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EFFECTS OF MONOMETHYLHYDRAZINE ON THALAMOCORTICAL EXCITABILITY AND PATTERNS OF SLEEP IN THE CAT

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FOR THE COMMANDER

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The influence of subconvulsive exposure was examined with reference to a more basic aspect of physiological function than previous sensorimotor and performance studies; namely, the organization of sleep-waking patterns. Polygraphic recordings providing for classification of states of sleep and wakefulness were obtained over a 10-hr period following either saline or MMH (5mg/kg, IP) injections. MMH caused no overt behavioral disruption on transient observation

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at this dose; however, analysis of polygraphic data disclosed a significant depression of sleep and disruption of normal diurnal rhythms. Sleep suppression lasted approximately 6 hours and was followed by a profound sleep rebound. The behavioral effects of MMH exposure extended beyond the realm of sensorimotor functions. The influence noted upon sleep could have equally serious and different consequences in performance. In a second study the effect of MMH upon thalamocortical conduction was examined. Cats were operantly trained to suppress movement by rewarding a sensorimotor EEG rhythm (the SMR) with positive hypothalamic brain stimulation. Other cats received similar but noncontingent reward. Following training, the two groups were administered MMH (10 mg/kg, IP) and thalamically induced somatosensory evoked potential responses measured until seizures occurred. The noncontingent group showed an expected increment in response prior to seizures, while the SMR-trained cats showed a decrement or reduced increment. Other aspects of response to this dose, and the implications of these findings, are discussed herein.

PREFACE

This research was initiated by the Toxicology Branch, Toxic Hazards Division, Aerospace Medical Research Laboratory, under Project 7163. Experiments were performed under Contract AF F33615-73-C-1855 by the Department of Anatomy and the Brain Research Institute, School of Medicine, University of California, Los Angeles, California 90024.

The experiments were conducted by M. B. Sterman, PhD, of the Veterans Administration Hospital, Sepulveda, California. Kenneth C. Back, PhD, was contract monitor for the Aerospace Medical Research Laboratory.

INTRODUCTION

Previous studies in our laboratory have focused on the effects of subconvulsive exposure to monomethylhydrazine (MMH) upon motor behavior in the cat. They have documented the influence of this propellant upon performance and provided clues to the central mechanisms mediating these effects. Specifically, it was found that intraperitoneally administered MMH significantly altered food motivated behavior in a runway apparatus at a dose as low as 2 mg/kg (Sterman et al., 1969a). In this study, drug performance was compared with performance after saline injections, and significant drug effects were noted during the period 30-300 minutes after MMH administration. The CD_{50} for MMH in the cat was established previously at 7 mg/kg (Sterman et al., 1969b).

Other studies demonstrated that immobility (neuromuscular blocking agent) or trained suppression of movement increased latencies to electrical (EEG) seizure induced by MMH (Sterman et al., 1969b; Sterman et al., 1974). Additionally, evoked cerebral neuroelectric responses were enhanced following convulsive doses of MMH in the cat (Sterman et al., 1972). The primary negative response of somatic sensory cortex was progressively facilitated during a period of approximately 1 hour preceding seizures. Taken together, these findings suggest that sensorimotor excitability is altered as a result of exposure to MMH, with a consequent disturbance of associated motor behavior.

In the studies reported here the effects of low dose exposure to MMH were evaluated in relation to a dimension of behavior not

directly associated with motor functions, namely the organization of sleep-waking patterns. The measurement of these patterns and their normative characteristics are well documented in the cat (Sterman et al., 1965; Ursin, 1968). Additionally, to further explore the effects of immobility on seizure mechanisms, sensory evoked potentials were studied in animals trained to suppress movement through EEG operant conditioning. We have previously found that reinforcement of a sensorimotor cortex EEG rhythm, termed the SMR, resulted in learned motionlessness (Wyrwicka and Sterman, 1968; Sterman et al., 1969). This paradigm was utilized here to evaluate the effects of trained immobility upon evoked response changes previously associated with MMH.

The two studies described here focused upon separate physiological questions. Accordingly, the methods and results of these studies will be presented separately. A common discussion will follow.

Experiment 1: Effects of Subconvulsive Exposure to MMH on Sleep-Waking Patterns in the Cat

METHOD

Six adult cats were prepared surgically for monitoring of polygraphic variables utilized in the definition of sleep and waking states in the cat. These included cortical EEG, eye movements (EOG) and neck muscle tone (EMG). Under barbiturate anesthesia, pairs of small (1/8 in. diameter) stainless steel screws were threaded into the calvarium over sensorimotor cortex, bilaterally, for recording EEG activity. Similar screws were threaded into the exposed frontal sinus laterally over the orbits, for recording EOG activity. Fine insulated wires were inserted into the neck musculature, bilaterally, with exposed tips imbedded in the body of the longus capitus

muscle, for recording EMG activity. Leads attached to these electrodes were soldered into a 20-contact female Winchester plug. The frontal sinus was filled with Gelfoam and sealed with dental acrylic together with all screw and wire electrodes. The plug was fixed similarly to the skull, and all wound edges were closed with silk sutures. Animals were provided with standard postoperative care and allowed to recover for a four week period before experiments were begun.

All monitoring was carried out in a large, sound-attenuated behavior chamber equipped with a one-way mirror and independent ventilation system. The animal was attached via a suspended, shielded cable to an 8-channel Grass Model 6 polygraph and allowed to adjust to the chamber during several 12 hr. adaptation periods. On the control test day the animals were injected with saline solution intraperitoneally and placed in the chamber. The cable was connected, and recording initiated between 8-10 A.M. Continuous polygraphic sleep-waking data were obtained during the subsequent 10 hr. period, which previous studies have demonstrated to be the period of most stable sleep-wake cycling in the cat (Sterman et al., 1965). One week later each animal was recorded under identical conditions, except that the initial injection consisted of a 5 mg/kg dose of MMH administered into the abdominal cavity.

Data were analyzed according to standard polygraphic pattern scoring procedures. This involved the classification of each successive 1 minute epoch of the record into 1 of 4 basic functional states, including: awake (A), drowsy (D), quiet (or slow wave) sleep (QS) and active (or REM) sleep (AS). The defining characteristics of these states have been described in detail within the sleep literature. Percentages of

the various polygraphic states as well as their distribution over the period of recording were tabulated and statistically compared between control and drug recordings.

RESULTS

No significant behavioral effects were noted after saline injections. Similarly, except for the sleep-waking effects to be detailed below, no unusual or abnormal behaviors were displayed following administration of 5 mg/kg MMH. None of the animals showed any prodromal or seizure activity, and no overt signs of emesis were apparent.

Sleep-waking patterns were altered significantly by subconvulsive exposure to MMH. The total percentages of the 4 states tabulated over the 2 test recording periods are shown in Table I. Individual as well as group data are presented. The distribution of pattern percentages after saline injection suggests that sleep was somewhat depressed in this test, since 24 hr. control studies (Sterman et al., 1965) report values of 40-60% as compared with the 31% figure found here (QS + AS = total sleep). Administration of MMH caused a significant increase specifically in the percent of alert waking activity; however, no significant changes were obtained in tests of the other patterns.

Analysis of the distribution of patterns across the period of recording under the two test conditions is shown in Figure 1 and Table II. In this analysis the total occurrence of a given pattern is displayed as the percentage of that total present in successive 2-hr. blocks during the 10 hours of recording. In the saline control condition, the 2 sleep

TABLE I

Effects of intraperitoneally administered saline and MMH (5 mg/kg) upon the percentage occurrence of alert (A), drowsy (D), quiet sleep (QS) and active sleep (AS) patterns during 10 hr. polygraphic recordings in six adult cats.

	SALINE				MMH			
	A	D	QS	AS	A	D	QS	AS
	32	44	15	9	45	39	9	7
	27	22	39	13	35	50	10	5
	32	26	28	14	42	26	22	10
	18	48	22	12	29	25	29	17
	35	56	8	1	29	60	4	7
	20	54	23	3	27	45	23	5
$\bar{X}$	27.33	41.67	22.5	8.67	34.5*	40.83	16.17	8.5
σ	6.98	14.39	10.6	5.46	7.53	13.73	9.83	4.55

*t = 2.5835

df = 5, $p < .05$

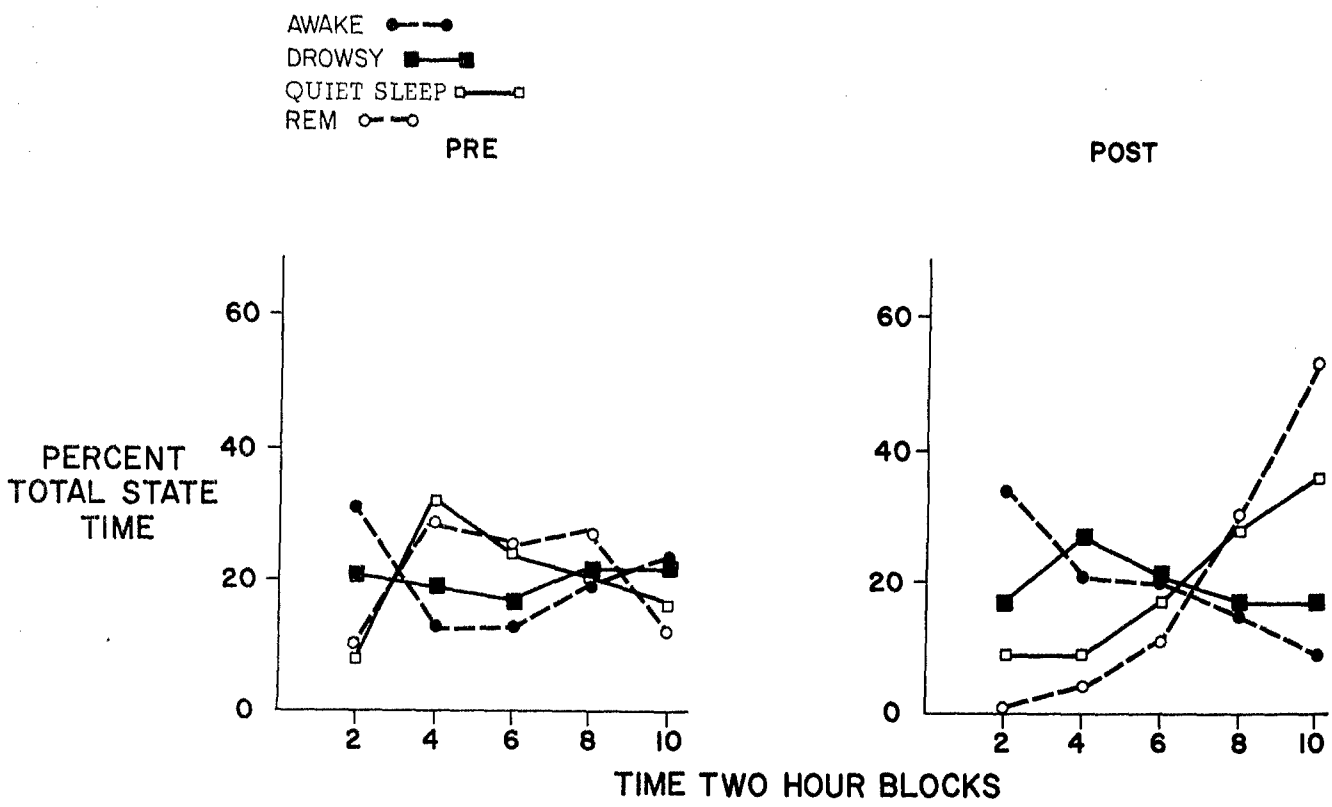

Figure 1: Effects of saline (Pre) and 5 mg/kg MMH (Post) on states of sleep and wakefulness in the cat. Mean 2-hour percentage values are shown for 6 animals. Under saline condition, diurnal patterns emerge from parallel awake and drowsy curves (waking) and the reciprocal distribution of quiet and active sleep. MMH not only depressed sleep states during first half of recording, but disrupted diurnal patterning as well.

TABLE II

Comparison of state pattern mean percentage distributions during successive two hour epochs over 10 hour recording periods after intraperitoneal saline and monomethylhydrazine (5 mg/kg) in 6 cats.

STATE PATTERN	SALINE TEST					MMH TEST				
	2	4	6	8	10	2	4	6	8	10
Awake	31.17 (±9.60	13.33 (±14.85)	13.0 (±11.36)	19.83 (± 8.23)	23.0 (±2.09)	34.33 (±6.34)	20.83 (±5.26)	20.0 (±9.20)	15.0 (± 9.20)	9.5** (±3.14)
Drowsy	20.83 (±9.10)	18.67 (±5.07)	16.67 (±7.14)	21.83 (±3.31)	21.83 (±5.03)	17.50 (±5.43)	27.17* (±7.13)	21.0 (±5.86)	17.50* (±2.42)	17.0 (±7.92)
Quiet Sleep	8.0 (±9.65)	31.67 (±9.81)	23.67 (±12.06)	20.50 (±13.78)	16.0 (±5.36)	9.0 (±12.18)	9.0** (±12.18)	17.33 (±8.82)	28.50 (±15.20)	36.17* (±24.07)
REM	10.33 (±14.55	27.5 (±28.96)	24.66 (±18.90)	26.50 (±15.68)	12.33 (±6.65)	0.83 (±1.32)	4.50 (±9.58)	11.0 (±10.63)	30.50 (±19.14)	53.16** (±23.15)

* $p = < 0.05$

** $p = < 0.01$

patterns (QS and AS) were predominant during a period 2-8 hours after recording was initiated, with the 2 waking patterns (A and D) dominating the first and last two hours of recording. This pattern reciprocity and diurnal curve is consistent with previous findings in the cat (Sterman et al., 1965). Following MMH administration an entirely different pattern was observed. Sleep was suppressed significantly during the second 2-hour block of recording and showed a marked recovery and rebound during the final 2 hours. Conversely, waking patterns accounted for most of the first half of the record, but were progressively depressed during the remainder of the time. Inspection of individual recordings indicated that long periods of sustained, but not unusually active, waking patterns characterized the initial period. The diurnal curves for sleep and waking patterns were abolished and the resulting distributions indicated clearance of toxic influences after 6 hours, followed by a marked rebound recovery. It may be concluded that significant sleep deprivation was produced following 5 mg/kg MMH.

Experiment 2: Effects of Monomethylhydrazine and Operant EEG Conditioning on Thalamocortical Evoked Potentials in Somatosensory System

METHOD

For this study 6 adult cats were prepared surgically for EEG operant conditioning and thalamocortical somatosensory evoked potential experiments. Under barbiturate anesthesia, electrodes were placed stereotaxically into the posterolateral hypothalamus (medial forebrain bundle, A9-10, L3, H-4), bilaterally, and into the nucleus ventralis posterolateralis of the thalamus (A18, L9-10, H+7.5). Three stainless

steel screws were threaded, bilaterally, into the calvarium over somatosensory cortex in a triangular array, in order to record both sensorimotor cortex rhythmic EEG activity and primary somatosensory evoked potentials in subsequent experiments. All leads were attached to a 20-contact female plug and insulated with dental acrylic. The plug was then fixed to exposed bone with the dental cement and wound margins closed with silk suture. A period of at least 4 weeks of postoperative care preceded initiation of experimental manipulations.

Following recovery, test somatosensory EEG and oscilloscopic recordings were obtained from all animals in order to determine the quality of sensorimotor EEG patterns and somatosensory evoked potentials. The animals were studied in a behavior chamber as described above. EEG patterns were recorded polygraphically and evoked potentials visualized on a Tectronix Model 502A oscilloscope. Evoked responses were elicited with a Grass Model S8 stimulator connected to either deep thalamic electrode. Thresholds and amplitudes of the various somatosensory evoked potential components were determined. The hemisphere showing the best combination of sensorimotor rhythm (SMR) activity and primary somatosensory evoked response was chosen for systematic study.

The 6 animals were divided randomly into two groups of 3 cats each. One group received EEG operant conditioning with positive brain stimulation reward delivered to the medial forebrain bundle electrode found most effective in shaping behavior. Production of 0.5 sec. trains of 12-15 Hz sensorimotor rhythm activity at a voltage 100% above baseline was rewarded. Details concerning the method for operant conditioning of EEG patterns in the cat have been described elsewhere (Wyrwicka and Sterman, 1968). The other group received similar stimulation delivered,

however, by an automatic random programming system. All animals obtained approximately 20,000 positive stimulation rewards during 3-per-week, 1-hour sessions over a 2 month period of training.

At the end of this period of systematic or sham training, evoked potential studies were begun. Ventrobasal thalamus was stimulated with progressively higher currents until thresholds for each of the 5 components of thalamocortical somatosensory evoked responses described by Allison (1965) were determined. Stimuli were single pulses delivered at a fixed stimulus duration of 0.1 msec. Accurate current settings were determined for the stimulus necessary to elicit components 1, 2 and 3 and at threshold for component 4 of this complex. This stimulus level (i.e., threshold for component 4) and a level 7 times the absolute or minimal response threshold were used as test stimuli for the study of MMH effects upon thalamocortical excitability.

Following these determinations, each animal was administered a 10 mg/kg dose of MMH, intraperitoneally. Pre-injection response amplitudes were subsequently compared with responses recorded at 5 min. intervals following drug administration for both SMR and control groups. Multiple responses were photographed with a Tectronix Model C-15 Polaroid camera mounted on the oscilloscope screen. Monitoring continued until major motor seizures occurred, at which time protective barbiturate was administered. Response amplitudes were measured also during the tonic phase of the seizure and post-ictally, approximately 10 minutes after barbiturate.

RESULTS

The data reported here deal only with evoked potential amplitudes resulting from thalamic stimulation at threshold current intensity for component 4 of the somatosensory evoked response. Accordingly, the values tabulated derive only from measurement of components 1-3, according to the method described by Allison (1965). Moreover, to summarize the extensive data collected, amplitudes were sampled prior to MMH administration (base), during the tonic phase of resulting major motor seizures (seiz.), at the point midway in time between drug injection and seizure (pre 1), during the 10 min. period immediately preceding seizure (pre 2) and during the 10 min. post-ictal period after barbiturate had been administered (post). Each sample represented an average of 5-10 individually elicited evoked responses for each animal in each test period.

The results of this analysis are shown in Table III and Figure 2. Base amplitudes tended to differ between the 2 groups with the SMR trained animals showing larger responses for component 1 and smaller responses for component 3 than the random control group. There were no apparent differences for component 2. Due to the small number of animals in each group (N = 3) it is inappropriate to apply statistics to these data. Nevertheless, comparison of relative trends suggest that the control animals showed the previously documented facilitation of somatosensory transmission (components 1 and 3) following exposure to MMH. Conversely, the SMR trained animals showed either a decrease (component 1) or an attenuated increment (component 3) in these same responses following MMH exposure. Responses recorded during the tonic phase of seizures

TABLE III

Comparison of mean somatosensory evoked potential amplitudes (μv) following monomethylhydrazine (10 mg/kg) in 2 groups of cats previously given either random (C) or EEG contingent (SMR) positive brain stimulation reward.

	SOMATOSENSORY EVOKED POTENTIAL COMPONENT					
SEQUENCE	1		2		3	
	C	SMR	C	SMR	C	SMR
BASE	26.32 (±8.98)	40.55 (±8.04)	4.48 (±1.82)	5.10 (±6.44)	32.14 ±8.12	26.48 (±18.96)
PRE 1	31.06 (±6.46)	38.50 (±7.22	5.86 (±2.38)	4.80 (±5.78)	36.96 (±8.38)	27.42 (±19.54)
PRE 2	35.08 (±10.20)	29.74 (±16.64)	6.06 (±2.64)	6.22 (±7.12)	40.44 (±4.43)	31.60 (±15.62)
SEIZ.	40.66 (±4.28	31.44 (±18.28)	6.00 (±2.36)	6.26 (±6.40)	37.04 (±2.14)	46.10 (±27.54)
POST	31.44 (±15.82)	28.46 (±24.72)	3.34 (±2.34)	4.66 (±5.04)	28.00 (±7.62)	44.46 (±28.76)

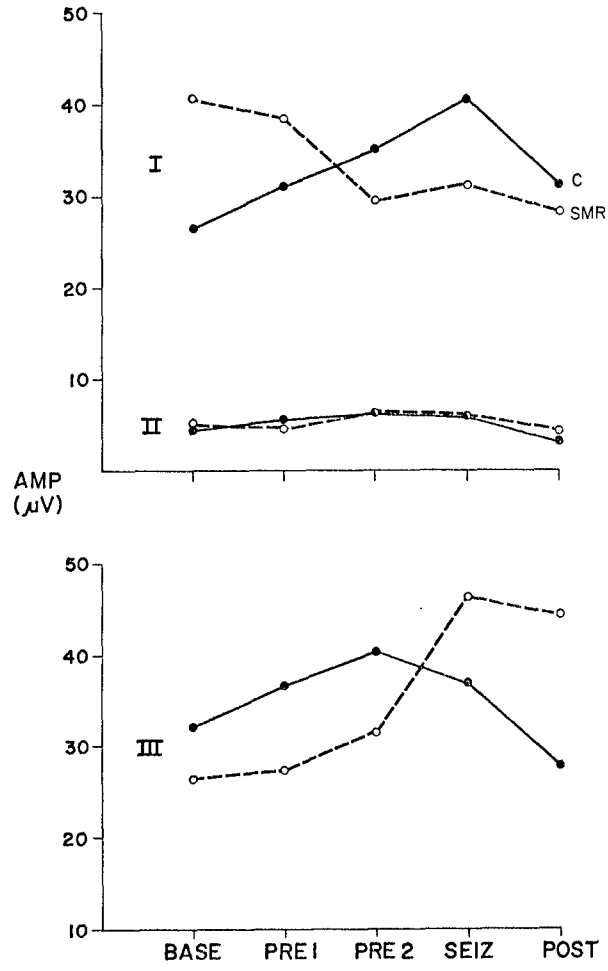

Figure 2: Mean evoked potential amplitudes for components 1-3 of somatosensory cortex response induced by thalamic stimulation are compared here in animals trained to suppress movement (SMR) and controls (C). Average amplitudes were measured before injection of 10 mg/kg MMH (base), during tonic phase of resulting seizure (seiz.), at a point midway in time between injection and seizure (pre 1), at a point just prior to seizure (pre 2) and after barbiturate was administered (post). Stimulation parameters are provided in text.

and after barbiturate administration were extremely variable, the latter, however, indicating a consistent trend toward recovery. In general, the data obtained from the SMR group were more variable than those of the control group (Table III).

It is interesting to note that seizure latencies in the 2 groups of cats did not appear to differ significantly, averaging 70-80 minutes post-injection. This fact tends to obscure interpretation of the evoked potential results. However, findings from other ongoing studies may help to clarify this question, as discussed below.

DISCUSSION

In these studies both convulsive and subconvulsive doses of MMH in the cat were found to have significant effects upon covert aspects of physiology. Evaluation of subconvulsive exposure (5 mg/kg) utilizing the complex structural organization of sleep-waking patterns proved to be most useful. The neural substrates for sleep and wakefulness provide a framework within which all behavior is organized. Careful measurement of these processes provides not only a subtle means of evaluating physiological disruption but, also, a basis for determining the duration of effects.

In the present context, injection of 5 mg/kg of MMH produced no overt disturbance detectable by virtue of transient behavioral evaluation. However, a significant alteration of sleep-waking patterns was observed, lasting approximately 6 hours. The duration of this influence is consistent with the effects noted on motor performance from low doses of MMH in previous studies (Sterman et al., 1969a). The present findings indicate that toxic CNS effects are generalized

beyond the realm of sensorimotor function, extending to the most fundamental aspects of behavior organization. There is no doubt that the depression of sleep and subsequent rebound noted would have profound influences upon the performance of even the most simple tasks, with the rebound phase posing the greatest problem. Moreover, pharmacologic studies of sleep alteration and rebound resulting from other activating drugs have shown that enhancement of the active or REM sleep pattern associated with rebound is usually accompanied by severe psychological disturbances in man (Oswald, 1969; Dunleavy et al., 1972).

The study of somatosensory evoked potential responses to MMH following trained immobility provided information at a different level of evaluation. While this complex experiment requires replication with a larger number of animals before firm conclusions can be drawn, the present findings suggested several paradoxes.

Animals trained to suppress movement with EEG operant conditioning tended to have larger component 1 responses during pre-drug baseline measurement than did the non-contingent reward group. Component 1 represents the direct cortical response to thalamic stimulation. Accordingly, enhancement of this response could reflect increased cortical or thalamic excitability as a result of SMR training. While control animals showed a significant facilitation of this response following a 10 mg/kg dose of MMH, a pattern previously documented with comparable aspects of the peripherally evoked somatosensory response (Sterman et al., 1972), SMR trained animals showed a parallel suppression of response amplitude prior to seizure. It is possible that this reciprocal response pattern

reflects a process of homeostatic control similar to that ascribed to autonomic nervous system function by the "Law of Initial Value" (Wilder, 1958), since the trained animals may have had significantly elevated baseline excitability. Alternately, these animals may have achieved increased control of thalamocortical conduction by virtue of the training. The latter interpretation is supported by the fact that component 3 (intracortical origin) responses were attenuated also in these animals following MMH, in spite of a tendency toward reduced initial excitability when compared to controls.

The significance of these suggested differences between groups, in terms of protection against seizures, is made questionable by the fact that both groups tended to convulse with approximately the same post-injection latencies. However, in another study currently under way in our laboratory we have found evidence which suggests that the excessive positive brain stimulation used in the present study, or the mere placement of deep electrodes in either ventrobasal thalamus or posterolateral hypothalamus, or both, may facilitate seizures resulting from exposure to MMH. Such an effect could operate via extralemniscal pathways and swamp any marginal protection afforded by EEG operant conditioning. More investigation will be required in order to separate the possible interactions suggested by these recent observations.

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