximal seizures than after clonic seizures elicited by shocks just above threshold. This was true even though the clonic seizures were usually longer in duration than the maximal seizures. In rabbits in which the tonic extensor component had been abolished by repeated supramaximal shocks at intervals of ten minutes or less, the complete maximal seizure pattern could often be restored by increasing the shock strength or duration, or by delivering additional shocks during the course of a clonic or tonic flexor seizure. During submaximal seizures, the brain is therefore capable of reinitiating and sustaining maximal seizures.
PROPERTIES OF MAXIMAL SEIZURES

Effect of anticonvulsant drugs on maximal seizures. The alterations produced by anticonvulsant drugs were similar to those following repeated seizures in untreated animals. Progressive changes in the character of seizures with increasing doses of diphenylhydantoin are illustrated in Figure 3.

Table 1. Relative efficacy of various agents in modifying maximal electroshock seizures

<table>
<thead>
<tr>
<th>Species</th>
<th>Agent</th>
<th>Route</th>
<th>Protective Dose mg./kg. (P)</th>
<th>Toxic Dose mg./kg. (T)</th>
<th>Protective Index (I = T/P)</th>
</tr>
</thead>
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<tr>
<td>Rat</td>
<td>Diphenylhydantoin</td>
<td>i.p.</td>
<td>50</td>
<td>100</td>
<td>2.0</td>
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<tr>
<td>Rabbit</td>
<td></td>
<td>s.c.</td>
<td>60</td>
<td>180</td>
<td>3.0</td>
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<tr>
<td>Cat</td>
<td></td>
<td>i.p.</td>
<td>10</td>
<td>40</td>
<td>4.0</td>
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<tr>
<td>Rat</td>
<td>Phenobarbital</td>
<td>i.p.</td>
<td>12</td>
<td>30</td>
<td>2.5</td>
</tr>
<tr>
<td>Rabbit</td>
<td></td>
<td>i.p.</td>
<td>15</td>
<td>35</td>
<td>2.3</td>
</tr>
<tr>
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<td></td>
<td>i.p.</td>
<td>2</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>Rat</td>
<td>Pentobarbital</td>
<td>i.p.</td>
<td>12</td>
<td>14</td>
<td>1.2</td>
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<tr>
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<td></td>
<td>s.c.</td>
<td>8</td>
<td>12</td>
<td>1.5</td>
</tr>
<tr>
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<td></td>
<td>i.p.</td>
<td>3</td>
<td>3</td>
<td>1.0</td>
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<tr>
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<td>350</td>
<td>400</td>
<td>1.1</td>
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<tr>
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<td></td>
<td>i.p.</td>
<td>500</td>
<td>675</td>
<td>1.7</td>
</tr>
<tr>
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<td></td>
<td>i.p.</td>
<td>200</td>
<td>300</td>
<td>1.5</td>
</tr>
<tr>
<td>Rat</td>
<td>Benimidazole</td>
<td>i.p.</td>
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<td>50</td>
<td>1.0</td>
</tr>
<tr>
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<td></td>
<td>s.c.</td>
<td>135</td>
<td>180</td>
<td>1.3</td>
</tr>
<tr>
<td>Cat</td>
<td></td>
<td>i.p.</td>
<td>100</td>
<td>50</td>
<td>0.5</td>
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<td>Rat</td>
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<td>1.0</td>
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<td>250</td>
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<tr>
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<td>i.p.</td>
<td>200</td>
<td>200</td>
<td>1.0</td>
</tr>
<tr>
<td>Cat</td>
<td></td>
<td>oral</td>
<td>16</td>
<td>35</td>
<td>2.3</td>
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<tr>
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<td>Glutamic Acid</td>
<td>i.p.; oral</td>
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<tr>
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<td></td>
<td>i.p.</td>
<td>*</td>
<td>1500</td>
<td>0</td>
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<tr>
<td>Cat</td>
<td></td>
<td>i.p.; oral</td>
<td>*</td>
<td>8000</td>
<td>0</td>
</tr>
</tbody>
</table>

† Current strength: rabbits 300 mA., cats 400 mA., rats 150 mA. Current duration: 0.2 sec.

P = dose required to abolish extensor tonic phase of seizure induced by supramaximal electroshock.
T = dose required to produce signs of central impairment.
* Failed to alter seizures in any dose.

The ability of several agents to modify maximal seizures is summarized in Table 1. In all three species, diphenylhydantoin and phenobarbital were effective in doses 50 per cent or less of that required to produce signs of central impairment (ataxia, loss of placing reactions, etc.). Tridione, pentobarbital, benimidazole, AN 22 and AN 23 were all effective, but their protective indices were lower. In preliminary observations in rabbits, ether
and sodium bromide were found effective but only in depressant doses. L(+)-glutamic acid was completely ineffective in all animals even at lethal doses.

The purely clonic seizure produced by supramaximal electroshock in an animal protected by diphenylhydantoin was almost always longer in duration than the control maximal tonic seizure in the same animal. Prolonged and violent clonus often continued for a minute or longer. Yet the central impairment in the post-ictal period was less severe and the rate of recovery more rapid in the diphenylhydantoin-treated animals. The alteration of seizure pattern by diphenylhydantoin was of particular interest because of the inability of this drug to increase the electroshock threshold for minimal seizures in any dosage. For example, electroshock thresholds in the same rabbits as shown in Figure 3 remained within the control range of 45 to 65 mA. after treatment with 100 mg./kg. of diphenylhydantoin and no individual animal showed an increase over its control level. Similar observations over a wider dosage range were made in five additional animals whose EEG's were recorded from implanted epidural electrodes. No significant alteration occurred in the EEG seizure threshold. This was true for long (9 sec.) as well as for short (0.2 sec.) duration of electroshocks. However, the EEG seizure pattern following supramaximal shocks was altered toward a more clonic type, as shown in Figure 4, with a reduction particularly in the surface-negative spikes recorded from the motor cortex, and a general slowing of frequency of discharge. This last-named effect was seen with other agents capable of modifying maximal seizures.

Experiments in rats (20) as well as in cats and rhesus monkeys (7, 8) have also demonstrated the inability of diphenylhydantoin to raise the
normal seizure threshold, although this agent in non-depressant doses protects against the tonic phase of seizures in all species. Diphenylhydantoin was found to modify maximal seizures in rats even when seizure threshold was reduced by cellular hydration. An additional point of interest revealed in the cat experiments was the prolonged duration of action of single doses of diphenylhydantoin. Doses of 20 mg./kg. abolished tonic seizures for an average of seven days (seven cats) while 40 mg./kg. extended the period of protection to 11 days (six animals). Other agents even in large doses failed to show such prolonged action. Diphenylhydantoin protection lasting for more than a day was also noted in rabbits and rats.

The most convenient animals for assay of anticonvulsant drugs were found to be rats of the Sprague-Dawley strain because of their docility and uniformity of response.

DISCUSSION

Rosenblueth and Cannon (17) reported a direct relation between seizure duration and "quantity" of stimulation. Their observations were made on chloralose-anesthetized animals. If such a relation exists in normal unanesthetized animals, it must hold true for only a portion of the range of stimulus strength. Tonic extensor seizures are of relatively constant duration for the individual animal over a wide range of stimulus conditions. Such maximal seizures can be elicited in most animals by shocks not far above threshold. The present studies indicate that during a tonic extensor seizure all neuronal circuits capable of contributing to the discharge are maximally active, and that the seizure cannot be further modified once it has begun. It would seem that the brain, like the individual neurones of which it is composed, is normally capable of responding in an all-or-none manner.

The constancy in form and duration of maximal seizures in normal animals suggests a fixed quantity of energy expended in each cerebral "explosion." With antiepileptic therapy this quantity of energy may be reduced, as indicated by the more rapid recovery from the purely clonic type of seizure following diphenylhydantoin treatment, while at the same time the dissipation of this energy may be spread out over a longer period, as indicated by the greater duration of such clonic seizures.

Clinically established anticonvulsants (diphenylhydantoin, bromide, phenobarbital, tridione) have in common the ability to abolish the tonic extensor component of a maximal seizure produced by a brief electroshock several times greater than the normal threshold current. This property is particularly significant with respect to diphenylhydantoin which is ineffective in altering the normal electroshock threshold or in protecting against the standard convulsive dose of metrazol. The results reported suggest the possibility that the efficacy of clinical antiepileptic agents may be better correlated with a reduction in the ability of the brain to support self-sustaining discharges than with a simple increase in the electrical or chemical thres-
hold for initiation of such discharges. Not all investigators are agreed that
the electroshock seizure threshold in epileptic patients is abnormally low
(4, 9, 14).

As a procedure for laboratory identification and assay of antiepileptic
drugs, the supramaximal electroshock method possesses the following ad-
vantages over more usual techniques involving threshold determinations:
(i) The ability of the brain to maintain a maximal seizure is studied inde-
pendently of the threshold for minimal seizures. (ii) The endpoint chosen is
sharp and easily recognized, whereas threshold determinations involve an
element of judgment between mild seizures and simple hyperactivity unless
EEG tracings are simultaneously taken. (iii) Only one electroshock is ad-
ministered per animal per determination, thus eliminating the effect of sub-
convulsive shocks or alterations due to unrecognized minimal seizures.

In spite of these advantages it is felt that this method should supplement
rather than displace other techniques. The simultaneous use of several inde-
pendent criteria may yield information on the different mechanism of action
of particular antiepileptic agents and thereby help to differentiate the
neurological and metabolic disturbances underlying the several clinical types
of convulsive disorders.

SUMMARY

1. Seizures produced in rabbits, cats, and rats by electroshock intensities
not far above threshold are usually characterized by extreme tonic exten-
sion, and are relatively constant in duration. This tonic extensor type of
seizure is not altered by further increase in stimulus intensity or by lowering
of threshold. Once it has begun it cannot be modified by additional stimula-
tion while in progress. When the tonic extensor component is abolished by
repeated electroshock, it may be restored by stimulation during a seizure.
The depression following tonic extensor convulsions is uniform in duration
and greater than for purely clonic seizures, although the latter are often
considerably longer. The tonic extensor seizure would appear to represent
the maximum rate of dissipation of energy of which the brain is capable.

2. The clinically recognized antiepileptic agents abolish the tonic phase
of major seizures even when these drugs fail to raise appreciably the thresh-
hold for electroshock or metrazol seizures. Diphenylhydantoin and pheno-
barbital show the highest protective index. Several new agents including
tridione rank with pentobarbital in efficacy.

3. A rapid and simple method for detecting and evaluating experimental
antiepileptic agents is presented.

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