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# Changes in Brain Metabolites Induced by Convulsants or Electroshock: Effects of Anticonvulsant Agents

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SUMMARY

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In general, cyclic 3',5'-GMP concentrations in the cerebellum are elevated by convulsants and diminished by anticonvulsant agents, whereas the levels of cyclic 3',5'-AMP remain unchanged by either treatment. Furthermore, the effect of convulsants on cerebellar cyclic GMP is antagonized by anticonvulsants, and the anticonvulsant activity persists concurrently with the biochemical changes. Maximal electroshock (MES) causes an elevation of cerebellar cyclic AMP during the excitable phase. It is suggested that the elevation of cyclic AMP is inhibitory to the Purkinje cell output and thus favors the seizure state. Phenytoin suppresses the increase in cerebellar cyclic AMP, which would reduce seizure activity. Phenytoin also prevents other metabolic changes induced by MES in the cerebellum, but not the cerebral cortex, indicating that these effects are not simply prevention of anoxia. It is proposed that phenytoin has a locus of action that attenuates the electroshock signal to the cerebellum or suppresses the response by a direct effect on the metabolic machinery.

## INTRODUCTION

Recent studies have indicated that the concentrations of cyclic nucleotides *in vivo* vary according to the level of excitability in the brain. It has been demonstrated that the levels of cyclic 3',5'-GMP increase in certain regions of the brain after the administration of central nervous system stimulants, and decrease following administration of depressant drugs (1-8). In addition, both cyclic 3',5'-AMP and cyclic GMP increase in the cerebellum and cerebral cortex during or after electrically induced seizures (9, 10). The apparent association between the cyclic nucleotides and neuronal excitability is further supported by the neurophysiological investigations of Siggins *et al.* (11) and Stone *et al.* (12). Iontophoretically applied cyclic AMP inhibited the output of Purkinje cells of the cerebellum and pyramidal tract neurons of the cerebral cortex; a similar application of cyclic GMP increased the electrical output of pyramidal tract neurons. In sum, the evidence suggests that the pharmacological alterations of seizures may be reflected by the levels of these neural modulators *in vivo*.

In the present investigation the levels of various metabolites were measured in the cerebellum and cerebral cortex of mice after the administration of anticonvul-



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sants alone and in combination with convulsants, and after maximal electroshock in mice given either no drug or phenytoin. The results support the concept that the cerebellum is involved in the control of seizures. Anticonvulsants generally depress the levels of cerebellar cyclic GMP and prevent the cerebellar metabolite changes that occur following the administration of convulsants. Furthermore, phenytoin inhibits the metabolite changes caused by MES[1] to a greater extent in the cerebellum than in the cerebral cortex. By modification of the electroshock signal, phenytoin may exert its anticonvulsive action through the inhibitory influence of the cerebellum. A preliminary report has been presented elsewhere (3, 10).

## MATERIALS AND METHODS

NIH general-purpose mice weighing 25–35 g and fed ad libitum were used. Following treatment, the mice were frozen intact in liquid nitrogen and stored at −65°. The outer 1–2 mm of cerebral cortex and the cerebellum were removed in a cryostat maintained at −20°, and extracted at 0° in 1 ml of 0.3 N perchloric acid containing 1 mM EGTA. The homogenate was centrifuged, and the supernatant was decanted and neutralized with 0.1 ml of 3 M potassium bicarbonate. The remaining pellet was dissolved in 1 ml of 1 N NaOH for protein determination. Cyclic nucleotides were measured using either a modification of the Gilman protein binding assay for cyclic AMP (13) or the radioimmunoassay described by Steiner *et al.* (14) for cyclic AMP and cyclic GMP. Lactate was measured according to Lowry and Passoneau (15); 5′-AMP, according to Barbehenn *et al.* (16); and GABA, according to Passonneau *et al.* (17).

The materials for the cyclic nucleotide radioimmunoassay were purchased from Collaborative Research (Waltham, Mass.); tritiated cyclic AMP, from New England Nuclear; and resins, from Bio-Rad Laboratories. Enzymes were obtained from Boehringer/Mannheim, and substrates and cofactors, from Sigma Chemical Company. The various agents were obtained from the following sources: clonazepam, Hoffmann-La Roche; acetazolamide and isoniazid, Sigma; trimethadione and sodium valproate, Abbott Laboratories; carbamazepine, Ciba; ethosuximide, U.S.P.C. (Rockville, Md.); pentylenetetrazole (Metrazole), Knoll Pharmaceutical Company; phenobarbital, Merck & Company; phenytoin, Parke, Davis; procyclidine hydrochloride, Burroughs Wellcome; and theophylline, K & K Laboratories.

Statistical significance was determined using Student's *t*-test. Proportionate change was used to give a value for a reduction in metabolite levels equivalent to that for an increase. As previously described by Veech and Mehlman (18), proportionate change (PC) was calculated from the formula

$$PC = x\left[\frac{\text{experimental value}}{\text{control value}}\right]^{x}$$

where $x = +1$ when experimental > control and $x = -1$ when control < experimental.

*Maximal electroshock.* Maximal electroshock was applied by corneal electrodes for a duration of 0.2 sec and at an intensity of 50 mamp. In the group treated with phenytoin, MES was applied 30 min after the administration of the drug.

*Treatment with convulsant and anticonvulsant agents.* Two convulsants—isoniazid and Metrazole—and nine anticonvulsants—clonazepam, acetazolamide, trimethadione, sodium valproate, carbamazepine, ethosuximide, phenobarbital, phenytoin, and procyclidine—were tested. The drugs were dissolved in 0.9% NaCl, except for carbamazepine, which was dissolved in 30% polyethylene glycol; clonazepam, which was dissolved in 95% ethanol at a concentration of 1 mg/ml and then diluted to a concentration of 20 μg/ml with water; and acetazolamide, which was dissolved in dilute sodium hydroxide and then neutralized. Controls were injected with the same vehicle as that containing the drugs. The dose level, route of administration, and time course for each drug are given in

[1] The abbreviations used are: MES, maximal electroshock; EGTA, ethylene glycol bis(β-aminoethyl ether)-*N*,*N*′-tetraacetic acid; GABA, γ-aminobutyric acid.

the legends to the appropriate tables and figures. In an effort to distinguish between the effects of the drugs and the effects of seizure activity, only seizure-free mice were included in this series of experiments. In the long-term studies on the combined effects of sodium valproate and isoniazid, some animals convulsed, but none were frozen during the seizure.

## RESULTS

*Effects of anticonvulsants on brain cyclic GMP and GABA.* Following our observations that phenobarbital at an anticonvulsant dose (20% of the sedative dose) depressed cerebellar cyclic GMP (3), eight other structurally different anticonvulsants were tested to determine whether they would elicit a similar response. GABA, another brain metabolite thought to be involved in the suppression of seizures, was also measured (Table 1). The doses of the various anticonvulsants tested approximate the $ED_{80}$ against experimental seizures as determined in our laboratory. The only agent that significantly increased the steady-state levels of GABA was sodium valproate, which had a comparable effect in both cerebellum and cerebral cortex. The concentrations of cerebellar cyclic GMP decreased following treatment with all the anticonvulsants tested, with the exception of acetazolamide. There were no significant decreases in cyclic GMP in the cerebral cortex. In contrast, the convulsant drugs, isoniazid and Metrazole, increased cyclic GMP in both the cerebellum and the cerebral cortex. Cyclic AMP levels were unchanged after treatment with anticonvulsant agents (data not shown).

*Antagonism of convulsant-induced changes in cerebellar metabolites following treatment with anticonvulsants.* Generally, cerebellar cyclic GMP was elevated by convulsant drugs and depressed following administration of anticonvulsants. In view of this relationship, experiments were performed to determine whether the elevation of cerebellar cyclic GMP by convulsants would be prevented by anticonvulsants. The doses of the convulsant drugs were selected to minimize the likelihood of seizures during the experimental periods. The onset and characteristics of the convulsive behavior were determined in a separate group of mice. After administration of isoniazid, 200 mg/kg subcuta-

TABLE 1

*Effects of various anticonvulsants on concentrations of cyclic GMP and GABA in mouse cerebral cortex and cerebellum*

Mice were injected intraperitoneally with the various anticonvulsants at the doses shown. The tissues were dissected and extracted as described under MATERIALS AND METHODS. Results are expressed as a percentage of control for the number of mice shown in parentheses; C, cerebellum; X, cerebral cortex. The GABA concentrations in control animals were 9.16 ± 0.40 (SE) and 8.97 ± 0.43 nmoles/mg of protein for cerebellum and cerebral cortex, respectively; the corresponding values for cyclic GMP were 5.51 ± 0.49 and 0.67 ± 0.07 pmoles/mg of protein. Control values represent the means of 26 determinations in cerebellum and 17 in the cerebral cortex.

| Treatment | Dose | GABA | | Cyclic GMP | |
|---|---|---|---|---|---|
| | | C | X | C | X |
| | *mg/kg* | *% control* | | *% control* | |
| Control | | 100 | 100 | 100 | 100 |
| Acetazolamide (5) | 50 | 100 | 97 | 83 | 83 |
| Carbamazepine (6) | 25 | 99 | | 21[a] | |
| Clonazepam (5) | 0.2 | 111 | 106 | 61[a] | 86 |
| Ethosuximide (5) | 200 | 111 | 103 | 35[a] | 106 |
| Phenobarbital (5) | 50 | 115 | 109 | 17[a] | 86 |
| Phenytoin (5) | 25 | 92 | 98 | 48 | 82 |
| Procyclidine (6) | 40 | 110 | | 23[a] | |
| Trimethadione (5) | 300 | 108 | | 20[a] | |
| Valproate (4) | 400 | 165[a] | 158[a] | 16[a] | 154 |

[a] Significantly different from control; $p < 0.05$.

neously, the mice developed twitches at 40 ± 4 min, tonic extension at 54 ± 3 min, and death (in four out of the five mice) at 67 ± 4 min. The period chosen for the examination of the isoniazid effects on metabolites was therefore limited to 30 min, a preconvulsive period essentially free of overt behavioral seizures. Metrazole (85 mg/kg subcutaneously) produced seizures 5 min after injection; therefore mice treated with Metrazole were frozen 3 min after injection.

In the preconvulsive state, both convulsants elevated cerebellar cyclic GMP 4–7-fold (Table 2). Only isoniazid affected cerebellar GABA levels, decreasing them to 63% of control. Clonazepam, at a dose that protects mice against chemically but not electrically induced seizures, decreased cerebellar cyclic GMP to 20% of control values. In combination with either isoniazid or Metrazole, clonazepam not only prevented any convulsant-induced increase in cyclic GMP, but in fact reduced the levels to about 50% of control. While clonazepam alone had no effect on GABA levels, it prevented the decrease observed after isoniazid alone. Thus clonazepam at an anticonvulsant dose prevented the changes in GABA and cyclic GMP that resulted from treatment with these two convulsants.

TABLE 2

*Effects of clonazepam on convulsant-induced changes in cerebellar cyclic GMP and GABA*

In combination treatments, clonazepam and isoniazid were administered simultaneously, whereas Metrazole was injected 27 min after clonazepam. The mice were frozen 30 min after clonazepam and/or isoniazid treatment, or 3 min after the injection of Metrazole. Metrazole and isoniazid were administered subcutaneously, and clonazepam was injected intraperitoneally. The results are based on at least four determinations for each group. For control values of the cerebellar metabolites, see Table 1.

| Treatment | Dose | GABA | Cyclic GMP |
|---|---|---|---|
| | *mg/kg* | *% control* | |
| Control | | 100 | 100 |
| Metrazole | 85 | 100 | 680[a] |
| Isoniazid | 200 | 63[a] | 456[a] |
| Clonazepam | 0.16 | 103 | 20[a] |
| Clonazepam + Metrazole | 0.16, 85 | 89 | 44[a] |
| Clonazepam + isoniazid | 0.16, 200 | 86 | 58[a] |

[a] Significantly different from control; $p < 0.05$.

The temporal relationship between the convulsive behavior and cerebellar metabolites was investigated. The drugs chosen were sodium valproate, a new and structurally unique anticonvulsant, and isoniazid, a convulsant. Studies on the blood levels of valproate (data not included) have shown that it is a relatively short-lived drug; this is confirmed by the brevity of its activity. Anticonvulsant activity, defined here as the ability to block electrically induced hindlimb extension, was assessed in a separate group of mice. At 0.5 hr after administration, 100% of the mice were protected; at 1 hr, 60% were protected; at 2 hr, 37%; and at 4 hr, all protection was lost. The maximal protection coincided with the highest levels of GABA and the lowest levels of cyclic GMP (Fig. 1a). At 2 hr after administration of valproate, when the anticonvulsant activity was decreasing, the GABA levels decreased to values less than control while those for cyclic GMP increased above control (Fig. 1a). At 2 and 4 hr, when cyclic GMP was elevated and GABA depressed, a greater susceptibility to seizures might be expected. However, the sensitivity of the test used for anticonvulsant activity was not sufficient to distinguish such an effect.

When the two drugs were administered simultaneously, valproate antagonized the GABA decrease induced by isoniazid at 0.5 hr (Fig. 1b and Table 2). However, GABA was significantly lower than control values 1, 2, and 4 hr after the combination of drugs was given. Similarly, the increase in cyclic GMP observed 0.5 hr after isoniazid was suppressed in the presence of valproate. Cyclic GMP concentrations subsequently increased to greater than control values 1 and 2 hr after valproate. The changes in metabolite levels and the appearance of some seizure activity indicate that after 1 hr the effect of isoniazid was predominant. By 4 hr the levels of cyclic GMP and GABA were near normal. Following the combined treatment with isoniazid and valproate at the

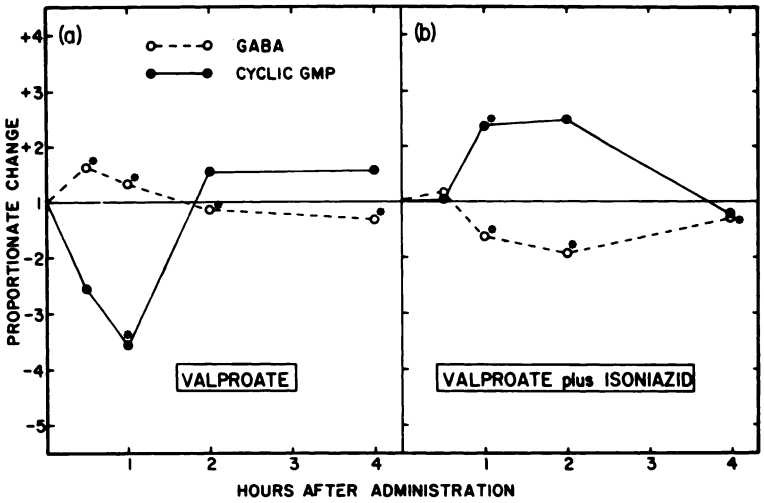


FIG. 1. *Time course of GABA and cyclic GMP levels in cerebellum after valproate either alone or in combination with isoniazid*

Mice were treated with 400 mg/kg (intraperitoneally) of valproate alone (a) or in combination with 200 mg/kg (subcutaneously) of isoniazid (b) and frozen in liquid nitrogen at the designated times. The results are expressed in terms of proportionate change as described in MATERIALS AND METHODS. Each value is the mean of at least four determinations.

* Significantly different from control; $p < 0.05$.

described doses, there appeared to be three distinct stages: (a) valproate antagonizes the isoniazid effect (0.5 hr), (b) isoniazid predominates as the valproate effect disappears (1-2 hr), and (c) the isoniazid effect is lost (4 hr). It should be noted that even though the ability of valproate to affect seizures and metabolites diminished by 1 hr, another action of valproate was evident after 1 hr. Normally the mortality rate of mice treated with this dose of isoniazid is 80%; however, when it was administered in combination with valproate, all the mice survived for 4 hr.

*Effect of phenytoin on MES-induced changes in brain metabolites.* The anticonvulsants discussed above antagonized the chemically induced seizures and depressed the concentrations of cerebellar cyclic GMP in the preconvulsive period. To determine whether a similar effect would be evident during a seizure, anticonvulsant activity was tested during MES. The advantage of MES over chemically induced seizures is that the time course of convulsive behavior is predictable and reproducible. MES elicits convulsive behavior characterized by a 2-sec tonic flexion, followed by a 11.4-sec tonic extension, a 10-sec period of intermittent clonic movements, and, finally, a postictal period. In order to relate the changes in metabolites to seizure activity, it should be emphasized that the excitable phase of MES convulsion is over by 25 sec after electroshock. Treatment of the mice with phenytoin (25 mg/kg intraperitoneally) 30 min prior to MES prevents the tonic extension; instead the mice exhibit a bilateral clonic movement. The obliteration of the tonic extension and associated apnea by phenytoin should reduce the anoxic component of MES.

The levels of GABA gradually increased in both the cerebral cortex and cerebellum following MES (Fig. 2). When phenytoin was given prior to MES, there was little effect on the GABA increase. The levels of cyclic AMP increased in both regions examined after MES; however, the magnitude and duration of the changes in the cerebral cortex were far greater than in the cerebellum, and were unaffected by prior phenytoin treatment (Fig. 3). In contrast, the cyclic AMP increase in the cerebellum was significantly reduced at 0, 10, and 30 sec after MES in the phenytoin-treated mice ($p < 0.05$).

Following electroshock the concentra-

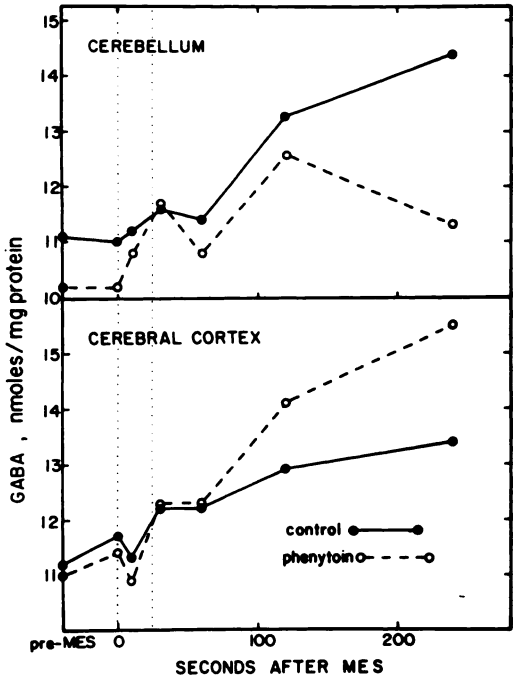


FIG. 2. *GABA levels in cerebellum and cerebral cortex after MES*

Treated mice received 25 mg/kg of phenytoin (intraperitoneally) 30 min prior to electroshock. The experiments were performed as described in MATERIALS AND METHODS. The vertical parallel dotted lines denote the excitable stage of convulsion, which includes tonic extension and clonus. A total of 57 mice were used, with at least four in each group.

tions of cyclic GMP increased in the cerebral cortex and cerebellum (Figs. 4 and 5). In the cerebral cortex the control levels (pre-MES) and the post-MES accumulation of cyclic GMP were slightly depressed in the presence of phenytoin; however, the differences were not significant ($p > 0.05$). In contrast, the differences in cyclic GMP concentration in the cerebellum in the presence of phenytoin were significant at all times after MES (Fig. 5). The accumulation of the nucleotide after MES was reduced more than 50% in the phenytoin-treated animals. With respect to cyclic GMP changes, the predominant effect of phenytoin was on the cerebellum.

The effects of anoxia on cyclic nucleotide concentrations are important in the interpretation of the effects of MES on these compounds, since the convulsions have an anoxic component. There appear to be conflicting reports on the effects of anoxia on the levels of cyclic GMP in the brain (19, 20). Therefore this compound, as well as GABA and cyclic AMP, was measured in

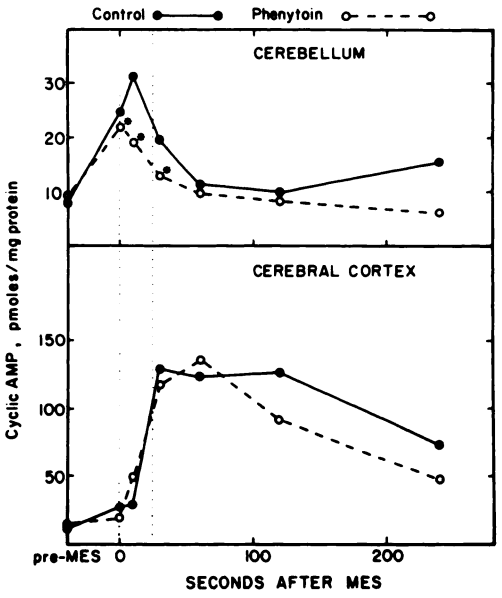


FIG. 3. *Cyclic AMP levels after MES*

The experiments were performed as described in Fig. 2.

* Significantly different from untreated controls; $p < 0.05$.

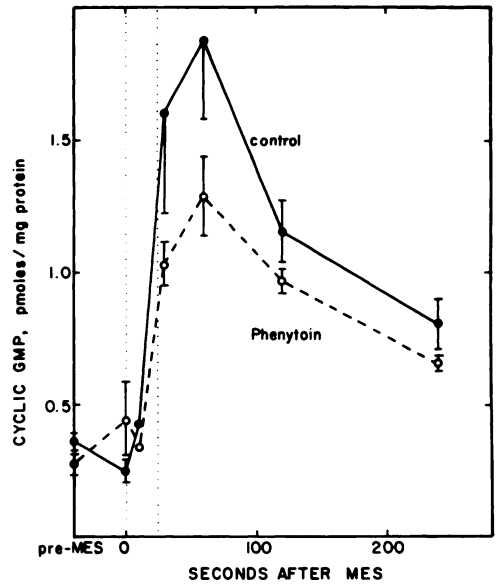


FIG. 4. *Cyclic GMP levels in cerebral cortex after MES*

For details, see Fig. 2.

the cerebral cortex and cerebellum 15 and 60 sec after decapitation (Table 3). Cyclic GMP concentrations decreased during the anoxic period. There were no measurable changes in GABA after 15 sec, whereas cyclic AMP concentrations increased 3–4-fold in both regions of the brain. The increases in cyclic GMP observed after MES are in direct contrast to the effect of anoxia, which indicates that the effect of MES is not due to oxygen deprivation. However, the accumulation of cyclic AMP after electroshock may be accounted for in part by the concomitant anoxia.

Ferrendelli and McDougal have established that after MES the energy demand exceeds the supply, and as a result there is a decrement in high-energy phosphate compounds and an increase in lactate in the cerebral cortex and cerebellum (21). In this study the energy status of the cerebral cortex and cerebellum was investigated after the insult of electroshock, with and without phenytoin treatment. Lactate was increased in both brain regions; the increase elicited by MES was significantly suppressed in the cerebellum in the presence of phenytoin, whereas there was no effect of the drug in the cortex (Fig. 6). Concentrations of 5′-AMP, which are a sensitive indicator of enhanced ATP use (22), increased in both the cerebral cortex and cerebellum (Fig. 7). When phenytoin was given prior to MES, the increases in 5′-AMP were diminished in both regions of the brain, and were almost obliterated in the cerebellum. The results indicated that phenytoin partially prevents the changes in cyclic nucleotides, lactate, and 5′-AMP caused by MES in the cerebellum, while it has only a slight effect in the cortex. The evidence suggests that there may be a phenytoin-specific locus in the pathways to the cerebellum, and that phenytoin minimizes the energy imbalance by preventing the electroshock signal from reaching the cerebellum.

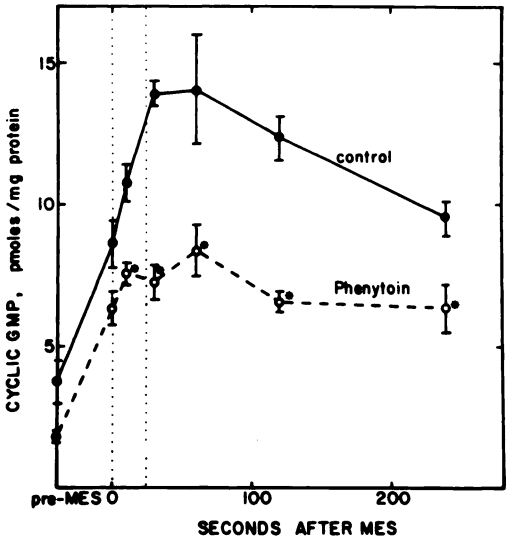


FIG. 5. *Cerebellar cyclic GMP levels after MES*
For details, see Fig. 2.

## DISCUSSION

The structural differences among the many anticonvulsant agents, as well as

TABLE 3

*Effect of decapitation on cyclic nucleotide and GABA concentrations in mouse cerebral cortex and cerebellum*

Mice were frozen intact (controls) or were decapitated and the heads frozen in liquid nitrogen after either 15 or 60 sec. The analyses were performed as described under MATERIALS AND METHODS. Values are means and standard errors for the numbers of animals shown in parentheses. C, cerebellum; X, cerebral cortex.

| Treatment | Cyclic GMP | | Cyclic AMP | | GABA | |
|---|---|---|---|---|---|---|
| | C | X | C | X | C | X |
| | *pmoles/mg protein* | | *pmoles/mg protein* | | *nmoles/mg protein* | |
| Intact | 7.1 ± 1.2 (9) | 0.67 ± 0.04 (9) | 3.80 ± 1.0 (5) | 5.51 ± 0.6 (5) | 8.7 ± 0.7 (5) | 8.9 ± 0.1 (5) |
| Decapitation | | | | | | |
| 15 sec | 6.3 ± 0.8 (8) | 0.55 ± 0.06 (9) | 18.9 ± 2.7 (5) | 15.3 ± 2.2 (5) | 8.9 ± 1.2 (5) | 9.3 ± 0.3 (5) |
| 60 sec | 4.4 ± 0.6 (7) | 0.23 ± 0.05 (7) | | | | |

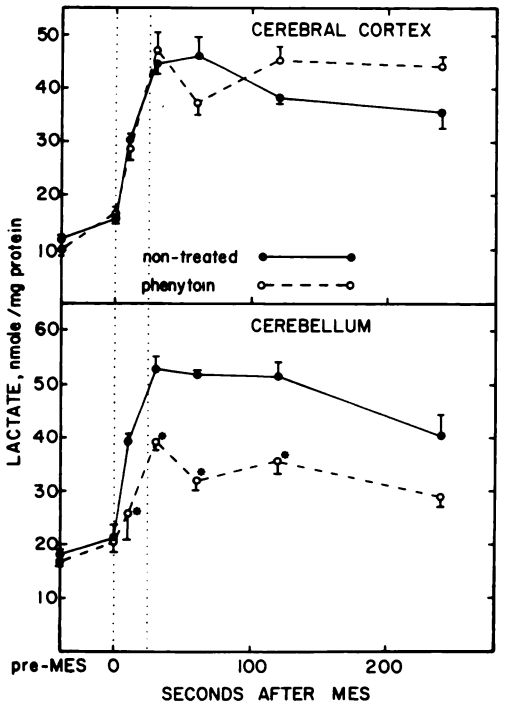


FIG. 6. *Lactate levels in cerebral cortex and cerebellum after MES*

For details, see Fig. 2.

their variable efficacy toward the many different types of seizures, make it unlikely that these compounds share a universal mechanism of action. It is possible, however, that the drugs used in seizure therapy may share some common pathways, or may cause a similar biochemical response related to the anticonvulsant action. Of the drugs tested in this study, all but one (acetazolamide) markedly decreased the levels of cyclic GMP in the cerebellum. Other investigators, using different anticonvulsants, including diazepam, aminooxyacetic acid, hydrazine, and phenobarbital, have reported similar decreases in cerebellar cyclic GMP (5, 6).

In direct contrast to the decrease in cyclic GMP concentrations produced by anticonvulsant drugs, the level of this cyclic nucleotide in the cerebellum is increased by experimental seizures. It appears that cyclic GMP concentrations are elevated in chemically or electrically induced excitation and reduced by anticonvulsant or depressant drugs. The antagonism of convulsants by anticonvulsant drugs is a further demonstration of the relationship between cerebellar cyclic GMP concentrations and neuronal excitability. When valproate or clonazepam is given in conjunction with either isoniazid or Metrazole, both the increases in cyclic GMP levels in the cerebellum and seizure activity are prevented. Furthermore, a temporal relationship between anticonvulsant activity and antagonism of metabolite changes induced by convulsant drugs can be demonstrated. When valproate is given with isoniazid, the anticonvulsant activity persists as long as the valproate prevents the biochemical changes induced by isoniazid alone. When serum valproate declines, the isoniazid effect prevails; cyclic GMP levels increase and GABA concentrations decrease in the cerebellum, and seizures occur.

Although the correlation between cyclic GMP concentrations in the cerebellum and neuronal excitability is attractive, there are exceptions. There are a number of central nervous system depressants, including ethanol, reserpine, and chlorpromazine, that decrease cyclic GMP levels in the cerebellum but do not exhibit significant anticonvulsant properties (2). The

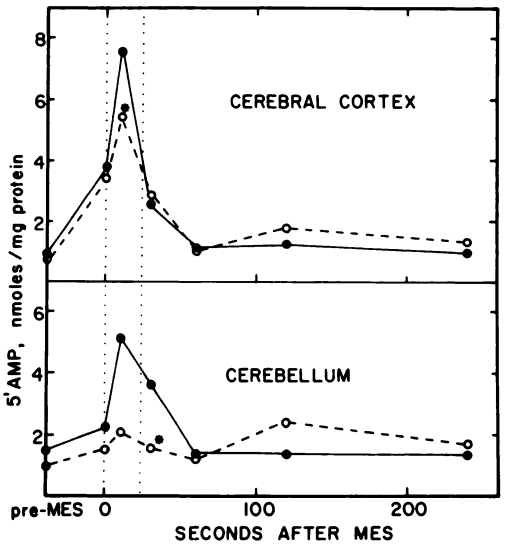


FIG. 7. *5'-AMP concentration in cerebral cortex and cerebellum after MES*

For details, see Fig. 2.

effect on a single component may not be sufficient to affect seizure activity; other changes, as yet undetected, may be implicated. Conversely, there are agents such as acetazolmide which have anticonvulsant activity but do not affect the concentration of cyclic GMP in the cerebellum. Despite these reservations, the fluctuations in cerebellar cyclic GMP may offer a biochemical clue to events involved in hyperexcitable states, and the modification of such states by anticonvulsants.

The changes in cyclic GMP concentrations tend to emphasize the role of the cerebellum in seizure activity. Furthermore, direct stimulation of the cerebellum has been used to suppress seizure activity in patients refractory to pharmacological management (23). Additional evidence for the involvement of the cerebellum in anticonvulsant activity has been reported by Halpern and Julien (24). These investigators demonstrated that the anticonvulsants diazepam, phenobarbital, and phenytoin increase Purkinje cell output and consequently enhance the inhibitory influence of the cerebellum. However, the same investigators have reported that some anticonvulsants do not affect firing of Purkinje cells. As with the evidence for changes in cyclic GMP concentrations in the cerebellum, there were exceptions that indicate a more complex situation.

The elevation of cerebellar cyclic AMP in the cerebellum that occurs during the excitable phase of MES is suppressed by as much as 40% in the presence of phenytoin; in contrast, phenytoin has no effect on the cyclic AMP increase in the cerebral cortex. The difference in response between the two brain regions indicates that the anoxic component of MES alone cannot be responsible for the changes in cyclic AMP. Furthermore, the MES-induced changes in lactate concentrations are unaffected by phenytoin in the cerebral cortex, but are minimized in the cerebellum by the drug. The results offer a further distinction between the effects of anoxia and electroshock. Cyclic AMP has been shown to be inhibitory to Purkinje cells (11); the increases in cyclic AMP would thus favor the seizure state. The suppression of the increase in cyclic AMP in the cerebellum by phenytoin would favor reduction in seizure activity.

The action of phenytoin with respect to electroconvulsive shock was primarily in the cerebellum, with only minor effects observed in the cerebral cortex. The diminution of the effects of MES by phenytoin might be explained either by attenuation of the electroshock signal or by suppression of the response by a direct effect on the metabolic machinery. Since phenytoin has been shown to prevent the spread of hyperexcitable foci (25, 26), it seems possible that the cerebellum may be protected from the electroshock and the consequent massive neuronal depolarization with increased energy demands. Although phenytoin at substantially higher doses has been shown to decrease the metabolic rate of the brain, such an effect would not be expected to be limited to the cerebellum. A diminished input of the electroshock signal appears to be more plausible; seizures induced by less intense electroshock might serve to answer this question.

The measurement of key brain metabolites may be useful in the study of the mechanism of action of anticonvulsants, and also serve to classify the agents on a biochemical basis. The biochemical correlates that determine the efficacy of anticonvulsant agents against different types of seizures may be delineated by future investigations.

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