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Effects of Restraint on Electroencephalographic Variables and Monomethylhydrazine-Induced Seizures in the Cat

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The toxic derivative of hydrazine, monomethylhydrazine, at a dosage of 10 mg/kg is a potent convulsant, producing tonic-clonic seizures in the cat. In this study the effects of enforced restraint on susceptibility to MMH-induced seizures was examined in naive animals and in cats prepared neurosurgically with indwelling polygraphic recording electrodes. Using a counterbalanced design, latency to seizure following the intraperitoneal administration of the drug (10 mg/kg) was measured twice in all animals, under restraint and in freely moving conditions. Susceptibility to seizures was significantly decreased under the condition of restraint. Additionally, polygraphic recordings showed that restraint was accompanied by an increased incidence of "synchronous" EEG patterns. These results were not explained by metabolic variables, duration of intertrial interval, or changes in weight. The relationship between observed polygraphic patterns and seizure response is discussed in terms of the physiological alterations attendant upon restraint.

INTRODUCTION

The toxic hydrazide, monomethylhydrazine (MMH), is known to induce tonic-clonic seizures in a variety of animal species (39). It is an effective and reliable convulsant in the cat when administered intraperitoneally at dosages of 10 mg/kg (31). Monomethylhydrazine is known to bind pyridoxal competively and is assumed to interfere with the synthesis of

Abbreviations: EEG—electroencephalogram; MMH—monomethylhydrazine; GABA—γ-aminobutyric acid; SMR—sensorimotor rhythm.

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the putative inhibitory neurotransmitter, γ-aminobutyric acid (GABA) (7). Seizures are thought to be due to the diminution of tonic inhibitory influences on central motor mechanisms (33). Monomethylhydrazine intoxication is characterized by stereotypic preconvulsive behaviors (piloerection, hyperventilation, emesis, salivation, and hyperactivity) followed by generalized tonic-clonic seizures (3, 31). The mean latency to seizure in naive, adult cats is 180 ± 83 min postinjection (27). Cats prepared with surgically implanted chronic brain electrodes have significantly shorter mean latencies (60 ± 13 min) (26). Previous investigations in this laboratory showed that the latency to MMH-induced seizures in the cat is influenced by electroencephalographic (EEG) phenomena accompanying the suppression of movement (26). We therefore undertook to examine in detail the role of motor suppression in the MMH-induced seizure response.

A relationship between restraint and susceptibility to seizure has been previously described in rodents. Audiogenic seizures were reduced in rats restrained in cylinders (17), modified Camichael socks (11), and in mice restrained with their anterior limbs extended and their posterior limbs flexed ["hogtied"] (37).

The present investigation was designed to examine the relationship between physical restraint and susceptibility to MMH-induced seizures in the adult cat. Attention was given to behavioral and EEG phenomena associated with the restraint paradigm and their possible role in MMH-induced seizure processes.

METHODS

Nine adult female and three adult male cats, weighing between 2.7 and 5.5 kg were used for this experiment. All animals were given physical examinations and then quarantined for 30 days prior to the experiment. Animals showing signs of illness were excluded from the study.

The animals were divided into two groups of six each. Group I consisted of naive, unoperated animals (five females and one male). Group II consisted of animals prepared with surgically implanted electrodes for monitoring the EEG (four females and two males). Each animal was subjected to two trials of intraperitoneally (ip) administered MMH at the convulsive dose of 10 mg/kg. The drug was obtained from Matheson, Cole and Bell, Norwood, Ohio (MW 46.07 g/mol, sp gr = 0.874) and was diluted to 20 mg/ml in normal saline.

Operated Group. Surgical procedures were carried out under pentabarbital sodium (Nembutal) anesthesia. Pairs of $\frac{1}{8}$-in. stainless-steel jeweler's screws were placed stereotaxically over the cruciate gyrus (A23, L8, 10) in all animals. Three of the animals were equipped with subcortical

recording electrodes; stainless-steel wire electrodes (250 μm in diameter), insulated to within 1 mm of their tips, were inserted into the thalamus (n. ventralis posterolateralis, lateral geniculate nucleus) and pontine reticular formation, with reference to the atlases of Jasper and Ajmone-Marsan (15) and Snider and Neimer (24). Bilateral electrodes were inserted into the dorsal neck musculature. The recording electrodes were soldered to a 20-lead Winchester plug which was then secured to the skull with dental acrylic. A low-noise, Microdot coaxial cable suspended by a counterweight system connected the subject to the polygraph.

Procedure. Seizure latencies for each animal were recorded under two behavioral test conditions, restrained and unrestrained. A counterbalanced design was used to control for order effects. Half the subjects in each group were tested first in the restrained condition and the other half first in the unrestrained condition. A minimum intertrial interval of 30 days was maintained for each subject.

Restraint was accomplished by securing the animal in a tightly fitting nylon net bag which was drawn closed around the neck. One-quarter-inch spacings in the net allowed unimpeded airflow. Animals were confined in a crouching position. While twisting motions and slight postural adjustments were possible, gross movements, including the extension of the limbs, were prevented.

Each animal was deprived of food for 12 to 16 h preceding the trial. After the cat was weighed and the appropriate dosage of MMH computed (10 mg/kg), it was placed into a modified LeHigh Valley recording chamber (61 × 61 × 76 cm) for a 30-min adaptation period prior to drug injection. The chamber had triple walls to provide sound attenuation and was equipped with positive-pressure ventilation and a one-way viewing window. Illumination was provided by a 300-W bulb placed over a translucent plastic ceiling.

Immediately after the administration of MMH, the animal was returned to the observation chamber. Latency to seizure was measured from the time of drug injection to the initial onset of tonic-clonic convulsions. Pentabarbital sodium was administered (35 mg/kg, ip) during the tonic phase of the seizure to prevent further convulsions.

The EEG was recorded both on polygraphic paper and analog tape. Movements were monitored via an electrostatic movement sensor mounted under the floor of the observation chamber.

The polygraphic records were scored in 1-min epochs using standard state pattern criteria (34). Drowsy and slow-wave sleep states were combined to define a more general measure of quiescence characterized by "synchronized" EEG patterns. Behavioral observations were used to facilitate scoring. These observations were also correlated with the movement

channel of the polygraphic record to establish scoring criteria for the measurement of movements. Movement episodes of 5 s or more, measuring in excess of 200 μV on the electrostatic movement sensor, were used as the standard scoring unit. This voltage corresponded to the amplitude of vigorous movements such as pacing, backward walking, or escape behaviors. Smaller movements such as head-turning or grooming did not meet this criteria. Successive movement episodes were scored as one unit if the interval between episodes was 6 s or less.

RESULTS

Ten of the twelve animals had increased seizure latencies in the restrained condition compared to the unrestrained condition (Table 1). Of the remaining animals, one did not have a seizure under either condition, and one had an earlier seizure under the restrained condition. To include non-seizure trials in group calculations, a latency value of 290 min was assigned to animals who failed to demonstrate seizures. This value represents the maximum seizure latency recorded for a larger group of naive animals ($N = 20$) observed in an earlier study (*27*) and was thus established as the maximum duration of observation in the present investigation. The

TABLE 1

Latency to Monomethylhydrazine Seizures in Restrained vs Unrestrained Cats

Cat number	Condition	Restrained	Unrestrained
1	Naive	290 min (no seizure)	48 min
2	Naive	290 min (no seizure)	95 min
3	Naive	91 min	65 min
7	Operated[a]	290 min (no seizure)	60 min
8	Operated[a]	178 min	67 min
9	Operated[a]	290 min (no seizure)	290 min (no seizure)
		Unrestrained	Restrained
4	Naive	172 min	209 min
5	Naive	222 min	290 min (no seizure)
6	Naive	62 min	102 min
10	Operated[b]	62 min	>89 min[c]
11	Operated[b]	191 min	53 min
12	Operated[b]	91 min	123 min

[a] Cortical + subcortical electrodes.

[b] Cortical electrodes only.

[c] No seizure observed; technical problems necessitated termination of trial.

TABLE 2

The Intertrial Interval, Change in Weight between Trials, and Change in Latency to Monomethylhydrazine-Induced Seizures

Cat number	Change in latency (min)[a]	Intertrial interval (days)	Change in weight (kg)[b]
1	>242	32	−0.10
2	>195	51	+0.15
3	26	52	−0.33
7	>230	137	+0.21
8	111	56	+0.38
9	0	52	−0.03
4	37	43	+0.41
5[c]	68	104	+0.98
6	40	39	+0.06
10[c]	>27	51	−0.20
11	−138	108	−0.40
12	32	45	−0.01

[a] The negative value for cat 11 indicates an earlier seizure in the unrestrained condition. Numerical differences between no seizure and seizure events represent minimal values and are so indicated by the ">" notation.

[b] Change in weight from the unrestrained to the restrained condition. Positive values indicate a higher weight in the restrained conditions.

[c] Subjects 5 and 10 were eliminated from the statistical analyses as it was impossible to place them accurately in the ranked order.

greatest number of "no seizure" events occurred in the restrained condition. In agreement with our initial hypothesis, restraint significantly increased seizure latency in these animals ($p < 0.001$, Wilcoxon matched-pairs signed-rank test, one-tailed). Spearman rank order correlation analysis did not indicate significant correlations between change in latency and either the intertrial interval ($r_s = -0.26$, $P = 0.23$) or the change in weight between trials ($r_s = 0.35$, $P = 0.17$) (Table 2).

Piloerection appeared as the first behavioral sign of monomethylhydrazine intoxication in a majority of the animals studied. Hyperventilation and emesis, followed by panting, then salivation were the next most common responses. The motor symptoms of intoxication such as backward walking, hyperactivity, and escape behaviors (31) were differentiated only in the unrestrained animals, as bagging restraint made it impossible to identify these responses adequately. All prodromal signs did not occur in every animal. The most frequently observed prodromal sign common to both experimental conditions was panting, followed by piloerection, emesis, and salivation (Table 3). The time to onset of piloerection, emesis, and salivation was longer in the restrained condition: however, statistical analysis

TABLE 3

Differences in the Time to Onset of Prodromal Behavior between Paired Trials[a]

Prodromal sign	Number of subject pairs	Mean difference, M_D between pairs (min)	Standard deviation (min)
Piloerection	6	−0.83[a]	3.89
Emesis	5	−19.6[b]	3.58
Panting	10	1.1	4.58
Salivation	3	−10.67	12.38

[a] Negative values represent a greater time to onset in the restrained condition.
[b] Significant at $P > 0.05$ (Matched Pairs t test, $t = 5.47$, two-tailed).

showed that the difference in the time to onset of emesis was the only variable that was significantly different between conditions (matched pairs t test, $t = -5.47$, $p > 0.05$). The time to first onset of panting tended to be shorter in the restrained condition than in the unrestrained condition. This difference, however, was not significant.

The incidence of "synchronized" EEG patterns prior to the earliest seizure in each subject's pair of trials increased under the restrained condition for all six of the EEG-monitored animals (Wilcoxon matched-pairs signed-rank test, $T = 2$, $P = 0.047$, one-tailed). Four of these animals had increased seizure latencies in the restrained condition. In three of these, the incidence of these patterns approximately doubled. One animal (#9) did not have a seizure under either condition. The amount of synchronized EEG activity displayed in the unrestrained condition was greater in this animal than for any of the other unrestrained subjects. Another animal (#11) had a seizure earlier in the restrained condition. This cat showed the least synchronized EEG pattern activity of all EEG-monitored, restrained animals.

In all cats, periods of wakefulness in the restrained condition were characterized by frequent episodes of vigorous escape behaviors. Twisting, writhing, and straining movements typified these episodes. In addition, oral behaviors consisting of biting and gnawing the restraint were often observed. These behaviors were marked by a gradual onset and usually ended abruptly. They did not appear to be convulsive and were not accompanied by paroxysmal EEG activity when observed in the EEG-monitored cats. Wilcoxon matched-pairs signed-rank test analysis showed that the frequency of movement episodes prior to the earliest seizure in each subject's pair of trials was not significantly different between conditions ($T = 5$, $P = 0.156$, one-tailed). Seizures appeared to be triggered during the alert, waking state, and never developed during sleep (Table 4).

TABLE 4

Movement and Synchronized EEG Pattern Activity in Monomethylhydrazine-Challenged Cats: Restrained vs Unrestrained

Cat	Condition	Latency (min)	Median movement duration (s)	Median movement duration to earliest seizure of pair (s)	Total number of movement episodes	Number of movement episodes to earliest seizure of pair	Total time exhibiting synchronous EEG patterns (%)	Amount of synchronous EEG pattern activity to earliest seizure of subject pair (%)
7	Restrained	290[a]	8.19	10	49	15	57.39	34.84
	Unrestrained	60	12.00	—	13	—	32.56	—
8	Restrained	178	16.75	20	29	25	30.00	46.00
	Unrestrained	67	9.00	—	14	—	18.00	—
9	Restrained	290	11.75	—	46	—	64.82	—
	Unrestrained	290	8.00	—	9	—	57.70	—
10	Restrained	89	8.00	7	13	8	68.71	71.50
	Unrestrained	62	13.00	—	18	—	26.88	—
11	Restrained	53	8.25	—	7	—	18.47	—
	Unrestrained	191	7.00	7	31	9	18.30	11.37
12	Restrained	123	23.00	28	27	23	34.00	42.00
	Unrestrained	91	9.00	—	13	—	26.00	—

[a] No seizure.

DISCUSSION

The results presented here indicate that bagging restraint increased the latency to seizure following convulsive exposure to MMH in cats. These findings are in agreement with those of other investigators who examined the effects of restraint on audiogenically elicited seizures in rodents (11, 17, 37). The present experiment showed that the restraint paradigm is also effective in altering drug-induced seizure susceptibility in the cat.

It is possible that these results were due to behavior-related alterations in drug absorption, distribution, biotransformation, and/or excretion. The onset of three of four prodromal signs was delayed in the restrained condition; however, only one, emesis, was significantly altered. The metabolic effects of MMH were shown to be similar in toxicity whether entry was via the lungs, the stomach, the peritoneal cavity, or direct intravenous injection (39). Consistently stable latencies were observed when MMH was administered by a variety of routes, including intracisternally (Sterman, unpublished finding). In the present experiment, no correlation was found between intertrial weight change and the corresponding change in seizure latency. Collectively, these findings support the hypothesis that behaviorally dependent metabolic variables had no significant effect on MMH toxicity as studied here.

Monomethylhydrazine has strong reducing properties and is known to undergo rapid oxidation in air (35). The experiment used a counterbalanced design to provide an internal control for the potential effects of MMH degradation over multiple exposure trials. The absence of a significant correlation between intertrial interval and latency to seizure indicates that a loss of MMH toxicity due to oxidation was not responsible for observed differences.

The bagging restraint was accompained by episodes of escape behavior. The frequency of these episodes did not differ significantly from the quantity of general movement observed in the unrestrained condition. It may be speculated that psychological variables associated with these intermittant motor behaviors provided protection against seizures. Complex escape behaviors, aggravated by the bagging restraint, may have served substitutive functions to the convulsive response. This role of substitutive behaviors was previously suggested to account for the resistance to audiogenically elicited seizures sometimes observed in restrained or distracted rodents (2, 10, 17). There is evidence also that arousal level is related to seizure susceptibility. Cortical activation was found to both facilitate (23, 32) and suppress (36) interictal discharges in human epileptic patients. Although an antagonism was frequently observed between sensory evoked cortical activation and seizure activity (6, 8, 12, 16, 20), arousal produced by emotional stress (23, 32), and decision conflict (19) were reported to increase seizure susceptibility.

The relationship between prodromal EEG patterns and seizure latency was of primary interest to us in the present experiment. It is generally believed that seizure thresholds are reduced during states characterized by synchronous EEG patterns (21). Our results showed the opposite, namely, that increased seizure latency was associated with a significant increase in the incidence of these patterns. Thus, under the restrained condition, a facilitation of synchronous EEG activity did not potentiate seizure activity and may, in fact, have exercised a protective influence.

As mentioned above, operant conditioning of sensorimotor cortex EEG patterns associated with learned immobility also extended seizure latencies in MMH studies (26). Specifically, a 12- to 15-Hz rhythmic activity termed the sensorimotor rhythm (SMR) was the EEG pattern rewarded in those investigations (22). SMR training in human epileptic patients was shown to be of therapeutic value in controlling seizure episodes (9, 18, 28). In the monkey, enforced restraint facilitates SMR activity (29). Studies have related the SMR to spindle-burst activity during sleep (14, 25, 30). Thus, it is possible that restraint-induced EEG synchronization can invoke the same protective mechanism as that demonstrated in EEG operant conditioning studies. Lesions of primary afferent pathways to ventrobasal thalamus were found also to facilitate these EEG patterns (1). In this regard it is interesting to note that lesions of the dorsal funiculi were reported to increase the latency to audiogenically induced seizures in susceptible strains of mice (4). Reduced audiogenic seizure severity was also observed in hemicordotomized mice when stimuli were presented to the ear ipsilateral to the lesion site. No reduction in seizure severity was obtained when stimuli were presented to the contralateral ear (38).

In the cat, cortically recorded SMR activity is accompanied by phasic decreases in muscular tone, reflex excitability, and unit discharge in motor pathways (5). As with the SMR, the sleep spindle is associated with a reduction of motor excitability. Hongo *et al.* (13) reported that cortical sleep spindles were accompanied by an inhibition of spinal gamma efferent discharges, and, consequently, decreased discharge rates from muscle spindle afferents in both flexor and extensor muscles. Thus, it is possible that central and/or peripheral manifestations of reduced gamma motor system activity can alter the seizure process. This effect can apparently be achieved by learned manipulation of central thalamocortical organization, by surgical interruption of primary somatosensory pathways, or by active restraint.

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