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Cognitive impairment and spontaneous epilepsy in rats with malformations of cortical development

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ABSTRACT

Purpose: To examine the cognition, spontaneous epilepsy, and electroencephalography (EEG) characteristics of rats with malformations of cortical development (MCD) and their use as an animal model for investigating the pathogenesis of intractable epilepsy and screening novel antiepileptic drugs.
Methods: An epileptic rat model of MCD was established with the F1 generation of pregnant rats after X-irradiation with 175 cGy (Group L), 195 cGy (Group M), or 215 cGy (Group H). Long-term video-EEG monitoring was used to record the seizures in the rats with MCD. Cognition was assessed with the Morris water maze. The EEGs were recorded and analyzed in the frontal and parietal lobes and hippocampi of adult rats. Finally, the brain tissues were processed for Nissl staining.
Results: The model groups exhibited markedly prolonged escape latencies and distinct decrements in the percent distance traveled in the target quadrant and platform-crossing frequency. These findings were dose-dependent. Frequent interictal epileptiform discharges were observed in the frontal and parietal lobes and hippocampi of adult rats, and their incidences were markedly higher in the model groups compared with that in the normal controls, with Group M having the highest incidence. Spontaneous seizures were observed in the model groups (mean incidence, 46.7%). The daily mean frequency of seizures and the incidence of spontaneous seizures were highest in Group M. Nissl staining revealed a dose-dependent pattern of hippocampal abnormalities, cortical and subcortical nodular heterotopia, and callosal agenesis in the model groups.
Conclusion: The 195 cGy dose was most appropriate for establishing an epileptic model of MCD with X-irradiation.

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1. Introduction

Malformations of cortical development (MCD), which are also known as cortical dysplasia and neuronal migration disorder [1–3], result in greatly heterogeneous brain anatomy alterations and clinical manifestations, and these abnormalities are related to many neurological and psychiatric diseases, including epilepsy, mental retardation, dyslexia, schizophrenia, and autism [1]. MCD has been accepted in recent years as one of the main causes of intractable epilepsy. The use of imaging and pathological and genetic techniques has shown that MCD is one of the causes of cryptogenic and symptomatic epilepsies [4]. Previously, a low incidence of spontaneous seizures (<20%) was reported in MCD models, and this was due to the short observation period (≤1 month) of rats with MCD [5]. In recent years, attempts by both Chinese and international researchers to establish models of MCD with X- and γ-irradiation in pregnant rats [6–9] were easily accessible and had high success rates, but an absence or an extremely low incidence of spontaneous seizures was observed in the models. This was also thought to be due to the short observation periods. Therefore, in this study, we used different doses of in utero X-irradiation in pregnant rats to establish an animal model of MCD and observed the incidence of spontaneous seizures with long-term (≥6 months) video-electroencephalography (EEG) monitoring. We examined spatial

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learning and memory, EEGs, and pathologies in these rats at different ages in order to investigate the behavioral and EEG characteristics of these rat models in detail. In so doing, we attempted to obtain an ideal rat model of MCD that shows a high incidence of spontaneous seizures in order to provide a foundation for investigations of the pathogenesis of intractable epilepsy and the screening of novel antiepileptic drugs.

2. Materials and methods

2.1. Grouping of experimental animals and establishment of the rat model of MCD with epilepsy

On embryonic day 17, eight healthy pregnant Sprague-Dawley rats were randomized into the following four groups: normal (N; 0 cGy; without X-irradiation; $n = 2$), low dose (L; 175 cGy; $n = 2$), medium dose (M; 195 cGy; $n = 2$), and high dose (H; 215 cGy; $n = 2$). As previously described [7–10], the animals were restrained in a 25-cm × 20-cm × 15-cm custom-made irradiation box, and the box was placed in a Elekta Precise Linear Accelerator (Elekta AB, Stockholm, Sweden) for in utero irradiation with 0, 175, 195, or 215 cGy. The X-irradiation was delivered at a dose rate of 200 MU/min. The mean irradiation time was 0 min for the N group and 1.7, 1.5, and 1.3 min for the L, M, and H groups, respectively. The rats' offspring (F1 generation) were assigned to Group N or the MCD model groups (Groups L, M, and H). Five rats were randomly selected from each group for the experiments. All of the procedures were performed in strict compliance with the relevant provisions of the Regulations for the Administration of Affairs Concerning Experimental Animals and with animal ethics.

2.2. Behavior observation and seizures

All of the groups of F1 generation rats were dynamically monitored daily over 24 consecutive hours in natural light with a net-hard disk video recorder (Network Video Recorder HD4201; KINO KN-1352, Shenzhen Univision Electronic Engineering Ltd, Shenzhen, Guangzhou, China). All rats were monitored for 183 days (six months). Spontaneous seizures were observed in the F1 generation rats. Statistical analyses were conducted on the data on Racine stage-3 and above seizures [11]. All of the groups were analyzed for the number of rats with seizures, the mean seizure duration, and the mean daily seizure frequency.

2.3. Morris water maze

Information acquisition and processing in the Morris water maze were conducted with a Morris200 Video Tracking System (Chengdu Taimeng Science and Technology Co., Ltd., Chengdu, Sichuan, China). The Morris water maze consisted of a circular pool with a diameter of 120 cm and height of 80 cm. The inner wall of the pool was painted white. Four equidistant insertion points divided the pool wall into four quadrants. A white circular platform (diameter, 5 cm; height, 20 cm) was placed in the very center of the target quadrant, which was defined as the fourth quadrant. The water temperature was maintained around 22 °C in each trial, and the water level was 1.5 cm higher than the platform. The total sample is 20 and the sample size of each group is 5. Five immature [postnatal day (P) 27–31], adolescent (P47–51), and mature (P86–90) rats were selected from the F1-generation rats in each group (Groups N, H, M, or L) and tested. For each group, hidden platform trials were performed on the first four days, and the probe trial was performed on Day 5. Escape latency, platform crossing frequency, and percent distance traveled in the target quadrant were the measures that were analyzed.

2.4. Intracranial EEG recordings

The EEGs were measured in the mature rats (P86–90). The animals were anesthetized with an intraperitoneal injection of 3.5% chloral hydrate (1.0–1.5 mL/100 g). The rats were then fixed in a stereotaxic apparatus and placed in a shielding box. The bregma, coronal suture, and lambdoid suture were exposed after disinfection. The bregma was set as the zero point, and standard electrode implantation was performed in both frontal lobes (F: A, 1.0 mm; L/R, 2.0 mm; D, 1.0 mm from bregma), parietal lobes (P: A, 2.0 mm; L/R, 2.0 mm; D, 2.0 mm from bregma), and hippocampi (H: A, 3.0 mm; L/R, 2.5 mm; D, 3.5 mm from bregma) on both sides. The distance between the anterior and posterior fontanelle (M) was measured in the rats in order to calculate the correction factor, $K = M/9.0$, and the actual coordinate was equal to each standard coordinate times K [12]. The EEGs were acquired and analyzed with a RM6240C multichannel physiological signal acquisition and processing system (RM6240C, Chendu, China). Each site was measured and analyzed for 30 min. Sharp activities, spikes, sharp (spike)-and-wave complexes, and polyspike-and-slow-wave complexes with ictal epileptic durations over 20 ms and amplitudes more than 5 times the background EEG activity were defined as EEG epileptiform discharges or epileptic activities [13]. The main outcome measure was the seizure frequency per minute.

2.5. Histopathology

All of the animals were perfused with a 4% paraformaldehyde phosphate-buffered solution. Their brains were then harvested and cryosectioned. With reference to the stereotaxic atlas of the rat brain [13], each brain, including the hippocampus, was cryosectioned in the coronal plane posterior to the septal region (2–3 mm). Each section was 40 μm in thickness. One out of every 10 sections was used for Nissl staining and examination.

2.6. Diagnostic criteria of MCD

All of the diagnostic criteria of MCD include gray matter heterotopia, focal cortical dysplasia (FCD), and tuberous sclerosis [14–16].

2.7. Statistical analysis

All of the data were statistically analyzed with SPSS17.0 software (IBM Corporation, Armonk, NY, USA). The measurement data are presented as mean ± standard deviation. One-way analysis of variance was used to compare multiple groups with normal distributions. Independent-sample t-tests were used for the inter-group comparisons. P values less than 0.05 were considered statistically significant.

3. Results

3.1. Survival of the MCD model rats

Parturition did not differ significantly among the groups of pregnant rats, and it was not related to the irradiation dose. Compared to the natural mortality of young rats, the rates of mortality increased with increasing irradiation doses, and the mortality was greatest in Group H (29.2%).

3.2. Behavioral analysis

Dynamic video recordings were conducted for 24 h/day for six months (total of 183 days). The rat behaviors were examined in detail every five days (total of 37 days). The rat behavior exhibited

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