Intrinsic and drug-induced seizures of adult and developing gerbils

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Seizures elicited by posture change and intraperitoneal administration of convulsants were studied ontogenetically in the Mongolian gerbil (*Meriones unguiculatus*). In posture change, the first signs of seizure appeared after age 6 weeks with maximal frequency at 8–9 weeks. Adults developed complex, but stereotyped, seizures. Facial twitch was followed by the generalized convulsion, further progressing to trembling of the limbs and then kicking of the hindlimb (full seizure) after 55 days of age. Pentylenetetrazole induced a seizure similar to the full event in gerbils as young as 37 days of age. The seizure pattern elicited by strychnine or glutamate was different from that of pentylenetetrazole.

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The Mongolian gerbil (*Meriones unguiculatus*) is known to be prone to chronically recurrent spontaneous motor seizures with stress-induced properties (1); the clinicoelectrical manifestation is evidently epileptic (2). Seizure manifestation changes according to developmental stage. Short episodes such as twitches of the pinnae begin at around 2 months and seizures then develop into complex, but stereotyped, motor manifestations. The mechanism underlying the ontogenical change of the seizure in the gerbil is not yet known.

Age-related epilepsies are well-known in humans (3), and that there are seizure differences between infantile and adult epilepsies (4).

We developed a seizure-prone strain of gerbil in which epileptic seizure occurred in 100% of animals during development. This strain may serve as a useful genetic animal model to elucidate the mechanism underlying age dependency in human epilepsy, especially in some types of reflex epilepsy.

We analyzed ontogenical changes in spontaneous seizure and then examined the capability of some convulsants to elicit seizures with similar characteristics in adult animals and also studied the effects of such convulsants on developing gerbils.

Various genetically seizure-prone animals including mice, rats, baboons and birds have been developed as animal models to elucidate the mechanism underlying epileptic seizure (review 5, 6). These animals have their own genetically determined abnormalities which result in seizures with characteristic patterns. The spontaneous seizure pattern of the gerbil is, for example, different from those of many other seizure-prone animals including El mouse (7), SER (spontaneously epileptic rat, 8) or GEPR (genetically epilepsy-prone rat, 9). A characteristic point of the seizure of the gerbil is that the violent kicking of the hind legs occurs after the seizure motor manifestation has faded except for fine tremor of the forelegs. This was used as a characteristic marker in comparing the similarity between the spontaneous and the drug-induced seizures, in addition to other seizure behavior and electrophysiological patterns.

Materials and methods

Animals. The gerbils used are from a colony of a strain (MGS/Idr) of Mongolian gerbils (*Meriones unguiculatus*) which was established at the Institute for Developmental Research (Aichi, Japan) by selective inbreeding for more than 20 generations. Selective inbreeding with sister-brother mating for the abnormal character of spontaneous motor seizures was started by Shoji in 1973 (10). Every gerbil in this strain has had seizures.

The gerbils were bred with free access to pelleted food and water, temperature and humidity were kept at 24°C and 50%, respectively. Light was provided between 06:00 and 18:30 h. When cages were changed once a week, all gerbils were suspended by their tails and their backs pressed to check for pregnancy. This treatment was very effective in eliciting seizures in both sexes, though changing the position of their cages itself often caused seizures. We recorded the seizure type elicited after this posture change had been maintained for 5 s, using the classification described below.

Seizure in the adult gerbil is stereotypical evolving sequentially. Sequential evolution of seizure pattern was classified as follows: Stage 1 (flattening of the ears against the head and twitch of the vibrissae with occasional closing of the eyes); Stage 2 (clonic-tonic convulsion with body rollover); Stage 3 (sudden return to normal posture with trembling, mostly of the forelimbs); Stage 4 (strong kicking of hindlegs); Stage 5 (exhaustion) followed. After a moment, the animal returned to pre-ictal behavior (Fig. 1). We termed this sequential seizure evolution "full seizure" when the seizure evolved sequentially from Stage 1 to post-ictal Stage 5.

To study ontogenically seizure development under the stimulus of posture change, we observed 140 animals for 18 months. To study the effects of drugs, 30 adult gerbils (older than 3 months weighing 65–95 g) and 15 young (older than 22 days) of both sexes were used.

Sprague-Dawley rats were raised under the same conditions as the gerbils except that their cages were cleaned every 4 days. For drug-induced seizure experiments, 7 rats aged between 30 and 50 days old were used.

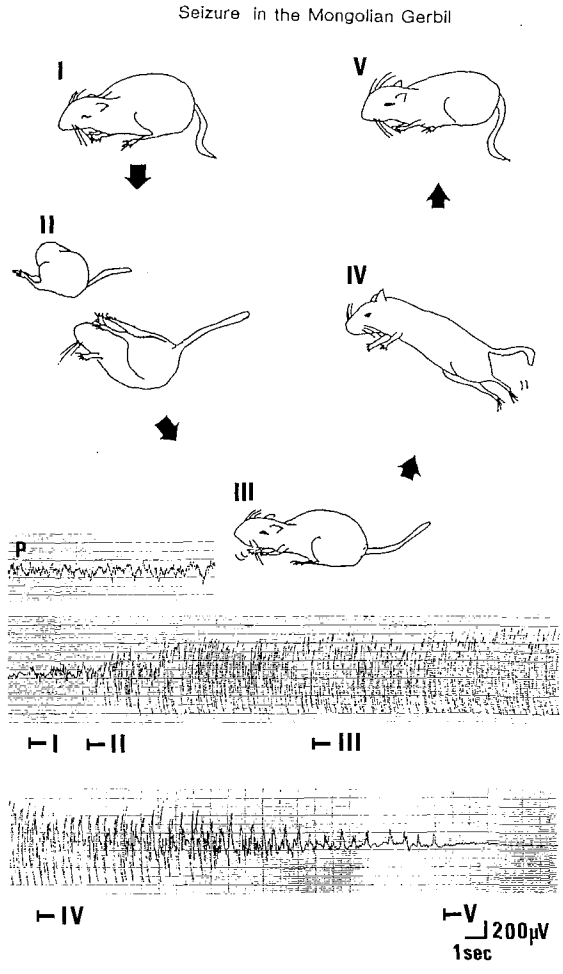

Fig. 1. Seizure behaviors and EEG pattern of the gerbil. Behavior during full seizure (Stages 1–4) and exhaustion stage (Stage 5) are drawn schematically with EEG pattern. P: pre-ictal state.

Electrophysiological study. For the electrocorticogram, epidural stainless steel screw electrodes (1 mm in a diameter for young animals and 2 mm, for adults) were placed for the duration on the forelimb motor area unless otherwise mentioned (in some cases, the hindlimb site was selected). The respective motor areas for forelimb, trunk and hindlimb were determined using the method of Hall & Lindholm (11), and were essentially the same as those of the rat reported (11) (data not shown). Burr holes were made through the bone with a dental drill under nembutal anesthesia (50 mg sodium pentobarbiturate/kg body weight). EEG recordings were made with a Multipurpose polygraph RM-150 (Nihon Kohden, Japan) with the animals able to move freely. The time constant of recording was 0.3 s and high-cut frequency was 100 c/s. In our EEG study, 27 gerbils and 3 rats were used. After the experiments, the animals were given a lethal dose of nembutal. The brains were removed and preserved in Bouin's fluid for staining of the frozen microtome sections with thionin to establish the position of the electrodes.

In both gerbils and rats the implanted electrodes produced no detectable effect on their behavior.

Drugs. Pentylenetetrazole (PTZ, Sigma, USA) and strychnine (Wako Pure Chemical, Osaka, Japan) were dissolved in 0.9% saline at concentrations of 10 mg/ml and 0.5 mg/ml, respectively and injected intraperitonially (ip) at intervals of 5 min, at doses of 10 mg/kg body weight for PTZ and 0.25 mg/kg body weight for strychnine. L-glutamic acid (Wako, Osaka, Japan) was dissolved by addition of 8 M NaOH to the aqueous suspension, neutralized with 1 M HCl, and the volume was adjusted with H_2O to the calculated concentration of glutamate, dimethyl sulfoxide (DMSO) was then added at a final concentration of 15%, as described by Sato et al. (12).

Results

Ontogenical profile seizure after posture change. When seizures were traced during development Stage 1 was observed as the first sign after 6 weeks of age, with maximal frequency at 8–9 weeks (Fig. 2). There was no significant sex-related difference. During chronological development, the animals began to show more developed types of seizure from Stages 1 to 2 and from Stages 1 to 3 further developing to full seizure. Full seizure always appeared after the gerbils had experienced Stage 1 at younger age,

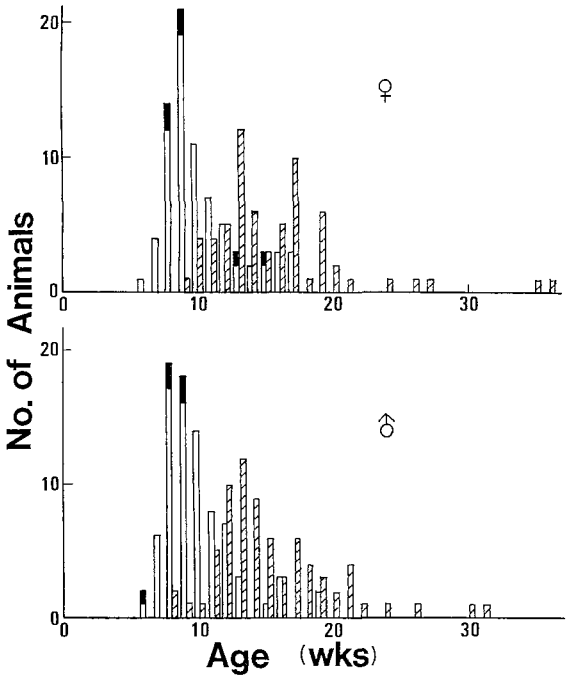

Fig. 2. The developmental profile of the intrinsic seizure. The numbers of gerbils showing the first sign of seizure (open bar + solid bar) and onset of full seizure (hatched bar) are plotted against age. Solid bar indicates the number of animals showing tapped response under the stress conditions described in Results: (♀) female, (♂) male.

though the interval required for development of the seizure pattern was very short in some (Fig. 3). The length of this interval did not correlate with the age at first appearance of Stage 1, though in some animals with a rather late Stage 1 seizure, the full seizure appeared extremely late (arrows in Fig. 3).

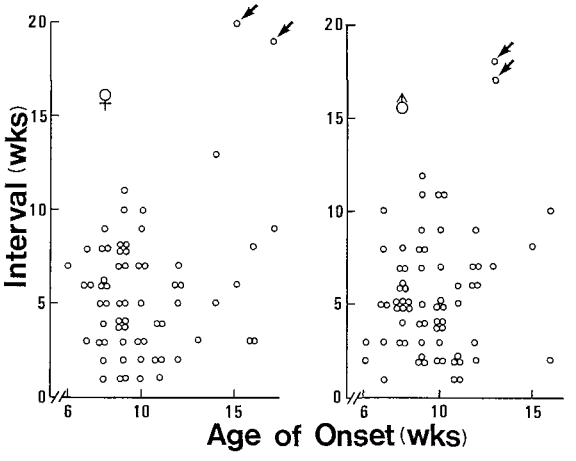

Fig. 3. The relationship between age at first seizure appearance and the time required to develop to full seizure. Age of first appearance is plotted as abscissa and the interval between the age of first appearance and the age at onset of full seizure, as ordinate in individual animals: (♀) female, (♂) male.

Seizure in gerbils is known to be effectively induced by the stress of a new environment (1). Some gerbils at around 40–50 days of age also appeared sensitive to the stress induced by the close proximity of larger, younger gerbils. These animals were often attacked by the larger gerbils and the dorsal fur on the rear half completely torn out. Under this stress, they tapped their hind legs at intervals of about 1 s, though there was no remarkable EEG change in the cerebral cortex motor area for the hindlimbs. The relationship between this sensitivity and that occasioned by posture change was examined by tracing the developmental profile of the seizures, but no specifically early onset of seizure was exhibited under stress of posture change and new environment (Fig. 2).

Effect of convulsants on adult gerbils. Three drugs, PTZ, strychnine and glutamic acid, were tested for their ability to provoke seizures identical to spontaneous seizures in adult gerbils.

The first injection of PTZ (10 mg/kg body weight) did not have any detectable effect on either behavior or EEG pattern. However, after the second injection (20 mg/kg body weight), the gerbils sometimes became motionless with an associated appearance of short duration EEG sharp wave bursts. They sometimes bit their pelleted food violently or wiped their mouths. Following further injections of PTZ, movement ceased more frequently. Occasionally, twitches of the vibrissae and later, of the pinnae also occurred. Correspondingly, repetitive sharp waves often appeared and the duration of each event increased. Higher doses of PTZ brought a strong jerk of the body accompanied by isolated high voltage sharp wave and/or spike (in some cases, more than 1 mV). These behavioral changes are summarized in Table 1. At a dose of 40–90 mg/kg of PTZ, the animals had generalized convulsions consisting of almost the same sequential events of behavior and EEG pattern to those of full seizure (Fig. 4). The average time from the onset of Stage 1 to the end of Stage 2 was 15 s (10–24 s) and to the end of Stage 3 was 29 s (20–45 s). Average time to

Table 1. Minimum amounts of PTZ necessary to induce sezure–related behavior

Behavior	Minimum amount of PTZ
immobility	20
twitch of the vibrissae	23
flattening of the pinnae	34
body jerk	46
full blown seizure–like seizure	57

The minimum amount of PTZ (mg/kg body weight) was calculated mathematically as the average value of the minimum amount necessary to induce each event in 10 adult gerbills

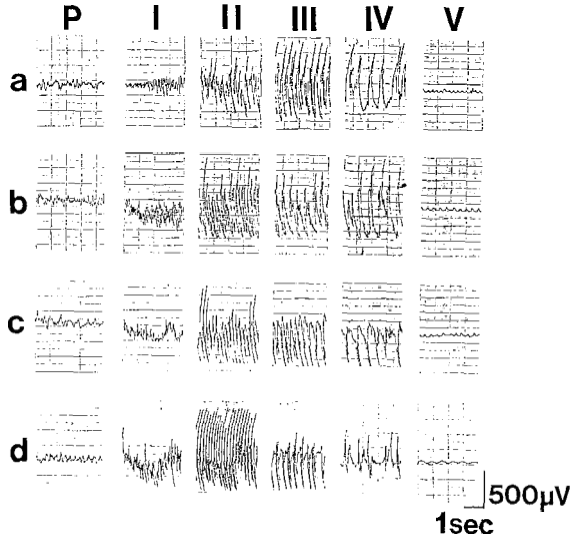

Fig. 4. EEG pattern during each stage of PTZ-induced seizures. Typical electrocorticograms obtained from the motor area of the cerebral cortex during each stage of seizures is shown: a) full seizure by posture change; b) full seizure-like event induced by PTZ in an adult gerbil; c) full seizure-like event induced by PTZ in a 38-day gerbil; d) full seizure-like event induced by PTZ in a rat. P: pre-ictal state, 1–4: Stages 1–4.

the termination of full seizure-like events was 47 s (28–70 s) (n = 12). Values for intrinsic seizure after posture change were 12 s (8–16 s), 21 s (14–30 s) and 31 s (26–53 s) (n = 23), respectively. In some cases, this full seizure-like event induced by PTZ repeated again after Stage 5 (exhaustion). The seizure repeated three times in one gerbil. The dose which provoked full seizure-like events was always a little lower than that for tonic seizure status with stretching of the limbs culminating in death. Repeated administration of saline did not induce the full seizure-like events, but PTZ administered after repeated saline administration did induce a full seizure-like seizure, as in those animals treated with PTZ alone.

Strychnine caused generalized convulsion at dose levels higher than 0.75 mg/kg body weight, but the convulsions induced were different in both the behavior and EEG pattern from the seizures caused by posture change. Animals floundered violently during clonic-tonic seizure, the type of seizure most often induced by touching the animals or suspending them by the tail, as for injection. The corresponding EEG pattern in the motor area of the cerebral cortex was not epiletiform.

Glutamate at a dose of 20 mmoles/kg body weight decreased movement and the animals stood on their hindlegs leaning against the wall of the cage. The body sometimes twitched. A dose of 40 mmoles/kg body weight caused convulsion with the animals trembling and shaking their forelimbs; sometimes they also jumped. Over all, these convulsions were different to the posture-change seizures. The solvent alone did not produce such convulsions.

Effect of PTZ on developing gerbils. Pentylenetetrazole which had the capacity to provoke spontaneous full seizure-like events in adult gerbils was examined for its effect on developing animals. Aliquots of PTZ solution injected repeatedly into young gerbils sequentially changed their behavior and EEG pattern if they were older than 37 days, as in adults. They exhibited full seizure-like seizure at a dose around 80–100 mg/kg body weight. This dose was again a little lower than that required to induce a lethal tonic seizure. Fig. 4 shows the EEG pattern during the full seizure-like event of a 38-day old gerbil after administration of PTZ at the dose of 80 mg/kg body weight. For the animals between 37 days and 2 months, that had not yet had a full seizure induced by posture change at the time of experiments, the average values for three time intervals of PTZ-induced seizures (counted as for the adults) were 11 s (8–13 s), 21 s (15–25 s) and 39 s (25–65 s), respectively (n = 7).

Animals younger than 30 days showed similar changes in EEG pattern and behavior with low and moderate doses of PTZ, although they tended to bite things more often. They also had generalized convulsions at a dose of approx. 80–100 mg/kg body weight, these were, however, different from spontaneous full seizure convulsions. Behavior during generalized seizure varied from one animal to another in detail, but mostly showed clonic-tonic convulsion with occasional bouncing of the body. The EEG pattern of 23-day-old gerbil during the generalized convulsion provoked by PTZ (80 mg/kg body weight) is shown in Fig. 5, which also shows the EEG pattern during drowsy phase and a typical adult pattern.

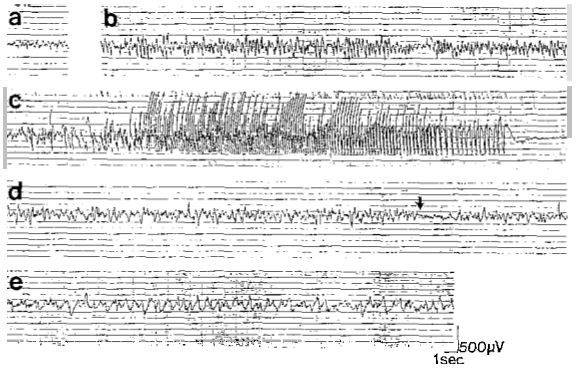

Fig. 5. EEG pattern of a 23-day gerbil. Electrocorticogram a) before injection of PTZ; b) after repeated injection of PTZ (final amount: 70 mg/kg body weight); c) at the PTZ-induced tonic-clonic convulsion (final amount: 80 mg/kg body weight); d) during drowsy phase (at the time indicated by the arrow, the researcher clapped her hands); e) EEG pattern during drowsy phase of an adult gerbil is shown for comparison.

The results of the ability of PTZ to provoke full seizure-like events in developing gerbils are summarized in Fig. 6.

The effect of PTZ on rats was examined to assess the specificity of the PTZ-induced full seizure-like seizures in the gerbil. Of 7 rats, 2 showed seizures similar to Stage 3, in 2 others, seizures proceeded like full seizures with rhythmical body movement rather than exact running, and 3 rats kicked violently similarly to the full seizure of the gerbil at a dose of 80–100 mg/kg body weight; the EEG pattern during such seizures is shown in Fig. 4.

Discussion

Ontogenic profile of seizure after posture change. The seizure behavior of our gerbils developed chronologically. As also reported by others (13–15), though we found some differences, especially in seizure behavior. The final seizure state in our colony (full seizure) is essentially the same as that reported by Suzuki (14), but differs from that described by Loskota et al. (15). In our results, the tonic component seems to be less marked and duration of seizure shorter than that reported by Loskota et al. (15). In their report, there was no description of running in the equivalent of Stage 4 of our full seizure, however, gerbils further bred selectively from their colony were reported to show wild running (16); they had deaths due to seizure (15), absent in our colony; they used an empty pan to stimulate the gerbils. The different methods of stimulation may have caused the differences in seizure behavior, but the exact reasons are not yet clear.

Our results showed that full seizure appeared after 55 days of age, always after each gerbil had experienced Stage 1 seizure at a younger age, however, the interval for the development of seizure was not constant. The mechanism underlying these phenomena is yet to be determined.

Seizures induced by drugs. A chemical which brings full seizure-like seizure in the adult gerbils, can be used, in turn, to examine whether the young gerbils which do not show full seizure under our condition, have capability to elicit full blown seizure-like seizure under some condition or they can not elicit it under any condition. To find out such a chemical, three chemicals, PTZ, strychnine and glutamic acid, were tested for their capacity to induce seizures which resemble full seizure in the adult gerbils. Among them, PTZ induces the full seizure-like seizure in gerbils older than 37 days of age. However, neither strychnine which is known to antagonize the function of glycine, an inhibitory neurotransmitter mostly located in the brainstem and the spinal cord (17), nor glutamic acid which acts as an exciting neurotransmitter when it passes through the blood-brain barrier with the aid of DMSO (12) elicits such sequential motor activities. The action of strychnine on the gerbils is similar to that on other animals reported previously (18). The mechanism of action of PTZ is complicated and a variety of effects on various nervous systems was reported, but at a synaptic level, it is thought to block GABA-mediated inhibition (19). It is to be noted that seizure-related differences in the GABAergic system in the gerbils were reported though in the brain of seizure-prone gerbils, in addition to the decrease of GABA receptor in several areas, some increase of GABAergic neurons in the hippocampus in comparison with that of seizure-resistant gerbils was observed. For the latter apparently paradoxical finding, disinhibition function of GABA which inhibited the inhibitory function of GABAergic system was suggested to work abnormally strongly to increase the output activity from the hippocampus, leading to seizure activity (16, 20). We do not know whether the mechanisms underlying full seizure and full seizure-like seizure induced by PTZ are common or not, but both seizures closely resemble each other. The GABAergic system may have some important role in both seizures but the situation is not simple and more experiments are required to clarify the roles of this neurotransmitter in these seizures.

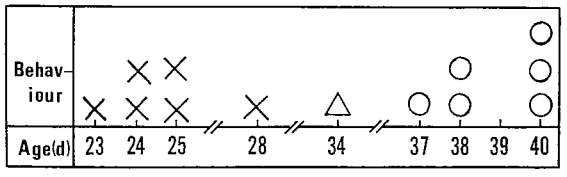

Fig. 6. Seizure pattern induced by PTZ in developing gerbils. The results of PTZ-induced seizure patterns in developing gerbils of different ages are summarized. Circles: the full seizure-like seizure; triangles: seizures in which the animals show rhythmical body movement like running after Stage 3, but without advance; crosses: seizures different from full seizure. Each symbol corresponds to the result from each animal.

Effect of PTZ on developing gerbils. PTZ can induce full blown seizure-like seizure in the gerbils as young as 37 days of age. The experience of Stage 1 seizure seems to be necessary to develop the seizure behavior into full seizure by posture change (Fig. 3) but it is not necessary for full seizure-like seizure by PTZ. The seizure behaviors induced by low dose of PTZ may be able to work as the replacement.

For the induction of full seizure-like seizure by PTZ, some maturation of the brain may be necessary because the gerbils younger than 30 days of age often showed the generalized convulsion different from full seizure. The rhythmic pattern in electrocorticogram during drowsy phase is formed already

at 23 days of age but we found that the development of gerbil brain proceeded more slowly than the rat or the mouse (21, 22, 23). The brain weight reaches its adult level at around 35 days of age (21). The immunohistochemical distribution of parvalbumin, a calcium-binding protein which colocalizes with GABA in the cerebral cortex and many other areas of the brain and is suggested to appear with functional maturation of the nervous system (22), reaches the adult pattern most slowly in the cerebral cortex by 38 days of age (23).

We observed that the seizure induced by PTZ in the Sprague-Dawley rats sometimes proceeded similarly to the full seizure of the gerbils. With the rat, it is thought that the initial phase of PTZ-induced seizure, facial and forelimb clonus, occurs under the activity of the forebrain, while the following phase of running-bouncing is under the activity of the brainstem (24). We do not know whether the mechanism underlying the seizure induced by PTZ in the rat is same as that in the gerbil or not. However, if they have common mechanism, the forebrain may be mostly responsible to Stage 1, 2 and 3 of full seizure-like seizure by PTZ and the brainstem may work for running during Stage 4, though both activities are probably not independent from each other as in both spontaneous full seizure and PTZ-induced seizure, running response in Stage 4 stops when the epileptiform pattern of the cerebral cortex ceased.

Maturation of forebrain which seems to participate in determining sequence of events may be important. However, there can be other explanations, such as the different effects of our method of PTZ administration including the volume of solution and the time of interval of injection, on the gerbils of different age. Thus, it is safe to say now that gerbils older than 37 days of age can exhibit full seizure-like seizure by repeated administration of PTZ.

Intrinsic seizure of the gerbil. In our colony, gerbils have never had a full seizure at 37 days of age with the stimuli we tested which included tossing the animals in the cage or observation of the animal in a new cage after hanging the animal by its tail. Some other stimuli may be able to elicit full seizure on the animal of this age but other researchers who employed other stimuli also reported the absence of full seizure at this age (14, 15). Thus, in the natural condition, some factor which is required to reduce the threshold to induce full seizure is absent at this age though the system which can show full seizure-like seizure by administration of PTZ is already formed. Stress is known to be an important factor to lower the threshold to trigger the seizure in the adult gerbil (1) but our results showed that the sensitivity to some stressful situation does not always mean the early onset of the spontaneous seizure (Fig. 2).

During development, the kind of factor(s) acting to induce the first episode of seizure and the processes working to make induce susceptibility to full seizure under investigation in our laboratory.

Acknowledgements

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