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Development of a Seizure and Epileptogenesis in EL Mouse

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Short Research Article

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ABSTRACT

To elucidate the mechnisms of epileptogenesis in the EL mouse which is an excellent animal model of epilepsy. All animals (EL/Suz) were stimulated by our routine tossing-up method once a week through their lives and exibited seizures.

The electric activities of the brain were recorded through implanted electrodes in the freely moving state. The following symptoms of an established seizure are observed: tiny auras, wild running, tonic convulsions, clonic convulsions, and finally, stupor repose lasting approximately 1 to 3 min. These symptoms are accompanied by major changes in paroxysmal discharges in the electro-corticogram and the electric activities of the deep brain parts. Paroxysmal activities start at the parietal cortex and are transmitted to other cortical areas. When the paroxysmal activities reach to the thalamus, hippocampus and striatum, the mouse runs; simultaneously, tonic-clonic convulsions start, for which the hippocampus plays a major role. Finally, paroxysms stop, and the animal stands still.

Abortive seizures do not occur until the age of 8 weeks and only occur after routine stimulation. At that time, some small paroxysmal activities are observed in the parietal cortex. After the age of 10 weeks, a running fit appears; however, it is not necessarily observed later in life. The most remarkable symptom of epilepsy, tonic convulsion, occurs after 10 weeks of age, and clonic convulsion continues until the death of animal.

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A common course of onset of individual seizures and abnormal plastic formation of seizures during the lifespan of the EL mouse are observed. All individual seizures repeat the developmental process of seizures in order. This paradigm can be demonstrated by longitudinal observations of seizure symptoms and electric activities in the EL mouse brain and by life-long investigations of many animals.
In conclusion one could observe all individual seizures repeat the developmental process of seizures in order by the EL mouse investigation.

Keywords: Epilepsy; EL mouse; seizure; development; abnormal plasticity.

1. INTRODUCTION

Epilepsy is known to be a highly complicated disease or syndrome [1]. The EL mouse is an excellent animal model of epilepsy. The pathogenesis or epileptogenesis of this disease in the EL mouse has been reported in some previous papers [2,3,4,5,6,7]. This work describes the common course of individual seizures and the plastic formation of seizures during the life of the EL mouse. This paradigm should be demonstrated by longitudinal observations of seizure symptoms and electric activities in the EL mouse brain and by life-long investigations of many animals.

1.1 Ethics

The author have read and abided by the statement of the ethical standards for research involving laboratory animals described by the US NIH Office of Laboratory Animal Welfare. All animal care and procedures were conducted in accordance with the IACUC (No.21-18, 2002) of our institution, which is officially approved by the Japanese Society of Experimental Animals, an internationally approved society. An important member of the committee is a veterinarian. In addition, all possible efforts were taken to avoid animal suffering and to minimize the number of animals used in the experiment. Additionally, the author referred to the standards for the publication of mouse mutant studies written by Crusio et al. [8] for all experiments conducted.

2. SUBJECTS AND METHODS

The details of the experimental animals and procedures were reported in our previous papers [6,9,10,7,11] and are briefly described again here.

2.1 Experimental Animals

One hundred animals each of the EL*/Suz line and DDY line were used for this study. Mice of both sex were used. They weighed 26-30 g and were 6 to 50 weeks old. No sexual difference in the occurrence of seizure was found.* This mutant mouse strain was named “ep” when it was first discovered, was later named “El”, and was then renamed “EL” at the International Symposium in Tokyo in 1992. The provider of the animals should manifest this strain to be the EL strain, which deprived from Suzuki (eg. Leussis, Heinrichs [12]).

All animals of the EL/Suz strain were inbred to the F128 generation, and those of the DDY strain were inbred to the F66 generation. The animals were, carefully reared at our institute and were treated with the routine provoking stimulation of being-tossed up in the air once a week since 4 to 5 weeks of age [7].

2.2 Experimental Procedure

The animals were anesthetized (pentobarbital, 50 mg/kg body weight) and fixed in a stereotaxic apparatus (Narishige, Tokyo, devised by the authors) during electrode implantation. The electric activities of several portions of the brain were chronically recorded while the mice were freely moving through thin stainless steel microelectrodes, which were stereotaxic according to the atlas [13]. After recording the data, the positions of the tips of the microelectrodes were verified by applying an electric current.

3. RESULTS

3.1 Establishment of Seizures

At first, no animal seized, but after theprovoking stimulation had been repeated several times, all animals easily seized and, eventually, they seized almost spontaneously. Thus, the threshold for seizing was lowered by repetition of the provoking stimulation as described in the literature [7], ensuring that they were highly prone to seizure. No animal of the DDY strain seized, even after being treated with similar repeated provoking stimulation.

3.2 Sequential Changes in Typical Seizure Symptoms

In an EL mouse with an established seizure, the symptoms of seizure are observed in the following order: tiny auras, such as trembling vibrissae, wild running, tonic convulsions of the whole body and limbs, clonic convulsions, and finally, stupor repose lasting approximately 1 to 3 min [5,10].

These sequence of symptoms were described earlier (Fig. 6 in Ref. [10]). The parallel phenomena of symptoms andelectrical activities incrucial brain areas are also described in Fig. 1 in Ref. [9]. When auras first present, very fast biphasic spikes and waves occur for several to ten seconds. Then, the animal runs violently, and this is accompanied by separated large spikes and waves of electrical activity lasting approximately for 5-10 seconds that then suddenly drop. Tonic convulsions of the limbs and body occur during the higher spikes, and clonic convulsions accompanied by a higher spike-and-wave burst lasting for about 20 seconds also occur. Finally, the mouse shows no movement or stands still with no electrical activity for several minutes.

Regarding the depth of the electrical activities, the paroxysmal activities propagate to different parts of the brain sequentially (Fig. 3. in Ref. [9]). Paroxysmal activities start at the parietal cortex and are transmitted to other cortical areas during the prodromal stage. Then, the paroxysmal activities reach the thalamus, hippocampus and striatum, at which time the mouse runs. Then, the paroxysmal activities become steeply high and very frequent and are associated with the initiation of tonic-clonic convulsions, for which the hippocampus plays a major role. Finally, the paroxysms stop, and the animal stands still.

3.3 Development of Symptoms of Seizures in EL Mouse

The abnormal plastic process of the development of seizures in the EL mouse was precisely reported by the author [7] in 1982. Here, the appearance and alteration of seizure symptoms are summarized through a direct observation and electroencephalographic investigation. The appearance of symptoms and electrical activities throughout the lifespan of an individual EL mouse are presented in Fig. 1.

Abortive seizures (descibed above) do not occur until the age of 8 weeks and only occur after administration of routine tossing-up stimulation once a week (Fig. 4 on Ref. [11]). At the same time, some small but violent paroxysmal activities are observed in the parietal cortex. After the age of 10 weeks, a running fit appears however, it is not necessarily observed later in life. The most remarkable symptom, tonic convulsion, occurs after 10 weeks of age, and subsequently intensifies and continues until the death of mouse. Clonic convulsion occurs around the age of 10-12 weeks, and interestingly, after being lost for 6 weeks, it reappears.

After these active symptoms present, the animal enters a stupor or motionless state, and the duration of that state increases gradually as the animal ages.

3.4 Commonality in the Development of Individual Seizures and Epileptogenesis in EL Mouse

Fig. 1 shows the sequential changes of typical seizure symptoms and the development of seizure symptoms in an EL mouse, and it is clear that these two phenomena involve from a common process. For an individual EL mouse, after routine stimulation, auras or abortive seizure are observed; then the mouse begins to run, tonic and clonic convulsions continue and, finally, the mouse enters a stupor or stand-still state. In regards to the formation of epileptic symptoms and the establishment of epileptic syndrome in all EL mice, the same process can be observed by both clinical observation of symptoms and measurement of electrical phenomena. The epileptic symptoms occur in the following order: aura or abortive seizure, running fit, tonic and clonic convulsions, and finally, stupor; these symptoms constitute the entire process of epileptogenesis in the EL mouse. As shown in the middle row of Fig. 1, paroxysmal electrical activities occur in several parts of the brain sequentially in parallel with the occurrence of symptoms. First, small but abrupt occurreing spikes are observed only in the parietal cortex, which correspond to the manifestation of auras, and no bursting activities are observed in other areas of the brain. Measurement of neuronal activity in the parietal cortices of EL and DDY mice in the resting state revealed that the neurons of EL mice are less active at rest than those of DDY mice but that the neurons of EL mice respond more actively to proprioceptive afferent input resulting from muscle stimulation than the neurons of DDY mice [11]).

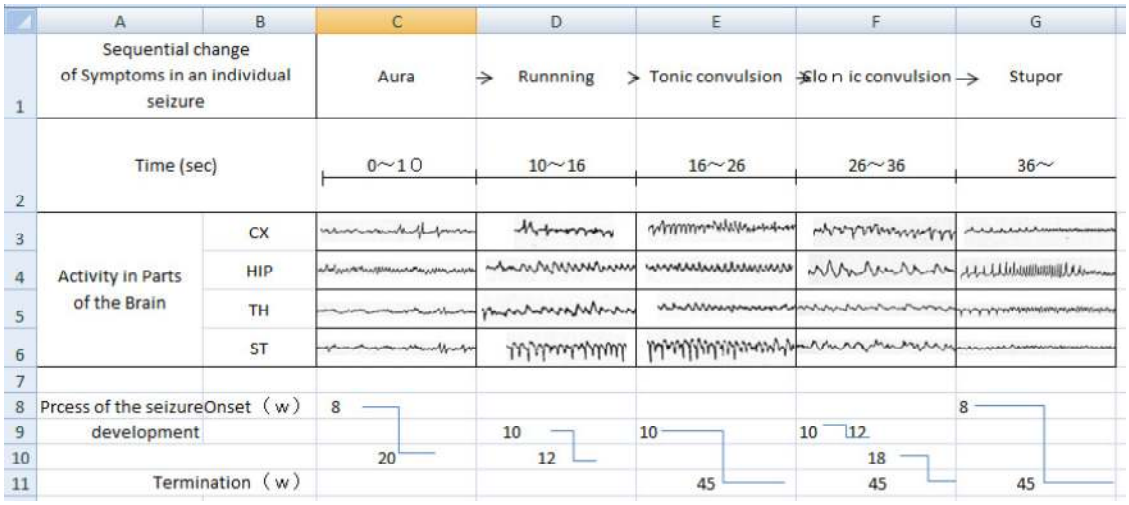

Fig. 1. Sequential changes in symptoms (aura, running, tonic convulsions, clonic convulsions and stupor) of an individual seizure are presented in the top row and the process of the development of seizure phenomena is presented in the bottom row (same as the symptoms shown in the top row). The unit of time in the top row is seconds, and the unit of measurement for the bottom row is age of mice in weeks. The chronic electrical activities of four areas of the brain are shown in the middle row. CX: Parietal cortex, HIP: Hippocampus, TH: Thalamus, ST: Striatum

These findings imply that repetitive stimulations cause some abrupt changes of electrical activities followed by biochemical and molecular changes to cellular systems of EL mice, including the GABAergic system or else in the parietal cortex [11,1]. After repetitive stimulation, small but paroxysmal activities grow at the parietal cortex and other cortices and are propagated more easily to the thalamus, hippocampus and other parts of the brain. These propagated activities cause neurons in the associated areas of the brain to be excited more easily and more intensely.

Based on the findings of this study, the order of symptoms that present during an individual seizure seem to be similar to the development process of seizures.

4. CONCLUSIONS

This work described the commonality of the course of onset of individual seizures and the plastic formation of seizures during the lifespan of the EL mouse. All individual seizures repeat the developmental process of seizures in order. This paradigm can be demonstrated by longitudinal observations of seizure symptoms and electric activities in the EL mouse brain and by life-long investigations of many animals.

Therefore, when any sign of epilepsy, even a trivial sign, is observed treatment for epilepsy should be initiated as quickly as possible.

Substantial changes in the process of the development of seizures will be discussed more precisely in upcoming work.

CONSENT

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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