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An analysis of various environmental and specific sensory stimuli on the seizure activity of the Mongolian gerbil

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Mongolian gerbils were subjected to different environmental and specific sensory stimuli to determine the ability of these stimuli to provoke seizures. None of the specific sensory stimuli, somatosensory, olfactory, auditory or visual, were effective in inducing convulsions. This finding does not implicate dysfunctions of the specific sensory pathways in seizure genesis in gerbils. In contrast, several novel environmental stimuli that exposed the animals to a difficult exploratory task (i.e., Y-maze, dish rack, etc.) could trigger seizures, and this suggests that the pathophysiology of epileptiform events in gerbils may have a unique association with exploratory behavior. However, the frequency, latency and severity of the seizures showed no correlation with each other, indicating that these parameters are probably determined by independent factors. Taken together with previous studies on the electrophysiology of the dentate gyrus during exposure to novel experiences, and the anatomical abnormalities found in the hippocampus of the seizure-sensitive gerbil, these behavioral data provide further support for a significant role of the hippocampus in the pathophysiology of seizures in this model of genetic epilepsy.

INTRODUCTION

Genetically epilepsy-prone animals are useful tools for the elucidation of the hereditary factors involved in epileptogenesis. The Mongolian gerbil (*Meriones unguiculatus*) is one of a number of animal species that have genetically determined seizure susceptibility¹⁰. Most of these seizure-sensitive strains display convulsions following well-

defined sensory stimuli. For example, convulsions can be induced in genetically epilepsy-prone rats (GEPRs) by auditory stimuli⁴ or in the Senegalese baboon, *Papio papio*, by visual stimuli²¹. Interestingly, Mongolian gerbils display seizures following certain environmental stimuli that are apparently not epileptogenic in other genetic models of epilepsy. Such stimuli include placement into a new cage and handling^{3,8–10,19}. However, a detailed analysis of the effects of specific sensory stimuli and various environmental exposures on the seizure activity of gerbils has not been described. Such an analysis will contribute to a better understanding of the pathophysiology of the seizures in these animals and the location in their brains where the circuitry and function are abnormal.

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Previous studies have indicated that several anatomical defects occur in the hippocampus of seizure-sensitive gerbils. Paul et al.¹⁴ showed that the number of spines on pyramidal cells was altered. Peterson et al.¹⁶ showed that hippocampal mossy fibers, the axons of granule cells, displayed a severe depletion of synaptic vesicles, a change commonly found in drug-induced seizures of the hippocampus. Also, the number of granule cells and GABAergic neurons in the dentate gyrus was increased in seizure-sensitive gerbils and in the seizure-naive offspring of these gerbils^{15,16}. Furthermore, bilateral lesions of the perforant pathway, which provides the hippocampal formation with its primary excitatory input from the entorhinal cortex, result in the abolition of the behavioral expression of seizure activity¹⁷. Taken together, these data suggest that the hippocampal formation, and particularly the dentate gyrus, has an abnormal circuitry that is significantly involved in the generation and/or propagation of epileptic activity in this model.

The present study shows that a number of specific sensory stimuli, somatosensory, auditory, visual and olfactory, were ineffective in inducing convulsions in gerbils, whereas several, although not all, novel environmental stimuli provoked seizures. The relationship of these new data to a possible dysfunction of the hippocampus is discussed in this paper.

METHODS

Twenty-six Mongolian gerbils of both sexes (evenly distributed) were used in this analysis. Their ages ranged from 6 to 18 months, and this age was well beyond the time (50 days of age) reported for the onset of seizure activity¹⁰. Some of these gerbils ($N = 11$) were bred from our own colony¹⁵, whereas others were obtained from Tumblebrook Farms ($N = 15$). The testing of various seizure stimuli occurred with a 2 day interstimulus interval; this period was long enough for the gerbils to fully recover from the postictal refractory period, which is considered to be 24 h (Ribak, unpublished observation).

The gerbils were tested with 10 environmental stimuli, an air blower and 5 specific sensory stimuli.

The environmental stimuli consisted of: (1) a white plastic cylindrical bucket, 9" in diameter and 6" high; (2) the top surface of a stainless steel cart, 24" long, 16" wide, with a 1" ridge on 3 sides; (3) a small room, 4 ft. by 4 ft.; (4) a stainless steel sink, 21" long, 16" wide and 7" high; (5) a long gray cylinder with a base of aluminum foil, 13" in diameter and 30" high; (6) a clear glass jar, 6" in diameter and 7" high; (7) a yellow plastic tupperware lid, 22" in diameter and 2" high; (8) a white styrofoam box, 14" long, 12" wide and 10" high; (9) a tan plastic dish-drying rack, 16" long, 14.5" wide, 4.4" high, with 0.5" parallel bars with a spacing of 0.75"; and (10) a Y-maze consisting of 5" white cardboard walls with a base of aluminum foil (one arm led to the gerbil's cage whereas the other was a dead end). The eleventh stimulus was an air blower that was pointed at the gerbil in its cage so that the air currents were directed toward its face.

The 5 specific sensory stimuli (stimuli 12–16) were administered to the gerbils while they were in their cages. They consisted of: (1) pain stimulation, squeezing the gerbil's tail with a hemostat; (2) odor stimulation, placing a mixture of 35% alcohol and 15% ammonia under the nose of the gerbil; (3) tactile stimulation, poking the neck and back of the gerbil with a narrow firm-bristled brush; (4) acoustic stimulation, ringing two doorbells used for inducing seizures in GEPRs¹⁸; and (5) intermittent light stimulation, 20 Hz by a strobe light.

Upon placement in a different environment, gerbils were monitored for seizures for a 3 min interval. Immediately thereafter, they were returned to their home cages. For the air blower test and the specific sensory stimuli, the gerbils were subjected to each stimulus for 1 min. Each gerbil was subjected to each test only once. The effectiveness of each stimulus was determined. It was defined as the percentage of animals that responded with seizures to a stimulus.

Seizure severity was rated using a 5 point scale from 0–4 that was modified from Loskota et al.¹⁰. A zero score was given when no seizure was observed. A score of 1 indicated a mild seizure in which vibrissae twitching and some flattening and flicking of the pinnae of the ear were observed at faster rates than usual. A score of 2 was given if the

twitching of vibrissae and pinnae occurred with motor arrest. A 3 indicated a gerbil with the same features in 2 but myoclonic jerks were present. Lastly, a 4 indicated a severe seizure in which the animal manifested tonic hindlimbs, clonic-tonic forepaw movements (forelimbs jerking, followed by tonic extension), head bobbing, extreme lordosis and falling followed by righting, wild running and jumping. None of the gerbils died following a seizure.

If a seizure were observed following a stimulus, the seizure score was recorded as well as the seizure latency. The seizure latency was defined as the time from placement into the novel environment until the onset of a convulsion. Furthermore, each gerbil was characterized by its seizure frequency. Seizure frequency was defined as the number of times the gerbil produced seizures divided by 10, the number of stimuli that caused seizures in the population. This parameter was expressed as a percentage. Linear regression analysis was used to determine whether seizure severity, seizure latency and seizure frequency correlated with each other. Linear regression analyses

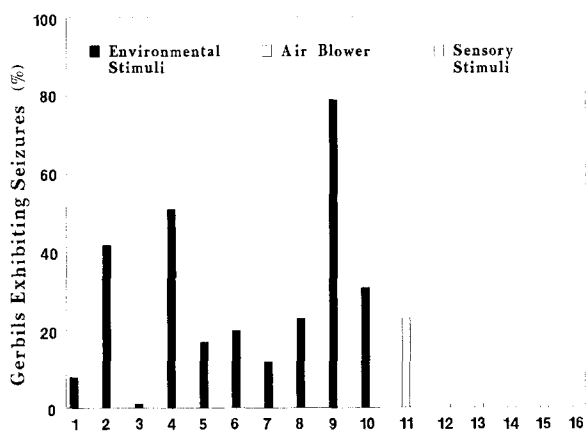


Fig. 1. Seizure provoking potential of different environmental stimuli, the air blower and 5 sensory stimuli (see Methods and Table I for the key to the numbered stimuli). The bars represent the percentage of animals ($N = 26$) that responded with seizures to a given stimulus. Note that the novel environmental stimuli caused marked differences in the percentage of gerbils exhibiting seizures whereas none of the 5 specific sensory stimuli induced seizures. The percentage values for stimuli 3 and 12–16 indicate 0%.

were made to determine whether any significant correlations existed for the data. First, the mean seizure score values were plotted against the mean seizure frequency values. Second, the mean seizure scores were plotted against the mean latency periods. And third, the mean latency periods were plotted against the mean seizure frequency values.

RESULTS

Effectiveness of stimuli

Fig. 1 and Table I show that the different stimuli had variable effects on the quantity and quality of seizure activity in the gerbils analyzed. Seventy-seven percent of the animals, the largest percentage in this study, had seizures following placement in the dish rack that had a ridged surface providing difficult footing for the gerbils. In contrast, another environmental stimulus that was very similar to the home cage of the gerbils, the 4×4 room, had no effect on seizure activity. This environmental stimulus was the only one that did not induce seizures. In the Y-maze that induced seizures in 31% of the gerbils, many of the animals had their seizures prior to entering either one of the arms of the

TABLE I

Effectiveness of novel environmental and specific sensory stimuli on the seizure activity, average latency and average score of gerbils ($N = 26$)

Stimulus	Gerbils with seizures (%)	Latency (sec) (mean \pm SE)	Score (0–4) (mean \pm SE)
(1) White cylinder	7.7	22.5 \pm 7.5	3.0 \pm 1.0
(2) Cart	42	49 \pm 13.4	2.2 \pm 0.3
(3) $4' \times 4'$ Room	0	0	0
(4) Sink	31	18.5 \pm 5.0	2.5 \pm 0.3
(5) Grey cylinder	15	12.5 \pm 3.2	3.0 \pm 0.6
(6) Glass jar	19	16.4 \pm 2.8	3.6 \pm 0.4
(7) Yellow lid	11.5	28 \pm 15.7	2.7 \pm 0.9
(8) Styrofoam box	23	24.5 \pm 8.3	2.8 \pm 0.5
(9) Dish rack	77	18.3 \pm 3.1	3.0 \pm 0.2
(10) Y-maze	31	34.5 \pm 4.7	3.5 \pm 0.3
(11) Air blower	23	22.0 \pm 0.9	3.7 \pm 0.3
(12) Pain	0	0	0
(13) Odor	0	0	0
(14) Tactile	0	0	0
(15) Acoustic	0	0	0
(16) Visual	0	0	0

Y-maze. A commonly used stimulus for inducing seizures, the air blower, produced seizures in 23% of the gerbils. Remarkably, none of the 5 specific sensory stimuli caused seizure activity.

The average latency time for seizure onset following placement into the novel environment varied without any relationship to the effectiveness of a seizure stimulus (Table I). For example, the grey cylinder had the shortest latency (12.5 sec) and it provoked seizures in only 15% of the gerbils whereas the steel cart had the longest latency period of 49 sec, yet it provoked seizures in 42% of the gerbils.

The quality of seizure activity was assessed by using the scores obtained following each seizure provoking stimulus. Only the animals that exhibited seizures following a specific stimulus were included in this analysis of seizure severity associated with environmental stimuli. The stimuli that elicited the most severe seizures included the clear glass jar, the Y-maze and the air blower (Table I).

Seizure activity of gerbils

Table II shows the frequency, latency and score of the seizures for the individual gerbils. Three gerbils had seizures in response to more than 50% of the environmental stimuli. Eight had seizures in response to 40–50% of the stimuli. The remaining group of 10 gerbils displayed seizures in response to 10–30% of the stimuli (Table II). It is important to note at this juncture that 20 of the 21 gerbils displayed a seizure in response to the dish rack. The one gerbil that failed to have a seizure when placed in this environment had the lowest score possible for seizures.

The gerbils had mean latency periods between placement into the stimulus and seizure onset that ranged from 15 to 94 sec (Table II). Six of the gerbils had latency periods under 20 sec. Thirteen or 62% of the gerbils had latency periods between 20–40 sec. Two gerbils had latency periods greater than 40 sec. The length of the latency period did not correlate with the frequency of seizures for an individual gerbil ($r = 0.33$). For example, the 2 gerbils (Nos. 5 and 9) that had the highest seizure frequencies (70%) had mean latency periods of 28 and 15 sec, respectively, whereas the 3 gerbils (Nos. 13, 17, 18, 19 and 20) with the lowest seizure

TABLE II

Parameters of the seizure activity of individual gerbils

The seizure activity of the individual gerbils was measured using the 10 stimuli that caused seizures. Five of the 26 gerbils were not used in this analysis because they never had a seizure.

<i>Gerbils</i>	<i>Seizure frequency (%)</i>	<i>Latency (sec) (mean \pm SE)</i>	<i>Mean score (\pm SE)</i>
1	20	49 \pm 11.0	2.5 \pm 0.5
2	40	20 \pm 3.7	3.3 \pm 0.5
3	50	18 \pm 3.2	3.6 \pm 0.4
4	50	21 \pm 6.6	3.0 \pm 0.6
5	70	28 \pm 12.1	3.7 \pm 0.3
6	60	16 \pm 4.0	2.3 \pm 0.4
7	50	18 \pm 10.2	1.8 \pm 0.2
8	40	36 \pm 24.2	2.5 \pm 0.3
9	70	15 \pm 3.1	2.9 \pm 0.3
10	40	28 \pm 11.5	3.3 \pm 0.5
11	20	94 \pm 46.5	4.0 \pm 0.0
12	50	30 \pm 6.9	3.0 \pm 0.5
13	10	19 \pm 0.0	4.0 \pm 0.0
14	50	32 \pm 4.5	3.6 \pm 0.4
15	20	25 \pm 3.0	2.0 \pm 0.0
16	30	24 \pm 7.5	3.3 \pm 0.7
17	10	34 \pm 0.0	4.0 \pm 0.0
18	10	30 \pm 0.0	4.0 \pm 0.0
19	10	23 \pm 0.0	1.0 \pm 0.0
20	10	22 \pm 0.0	2.0 \pm 0.0
21	20	50 \pm 0.0	1.0 \pm 0.0

frequencies (10%) displayed mean latency periods ranging from 19 to 34 sec (Table II).

Four of the gerbils that displayed the highest observed seizure score of 4.0 (Nos. 11, 13, 17 and 18) had that score in response to each environmental stimulus. However, these gerbils responded with seizures in only 10–30% of the environmental stimuli. The gerbils that responded most frequently to the stimuli (40–70%) had mean seizure scores ranging from 1.8 to 3.7. Kindling-like progression of the seizure severity during the course of successive stimulations was not observed. Linear regression analysis showed that there was no correlation between seizure scores and seizure frequency ($r = 0.11$). Also, there was no correlation between seizure latency and seizure scores ($r = 0.09$).

DISCUSSION

Three main findings were obtained from this study that examined the ability of various environmental and specific sensory stimuli to provoke seizures in gerbils. The first finding is that intense stimulation of specific sensory systems is not sufficient to induce seizures in Mongolian gerbils. Thus, dysfunctions of the somatosensory, olfactory, auditory and visual pathways are probably not involved in the pathophysiology of seizures in these animals. In contrast, placement of gerbils in various environments that were different from their home cage is highly effective in provoking seizures in gerbils. This observation is consistent with previous findings^{3,5,8-10,19}. Since spatial orientation plays a significant role in maneuvering in these unusual environments, it is likely that the hippocampal formation which plays an important role in this function^{12,13} is involved in generating seizures. Furthermore, recent studies by Green et al.⁷ and Sharp et al.²⁰ on rats have shown that novel environments which lead to an increase in the incidence of exploratory behaviors and hippocampal theta activity cause a substantial and persistent elevation in the size of the evoked field EPSPs from the dentate gyrus and a transient elevation in the evoked population spike amplitude in this structure whenever the animal was exposed to a novel experience, such as transitions between environments. These data suggest that exploratory behavior is accompanied by a substantial increase in evoked synaptic efficacy of granule cells. Taken together with previous data that showed an abnormality in the numbers of granule and inhibitory basket cells in the dentate gyrus of seizure-sensitive gerbils¹⁵ and the importance of intact bilateral perforant pathways for seizures to occur¹⁷, this study provides important behavioral data to indicate that the dentate gyrus plays a role in the pathophysiology of seizures in gerbils.

The second finding of this study is that the ten different environments used in this study are not equally effective in producing seizures. Many environmental stimuli induced seizures with a high probability, whereas others were much less effective or even ineffective. This finding indicates that changes from the familiar home environment must

be superimposed by other factors to increase the excitability of their brains above the seizure threshold. Certain environments that were similar to the home cages of the gerbils and were easy to explore, such as stimuli 1 and 3 (Table I) had little or no effect on provoking seizures. In contrast, those environments that were very different from the home cages of the animals in that they were hard to explore due to physical obstacles or a complicated structure, such as the dishrack and the Y-maze, respectively, were very effective in inducing seizures. Therefore, the environmental stimuli that were the most difficult to explore were most effective in provoking seizures.

Consistent with previous data⁵, the air blower stimulus was moderately effective in provoking seizures. This does not appear on the surface to fit into the discussed idea about the role of exploration and spatial orientation in the seizure genesis of gerbils. One may argue that the air blowing is a stressful stimulus and that this is why it provokes seizures. However, several stimuli that were stressful for the gerbils such as the tail-pinching and the 95 dB doorbell sound did not induce seizures. Thus, a stressful situation alone is insufficient to provoke seizures in gerbils; it must be associated with an exploratory task to trigger the pathophysiological event. It also can be considered that the air blowing may influence the relation of the gerbil to its environment and may profoundly disturb its spatial orientation.

The data for the Y-maze may have a special interest because they show that an exploratory task widely used for learning-memory research can trigger seizures. As it was pointed out by Buzsáki², information in the hippocampus is deposited in a relatively labile form during exploratory activity and the labile trace is converted into a long-lasting form at the termination of the exploration. Thus, exploratory behavior is a characteristic first step in learning and the efficacy of this step to induce seizures in gerbils suggests that the physiological processes underlying learning in these animals can eventually be transformed into epileptiform events. This conclusion is consistent with previous and intriguing discussions about the relationship between learning-memory processes and epilepsy^{1,6,11}. Thus, the Mongolian gerbil may be a

unique model for the examination of this relationship.

The last finding of this study is that frequency, latency period and scores of the seizures were not correlated with each other. It was interesting to observe that gerbils with high seizure frequency responded with low scores to many environmental stimuli whereas other gerbils that responded infrequently to the stimuli showed maximal seizure scores for each stimulus. Furthermore, the seizure latency can also vary independently of the seizure frequency. Although the exact meaning of this lack of correlation remains unclear, it may indi-

cate that the excitability of the input pathways connected to the seizure generator site(s) and the excitability of the structures involved in the propagation of epileptiform activity are determined by different neurochemical and neurophysiological factors in gerbils.

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