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CALIFORNIA UNIV LOS ANGELES SCHOOL OF MEDICINE F/6 6/15
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**SLEEP EEG POWER SPECTRAL PROFILES AND
ANTICONVULSANT DRUGS: COMPARISON OF PROTECTIVE
EFFECTS WITH MONOMETHYLHYDRAZINE.**

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APRIL 1982

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AFAMRL-TR-82-18

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FOR THE COMMANDER



ROGER C. INMAN, Colonel, USAF, BSC
Chief
Toxic Hazards Division
Air Force Aerospace Medical Research Laboratory

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER AFMRL-TR-82-18	2. GOVT ACCESSION NO. AD-A116056	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) SLEEP EEG POWER SPECTRAL PROFILES AND ANTICONVULSANT DRUGS: COMPARISON OF PROTECTIVE EFFECTS WITH MONOMETHYLHYDRAZINE.		5. TYPE OF REPORT & PERIOD COVERED Annual Report Feb. 1, 1981-Jan. 31, 1982
7. AUTHOR(s) M.B. Sterman, Ph.D. R.A. Kovalesky M.D. Fairchild, Ph.D.		6. PERFORMING ORG. REPORT NUMBER
9. PERFORMING ORGANIZATION NAME AND ADDRESS Departments of Anatomy and Pharmacology School of Medicine, University of California Los Angeles, California 90024		8. CONTRACT OR GRANT NUMBER(s) F33615-79-C-0506
11. CONTROLLING OFFICE NAME AND ADDRESS Air Force Aerospace Medical Research Laboratory Aerospace Medical Division, AFSC Wright Patterson Air Force Base, Ohio 45433		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 61102F, 2312 - VI - 21
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		12. REPORT DATE April 1982
		13. NUMBER OF PAGES 10
		15. SECURITY CLASS. (of this report) Unclassified
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE
16. DISTRIBUTION STATEMENT (of this Report) Approved for public release; distribution unlimited.		
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)		
18. SUPPLEMENTARY NOTES Prepared in cooperation with the Veterans Administration Medical Center, Sepulveda, California 91343		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) somatosensory system pyridoxine anticonvulsant drugs diazepam sleep EEG protection power spectral analysis		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) The effects of five known anticonvulsant compounds on electroencephalographic (EEG) power spectral density profiles during slow wave sleep were measured in a group of five chaired rhesus monkeys. Doses used corresponded to established clinical standard in children of similar weight to our primate subjects. Compared to saline controls, all five anticonvulsant drugs produced a specific pattern of spectral density change localized to sensorimotor cortex, bilaterally. This consisted of a sharp attenuation of activity below 7 Hz, and particularly in the 4-7 Hz band, and an increase and/or stabilization of power		

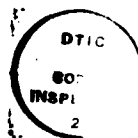
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In the 12-15 Hz band. A second, identical test series was carried out with 15 mg/kg of monomethylhydrazine (MMH) administered shortly after drug injections. Significant protective effects were obtained with pyridoxine and diazepam but not with valproic acid or carbamazepine. Reference to the spectral density changes produced by these groups of drugs suggested that compounds which protect against MMH primarily attenuated 4-7 Hz activity in the sensorimotor EEG. This outcome was consistent with evidence for an acute increase in cortical neuronal hyperexcitability following MMH, and with data indicating a mediation of this effect by disturbances in the inhibitory functions of GABA.

PREFACE

This research was initiated by the Toxicology Branch, Toxic Hazards Division, Aerospace Medical Research Laboratory, under Project 2312. Experiments were performed from February 1, 1981 to January 31, 1982 under Contract AF F33615-79-C-0506 by the Departments of Anatomy and Pharmacology, University of California, Los Angeles, California 90024.

The experiments were conducted by M. B. Serman, Ph.D. and R. A. Kovalesky of the Veterans Administration, Sepulveda, California 91343 and Department of Anatomy, University of California, Los Angeles, California 90024 and M. D. Fairchild, Ph.D., Department of Pharmacology, University of California, Los Angeles. Kenneth C. Back, Ph.D. was contract monitor for the Aerospace Medical Research Laboratory.



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INTRODUCTION

Previous studies in this program have focused primarily on neurophysiological processes which mediate monomethylhydrazine (MMH) induced generalized seizures and have provided a sound basis for exploring therapeutic strategies for this toxic compound. It has been clearly established that MMH ultimately disrupts normal sensory and motor regulatory mechanisms within the Central Nervous System (CNS). This may well reflect a disturbance in neurotransmitter synthesis and metabolism, but the functional implications of this disturbance can best be understood physiologically as a failure in sensory control processes at thalamic and cortical levels, a corresponding hyperexcitability in cortical neuronal populations and the eventual propagation of abnormal discharge throughout the CNS, resulting in generalized convulsions. During the hyperexcitable phase of this sequence virtually any stimulus can elicit seizures.

Studies of sensory regulatory mechanisms in ventrobasal thalamus, and of related sensorimotor cortex EEG patterns, provided a unique perspective on the mediation of these changes. The basic elements of this conceptual approach have been well documented (for reviews see Creutzfeldt, 1974; Sterman and Bowersox, 1981). Normally, when sensory signals are being processed within the somatosensory pathway, neuronal interactions mediated by both sensory specific and nonspecific neurons facilitate relevant conduction while suppressing activity in adjacent elements of the pathway. Activation is reflected by a low voltage, high frequency EEG pattern in localized areas of somatosensory cortex and suppression by a pattern of rhythmic activity in adjacent areas. The rhythmic EEG activity is mediated by recurrent inhibitory neurons which are central to an intrinsic "gate" mechanism in thalamic sensory relay nuclei. The activated pathway "closes" this gate in adjacent pathways, thereby producing a lateral inhibition which increases the sensory signal-to-noise ratio. When attention is directed to other sensory systems (i.e., visual or auditory), suppression becomes generalized within the somatosensory system and these rhythmic EEG patterns appear intermittently over the entire somatosensory cortex, again contributing to an increased signal-to-noise ratio.

The physiological importance of these neuronal dynamics was documented by studies of interactions between CNS state, EEG patterns, and neuronal excitability in the cat as determined through the application of evoked potential methods (Goff et al., 1967; Howe and Sterman, 1973). The presence of rhythmic 12-15 Hz EEG activity during both wakefulness and sleep is associated with an attenuation of conduction through the somatosensory relay nucleus of thalamus. In fact, during slow wave sleep (SW) with 12-15 Hz "spindles," this sensory pathway is maximally suppressed. However, as the states of sleep progress, the cortex itself becomes increasingly responsive to stimuli applied directly to extrathalamic somatosensory projections (SI). Nevertheless, even in the presence of intense phasic discharge during rapid-eye-movement (REM) sleep, seizures do not occur because the "gate" remains partially closed.

When a convulsive dose of MMH was administered several things happened. First, as seizures approached, both sleep and rhythmic EEG patterns were virtually abolished. Second, cortical excitability reached unprecedented levels; however, there was no attendant suppression of thalamic conduction. Instead, the thalamic "gate" appeared to be wide open. This combination of events within sensorimotor regulatory systems may account for the bizarre sensory and motor behavior seen in the preictal state following MMH exposure, and in the eventual "triggering" of generalized

seizures. It also provides a bridge between acute seizure susceptibility with MMH exposure and the chronic propensity for convulsions in epileptic patients suffering from primary or secondary motor seizures. This group of epileptics shows a consistent attenuation of normal rhythmic activity in the sensorimotor cortex EEG and a corresponding increase in slower (4-7 Hz) frequencies (Serman, 1981). These slower patterns are thought to result from abnormal excitation in cortical neurons (Kostopoulos and Gloor, 1982). Apparently, the thalamic gate mechanism is also disturbed in these epileptics but in a more fundamental sense, and this is associated with abnormal increases in cortical excitability.

The sensorimotor EEG can thus be used as a means of monitoring these neuronal dynamics and, together with a consideration of the concurrent state of consciousness, can be exploited as a tool for evaluating neuronal responses to both pathological and therapeutic interventions. The present study was directed to this concept in an effort to evaluate potential therapeutic strategies for protection against MMH neurotoxicity.

METHODS

Five adult rhesus monkeys (*macaca mulatta*) were prepared surgically for recording appropriate sensorimotor and alternative EEG activity during long-term polygraphic studies. After surgical recovery these animals were adapted to restraining chairs and habituated to a standardized sleep recording situation in a sound attenuated and isolated recording chamber. Successive six hour polygraphic recordings (2000-0200 hours) were obtained on paper and on magnetic tape during a week of baseline data collection, two nights of which included intramuscular saline injections administered just prior to the start of the recording period. During subsequent weeks each animal was administered a sequence of five anticonvulsant compounds with a two-week interval between each drug, using the identical paradigm. The drugs tested included carbamazepine (10.0 mg/kg), diazepam (0.75 mg/kg), phenobarbital (2.0 mg/kg), pyridoxine (10.0 mg/kg), and valproic acid (50.0 mg/kg). The sequence of drugs administered was counterbalanced for the group so that each compound was received first in one animal and at various stages in the test sequence in each of the others. Because of limitations in time and resources only one dose of each compound could be tested. The dose was estimated from experimental and clinical literature and in each instance was chosen to approximate established therapeutic levels in man for that compound. After two hours of recording, blood samples were drawn from the femoral vein to verify actual serum levels for each test compound. The polygraphic records were scored for sleep and waking stages according to standard criteria and a 10 min. sample of slow-wave-sleep identified at the end of the recording just prior to blood sampling. This EEG sample was drawn from the tape record, digitized, and subjected to Fast Fourier Transform in order to generate power spectral density profiles for comparison with similar baseline data. Standardized procedures for this analysis have been described elsewhere (Serman et al., 1977; Serman, 1981).

RESULTS

All of these compounds produced a similar pattern of spectral change in sensorimotor cortex relative to baseline while having little effect on the EEG of other cortical areas. This pattern consisted of a significant decrease in frequencies below 7 Hz, and particularly in the 4-7 Hz band, and an increase and stabilization of power in the rhythmic 8-15 Hz range (figure 1). This pattern of change is

the exact reciprocal of the pathological changes associated with both acute and chronic motor seizures, as discussed above, and may therefore constitute an "anti-convulsant signature" in the sensorimotor EEG. An evaluation of serum concentrations for these test compounds taken at the time of sleep EEG sampling indicated low therapeutic blood levels.

Following this phase of study, a second series of tests was performed. The animals were given essentially the same sequence of anticonvulsant compounds at the same dose levels, but in this case each trial was preceded by the administration of a 15 mg/kg dose of MMH 10 minutes prior to the test anticonvulsant compound. Therapeutic effects were measured in terms of latency to generalized seizures, a measure found in previous studies of the monkey to be a reliable indicator of protective effects (Serman et al., 1979). These values were compared with stable, normative, seizure latencies established in previous studies of untreated animals. The results of this comparison are shown in figure 2, with the exception of phenobarbital, which was not tested in this series.

By convention, any challenge which is not followed by generalized convulsions within three hours after exposure to MMH was terminated by the administration of an anesthetic dose of phenobarbital. As can be seen in figure 2, only two of the test anticonvulsant compounds provided significant protection at the dose levels administered. These were pyridoxine, which completely suppressed seizures, and diazepam, which more than doubled the mean latency to seizures. In contrast, carbamazepine and valproic acid provided no reliable protection.

A comparison of spectral profile changes associated with protective vs. non-protective compounds showed significant differences. It will be recalled that these data were collected during control recordings prior to MMH challenge. The major effect on the two drugs found to protect against MMH toxicity was a stable reduction in 4-7 Hz activity while the other compounds showed more of a tendency to preserve rhythmic and higher frequencies at more normal levels.

DISCUSSION

Evaluation of power spectral profiles during stable sleep conditions with reference to a specific sensory pathway provided clear evidence for functional anti-convulsant properties. The suppression of somatosensory cortex 4-7 Hz activity and/or the facilitation of 12-15 Hz activity characterized anticonvulsant compounds. From previous studies of somatosensory function (see above) we know that increased 4-7 Hz activity reflects cortical hyperexcitability while decreased 12-15 Hz activity is indicative of decreased thalamic regulation. Since drugs that protected against MMH convulsions (i.e., pyridoxine and diazepam) primarily suppressed somatosensory 4-7 Hz EEG activity, it may be suggested that the critical pathological effect of MMH resides in its alteration of cortical neuronal excitability. In previous work with evoked potential methods we found evidence for a disinhibition of somatosensory neurons just prior to hydrazine-induced seizures (Goff et al., 1967), and suggested that a disturbance in GABA synthesis could mediate this effect. The present findings reinforce this conclusion since pyridoxine and diazepam are known to restore the synthesis and facilitate the post-synaptic inhibitory actions of GABA, respectively (Tower, 1976; Costa et al., 1975).

The other anticonvulsant compounds tested here appear to exert a primary effect on thalamic inhibition, as indicated by changes in 12-15 Hz activity, which may also

attenuate cortical excitability and thereby reduce 4-7 Hz patterns. These drugs might be expected to be most effective in chronically developing seizure disorders, where abnormal cortical activating discharge is a part of the pathophysiology. In this case, a disturbance of thalamic regulatory function may be a primary factor in the etiology of seizures (Sterman and Shouse, 1982).

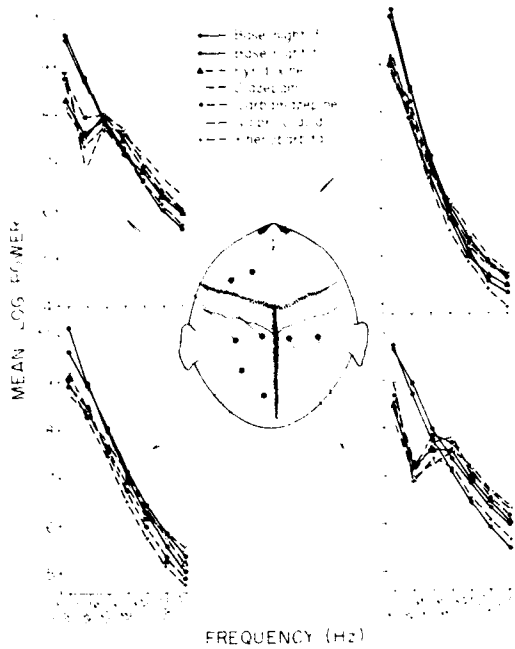
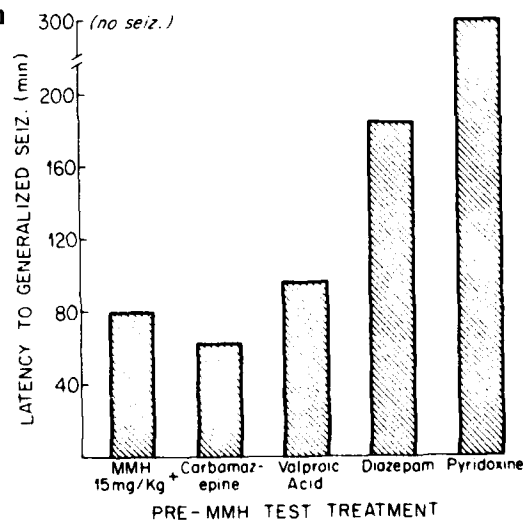


Figure 1. Mean power spectral density changes obtained from EEG patterns recorded two hours after administration of saline (base nights 3 and 5) and five anticonvulsant compounds in four rhesus monkeys. Data in each case are based on 10 minute samples drawn during sustained slow wave (nonREM) sleep from cortical areas indicated. Note specific profile changes localized to somatosensory cortex, bilaterally.

Figure 2. Mean latencies to generalized convulsions, measured in minutes post-MMH administration (15 mg/kg), in a group of four rhesus monkeys with and without subsequent treatment with four anticonvulsant drugs. In each case drugs were administered 10 minutes after MMH.



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