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EFFECTS OF MONOMETHYLHYDRAZINE (MMH) ON EVOKED CEREBRAL NEUROELECTRIC RESPONSES

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The experiments reported herein were conducted according to the "Guide for Laboratory Animal Facilities and Care," 1965 prepared by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences—National Research Council.

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13. ABSTRACT Studies of the effects of monomethylhydrazine (MMH) on the cerebral neuroelectric evoked response in the unanesthetized cat revealed that convulsive doses of this compound consistently produced a large increase in the primary negative response of the somatic sensory cortex which progressively changed with time and approached peak levels starting approximately 1 hour before seizure onset. Delay of seizures with neuromuscular paralysis was observed also. The possible significance of this finding in relation to mechanism of action in the nervous system was explored. These results obtained with MMH are consistent with those previously reported for unsymmetrical dimethylhydrazine (UDMH). As herein reported, the evoked response changes are similar to results obtained with the convulsant agent Metrazol, suggesting that these response changes may be a useful index of impending seizure in a variety of toxic and clinical conditions. Key Words: Monomethylhydrazine Cerebrospinal fluid glucose 1-methylhydrazine Cerebrospinal fluid formation Blood glucose			

FOREWORD

This research was initiated by the Toxicology Branch, Toxic Hazards Division, Aerospace Medical Research Laboratory, under Project 7163. Experiments were performed under Contract AF F33615-69-C-1441 by the Department of Anatomy and the Brain Research Institute, School of Medicine, University of California, Los Angeles, California 90024.

The experiments were conducted jointly by M. B. Sterman, PhD, of the Veterans Administration Hospital, Sepulveda, California, M. D. Fairchild, PhD, of the Veterans Administration Hospital, Long Beach, California, and T. Allison, PhD, and W. R. Goff, PhD, of the Veterans Administration Hospital, West Haven, Connecticut. Kenneth C. Back, PhD, was contract monitor for the Aerospace Medical Research Laboratory.

This technical report has been reviewed and is approved.

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Section I

INTRODUCTION

In a continuing series of experiments on the central nervous system effects in the cat of the biologically toxic liquid propellant hydrazine, and its derivative compounds unsymmetrical dimethylhydrazine (UDMH) and monomethylhydrazine (MMH), we have (1) established convulsive and lethal dose levels, (2) described behavioral and neurophysiological effects of subconvulsive doses, and (3) evaluated the effects of UDMH on cerebral neuronal excitability as indicated by neuroelectric responses (Fairchild and Sterman, 1964; Sterman et al., 1969; Goff et al., 1970). The latter, in particular, have provided some insight as to the central mechanisms of effects which are responsible for the toxic symptoms of these compounds in the realms of behavior and neurology. It was established that the convulsant action of UDMH is mediated primarily at the cortical level and not at subcortical relays of the somatosensory system. In the present experiments we have extended the previous investigation to a study of the effects of monomethylhydrazine (MMH) and to another convulsant agent, Metrazol, in order to test the generality of these convulsant effects.

Section II

METHODS

The methods used in these experiments are similar to those employed in the earlier studies (Goff et al., 1967; Goff et al., 1970). Experiments were performed on 10 cats prepared several weeks previously with chronically implanted electrodes. Small stainless-steel screws resting on the dura recorded the electrocorticogram (ECoG) and surface evoked responses. Stainless-steel depth electrodes with intertip distance of 1 mm were placed stereotaxically. Somatic evoked responses to stimulation (1-3 V, 0.1 msec pulses) of the ulnar nerve via an implanted cuff electrode were averaged by a four-channel analog device or by a Fabri-Tek 1074 averager. Evoked responses were recorded with reference to a screw in bone overlying the frontal sinus. Anterior and posterior cerebral cortex, and dorsal hippocampus activity was recorded to assess the electrographic manifestations of seizures.

After control evoked response and EEG recording, MMH (Eastman Organic Chemicals, practical grade) in a 10% saline solution was administered intraperitoneally in doses of 9-18 mg/kg. All experiments were carried out in unanesthetized animals; the epileptogenic action of MMH is readily blocked by barbiturate anesthesia, while chloralose itself has an excitant action which would have confounded the results. Recordings in freely-moving animals were made by means of a cable connected to a counterweighted slip ring (Lehigh Valley Electronics) allowing freedom of movement within a recording box. It was usually impossible to record evoked activity during a generalized seizure due to paroxysmal EEG activity and movement artifact. To eliminate movement artifact and to test the effects of immobilization on the development of seizures, most animals were studied after paralysis by gallamine triethiodide. They were first

tracheotomized and artificially ventilated; all wound margins were infiltrated periodically with xylocaine. To minimize the animal's discomfort the experiment was terminated with barbiturate sedation either when a stable pattern of results emerged (usually after two or three generalized seizures) or immediately upon onset of status epilepticus.

Section III

RESULTS

The results of these experiments were quite consistent with those obtained with UDMH. Typical results are shown in Fig. 1. As with UDMH intoxication, administration of convulsive doses of MMH resulted in a very large, consistent increase in the amplitude of the primary negative response of somatic sensory cortex (SI). The primary positive response was clearly increased also in some animals, as is shown in the data from animal 229 in Fig. 2. It was observed that these changes in response amplitudes usually preceded seizures by approximately one hour and were only temporarily suppressed by administration of Nembutal. When high doses were administered initially (i.e., 20 mg/kg, Fig. 1), a progressive increase was sometimes observed, with excitability being acutely increased within the hour preceding the onset of seizures. The magnitude of this effect can be appreciated by reference to Fig. 3, which shows samples of evoked somatosensory neuroelectric responses both before MMH administration and just prior to MMH seizures in the same animal.

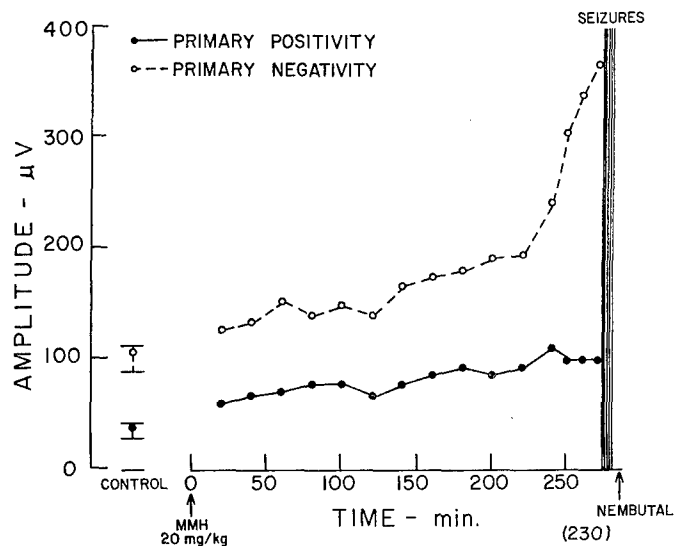


Figure 1. Amplitude of primary positive and negative waves of somatic cortex to stimulation of contralateral median nerve. Animal was paralyzed and artificially respiration. Control evoked responses were taken immediately before i.p. administration of MMH. Each response is the computer average of 10 individual responses. Note tremendous increase in amplitude of primary negativity prior to seizure. The primary positive wave also increased following drug administration, but does not predict seizure onset. Later components of the somatic response (not plotted) show no particular change following MMH administration. Following the first seizure the cat went almost immediately into status epilepticus, and was sedated with Nembutal shortly thereafter.

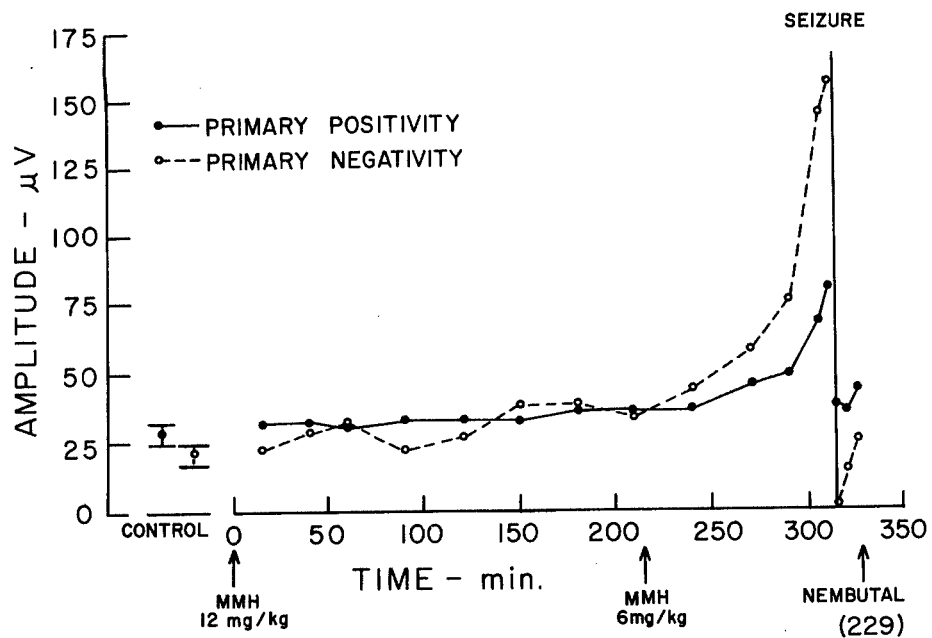


Figure 2. Another example, similar to Fig. 1, showing large increase in amplitude of primary negativity prior to seizure. In this experiment the primary positivity also shows a clear, although smaller, increase in amplitude prior to seizure. Cat 229, paralyzed, artificially respired, locally anesthetized. At 215 minutes it was decided that the original dosage was too low to elicit a seizure; therefore, an additional 6 mg/kg MMH was administered. Note that this dosage would be more than enough to induce seizures in a freely-moving animal.

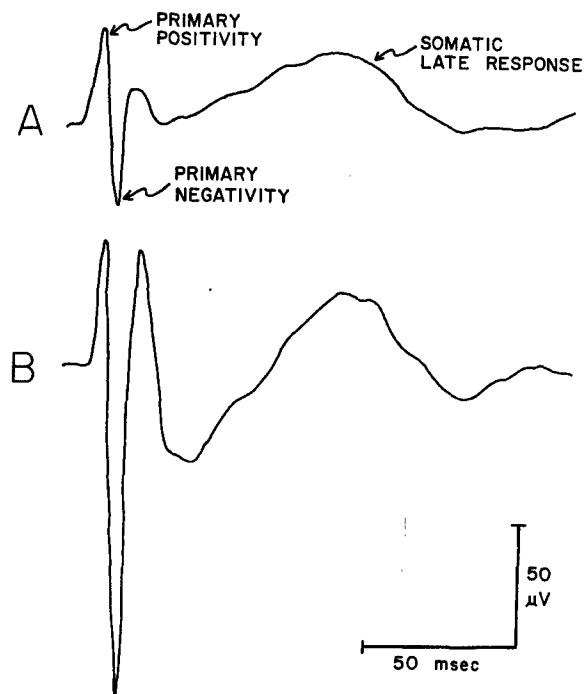


Figure 3. Characteristic changes in somatic evoked response after administration of MMH. A. Control response prior to drug administration. Response components measured in these experiments are labelled. B. Response just prior to generalized seizure. Note slight augmentation of primary positivity, very large augmentation of primary negativity. In this particular response, the somatic late response was also augmented, but this increase was not consistently seen. (Cat 228)

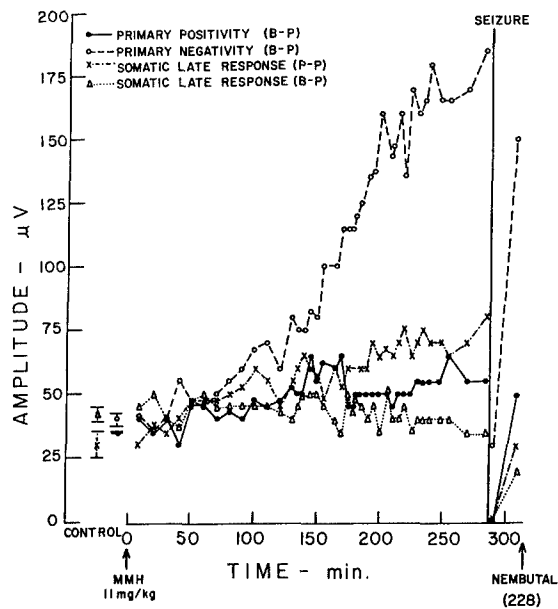


Figure 4. Changes in somatic early and late evoked responses after MMH administration. Primary responses were measured from baseline to peak (B-P). Median and range of response amplitudes prior to drug administration are shown to the left (control). Note that only the primary negativity showed a consistent, progressive increase in response amplitude prior to seizure. During and immediately following the seizure (during postictal depression of the EEG) all response amplitudes were considerably smaller than normal, but quickly recovered prior to next seizure. The animal then went into status epilepticus and was sedated with Nembutal at 311 minutes. (Cat 228, paralyzed, artificially respired, locally anesthetized.)

As in the previous studies, the only consistent change in neural activity prior to seizures resulting from MMH administration was the dramatic increase in the primary negativity of the somatosensory response. Fig. 4 presents measurements of evoked potential changes after 11 mg/kg of MMH, which included both primary and secondary components of the response. Once again it can be seen that the negativity was greatly increased beginning, in this case, 3 hours before seizures were manifest. This effect was again noted, after a very brief depression, following the administration of Nembutal.

In the freely-moving cat, the threshold dose for seizures following intraperitoneal administration of MMH was found to be 7 mg/kg (Stermann et al., 1969). Seizures were consistently observed within approximately 1 hour at a dose of 9 mg/kg. In contrast, the paralyzed preparations studied here required at least 4 hours before seizures were manifest, at doses ranging from 11 to 20 mg/kg.

Evaluation of the effects of Metrazol on somatosensory evoked responses indicated a similar increase in the amplitude of the primary negativity prior to seizures. The extreme rapidity of action of this convulsant, however, made it difficult to document drug related alterations. Nevertheless, it would appear that any convulsive agent, no matter what its pharmacological mode of action, can enhance the amplitude of the primary negativity of somatic cortex, prior to seizure onset.

Section IV

DISCUSSION

The present findings indicate that MMH and Metrazol, like UDMH, produce a relatively specific facilitation of the primary negative somatosensory evoked response in the cat. This effect may develop gradually after intraperitoneal injection and become acute, or develop abruptly, approximately 1 hour before the onset of seizures. As has been suggested previously (Goff et al., 1967), this observations could provide a basis for the prediction of seizures resulting not only from toxic poisoning but also from clinical conditions such as epilepsy. This possibility is presently being explored at the Seizure Clinic of the West Haven Veterans Administration Hospital.

Another general conclusion with significant implications for an understanding of the mechanisms of action in the nervous system of both MMH and UDMH relates to the observed delay of seizures resulting from neuromuscular blockade. It is probable that the reduction of background afferent somatosensory discharge resulting from muscular paralysis can delay the detrimental biochemical action of these compounds on cortical elements (Goff et al., 1970). This action is thought to be directed to inhibitory interneurons in the cerebral cortex, perhaps via interference with pyridoxine mechanisms. Recent findings suggest that the function of cortical inhibitory interneurons may be facilitated by a stable somatosensory input, which could explain this increased resistance to seizures (Sterman and Friar, 1972).

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