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Electroencephalographic features of familial spontaneous epileptic cats

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Summary A feline strain of familial spontaneous epileptic cats (FSECs) with typical limbic seizures was identified in 2010, and have been maintained as a novel animal model of genetic epilepsy. In this study, we characterized the electroencephalographic (EEG) features of FSECs. On scalp EEG under sedation, FSECs showed sporadic, but comparatively frequent interictal discharges dominantly in the uni- or bilateral temporal region. Bemegride activation was performed in order to evaluate the predisposition of epileptogenicity of FSECs. The threshold doses of the first paroxysmal discharge, clinical myoclonus and generalized convulsion in FSECs were significantly lower than those in control cats. Chronic video-intracranial EEG monitoring revealed subclinical or clinical focal seizures with secondarily generalization onset from the unilateral amygdala and/or hippocampus. Clinical generalized seizures were also recorded, but we were unable to detect the onset site. The results of the present study show that FSECs resemble not only feline kindling or the kainic acid model and El mouse, but also human familial or sporadic mesial temporal lobe epilepsy. In addition, our results indicate that FSECs are a natural and valuable model of mesial temporal lobe epilepsy.

Abbreviations: FSEC(s), familial spontaneous epileptic cats; FTLE, familial temporal lobe epilepsy; FLTLE, familial lateral temporal epilepsy; FMTLE, familial mesial temporal epilepsy; IHC, immunohistochemistry; IIDs, interictal discharges; KA, kainic acid; MTLE, mesial temporal lobe epilepsy; PD, paroxysmal discharge.

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Introduction

Recently, we identified a novel model of genetic epilepsy in a familial strain of spontaneous epileptic cats (FSECs) that was colonized and sustained at our institute (Nippon Veterinary and Life Science University) (Kuwabara et al., 2010). The FSEC colony has expanded to 30 cats (2 newly onset cats and 7 newborn F1 cats) from that reported previously. These FSECs show typical limbic seizures with secondarily generalizations similar to the feline amygdala/hippocampus kindling or kainic acid (KA) model (McIntyre, 2006; Morimoto, 1997; Shouse et al., 2004; Tanaka et al., 1992; Wada et al., 1974) and/or vestibular stimulation-induced generalized seizures such as that in the El mouse (King and LaMotte, 1989; Suzuki and Nakamoto, 1977; Wang et al., 1997), and are suspected to show autosomal recessive inheritance. FSECs have interictal discharges (IIDs), which are dominant in the uni- and/or bilateral temporal regions or are generally synchronized, on interictal scalp EEG under sedation. Three of the 6 F1 cats showed spontaneous and stimulation-induced seizures that were confirmed by 2 months of continuous video recording and a vestibular-stimulation test at 2 months after publication of the previous report. Therefore, FSECs are considered as a true spontaneous and genetic (autosomal recessive) model of mesial temporal lobe epilepsy (MTLE).

In our previous report, a detail analysis of scalp EEGs under sedation was not described and depth- or ictal EEGs were not performed. Here, we analyzed the EEG features of FSECs including IIDs counts and bemegride activation in scalp EEGs under sedation, and video-intracranial EEGs to detect predisposition and the epileptogenic zone (irritative zone and ictal onset/symptomatic zone) (Luders et al., 1993).

Material and methods

Study approval

This study, including maintenance of the FSEC colony, was approved by the Animal Care and Use Committee of Nippon Veterinary and Life Science University (accession # 09-1, 10-3, 11-51, 12-42; representative researcher is D.H.).

Interictal scalp EEG under sedation with medetomidine

Initially, we performed interictal scalp EEG under sedation with medetomidine to characterize IIDs in the FSECs. The frequency and the distribution of IIDs of FSECs were analyzed and compared to that of control cats.

Animals and sedation procedure

Twenty-three FSECs (FSEC group) and 13 clinically healthy cats (as control group) that were maintained in the same conditions (individual cages, food and water supplied twice a day, room temperature/humidity at 22—24 °C/45—55%) were used. Cats of the FSEC group consisted of 15 males and 8 females (1.6 to 7.3 years old; mean age, 4.2 years; 2.6 to 4.8 kg in body weight; mean weight, 3.6 kg), while those of control group were 8 males and 5 females (0.5 to 13.5 years old; mean age, 5.3 years; 2.4 to 5.2 kg; mean, 3.7 kg). Seizure frequencies of FSECs from the 2-month video monitoring varied from 0 sz/month to 3 sz/month (mean, 0.7 sz/month).

All cats were restricted in feeding and drinking for 12 h before the EEG recording. Sedation was performed by intramuscular injection of 40 μg/kg of medetomidine (Domitor®, Zenoaq, Japan). During the EEG recording, all cats were administered lactated Ringer solution at 3.0 ml/kg/h intravenously, and their body temperatures were maintained at 37—38 °C by blanket and/or hot-water bags, if necessary. After the EEG recording, all cats were administrated 120 μg/kg of atipamezole (Antisedan®, Zenoaq, Japan) intramuscularly, which is an antagonist of medetomidine.

EEG recording

After the cats were sedated (approximately 15 min after the injection of medetomidine), they were positioned in prone position. Recording needle electrodes were placed subcutaneously on the bilateral frontal (LF/RF), parietal (LP/RP), temporal (LT/RT), and occipital (LO/RO) regions, and the reference and the ground electrodes were placed on the apex of the nose and neck, respectively. ECG was recorded simultaneously. EEGs were recorded using a digital EEG system (Neurofax® EEG-1200, Nihon Kohden, Japan), and the recording conditions were sample frequency at 1000 Hz, Hi-cut filter at 60 Hz (AC filter, on), and TC at 0.1. Total recording time was 20—30 min for each cat.

Evaluation of IIDs

All recorded EEGs were reviewed by an investigator who was blinded to the conditions of each case. To review the recorded EEGs, the montage was set up as reference (LF, RF, LP, RP, LT, RT, LO, RO) and bipolar (both side of F-P, P-O, F-T, T-O, T-P) derivations. For evaluating the frequency of IIDs, 10 min of stable recording were selected randomly from each recording. IIDs, including spikes, polyspikes, spike-and-waves, and sharp-waves, were counted and localized. If the IIDs appeared on multiple channels, the localization of IID was detected as the region of the highest amplitude or the fastest duration (reference derivation) and/or phase reversing (bipolar derivation). When IIDs were completely synchronized generally, all regions were given a 1 count. IIDs counts (frequency, IIDs/min) and distributions of each group were calculated and analyzed statistically by the Mann—Whitney *U* test and Tukey—Kramer test, respectively. In addition, IIDs frequency and distribution in the FSECs group were also analyzed for statistical correlations with gender (Mann—Whitney *U* test), body-weight and age (Spearman's rank correlation coefficient). The significant difference of all statistical analyzes was defined as $p < 0.05$.

Bemegride activation under sedation with medetomidine

To investigate the predisposition of epileptogenesis in FSECs, bemegride activation on scalp EEG under sedation with medetomidine was performed. Bemegride is a central nervous system stimulant, especially in the cortex, that is used historically to activate abnormal EEGs in the diagnosis of epilepsy and to induce convulsion with a certain