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Authors: Seto-Ohshima, Akiko, Ito, Muneyuki, Katoh, Miyuki, Kitajima, Satoko, and Kishikawa, Masao

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Manipulation of the Somatosensory Cortex Modulates Stimulus-Induced Repetitive Ear Movements in a Seizure-Sensitive Strain of Gerbil

Akiko Seto-Ohshima[1,2]*, Muneyuki Ito[1], Miyuki Katoh[1], Satoko Kitajima[1], and Masao Kishikawa[1]

[1]*Institute for Developmental Research, Aichi Human Service Center, Aichi 480-0392, Japan,*
[2]*Laboratory for Neurogenetics, Brain Science Institute, Institute of Physical and Chemical Research (RIKEN), Saitama 351-0198, Japan*

ABSTRACT—Some Mongolian gerbils (*Meriones unguiculatus*) respond to stimulation by seizures, the pattern of which changes progressively during development. We previously established a seizure-sensitive strain, MGS/Idr, in which all animals exhibit such stimulus-induced seizures. We have now noted that all adults of this strain also show repetitive backward movements of the ears at the beginning of stimulus-induced seizures, although the incidence varies with the individual. We examined whether the cerebral cortex was involved in these movements and found that electrical stimulation of an area of the somatosensory cortex elicited strong backward movement of the ear on the contralateral side, and that unilateral application of bicuculline, a $GABA_A$ receptor antagonist, induced spontaneous repetitive backward movements of the same ear. In this area, sharp waves appeared in the electrocortigram during the repetitive ear movements induced by seizure-inducing stimuli. Unilateral ablation of this area abolished stimulus-induced repetitive movements of the contralateral ear, but had no effects on those of the ipsilateral ear. These results suggest that, in certain types of seizure-susceptible subjects, it may be possible to modify stimulus-induced repetitive movements by manipulating a certain area of the somatosensory cortex which is related to these movements and that this gerbil strain may be useful in research on this subject.

Key words: gerbil, somatosensory cortex, ear movement, seizure, model animal

INTRODUCTION

The Mongolian gerbil (*Meriones unguiculatus*) has been used in a variety of scientific and medical fields, including research on epilepsy, since some gerbils show stimulus-induced epileptic motor seizures (reviewed by Jobe *et al.*, 1991). This epileptic disorder has hereditary characteristics. To clarify the mechanism underlying epileptic seizures in seizure-sensitive gerbils, we previously established a seizure-sensitive strain, MGS/Idr, by selective inbreeding for motor seizures elicited by suspending the gerbils by their tails and pressing their backs for 5 sec (S method), a method that elicits epileptic seizures in all adults of this strain (Seto-Ohshima *et al.*, 1992).

The pattern of behavior elicited by application of the S method once a week changes in a stepwise fashion. The first signs are repetitive (about 1–1.5 / sec) backward movements of the ears (RBME) that appear transiently immediately after the stimulus (usually for less than 15 sec); this behavior appears after postnatal day 40, and is considered to be an early episode, if not the first stage, in the development of epileptic motor seizures (Seto-Ohshima *et al.,* 1997). This is later replaced by repetitive movements of the ear, head, and neck in response to stimulation by the S method, and gait disturbances also gradually appear. This is, in turn, replaced by stage 1 of the full-blown seizure, in which the ears remain flattened, the eyes are closed, and the head drops, followed by full-blown seizure consisting of 4 stages (stages 1–4) (Seto-Ohshima *et al.,* 1992, 1997-diagram).

Recently, we noticed that, among those gerbils that became sufficiently susceptible to stimulation by the S method to enter stage 1 directly, some showed stimulus-induced RBME immediately before the ears became continually flattened in stage 1. This “pre-stage 1” RBME behavior is similar to that seen during the early episode, but evolves into stage

* Corresponding author: Tel. +81-568-88-0811 (Ext. 3524); FAX. +81-568-88-0829.
E-mail: aohs@inst-hsc.pref.aichi.jp

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1, whereas, after early episode RBME, the gerbil returns to normal behavior and does not enter stage 1.

Rhythmic twitches or clonuses of certain body part(s) are sometimes observed at the beginning of convulsions in other epileptic animal species, including human beings, and, in some cases, involvement of the cerebral cortex has been either suggested or demonstrated (Suzuki and Nakamoto, 1982; Vergnes *et al.*, 1990; Noda *et al.,* 1998; Pedersen and Petersen, 1998). In this study, we investigated the relationship between the cerebral cortex and stimulus-induced pre-stage 1 RBME in our seizure-sensitive gerbils and found that unilateral ablation of an area of the somatosensory cortex, electrical stimulation of which elicited backward movement of the contralateral ear, abolished stimulus-induced RBME on the contralateral side, but did not affect that on the ipsilateral side. Some of these results have been briefly described in abstract form (Seto-Ohshima *et al.*, 1998a; Seto-Ohshima *et al.,* 1999).

MATERIALS AND METHODS

MGS/Idr strain gerbils were inbred and housed in the Institute for Developmental Research, Japan. Their behavior elicited by the S method was recorded once a week, as described previously (Seto-Ohshima *et al.,* 1992; Seto-Ohshima *et al.,* 1997). In this study, we used a total of 120 MGS/Idr gerbils (F26–31) of both sexes, aged 3–10 months, which had already experienced stage 1 or more advanced stages of full-blown seizure when stimulated using the S method.

The cerebral cortex area responsible for the backward movement of the contralateral ear was located by removing the unilateral skull under Nembutal anesthesia (65 mg sodium pentobarbiturate / kg body weight, i.p.) and applying a 1-msec, 300 Hz stimulus for 1 sec, the same method used to map the rat motor cortex (Hall and Lindholm, 1974), the voltage being varied from 5 to 25 volts. The stimulating electrodes, consisting of two stainless steel wires (100 μm diameter) insulated with urethane, except for 0.3 mm at the tip, were separated by less than 0.7 mm. A SEN-7203 stimulator (Nihon Koden, Tokyo, Japan) was used.

As electrophysiological methods to detect ear movement using needles (26G) inserted into the posteroauricular muscle (Seto-Ohshima *et al.*, 1997) and a reference muscle in the back or hind leg often fail to detect slight movements of the ear, ear movement and other behavior were recorded using a video camera (Handycam DCR-TRV10, SONY, Tokyo, Japan) and assessed visually. In some experiments, the pictures on the video tape were captured using a computer equipped with a digital video still image capture board (SONY DVBK-1000, SONY, Tokyo, Japan).

To determine the number of pulses required to induce backward ear movement, the site in the somatosensory cortex at which ten 5 volt rectangular pulses (duration: 0.5 msec; interval: 4 msec) induced ear movement was located, then the pulse interval was increased in 1 msec steps from 1 msec to 12 msec; at each pulse interval, the number of pulses was increased in 1 pulse increments from 1 pulse until either ear movement was elicited or the number of pulses reached 25 without ear movement.

To locate the sensitive site in the somatosensory cortex responding even to a small number of electric pulses, five rectangular pulses (duration: 0.5 msec; interval: 4 msec) were applied, moving the electrode by a distance of about 1 mm between tests. At each site, the stimulation voltage was increased in 1-volt increments from 5 to 17 volts, then in 3-volt increments up to 23 volts. When either a contralateral ear movement was elicited or stimulation at 23 volts failed to elicit movement, the electrode was moved to the next site. Consecutive trials were separated by more than 10 sec.

To apply (–)-bicuculline methiodide (BMI, Sigma-Aldrich Co., U.S.A.), an antagonist of $GABA_A$ receptor, a small block of gelatin sponge soaked in BMI solution (0.5–2.5 mM in saline) was placed in a hole made in the skull, as described by Fishman and Parks (1998). The diameter of the hole was about 2 mm and its center 1 mm posterior and 4.5 mm lateral to the bregma. The electrocorticogram (ECoG) was recorded in animals under anesthesia and after waking, using a radio telemeter (ITE1000TE, Unimec Ltd., Tokyo, Japan) essentially as in a previous study in which it was used to record the ECoG in the somatosensory area of free-moving gerbils without movement artifacts (Seto-Ohshima *et al.*, 1998b). Two screws with wires were implanted near the hole (at around 0 mm posterior and 4.5 mm lateral and at 3–3.5 mm posterior and 4.5 mm lateral to the bregma) and cemented to the skull using fast curing dental acrylic, which covered them completely. Control gerbils underwent surgery, but were treated with saline.

The ECoG of free-moving animals given seizure-inducing stimuli was recorded using the same ratio telemeter. One screw was placed at 0 mm posterior and 4.5 mm lateral to, and the other at 1.5 mm posterior and 4.5 mm lateral to, the bregma. In this case, as seizure-inducing stimuli, we used both the S method and the H method in which a researcher moved his (her) palm back and forth over the gerbil's head at a frequency equal to, or greater than, 1 movement / sec.

To determine the effect of cerebral cortex ablation on behavior, as in the BMI application experiments, a burr hole was made unilaterally in the skull over the area marked **b** in Fig. 1A under anesthesia, and the cerebral cortex carefully removed by suction, the space formed filled with a block of gelatin sponge, and the skin sutured. After the gerbils recovered from the anesthesia and were showing normal behavior, a seizure-inducing stimulus was given to induce RBME and the behavior was recorded using a video camera. In control experiments, an area of the occipital cortex was removed unilaterally in the same way, except that the center of the burr hole was at 5 mm posterior and 4 mm lateral to the bregma.

In most experiments, the cortical site examined was marked with 1% thionine. Coronal sections (90 μm thick) of the brain were prepared on a freezing microtome as described previously (Seto-Ohshima *et al.*, 1994) and stained with cresyl violet. To locate the site in the brain, we made a rough atlas using freezing microtome sections of gerbil brain stained with pyronin G and methyl green. Some sections were also immunostained using anti-parvalbumin antibody or stained histochemically for cytochrome oxidase activity as described previously (Seto-Ohshima *et al.*, 1994). The anatomical information from these sections was combined to make a rough atlas with reference to a rat brain atlas (Paxinos and Watson, 1986).

Differences between the number of pulses required at various stimulation intervals and between the number of positive animals in the experimental and control groups were evaluated by Student's t test and Fisher's exact probability test, respectively.

RESULTS

Initially, the behavior elicited by application of the S method once a week was recorded for 8 weeks on 51 gerbils. Of the 227 seizures observed, 94 started directly with stage 1, while, in the other 133, RBME occurred immediately before stage 1. During this 8 week period, 2 of the 51 gerbils did not show RBME before entering stage 1, but did so when examined for a further 6 weeks, showing that all the gerbils exhibited stimulus-induced RBME as pre-stage 1, the incidence varying with the individual, but not with the sex. No repetitive movements were observed in the absence of seizure-inducible stimuli.

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The frequency of stimulus-induced pre-stage 1 RBME was usually similar to that in early episode RBME (i.e. 1–1.5 / sec), but, in some cases, it was up to ten times lower and not constant. Such RBME soon changed to movements at a frequency of 1–1.5 / sec and finally, the behavior changes to stage 1.

When the cerebral cortex of gerbils under anesthesia was stimulated at 300 Hz for 1 sec (n=25), two areas elicited backward movement of the contralateral ear. One was anterior to the bregma and near the midline and the other was lateral and posterior to the bregma; these are indicated, respectively, in Fig. 1A as **a** (at 1–3 mm anterior and 0.5–2 mm lateral to the bregma) and **b** (at 0–2.5 mm posterior and 4–5 mm lateral to the bregma). On electrical stimulation of area **a**, the upper part of the contralateral ear moved slightly; this was often difficult to reproduce, as reported for the motor area for ear representation in the rat (Hall and Lindholm, 1974). In contrast, stimulation of area **b** elicited strong backward movement of the contralateral ear, this effect being entirely reproducible. As described above, area **b** was localized using a stimulation at 300 Hz for 1 sec (i.e. 300 pulses), but, as shown in Fig. 1B, the susceptible site in area **b** required far fewer pulses to induce contralateral ear movement, only 3 being required at an interval of 2–6 msec. Using an interval of 1, 2–6, 7, 8, 9, or 10 msec, the number of 5-volt pulses required (mean±SD) was, respectively, 5±1.4, 3±0, 3.5±1, 6.5±3, 11±5.6, and 15±9.1 (n=4), the values at 1, 9, and 10 msec being significantly different from that at 2–6 msec ($p<0.04$, 0.03 and 0.04, respectively). Fig. 1C shows the site in area **b** at which stimulation with 5 pulses at less than 20 volts elicited ear movement. This area was mainly in the primary somatosensory cortex defined previously by cytochrome oxidase staining (Seto-Ohshima *et al*., 1994).

As shown in Figs. 2A, 2B, and 2C, when BMI was applied to area **b** in one hemisphere, recurrent sharp waves on the ECoG (n=5) and repetitive backward movements of the contralateral ear (n=12) started spontaneously and lasted for several hours (sometimes for up to 24 hr) in all gerbils examined. Gerbils treated with saline showed neither ear movement nor sharp waves on the ECoG (n=5). Fisher's exact probability test showed a significant increase, in BMI-treated animals compared to saline-treated animals, of both sharp waves (5/5 and 0/5 animals, respectively) ($p<0.005$) and repetitive ear movements (BMI-treated, 12/12 animals; saline-treated, 0/5) ($p<0.005$). After recovery from anesthesia, the BMI-treated animals behaved normally except for ear movements. Ear movement was often initially weak and synchronous with

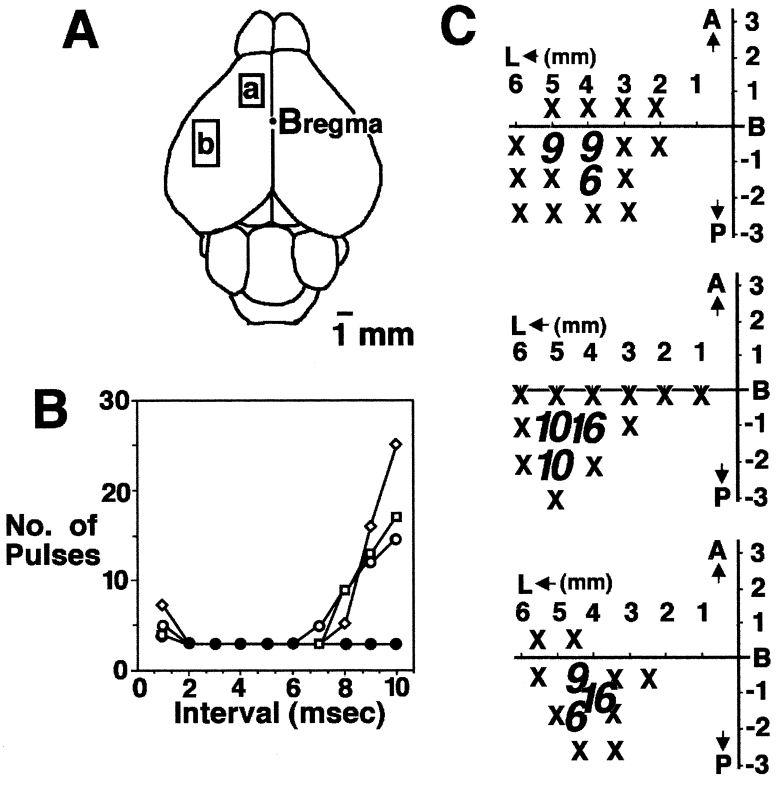

Fig. 1. Ear movement elicited by electrical stimulation of the cerebral cortex.
A. Two areas of the cerebral cortex that elicited movement of the contralateral ear on electrical stimulation at 300 Hz for 1 sec are shown as rectangles, **a** and **b**. Results from 25 gerbils were combined. B. The minimum number of pulses of stimulation applied to area **b** to elicit ear movement is plotted against the inter-pulse interval (duration: 0.5 msec; 5 volts). Results for 4 different gerbils are shown. In one gerbil indicated with a black circle, six pulses were required at an interval of 11 msec. C. Sites that elicited ear movement on application of 5 pulses (duration: 0.5 msec; interval: 4 msec) at less than 20 volts are shown, with the minimal voltage required (in italics). X denotes the sites, stimulation of which did not generate ear movement at this voltage range. The results are from 3 different gerbils. A: anterior, B: bregma, L: lateral, P: posterior.

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some, but not all, of the sharp waves, but soon became stronger and a 1:1 temporal correlation between ear movement and the appearance of sharp waves became clearer. A typical pattern is shown in Fig. 2D.

Following these experiments, the ECoG for area **b** during stimulus-induced pre-stage 1 RBME was recorded in free-moving gerbils using a radio telemeter. Fig. 3 shows a typical case in which RBME and sharp waves in the ECoG appeared after the end of a period of seizure-inducing stimuli applied by the H method, each sharp wave being synchronous with an

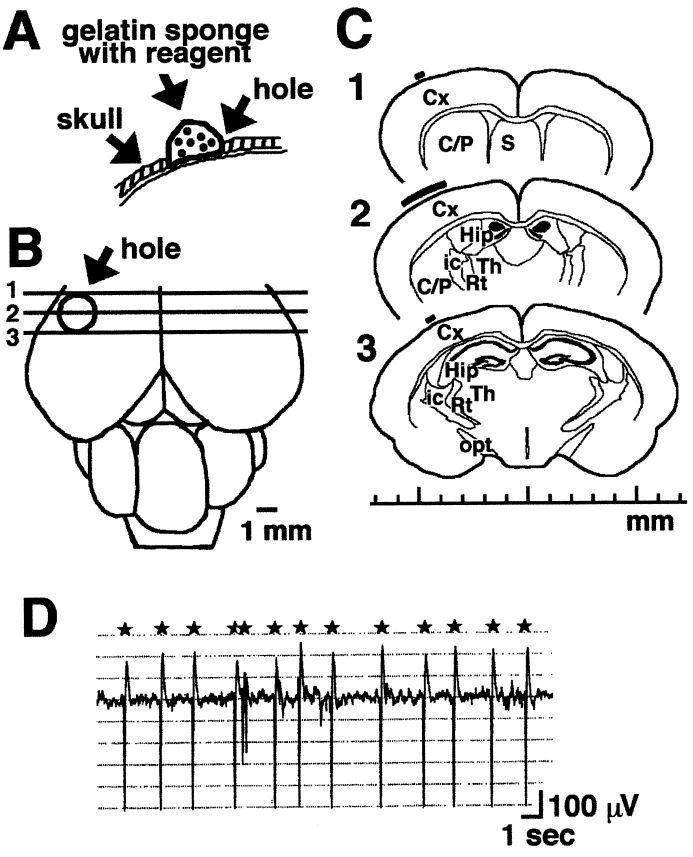

Fig. 2. Effects of BMI application on ECoG pattern and ear movement.
The procedures for the application of BMI (A) and the location of the hole (B) are shown schematically. The figures in C are those from the atlas at –0.1 mm from the bregma (#1 in B and C, the most anterior position of the hole), –0.98 mm from the bregma (#2 in B and C, the middle position), and –1.97 mm from the bregma (#3 in B and C, the most posterior position). The location of the hole is indicated by a line over the cerebral cortex of each figure. A typical ECoG pattern after BMI application is shown in D. Asterisks denote movements of the contralateral ear.
C/P: caudatus putamen, Cx: cerebral cortex, Hip: hippocampus, ic: internal capsule, opt: optic nerve, Rt: reticular thalamic nucleus, S: septum, Th: thalamus.

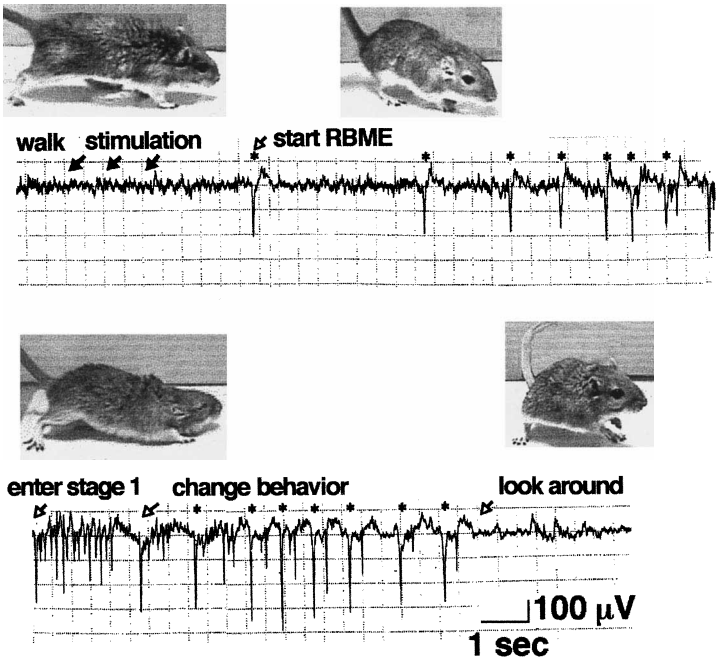

Fig. 3. ECoG pattern in area **b** and behavior of a freely-moving gerbil stimulated using the H method.
Stimulation was applied three times (arrows). After the end of the stimulus, at 2.2 sec, strong RBME appeared ("start RBME"). At 12 sec, the gerbil stopped walking and lowered its head; its ears were flattened and its eyes remained continually closed ("enter stage 1"). At 14 sec, the gerbil started walking again, with its ears, head and neck moving rhythmically ("change behavior") and, at 21 sec, the repetitive movement suddenly stopped and the gerbil looked around and started walking normally ("look around"). The asterisks denote movements of the ear.

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ear movement. When the gerbil entered stage 1, in which the ears were flattened, the ECoG profile became complicated. Behavior then returned to repetitive movement of the head, neck, and ears and the profile of the ECoG waves also became simpler, although it was still more complex than the apparently simple, sharp waves seen with ear movement alone. The gerbil then began to look around and to walk normally and the ECoG pattern returned to normal. Sharp waves, each apparently synchronous with each ear movement, appeared in all gerbils examined (n=7) with minor variation; for example, a small broad wave occasionally followed sharp waves.

Following unilateral ablation of area **b**, recovery from anesthesia, and a return to normal behavior, when a seizure-inducing stimulus was applied, RBME was no longer seen in the contralateral ear (n=5). Fig. 4 shows brain sections of three gerbils showing different degrees of ablation and pictures showing unsymmetrical ear movement in one of the gerbils. In control gerbils with unilateral ablation of part of the occipital cortex (n=3), RBME were elicited normally on both sides by seizure-inducing stimuli. Fisher's exact probability test showed a significant increase in the abolition of stimulus-induced RBME after unilateral ablation of area b (5/5) compared to after unilateral ablation of part of the occipital cortex (0/3) ($p<0.025$).

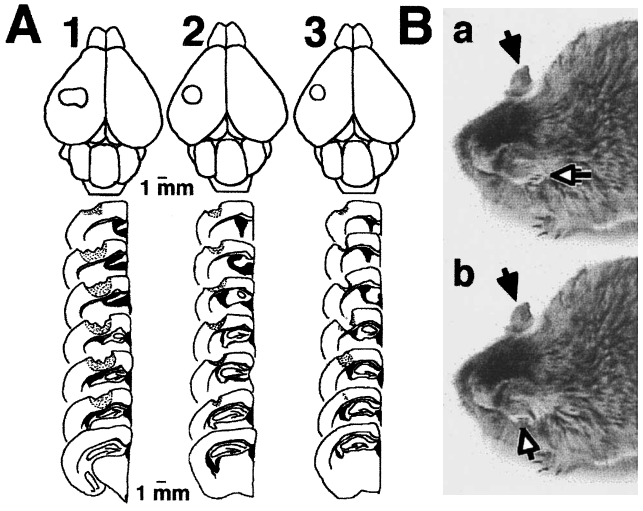

Fig. 4. Effect of ablation of area **b** on stimulus-induced RBME in free-moving animals.
A. The lesions made in the cerebral cortex are shown as an encircled area in a bird's eye view of the brain and in coronal sections (three gerbils). The most anterior section is 0.3 mm posterior to the bregma (case #1), at the level of the bregma (case #2), or 0.3 mm anterior to the bregma (case #3). The distance between pictures of sections is 0.45 mm. The dotted area indicates the affected area in which neurons were lost or greatly reduced in number. B. (a) The picture captured from the video tape (case #2) shows that the ipsilateral ear (left) was moving backwards (note the vertical lines on the pinna made by the backward movement itself) in RBME induced by the H method, while the contralateral ear (black arrow) was not affected. (b) The corresponding picture, taken 0.05 sec before (a), when both pinnae show a normal profile. When RBME occurred in the ipsilateral ear, the contralateral ear never moved backwards.

DISCUSSION

The results of this study showed that pre-stage 1 RBME induced by seizure-inducing stimuli can be considered one of the characteristics of our seizure-sensitive strain, MGS/Idr, since it was seen in all adults, although the incidence varied between individuals. It is currently unclear why, in a given gerbil, some seizures start with RBME, while others do not, and why there are different types of RBME with either short and constant or longer and less constant intervals.

Using conditions of electrical stimulation similar to those used to map the motor cortex area responsible for the movement of individual body parts, we found that, under anesthesia, stimulation of an area of the primary somatosensory cortex (area **b**) elicited strong backward movement of the contralateral ear. We then applied the $GABA_A$ receptor antagonist, BMI, to this area to see the effect of artificially inducing an imbalance between excitatory and inhibitory systems in this area, since such an imbalance is believed to be a factor in the genesis of epileptic disorders. We chose BMI because GABA is the major inhibitory neurotransmitter in the brain, and its dysfunction, especially in terms of the $GABA_A$ receptor, has been observed in some epileptic patients, which fits the so-called GABA hypothesis of epilepsy (reviewed by Lloyd *et al*., 1985), although the major excitatory neurotransmitter, glutamate, and other neurotransmitters also contribute to some forms of epilepsy (reviewed by Engelborghs *et al*., 2000). Surprisingly focal application of BMI to this area spontaneously induced similar, but long-lasting, RBME. When BMI is injected into the forelimb sensorimotor cortex of the rat, rhythmical electrophysiological activity, accompanied by rhythmical forelimb movement, is seen (Castro-Alamancos and Borrel, 1995) and, in the cat, injection of BMI into the suprasylvian cortex elicits paroxysmal EEG spikes to which the cerebral cortex is considered to be a main contributor (Steriade and Contreras, 1998). These studies demonstrate that inhibition of $GABA_A$ receptors in at least certain areas of the cerebral cortex can elicit synchronous and repetitive electrophysiological activity, and that, if the application site is related to the movement of some body part, repetitive movement of the body part can also be induced. Taken together with these results, the results of our study show that area **b** is related to movement of the contralateral ear, although the exact route is not known.

During pre-stage 1 RBME elicited in waking gerbils, area **b** showed sharp ECoG waves that were apparently synchronous with individual ear movements. With the extracellular recording method used in this study, sharp ECoG wave basically indicates highly synchronized firing in a substantial number of cells in the area. As the epileptic behavior proceeded, the ECoG profile became more complicated, suggesting that the sharp waves observed synchronously with individual ear movements were not artifacts due to the movement, but reflected electrical activity occurring in area **b**.

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In patients, the jerk-rocked back averaging method is used to see whether the cortical spikes precede the individual muscle jerks within a reasonable time, evidence that the jerks are "cortical myoclonus" caused by cortical activity, but, in our study, we cannot use such a precise method to say whether there is an exact relationship between the cortical sharp waves and ear movement. However, it is interesting that the somatosensory cortex is one of the areas known to generate cortical myoclonus, especially the stimulus-sensitive type (Uesaka *et al.*, 1996); in this case, the exact route to elicit movement is still debated, but one possibility is via the motor cortex activated through the connection between these two areas, while another does not involve the motor cortex. In our experiments, area **a** may be the motor area for ear representation, since both the location and the poor reproducibility of movement induction are similar to those seen with the motor cortex of the ear in the rat (Hall and Lindholm, 1974). Since a connection between the primary somatosensory cortex and corresponding motor cortex has also been reported in rodents (Izraeli and Porter, 1995), the ear movement induced by electrical stimulation of, or BMI application to, area **b** may be due to activation of the motor cortex (presumably area **a**) via a connection between these two areas, although we did not examine whether area **b** was truly a somatosensory cortex receiving somatic sensory information from the ear. In the rat, the somatosensory cortex for the ear is located in a more posterior area (Welker, 1971), but there may be a species difference in the cortical map, as seen with the vestibular cortex. In the gerbil, or at least in our strain, the vestibular cortex responding to peripheral utricular stimulation is located at an area overlapping area **b** which is more lateral than that in other animals, including man (Ito and Seto-Ohshima, 1998).

The abolition of ear movement by ablation of area **b** may also result from inactivation of the motor cortex via the connection between the two, if this, in fact, exists. Alternatively, damage to some specific cells in this area, including those responsible for vestibular stimulation, may affect other cells necessary for these movements. The possibility that the surgical operation nonspecifically affected one hemisphere is unlikely, since ablation of part of the unilateral occipital cortex did not result in this unsymmetrical phenomenon.

Under the condition of electric stimulation used, three pulses were sufficient to induce movement when repeated at around 300 Hz at the susceptible point (Fig. 1B). These results suggest that, when a small number of pulses (not necessarily highly repetitive stimulation) reach this area, they can trigger a backward movement of the ear in vivo. If seizure-inducing stimuli elicit repetition of such a set of pulses entering area **b** and/or temporarily cause some inhibition of the $GABA_A$ system in this area, the movement may repeat for some time. Although further experiments are required to clarify the exact role of this area of the somatosensory cortex in stimuli-induced RBME, our results suggest that manipulation of an area in the somatosensory cortex may modulate the stimulus-induced repetitive movements seen in some types of epilepsy in other species (Hallet, 1987), and that our strain may be useful in fundamental research on the mechanisms underlying such repetitive movements and approaches to their modulation.

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