Dissociation between *in vitro* and *in vivo* epileptogenicity in a rat model of cortical dysplasia

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ABSTRACT – **Objective.** Malformations of cortical development are frequent causes of human refractory epilepsy. The freeze-lesion model in rats shows histopathological features similar to those found in human polymicrogyria. Previous studies reported *in vitro* hyperexcitability in this model, but *in vivo* epileptogenicity has not been confirmed.

**Methods.** Neocortical freeze lesions were induced in Sprague-Dawley rat pups (n = 10) on postnatal day 0 or 1 (P0/P1). Sham-operated animals served as controls (n = 10). On P60, animals were implanted with epidural electrodes for long-term video-EEG monitoring (4 weeks). The threshold for pentylenetetrazol-induced seizures was determined. Animals were sacrificed and brain sections processed for histological staining and *in vitro* electrophysiological recordings. Epileptiform field potential repetition rate, amplitude and integral were compared between slices containing a cortical freeze lesion, and slices from sham-operated rats.

**Results.** No interictal spikes and no electrographic or clinical seizures occurred in either group. The median threshold for pentylenetetrazol-induced seizures was 60 mg/kg for lesioned, and 45 mg/kg for control animals (difference not significant). No spontaneous epileptiform field potentials were recorded from either freeze-lesion or control slices bathed in normal, artificial cerebrospinal fluid (ACSF). Upon omission of Mg\(^{2+}\) from the bath, epileptiform field potentials were elicited that showed a significantly higher burst integral in the freeze lesion slices compared to control slices.

**Conclusion.** Neocortical freeze lesions induced in newborn rat pups show histological characteristics reminiscent of human cortical dysplasia. Brain slices containing neocortical freeze lesions display hyperexcitability *in vitro*, but the same lesion does not appear to show spontaneous epileptogenicity *in vivo*.

**Key words:** cortical dysplasia, freeze lesion, electroencephalography, epileptogenicity
Malformations of cortical development (MCD) are among the most common pathological causes of medically refractory focal epilepsy in patients undergoing surgical resection (Annegers, 1994, Tassi et al. 2002). Post-surgical seizure-free outcome is less favorable in patients with MCD than in patients with other lesions, e.g. hippocampal sclerosis (Bast et al. 2006, Hamiwka et al. 2005, Lüders and Schuele, 2006, Wyllie et al. 1998).

However, reliable data about the pathophysiological mechanisms resulting in epilepsy in these patients remain scarce. Several animal models of MCD have been investigated, such as the focal freeze lesion model (Dvorak and Feit, 1977, Rosen et al. 1992), the in utero alkylating (MAM) model (Baraban and Schwartzkroin, 1995), and the in utero irradiation model (Roper et al. 1995), as well as genetic models (Amano et al. 1996; Chae et al. 1997). Among the injury-inducing models, spontaneous but rare seizures have only been demonstrated in the in utero irradiation and alkylating models (Kellinghaus et al. 2004, Kondo et al. 2001, Möddel et al. unpublished observations).

In addition, the anatomical changes in these 2 in utero models are multifocal (affecting both the archihippocampal formations and neocortex) and only remotely resemble the characteristics of focal cortical dysplasia in humans (Prayson and Estes, 1995, Taylor et al. 1971). In contrast, neocortical lesions induced by application of a freeze metal probe on neonatal rat pup skull (“freeze lesions”) share several anatomical and histological features with focal polymicrogyria in humans (Dvorak et al. 1978, Rosen et al. 1992). Freeze-lesioned neocortical brain slices have been extensively studied in vitro and were found to display hyperexcitability (Chevassus-Au-Louis et al. 1999, Jacobs et al. 1999a, Redecker et al. 2005). However, long-term, video electroencephalographic (EEG) recordings have not yet been performed using this model. Holmes (Holmes et al. 1999) found no difference in afterdischarge threshold and kindling rate in young freeze-lesioned rats as compared to controls. Thus, the clinical relevance of the anatomic and in vitro findings remains unclear.

This study was designed to investigate whether rats with neocortical freeze lesions display in vivo epileptogenicity, and to study the threshold of their response to a seizure-provoking agent (as compared to control animals). Furthermore, we aimed to correlate the in vivo observations with histological and in vitro electrophysiological findings.

**Methods**

**Animals**

Neocortical freeze lesions were induced in rats as initially described by Dvorak and Feit (Dvorak and Feit, 1977) with slight modifications. Newborn (post-natal day 0 or 1; PN0/1) Sprague-Dawley rat pups (n = 16; parent animals from Charles River, Wilmington, MA, USA) were anesthetized by hypothermia (5 minutes on dry ice covered by a plastic cover). A 6-7 mm incision was made in the skin overlaying the fronto-parietal cortex. After exposing the skull, a cold probe was placed on the skull covering the left primary motor and somatosensory cortex on three separate points along a line approximately 1 mm lateral from the midline for 8 seconds per contact. The cold probe consisted of a stainless steel rod of approximately 100 mm length and a contact surface of approximately 2 x 1 mm. It was cooled to -60°C in a methanol-filled centrifuge tube placed in dry ice. Following this procedure, the skin was closed with a single suture, and the animals were placed under a heat lamp and returned to their mother after 30 minutes. The control animals (n = 12) were treated in the same way with the exception that the steel probe was at room temperature (21-23°C). Rat pups remained with their mothers until they were weaned at PN21. All animals were maintained on a 12-hour light-dark cycle with food and water available ad libitum throughout the whole time, including the EEG recordings. The research protocol was approved by the Cleveland Clinic Foundation institutional animal care and use committee (IACUC).

**Electrode implantation**

After PN60, stereotactic electrode implantations were performed in 10 freeze-lesioned rats (8 males, 2 females) and 10 control rats (8 males, 2 females) under pentobarbital anesthesia (50 mg/kg, intraperitoneal, (i.p.)), using the Kopi stereotactic frame according to coordinates that were adapted from Paxinos’ stereotactic atlas of the rat brain (Paxinos, 1986). After preparation of the skull, stainless steel screw electrodes (MX-0090-2, Small Parts Inc., Miami, Florida) were placed bilaterally on the dura mater of the frontal cortex (LF: left frontal cortex, RF: right frontal cortex, A: 1.0 mm, L: ± 2.5 mm from the bregma) and the parietal cortex (LP: left parietal cortex, RP: right parietal cortex, P: 2.0 mm, L: ± 2.5 mm from the bregma). An additional screw electrode was placed in the frontal sinus and served as a reference recording electrode. The electrodes were connected to a plastic plug (SMP-06V-BC, Japan Solderless Terminal MFG., Tokyo, Japan) which was fixed to the skull using dental cement (Hygenic repair resin, Hygenic, Akron, OH, USA). In order to maintain electrodes and plugs in position for long-time monitoring, an extracranial fixation technique was employed (Mascott et al. 1994): a stainless steel suture (0.1 mm diameter) was wrapped around the posterior limb of the zygomatic arches after careful preparation of the temporalis muscles off the lateral skull surfaces. The steel suture was then embedded in the dental cement to anchor the electrodes and plug into the zygomatic arches. Rats were left unrestrained for 1 week for recovery from surgery before prolonged EEG recordings were performed.
Continuous digital EEG recordings from freeze-lesioned rats and the sham-operated control animals were performed in five custom-made, electrically shielded boxes with free access to food and water. Implanted recording electrodes were connected to pendulous electrocorticographic rings (MRS 35-06P, M-T GIKEN, Tokyo, Japan). This arrangement allowed the acquisition of real-time low-noise EEGs of the freely moving animals 24 hours per day. Monitoring of the rats was performed in 24-hour periods of recordings alternating with 24-hour periods without EEG recordings. The freeze-lesioned animals underwent a total of 28 days of monitoring (14 days before and 14 days after seizure threshold determination), the control animals were monitored for a total of 15 days (1 day before and 14 days after seizure threshold determination).

Five-channel digital EEG recordings were performed using the Vangard system (Lamont, Madison, WI, USA), consisting of a recording Hewlett-Packard workstation and a similar review system. A total of five rats were monitored simultaneously at any given time. EEG filter settings were: 1 Hz (low frequency filter) and 70 Hz (high frequency filter), sampling frequency was 100 Hz. Each cage was monitored with a digital video-camera fixed just in front of the cage. The time relationships between EEG events and clinical motor fits were assessed using a split-screen video monitoring system. The simultaneously-obtained EEG and video data were digitally stored in the hard drive of the recording workstation and later transferred to magneto-optical disks (MO).

**Data analyses**

The digitized EEG signals were reformatted to referential and bipolar montages. The EEG was analyzed by visual inspection for the presence of interictal and ictal epileptic activities. Interictal spikes were defined as sharp potential fluctuations with durations of between 20 and 150 ms and amplitudes of at least 5 times the background EEG activity. The interictal spikes were mapped to the area of maximum amplitude (on referential montages) and to the electrode of phase reversal (on bipolar montages) according to their location. The rates of occurrence of all interictal spikes were calculated and expressed as spikes/hour.

As previously described, EEG seizures were defined as rhythmic spiking or paroxysmal fast activity (15-25 Hz) that evolved in amplitude and/or frequency and lasted for at least 10 seconds. The rates of occurrence of ictal activity were calculated and expressed as seizure/day.

Behavioral seizures during the determination of the threshold for PTZ-induced seizures were graded according to the clinical manifestations on a scale modified from Racine (Racine, 1972): Grade 1: facial twitching, Grade 2: facial and forelimb twitching, Grade 3: axial twitching, Grade 4: generalized tonic-clonic seizure with preservation of posture, Grade 5: generalized tonic-clonic seizure with loss of postural balance.

Statistical testing was performed with a commercially available software package (SPSS Inc., Chicago, Illinois, USA). We used the Wilcoxon rank-sum test for inter-group comparison of interval- or ordinal-scaled data. Categorical variables were compared with the Chi-square test or Fisher’s exact test (2 x 2 tables). Significance levels were set at $p = 0.05$ (two-tailed tests).

**Determination of the threshold for PTZ-induced seizures**

The implanted animals ($n = 10$ per group) received a subthreshold PTZ dose of 10 mg/kg i.p. If there was no seizure of at least Grade 4 after 10 minutes, additional injections in 5 mg/kg PTZ increments were given once every 10 minutes until a seizure of at least Grade 4 occurred. The total dose needed to elicit a seizure of at least Grade 4 was defined as the threshold PTZ dose.

**Histopathological examination**

At the end of the EEG acquisition periods, rats were deeply anesthetized with pentobarbital (60 mg/kg, i.p.) and perfused intracardially with 4% paraformaldehyde (PFA) in phosphate-buffered solution (PBS, pH 7.4). The brains were saved in 4% PFA for 2 days and then transferred to 20% sucrose for 48 hours before processing. Serial sections (50 µm) were cut in the coronal plane using a cryostat. One out of 10 sections was cresylved with violet (CV) Nissl stained for histological examinations. Sections from the animals from both groups were analyzed regarding the presence or absence of a typical pathological lesions, and other histological abnormalities.

**Slice electrophysiology**

Freeze-lesioned ($n = 5$) and control ($n = 5$) rats (age 110-130 days) were deeply anesthetized with isoflurane, perfused with ice-cold preincubation artificial cerebrospinal fluid (pACSF; containing [in mM]: NaCl 124; KCl 3; CaCl$_2$ 1; MgCl$_2$ 1.4; NaHCO$_3$ 26; KH$_2$PO$_4$ 1.25; glucose 10), and then decapitated. The brains were quickly removed from the skull and immediately placed into ice-cold, oxygenated pACSF. The brainstem and cerebellum as well as the frontopolar regions were dissected. The central section of the cerebral hemisphere containing the macroscopically visible, freeze-lesion-induced microsulcus (or, in controls, the central section of the left hemisphere), including the sensorimotor cortical regions, was subsequently cut in the coronal plane, into slices of 400-500 µm thickness using a vibratome. Slices were kept in a preincubation chamber containing oxygenated (95% O$_2$: 5% CO$_2$) pACSF at room temperature and pH 7.4 for one hour. After 60 min of preincubation, the Ca$^{2+}$ concentration was increased to 2 mM to reach ion concentrations comparable to in vivo conditions of artificial cerebrospinal fluid,
Results

Histopathological abnormalities

The application of a freeze probe to the skull on PN0/1 produced similar, typical focal structural cortical abnormalities in all animals (n = 16) including those that were used for EEG recordings. The abnormalities consisted of a longitudinal microgyrus located in parallel to the midline with a length of 2-5 mm, which was clearly visible macroscopically (figure 1A) and appeared as a fissure spanning about two thirds of the cortical thickness on low-magnification microscopic images acquired from brain slices during field potential recordings (figure 1B) as well as from cresylecht violet-stained histological sections (figure 1C). The microscopic architecture was somewhat variable. Two-, three- or four-layered cortices, with a varying degree of loss of normal cortical architecture, were seen. In the most severe form, layers IV-VI were completely destroyed and substituted by scarring. No histopathological abnormalities were seen in the sham-operated rats (n = 12) (figure 1D).

Long-term video-EEG monitoring

All freeze-lesioned rats were monitored for 14 days before the determination of the seizure threshold to look for spontaneous seizures or epileptiform discharges. In addition, all control rats were monitored for 24 hours before the PTZ injection. No seizures or spikes were recorded in any animal of either of the groups during the evaluation period prior to the PTZ injection. One of the rats suffered an injury during the PTZ-induced seizure and was sacrificed immediately afterwards. The other nine freeze-lesioned rats as well as the ten control animals were monitored for 14 days after the threshold determination, beginning immediately after the clinical seizures had occurred. During the first twelve hours following the PTZ-induced seizures, generalized spikes were seen in all animals of both groups. We did not see any differences regarding frequency, localization or morphology between the animals of both groups. The frequency of the spikes decreased over a time-period of 10-12 hours, until no further epileptiform discharges were observed 12 hours after the PTZ injections. We considered these discharges to be an acute PTZ effect and excluded the first 12 hours after PTZ injection from further analyses. Thereafter, no spikes and no seizures were observed in any of the animals in both groups (figure 2). The recordings of the two groups showed normal alpha-background activity as well as normal sleep-wake cycles. There was no focal slowing and no evidence for other EEG abnormalities in either group.

Threshold for PTZ-induced seizures

PTZ was injected step-wise until the animals developed a generalized tonic-clonic seizure (stage IV or V). Seizure stages I or II were reached after injection of a median dose of 37.5 mg/kg body weight in the freeze-lesioned rats, and 40 mg/kg in the control animals. A generalized tonic-clonic seizure (stage IV or V) was elicited after injection of a median dose of 60 mg/kg in the lesioned group, and 45 mg/kg in the control group. The differences were not statistically significant. There were also no significant differences in age or body weight between both groups at the time of the PTZ injection (table 1). Practical and technical issues precluded EEG-recording during the threshold determination for PTZ-induced seizures.

In vitro electrophysiology

No spontaneous epileptiform field potentials (EFP) were recorded in either hemispheric brain slices containing a cortical freeze lesion (FL slices; 5 animals, one slice per animal) or in brain slices from sham-operated rats (CTRL slices; 5 animals, one slice per animal). Omission of Mg\(^{2+}\) ions from the bath reliably elicited EFP in both FL and CTRL slices. In FL slices, EFP were simultaneously recorded from the cortex directly adjacent to the freeze-lesion-induced microsulcus (LES, see figure 2B), as well as from the cortex 8 mm lateral to the microsulcus (LAT). EFP occurred synchronously at both recording sites, although the temporal relationship between the initial negative spikes at LES and LAT positions was inconsistent.
Discharges recorded from LES and LAT positions did not differ in any of the parameters measured (latency, repetition rate, maximum amplitude, burst integral). The latency time to first appearance of epileptiform activity was 24 +/- 6 min for the FL slices (n = 5) and 33 +/- 8 min for the CTRL slices (n = 5). The difference was not significant (p = 0.21).

EFP recorded from FL slices occurred at an average repetition rate of 3.3 ± 0.6 min⁻¹, which was not different from the EFP repetition rate in CTRL slices (3.3 ± 0.4 min⁻¹; figure 3A, B; left traces). In both FL and CTRL slices, single discharges consisted of an initial negative spike, followed by a repolarization phase (figure 3A, B; right traces). In FL slices, the repolarization phase was prolonged, with superimposed afterdischarges, giving the discharges the appearance of ictal-like events (figure 3A; right traces). In CTRL slices, the repolarization phase was shorter; these discharges were of the interictal type (figure 3B; right trace). EFP in FL slices had a slightly, although not significantly, higher, maximum burst amplitude than EFP recorded from CTRL slices (480 ± 130 μV, compared to 210 ± 60 μV, p = 0.1). The average burst integral was significantly higher in FL slices than in CTRL slices (1220 ± 324 μVs, compared to 261 ± 117 μVs, p = 0.02).

Discussion

Our current results show dissociation between the expression of in vitro hyperexcitability and the occurrence of in vivo epileptogenicity in pathologically-confirmed dysplastic neocortical lesions in the rat. In our study, we were able to consistently induce a focal cortical lesion by applying a freeze probe to the skull of newborn rat pups. The histological appearance and structure of these lesions are consistent with the findings originally reported Dvorak.*

In spite of the clear lesion, the animals did not develop spontaneous seizures, and long-term EEG recording did not show any epileptiform discharges in the absence of a seizure-provoking agent. Several animal models of focal epilepsy show that not all animals receiving the acute injury actually develop seizures (Bertram and Cornett, 1994, Kellinghaus et al. 2004, Kondo et al. 2001, Tanaka et al. 1985, Möddel et al. unpublished observations). Correspondingly, not all human patients with MCD develop epilepsy, even if the malformation is severe (Bertram and Cornett, 1994, Leventer et al. 1999), and healthy relatives of epileptic patients with MCD frequently also have subtle cortical abnormalities (Merschhemke et al. 2003). We may have monitored an insufficient number of animals for an insufficient amount of time. Nevertheless, the absence of spontaneous seizures (and spontaneous unprovoked interictal spikes) in animals harboring clear

Table 1. Induction of seizures by pentylenetetrazole (PTZ) injection in freeze-lesioned, compared to sham-operated control rats.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Freeze-lesioned rats (n = 10): median (range)</th>
<th>Controls (n = 10): median (range)</th>
<th>Mann-Whitney U-Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at PTZ injection</td>
<td>105 days (90-120 days)</td>
<td>97.5 days (90-105 days)</td>
<td>p = 0.30</td>
</tr>
<tr>
<td>Weight at PTZ injection</td>
<td>405 g (305-510 g)</td>
<td>418 g (255-505 g)</td>
<td>p = 0.91</td>
</tr>
<tr>
<td>Threshold for seizure stage II/III</td>
<td>37.5 mg/kg (25-70 mg/kg)</td>
<td>40 mg/kg (35-45 mg/kg)</td>
<td>p = 0.26</td>
</tr>
<tr>
<td>Threshold for seizure stage IV/V</td>
<td>60 mg/kg (35-80 mg/kg)</td>
<td>45 mg/kg (40-65 mg/kg)</td>
<td>p = 0.07</td>
</tr>
</tbody>
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Figure 2. Representative normal EEG recordings at resting stage at approximately day 10 after PTZ-injection: A) freeze-lesioned rat, B) control rat. LF = left frontal, RF = right frontal, LP = left parietal, RP = right parietal, REF = reference electrode (frontal sinus).
neocortical lesions which show in vitro hyperexcitability suggests that the development of behavioral seizures may require additional factors other than regional (focal) excitability changes.

Induction of a generalized tonic-clonic seizure by PTZ did not elicit spontaneous epileptiform activity beyond 12 hours after injection. Decreased threshold for PTZ-induced seizures has been demonstrated in different animal models of focal neocortical epilepsy, e.g. the cobalt oxide model in cats (Hocherman and Reichenthal, 1983) and the alumina-gel model in monkeys (Mayanagi and Walker, 1974), and also in a mouse model of cortical dysplasia (Gabel and LoTurco, 2002). However, the threshold for PTZ-induced seizures was not decreased in the freeze-lesioned rats. These results are consistent with those reported by Holmes (Holmes et al. 1999), who showed no difference in afterdischarge threshold and kindling rates between freeze-lesioned and control rats using amygdala-kindling. In contrast to the unchanged threshold for PTZ-induced seizures, there is a report of decreased seizure threshold for hyperthermia-induced seizures in immature, freeze-lesioned rats (Scantlebury et al. 2004). However, animals lesioned on postnatal day 1 were used, whereas our animals were lesioned within 30 hours after birth, most of them within the first 18 hours because they were born during the night and the procedure took place the following morning. In a study differentiating between lesions performed on P0 versus P1 found that animals lesioned on P0 showed decreased incidence of epileptiform activity as mature rats, compared to animals treated on P1 (Jacobs et al. 1999a), probably due to less extensive retargeting of fibers into the epileptogenic zone if the lesion was induced earlier.

In contrast to the in vivo findings that showed no evidence of spontaneous or differentially drug-induced epileptogenicity, our in vitro studies confirmed the presence of hyperexcitability in hemispheric brain slices of freeze-lesioned animals, with significantly higher epileptiform field potentials (EFP) burst integrals in FL slices, as compared to CTRL slices. Comparison of EFP recorded from the cortex directly adjacent to the freeze-lesion induced microsulcus (LES), with EFP recorded from the cortex 8 mm lateral to the microsulcus (LAT), showed no differences in any of the parameters measured. Jacobs (Jacobs et al. 1999b, Jacobs et al. 1999c) found that the epileptogenic region is not located within the lesion proper, but within 0.5-2.5 mm lateral to the lesion, and remains hyperexcitable even if the lesion itself is removed. They suggested that thalamo-cortical and intracortical afferents originally targeting neurons within the lesioned area may

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**Figure 3.** Zero-magnesium-induced epileptiform field potentials (EFP) recorded from coronal brain slices from freeze-lesioned rats (FL slices; A), compared to control animals (CTRL slices; B); 10 min periods depicting EFP repetition rate (left traces); single EFP bursts displayed at a higher time resolution (right traces). A) Field potentials (FP) recorded from a FL slice. FP were simultaneously recorded from the perilesional cortex in the immediate vicinity of the microsulcus (LES), and from a site 8 mm lateral of the microsulcus (LAT). Zero-magnesium-induced EFP were ictal-like, with an initial negative spike, followed by a prolonged repolarization phase with superimposed afterdischarges. EFP recorded from LES and LAT positions did not differ in terms of repetition rate, maximum amplitude, or burst integral. B) FP recorded from a CTRL slice. Zero-magnesium-induced EFP were of the interictal-like type, consisting of an initial negative spike and a slow repolarization phase which was significantly shorter than in FL slices. Calibration bars in B apply to all traces.
have been redirected to regions adjacent to the lesion, leading to hyperinnervation with excitatory connections (Jacobs and Prince, 2005). However, our recordings used the zero-magnesium model of epileptiform activity (Avoli et al. 1987, Avoli et al. 1991, Mody et al. 1987). The low-magnesium model induces robust epileptiform activity in both normal and lesioned cortex by augmenting the NMDA-component of the excitatory postsynaptic potential (EPSP), without pharmacological blockade of synaptic receptors (i.e. GABA-A receptors in the bicuculline model). In vivo conditions are therefore more closely mimicked, as recurrent and lateral inhibition remains intact. In addition, low-magnesium activity induces postsynaptic calcium influx, resulting in activation of the same calcium-dependent, second messenger mechanisms that underlie activity-dependent neuronal plasticity. Redecker (Redecker et al. 2005) used optical imaging to investigate the epileptiform activity of freeze-lesioned slices produced by the zero-magnesium model. In contrast to the spontaneous activity, epileptiform potentials induced by the omission of magnesium always originated from the more superficial layer of the lesion itself. Zilles (Zilles et al. 1998) reports widespread changes of GABA(A)- and non-NMDA glutamate receptor densities in the lesioned hemisphere including the lesion, whereas changes in GABA(B) and NMDA glutamate receptors were confined to the dysplastic cortex itself. This specific pattern of changes of receptor densities may be responsible for the increased excitability of the lesion itself when magnesium is omitted from the bath solution. Thus, following major changes in general brain excitability as modeled here, different generators of epileptiform discharges may be active. More studies are needed to identify the role of subcortical structures and/or other metabolic (focal or systemic) adaptations of the affected (and potentially epileptogenic) tissue in the development of epileptogenesis.

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