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Stimulus-Induced Behavior in F1 Hybrids of Seizure-Sensitive and Seizure-Resistant Gerbils

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ABSTRACT—We previously established two strains of Mongolian gerbil: a seizure-sensitive strain, established by selective inbreeding for motor seizures elicited by a stimulus called the S method and a seizure-resistant strain that does not exhibit inducible seizures. The behavior of the seizure-sensitive strain is characterized by a progressive increase in responsiveness to weekly application of the S method, from repetitive backward ear movements appearing after postnatal day 40, to a full-blown seizure, while the seizure-resistant strain is apparently unaffected by the stimulation. The difference between these two strains is presumably genetic. To determine the genetic factors underlying this difference, we first examined developmental changes in the stimulus-induced behavior of the F1 hybrids. When the S method was applied, most F1 hybrids had repetitive movements of the ears (and head) similar to the seizure-sensitive gerbils, but generalized seizures emerged considerably later than in seizure-sensitive gerbils. These results suggest that a half dose of the gene products involved renders most gerbils susceptible to the stimulus but is insufficient for the rapid accumulation of an as yet undefined change needed to spread the abnormal electrophysiologic activity to elicit generalized seizures.

Key words: gerbil, seizure, animal model, F1 hybrids

INTRODUCTION

Genetic factors that lead to epilepsy have been extensively investigated and recent progress in molecular biology indicates that increasing numbers of genes are involved in the emergence of epileptic seizures (Berkovic and Scheffer, 2001). Some of these genes encode ion channels. Many more genetic factors are expected to be implicated in epileptic dysfunction (Berkovic and Scheffer, 2001) and studies using animal models might help to identify them (Noebels, 2001).

Some populations of the Mongolian gerbil (*Meriones unguiculatus*) exhibit stimulus-induced epileptic motor seizures. This characteristic is hereditary and the gerbils are considered a genetic animal model of idiopathic epilepsy (reviewed by Jobe *et al*., 1991). The nature of the genetic factors involved, however, is unknown. To clarify the mechanism underlying epileptic seizures in these gerbils, we previously established a seizure-sensitive strain, MGS/Idr (MGS), from the colony maintained at the National Institute of Infectious Diseases (NIID, Japan) by selective sister-brother mating for motor seizures elicited by a method called the S method. (Seto-Ohshima *et al*., 1992). The S method consists of suspending the gerbils by their tails and applying

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Footnotes: Small colonies of MGS and MGR, maintained in the Tokyo Institute of Psychiatry (Japan), are available to interested workers.

pressure to the gerbil's back for 5 s. After postnatal day 40, repetitive backward movements of the ears (RBME) appear in MGS gerbils immediately after the stimulus and last for a short time (usually less than 15 s). These movements are the first detectable sign expressed in most gerbils of this strain. The behavior induced by the S method changes progressively with increasing exposure to the stimulus, and finally a full-blown seizure, composed of stages I to V, is elicited. (for details see Seto-Ohshima *et al*., 1992 and Seto-Ohshima *et al*., 1997).

From the same colony maintained at the NIID, a seizure-resistant strain (MGR) was established at the Tokyo Institute of Psychiatry (Japan) by selective sister-brother mating for a phenotype that did not exhibit stimulus-induced seizures even with more complicated stimuli than the S method (Seto-Ohshima *et al*., 1997).

These differential phenotypes have been stably maintained in MGS and MGR gerbils, indicating their hereditary natures. To gain further understanding of the genetic factors associated with seizure sensitivity, we examined the behavior elicited by the S method in MGS/MGR F1 hybrids.

MATERIALS AND METHODS

All experiments were performed following the "Principles of Laboratory Animal Care" (NIH publication No. 85–23, revised 1985) and the guidelines for animal experimentation at the Institute for Developmental Research, Japan.

The strains of gerbils used in this study were previously described as "SS" (seizure sensitive) and "SR" (seizure resistant) (Seto-Ohshima *et al*., 1997; Kato *et al*., 2000; Omori *et al*., 2002). For clarity, however, the terms "MGR" and "MGS" were used in this study. The gerbils were bred with free access to pelleted food and water at a constant temperature (24°C) and humidity (50%) at the Institute for Developmental Research. Light was provided between 0600 and 1830 hr.

Forty-eight pairs were mated, 24 MGS females (f) x MGR males (m) and 24 MGR (f) x MGS (m). Eighteen pairs successfully raised pups: 11 of the pairs were MGS (f) x MGR (m) (16 female and 19 male pups; F1S) and 7 MGR (f) X MGS (m) (9 female and 12 male pups; F1R). For controls, we used 14 females and 11 males from 8 MGS pairs and 15 females and 16 males from 8 MGR pairs; these gerbils were born over approximately the same period. The day of birth was designated postnatal day 0. The pups were weaned at postnatal day 30, after which they were subjected to the S method once a week and the elicited behavior was recorded using a video camera (Handycam DCR-TRV10, SONY, Tokyo, Japan).

There were no apparent differences in developmental profiles of MGS gerbils, MGR gerbils, and their F1 hybrids other than the stimulus-induced behaviors, although some developmental parameters, such as body weight, were not measured precisely to avoid providing additional stimuli to the gerbils.

Comparisons between the different strains were made with regard to the appearance of the first detectable seizure-related signs and that of generalized seizures (MGS vs F1S, MGR vs F1S, MGS vs F1R, MGR vs F1R, and F1S vs F1R). One of the authors moved to a different institute during the study and therefore, it was necessary to kill the animals at different ages. To evaluate the data under these conditions we used a non-parametric generalized Wilcoxon's test (Gehan, 1965). This method is used when the duration of the experiment differs between individuals tested due to reasons independent of the event being compared. Using this method, significance is achieved if the value from a chi-square analysis is greater than 3.841 (*degree of freedom*=1, $p<0.05$). Holm's procedure (Holm, 1979) was used to account for multiple comparisons.

RESULTS

The behavior elicited by the S-method in F1 hybrids was compared with that in MGS gerbils (Seto-Ohshima *et al*., 1992, 1997). The elicited behavior was recorded as described in "Materials and Methods". The behaviors elicited in MGS gerbils are classified as follows; (1) RBME, which is the first detectable seizure-related sign in most MGS gerbils, (2) repetitive movements of the head and neck in addition to the ears which can increase in frequency until stage I of a full-blown seizure is reached, (3) stage I that finished without following behaviors (In stage I, the ears remain flattened, the eyes are closed, the vibrissae vibrate vigorously, and the head droops.) (4) stage I followed by stage II (generalized convulsion with body rollover), (5) stage I followed by stage II and then stage III (sudden return to the normal posture with trembling, mostly of the forelimbs) and (6) stage I followed by stage II, stage III, stage IV (strong kicking of the hind legs) and stage V (exhaustion) in order. These behaviors are shown in Fig. 1. Their detail was described previously (Seto-Ohshima *et al*, 1992, 1997).

The behavior elicited by the S method in MGS and MGR gerbils and their F1 hybrids is shown in Fig. 2. The percentage of surviving gerbils at a given time point that exhibited either the first sign (Fig. 3A) or stage II (Fig. 3B) are plotted against the age when the signs first appeared. Because the age at which the gerbils were killed varied within each group (MGS, MGR, or the MGS/MGR F1), the percentage sometimes decreased.

Table 1 summarizes the comparisons between the groups. The appearance of the first seizure-related sign was statistically different between the original strains and the hybrids ($p<0.05$), but not between the two hybrids. Similar results were obtained for the appearance of stage II signs.

As shown in Fig. 3A, the number of MGS gerbils that exhibited the first seizure-related sign increased rapidly as a function of age. Generalized seizures also appeared soon after the first sign (Fig. 3B), although the time profile of the behavior indicated some individual variation (Fig. 2). Conversely, most MGR gerbils (97%, 30/31) had no stimulus-induced behavior, except for one female that had RBME and stage I.

In contrast to MGR gerbils, 91% of the F1 hybrids (51/56) responded to the S method with motor manifestations, and this was independent of the strain of the mother [F1S: 89% (31/35), F1R: 95% (20/21)]. The first detectable sign in 92% of MGS gerbils (23/25) was RBME. Among F1 hybrids that exhibited S method-induced behaviors, RBME was the first sign in 77% (24/31) of the F1S group and in 55% (11/20) of the F1R group. The remaining MGS and F1 hybrids had repetitive movements of the head, neck, and ears as

A

	level	behavior
mild ↓ severe	1	RBME
	2	repetitive movements of the ears, head and neck
	3	stage I without following stages
	4	stage I - stage II
	5	stage I - stage II - stage III
	6	stage I - stage II - stage III - stage IV - stage V

B

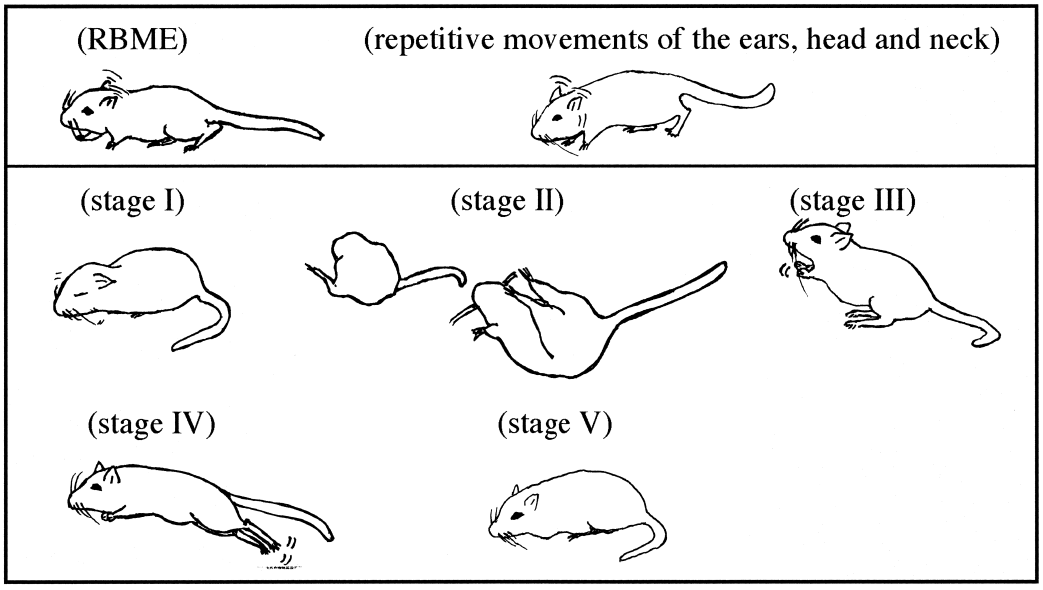

Fig. 1. Stimulus-induced behavior and classification levels. (A) Behaviors elicited by the S method are classified into six levels. They are shown in order of severity. (B) Each behavior is drawn schematically. The gerbil with RBME, the first detectable behavior elicited in most MGS gerbils, shows strong backward movements of the ears repetitively. At the next step, the rhythmical movements of the head and neck in addition to the ears occur. The frequency of the movements can increase until stage I is reached. In stage I, the ears remain flattened, the eyes are closed, the vibrissae vibrate and the head droops. Following behaviors are generalized convulsion with body rollover (stage II), sudden return to the normal posture with trembling of the forelimbs (stage III), strong kicking of the hind legs (stage IV) and exhaustion (stage V).

the first detectable sign, except for two gerbils in the F1S group whose first sign was stage I, which appeared late during development. The first detectable sign emerged at a similar age and the number of responding gerbils increased similarly in both the MGS group and the F1 hybrids (Fig 3); however, the average age of appearance of the first detectable sign was slightly delayed in F1 hybrids (F1S: 10.9±4.6 weeks, n=31; F1R: 9.3±0.7 weeks, n=20) compared with MGS gerbils and some F1 hybrids showed no detectable signs during their lifetime (4 F1S and 1 F1R). Thus, there was a statistical difference in the appearance of the first detectable sign between the MGS gerbils and the F1S and between the MGS and the F1R (Table 1).

In F1 hybrids, the change in stimulus-induced behavior was similar to that of the MGS gerbils. The rhythm of the induced repetitive movements increased and stage I appeared in the gerbils that exhibited the first seizure-related sign except for 4 gerbils (#6, 8 and 13 of F1S males and #6 of F1R male in Fig. 2). As in MGS gerbils, the generalized seizures (stage II) in F1 hybrids were always preceded by stage I within a seizure, and were only observed in gerbils that previously experienced milder seizure-related behavior induced by stimuli during development. The age when the stage II seizures appeared, however, was considerably delayed in the F1 hybrids, independent of the strain of the mother. All 25 MGS gerbils exhibited the stage II seizures between 10 and 20 weeks of age, while only 14% of F1S (4/28) and 6% of F1R (1/18) that were alive at 20 weeks of age exhibited the stage II seizures, although one F1 hybrid that lived for 17 weeks exhibited the stage II seizures during week 16. The average age at which stage II seizures were first expressed was 12.8±2.4 weeks in MGS gerbils (n=25), 20.9±3.0 weeks in F1S (n=10), and 21.0±3.8 weeks in F1R (n=7). Some F1 gerbils did not exhibit stage II seizures over the period of study (25 F1S and 14 F1R) and the difference in the first appearance of stage II seizures between all MGS and F1S and that between MGS and F1R was statistically significant (Table 1). Furthermore, body rollover in stage II seizures of the F1 hybrids was often not as violent as in MGS gerbils.

No MGR gerbils exhibited stage II seizures over the time period studied (Figs 2B and 3B). Because many of the

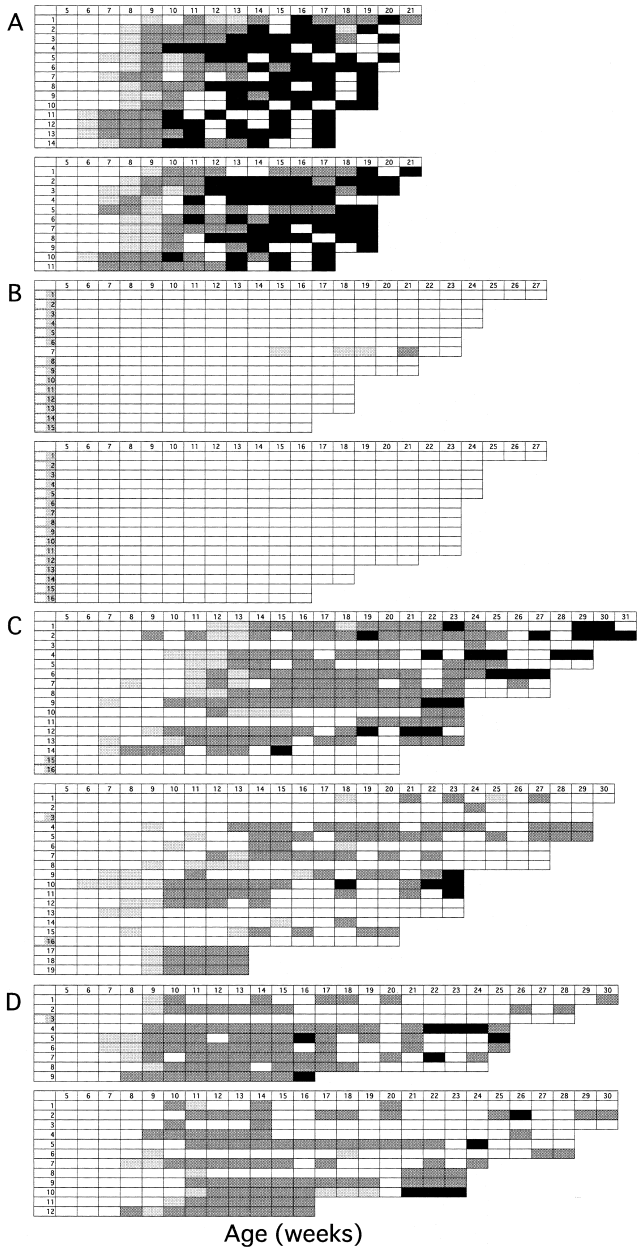

Fig. 2. Developmental changes in stimulus-induced behavior in MGS and MGR strains and their F1 hybrids. The S method was administered to MGS and MGR gerbils once a week. The elicited behavior was recorded as described in "Materials and Methods" and was classified into six levels shown in Fig. 1A. Behaviors (1), (2, 3) and (4, 5, 6) are shown as light gray, dark gray, and black, respectively, for each gerbil. The number on the ordinate corresponds to each gerbil and the number on the abscissa is the age in weeks after birth. The gerbil whose number is shaded gray showed no stimulus-induced behavior during the study. A: MGS, B: MGR, C: F1S, D: F1R. Upper columns represent data from females and lower columns represent data from males.

MGR gerbils examined were younger than the F1 hybrids, we compared the proportion of gerbils that exhibited stage II up to and including 23 weeks of age [8/26 (31%) for the F1S group, 3/18 (17%) for the F1R group and 0/18 (0%) for

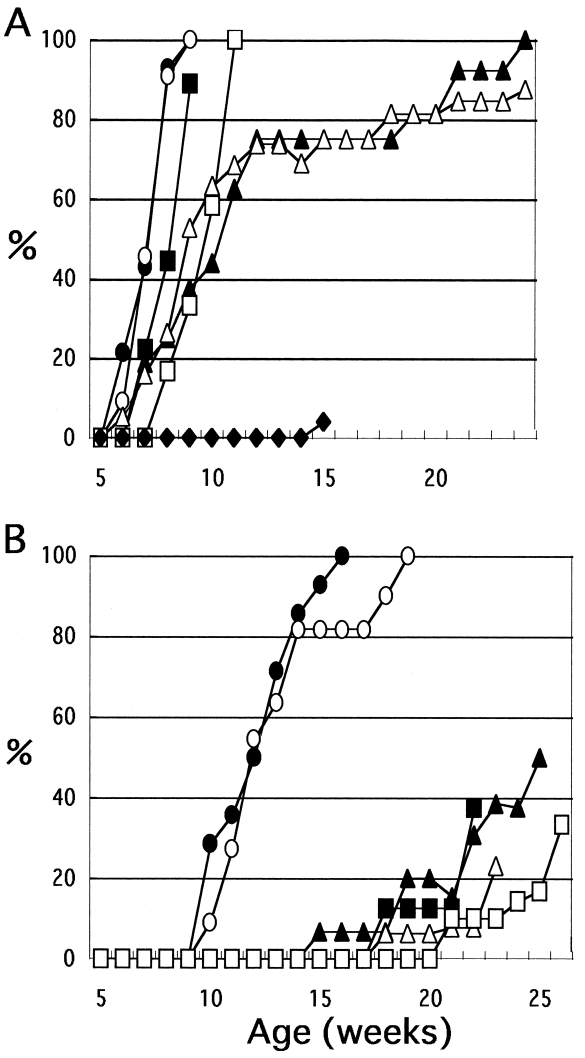

Fig. 3. Percentage of gerbils exhibiting either the first sign or stage II during development. The percentage of gerbils that exhibited the first sign (A) or stage II that emerged after stage I (B) is plotted against age. The circles, triangles, squares, and diamonds indicate MGS, F1S, F1R, and MGR, respectively; filled symbols indicate females and unfilled symbols indicate males. No male MGR gerbils showed the first sign and also no MGR gerbils exhibited stage II over the time period studied

Table 1. A comparison between the emergence of the first sign and the first appearance of stage II seizures. The statistics for the generalized Wilcoxon's test for differences in the date of the appearance of the first sign or the first appearance of stage II are shown. Corresponding P values of Wilcoxon's tests are shown in parentheses.

	First sign	Stage II
MGS/F1S	22.13* (<0.001)	60.36* (<0.001)
MGS/F1R	18.24* (<0.001)	37.29* (<0.001)
MGR/F1S	43.26* (<0.001)	8.48* (0.0036)
MGR/F1R	50.28* (<0.001)	8.22* (0.0041)
F1S/F1R	1.25 (0.26)	0.01 (0.92)

* specifies the significant difference by Holm's multiple comparison procedure with $P<0.05$.

the MGR group]. Further evaluation with the generalized Wilcoxon's test followed by Holm's multiple comparison procedure of all MGR and F1 hybrid gerbils, whether or not they had experienced stage II seizures, revealed a significant difference in the time of the appearance of stage II between MGR and F1S and between MGR and F1R (Table 1).

DISCUSSION

In MGS gerbils, the behavior elicited by the S method changed progressively from RBME (in some cases, also repetitive movements of the head and neck) to full-blown seizures with increased exposure to the stimulus during development. The results of this study revealed that most of the MGS/MGR F1 hybrids also exhibited the same type of first seizure-related signs at a similar, but slightly older age, independent of the strain of the mother. Upon continued stimulation during development, the stimulus-induced behavior progressed to repetitive movements with a faster rhythm and stage I behavior in both MGS gerbils and most F1 hybrids that exhibited first seizure-related signs. In these milder seizure-related behaviors, the affected body parts were the face and neck, which indicates that abnormal electrophysiologic activity was elicited and spread in a limited area of the brain. Some types of human epilepsy are caused by abnormal gene (Berkovic and Scheffer, 2001). Our results suggest that a half-dose of abnormal gene(s) makes most gerbils respond to the stimulus by creating abnormal electrophysiologic activity in some limited area of the brain, as in gerbils with only the abnormal gene (MGS). The results further suggest the existence of a main gene responsible for at least the initial phases of stimulus-induced seizures. The situation might be more complicated, however, because 1 of 31 MGR gerbils exhibited RBME and stage I, and 5 of 56 F1 hybrids showed no detectable stimulus-induced behavior over the time period studied. It is possible that there is modulation even if a main gene exists. It is also possible that the gene product mainly responsible varies with the amount or degree of activity of modulation in different individuals. Alternatively, several factors, each of which has a minor effect, might work together to induce seizures, as has been suggested for seizures in the EL mouse, a model animal of multifactorial idiopathic epilepsy (Rise *et al*., 1991; Todorova *et al*., 1999; Legare *et al*., 2000; Berkovic and Scheffer, 2001). In this case, summation of the contribution of individual factors might vary within each group.

Our results indicate that the age at which stage I turned into generalized seizures (stage II) in F1 hybrids was significantly older than in MGS gerbils, as observed with the generalized seizures elicited in EL mouse/non-seizure mouse F1 hybrids compared with EL mice (Fueta *et al*., 1986). This tendency was also independent of the strain of the mother. In generalized seizures, many body parts exhibited abnormal movements, in addition to the face and neck. In these regions, movement is usually induced by motor neurons in the corresponding area of the cerebral cortex sending information to the spinal cord, which is different from the pathways driving movements in the face and neck. Thus, to elicit generalized seizures with the same stimulus, there must be some change that allows the abnormal electrophysiologic activity to spread more widely in the cerebral cortex or in subcortical areas or in both areas. In F1 hybrids, the accumulation of the changes needed to generate abnormal activity in many more neurons needed for stage II might first occur slowly because of the half-dose of the abnormal gene or genes, including that of putative modulatory elements. The observation that the generalized seizures were often not as violent in F1 hybrids as in MGS gerbils might also reflect the slow increase in number of neurons involved in the developmental changes of the seizures.

Our previous study on the cortical evoked potential revealed that the somatosensory cortex (the barrel field for the vibrissa) of MGS gerbils shows an abnormal response to the electric stimulation of the whisker follicle: it lacks a component of evoked potential that reflects post-synaptic inhibitory potentials (Kato *et al*., 2000). This type of response was also observed in young gerbils of MGS that had not experienced seizures (unpublished data), suggesting that the impairment is likely the cause but not secondary effects of seizures. Further, this area of MGS gerbils was liable to fatigue under the stimulation condition we used. Inhibitory activity can be suppressed by lowering the energy level (Krnjevic, 1990), which is considered to be an underlying mechanism of epilepsy associated with mitochondrial disorders in humans (DiMauro *et al*., 1999; Naviaux, 2000). Hypometabolism in the focus area is observed in some types of epileptic patients (Semah, 2002).

In the barrel field, an area exists where blocking the inhibitory system elicits repetitive backward movements of the ear resembling RBME induced by a seizure-inducible stimulus (Seto-Ohshima *et al*., 2001, 2002). This area overlaps the vestibular cortex (Ito and Seto-Ohshima, 1998) that is stimulated by the S method. In MGS gerbils, when they are stimulated by the S method, supplying enough energy may be difficult, thus leading transiently to a weakened inhibitory system and RBME. In order to clarify the exact mechanism that elicits RBME as the first sign, precise morphological, biochemical and electrophysiological study of the cerebral cortex of MGS and MGR gerbils and of F1 hybrids that showed stimulus-induced behavior and those without showing such behavior, is required.

Stimulus-induced behavior evolved (epileptogenesis) in MGS gerbils and in many F1 hybrids although the time course of change varied between MGS gerbils and F1 hybrids or even within each group. Progressive alteration of the seizure-related behavior has been reported in different seizure-sensitive populations of gerbils (Scotti *et al*., 1998). Our results of electrophysiological study showed that with the barrel field of at least adult MGS gerbils, the component of evoked potential that corresponds to excitatory activity tended to be prolonged when electric stimulation of whisker follicle was repeated, although its peak height much

declined while such a phenomenon was not observed with MGR (Kato *et al*., 2000). This characteristic prolongation indicates some kind of neural plasticity and may be related to an underlying mechanism of epileptogenesis.

Progressive changes in severity of epileptic behavior are observed in several kinds of other genetic animal models of epilepsy, in animal models with epileptic seizures induced by chemical or electrical treatments and in some types of epilepsy of humans (Dreifuss, 1990; Jobe *et al*., 1991; Meldrum, 2002). Although we prefer to think that the cerebral cortex, particularly the somatosensory cortex or vestibular cortex or both, has a central role in seizure phenotypes in MGS, the hippocampus also may participate in these phenotypes. Evoked responses in the dentate gyrus of the hippocampus change as seizures become severe in a different type of seizure-sensitive gerbils (Buckmaster and Wong, 2002). Similar changes might occur in our MGS gerbils, although the triggers to elicit seizure used in these other studies and in the early phase of the seizures reported were different from those in our study.

Molecular basis of phenomena observed in MGS is unclear at present. We recently began a proteomic analysis of cerebral cortex proteins using MGR and MGS gerbils, and found differences in isoelectric points of a series of proteins between these two strains associated with some substitutions in the coding sequence (Omori *et al*., 2002). These proteins are highly homologous to human IMMT, a mitochondrial protein encoded in the nuclear DNA. IMMT is supposed to be anchored in the inner membrane extruding its majority part into the intermembrane space (Giffers *et al*., 1997), in which there were predicted to be coiled-coil domains that are known to participate in protein-protein interaction. The function of IMMT is unknown yet but its location, structure and its rather conserved character between humans and gerbils suggested that it may play an important role in mitochondria: it may work to transfer proteins or have a role as a chaperone, for example. If this protein is involved in mitochondrial function and the change of isoelectric point alters the function, the mutation in IMMT-like protein of gerbil might cause hypometabolism and eventually in epileptic seizures in MGS.

EL mice also show a process of epileptogenesis: they begin to respond to certain kinds of stimuli at a comparable age to that of MGS gerbils and there are corresponding changes that probably reflect abnormal neuronal plasticity (Suzuki and Nakamoto, 1982; Murashima *et al*., 2002). When a mild stimulus was used to elicit generalized seizures, however, the F1 hybrids from a DDY female x EL male pair were more susceptible at 90 to 150 d than those from an EL female x DDY male pair (Todorova *et al*., 1999). Our results do not indicate such a paternal effect, which suggests some difference in the mechanism underlying stimulus-induced seizure between these animal models. A more detailed comparison of the MGS and MGR strains as well as their F1 hybrids should provide novel insights on the mechanism of age-dependent and stimulus-induced types of idiopathic epilepsy.

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