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SHORT RESEARCH ARTICLE

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Diurnal burden of spontaneous seizures in early epileptogenesis in the post-kainic acid rat model of epilepsy

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Abstract

Patients with epilepsy can experience diurnal seizure patterns. However, few studies in rodent models of temporal lobe epilepsy (TLE) routinely quantify the diurnal pattern of spontaneous recurrent seizures (SRS), and those that have conducted such assessments used small groups. This study thus aimed to define whether there was a diurnal pattern of SRS in the early phases of epileptogenesis in a large cohort (n = 40) of post-kainic acid (KA)-induced status epilepticus (SE) male Sprague Dawley rats. Rats were monitored by continuous 24/7 video-EEG in two-week epochs up to 6 weeks post-KA-induced SE. The total number of SRS by 6 weeks post-SE correlated to body weight at the time of SE insult (R^2 = .1465, P = .0143). The total number of spontaneous behavioral and electrographic seizures, seizure severity, and seizure burden was recorded during lights ON (light) or lights OFF (dark) phases. All measures significantly increased with time post-SE; we detected significantly more seizures during the lights OFF phase of the post-SE monitoring periods. Moreover, a subset of rats demonstrated marked seizure preference in the lights OFF phase. Our study confirms that a diurnal pattern of SRS is variably detectable in early epileptogenesis in this model of TLE.

KEYWORDS

diurnal seizure patterns, Kainic acid, rat, status epilepticus, temporal lobe epilepsy

1 | INTRODUCTION

Epilepsy is a chronic neurological condition characterized by spontaneous recurrent seizures (SRS). SRS can occur more frequently during specific times of day or night in humans;[1–3] that is, some patients experience peak epileptiform activity at night or the late afternoon.[1,4] However, it is less clear to what extent rodent models of acquired temporal lobe epilepsy (TLE) also demonstrate similar SRS periodicity, especially in early epileptogenesis. Some studies have found an intrinsic SRS rhythm in various rodent TLE models,[5–9] whereas others have reported no circadian pattern.[10] Further, studies that have assessed SRS periodicity were often conducted with small cohorts or only monitored SRS for brief durations in fully established epilepsy.[6,7,9–11] Monitoring well after epilepsy is established does not inform on the potential to mitigate disease severity through pharmacological intervention shortly after the inciting epileptogenic event. Most drug discovery programs for epilepsy currently focus on the effect of treatments on established SRS,[12] rather than on early metrics

of disease onset.[13] Understanding the behavioral changes associated with early epileptogenesis is critical to accurately interpret disease modification studies.

Systemic kainic acid (KA) administration to rats is an accepted model of TLE, wherein an initial status epilepticus (SE) insult is followed by a sustained latent period that subsequently gives way to SRS, that is, epilepsy.[14] The post-KA-induced SE model of TLE is frequently used in the discovery of investigational treatments for epilepsy, including by the NINDS Epilepsy Therapy Screening Program (ETSP).[12,15] Yet, few studies routinely assess the diurnal periodicity of SRS in this model. No study has yet quantified diurnal seizures in early epileptogenesis, for example, 0-6 weeks post-SE, a time when investigational drugs may be administered in the search for disease-modifying agents.[13] In this regard, understanding the diurnal patterns of SRS in early epileptogenesis in the post-KA SE model of TLE is critical to potentially uncover chronopharmacological effects and further assess the suitability of this model for drug discovery. The main goal of this present study was to thus more completely characterize the early phases of epileptogenesis, better delineate SRS variability, and define the diurnal patterns of SRS in the post-KA SE rat model of TLE to support disease modification studies.

2 | METHODS

2.1 | Animals and EEG recording electrode implant surgery

Male Sprague Dawley rats (n = 82 total underwent surgery; 126-150 g on order, 4-6 weeks old, Charles River Laboratories strain 001) were implanted for chronic video-EEG (vEEG) recording 7-10 days prior to SE.[16,17] Rats weighed 234 ± 33 g at surgery (not shown). Stainless steel screw 3-channel electrodes (MS333/1-A; Plastics One) were implanted left and right of midline, and an additional ground electrode was placed rostral to the posterior skull ridge. Following surgery, rats were provided oral analgesic (Rimadyl, Bio-Serv, MD150-2) and recovered for 1 week in individual Plexiglass chambers before KA SE. Animals were housed in a specific pathogen-free vivarium with ad libitum access to irradiated chow (Picolab 5053) and filtered water. The University of Washington Institutional Animal Care and Use Committee approved all animal use.

2.2 | Kainic acid SE induction

Implanted rats were acclimated to the testing room for a minimum of 1 hour prior to repeated KA (Tocris, catalog #0222 dissolved in 0.9% normal saline) administration to induce SE. At time = 0 hour, rats were administered 10 mg/kg (ip) KA; 1 hour later, a subsequent injection of KA (5 mg/kg) was administered. A 5 mg/kg dose of KA was then administered every 0.5 hour (T = 1.5, 2.0 hour, etc) until onset of sustained electrographic spiking and generalized convulsive seizures (at least two Racine stage 4/5 seizures within 30 minutes), indicative of sustained SE.[16] Electrographic SE (ESE) was defined as continuous high-frequency EEG spiking with little to no interruption. Animals were vehicle-treated control rats from investigational drug studies contracted by the NINDS ETSP; thus, data obtained from these rats were pooled over the course of 3 years from multiple investigational drug studies. The severity and frequency of convulsive seizures were continuously monitored throughout SE (1.5 hours post-SE onset). At the conclusion of SE monitoring, rats were given 3 mL of sterile lactated Ringer's solution (subcutaneous) and provided supplemental chow moistened with pediatric electrolyte solution to restore SE-induced fluid loss. No pharmacological intervention was administered to stop behavioral or ESE. Animals were weighed daily after KA SE for up to 7 days post-SE and observed for signs of distress, but thereafter handled no more than 1x/2-weeks.

2.3 | Chronic vEEG monitoring

A total of 40 rats (48.8%) survived the surgery, KA SE insult, and retained head-caps throughout long-term vEEG monitoring post-SE. Rats were vEEG monitored 24/7 for 2 weeks (0-2 weeks post-SE), then had a 2-week recording-free period, before a second 2-week recording period (4-6 weeks post-SE). Rats were thus monitored up to 6 weeks post-SE; the early epileptogenesis period preceding the onset of high-frequency SRS expression.[11,17] Electrographic and behavioral seizures were recorded by vEEG during each 2-week session using a customized data acquisition system with an MP160 and EEC100 (Biopac).[18] The identification of electrographic and behavioral seizures from vEEG footage was conducted offline following in-life studies by a blinded investigator and using automated Assyst EEG analysis software (KaosKey). All seizures were independently confirmed by a secondary reviewer.

Seizures that occurred in potential "clusters" were scored as individual events along the Racine scale. Because there is no consensus definition of seizure clusters in rodent epilepsy models, but only the observation that seizures can arise in clear bouts within the rat post-KA SE model,[19] no specific definition of seizure "clusters" was applied to the analysis. The vEEG files and seizure scores were re-evaluated for rats that had an abnormally high seizure burden, defined as more than two generalized seizures in a single 12-hour recording period. In total, nine rats met these criteria (not shown). It

was then determined whether, in the instances of multiple seizures in a single recording session, events were "clusters" of multiple seizures in short succession, or whether events were distinct seizures separated by >20 minutes over the course of a 12-hour period. There were several days in the 4-6 weeks post-SE session where these nine rats in particular had 12-hour recording periods with multiple generalized seizures (ie, stage 4/5; not shown). All of these events were included in analysis as individual seizures.

2.4 | Seizure tracking during lights ON vs lights OFF phase

Seizures were reviewed and determined to have occurred in either lights ON (06:00-20:00; 14 hours) or OFF (20:00-06:00; 10 hours). Using these vEEG double-confirmed seizures, the lights ON/OFF seizure burden and number of events were then normalized to the total duration of light phase (14:10 hours) and binned for each 2-week session by an independent, tertiary blinded investigator. Seizure burden is an important metric of disease severity and was assessed by Racine stage seizure severity x number of seizures. Data are represented on the same graphs but analyzed separately for each 2-week session (Figure 2A-C).

2.5 | Statistics

The amount of KA to induce SE was correlated to body weight at SE induction. Body weight was also correlated to the total number of confirmed seizures during the 2-week monitoring sessions. Seizure burden and number of events during lights ON vs lights OFF phases was binned and compared by Wilcoxon signed-rank test or paired *t* test, respectively, with each rat serving as its own control between the 0- to 2- and 4- to 6-week monitoring period. The number of Racine stage seizures in the light ON/OFF phase at 4-6 weeks post-SE was compared by two-factor ANOVA. The percent of total seizure burden in the lights OFF period was correlated to the total 4-6 weeks post-SE monitoring session seizure burden. Statistical analysis was conducted in GraphPad v8.0 or later, with $P < .05$ significant.

3 | RESULTS

3.1 | Spontaneous seizure burden up to 6 weeks post-SE positively correlates to rat body weight at time of SE induction

This study was designed to characterize further the patterns of SRS presentation in the early epileptogenesis period after KA SE to ultimately support antiepileptogenesis drug discovery. Thus, we sought to further define influential factors associated with SRS onset and/or SRS rhythmicity in this TLE model. The total amount of KA to induce SE did not correlate to rat body weight (Figure 1A). However, body weight at the time of SE insult positively correlated, albeit modestly, to the total number of observed seizures during the two, 2-week-long recording periods up to 6 weeks post-SE (Figure 1B). This correlation was conserved in the 4- to 6-week post-SE period; there was a significant, albeit modest, correlation between body weight at SE induction and the average number of seizures/day in both lights ON and lights

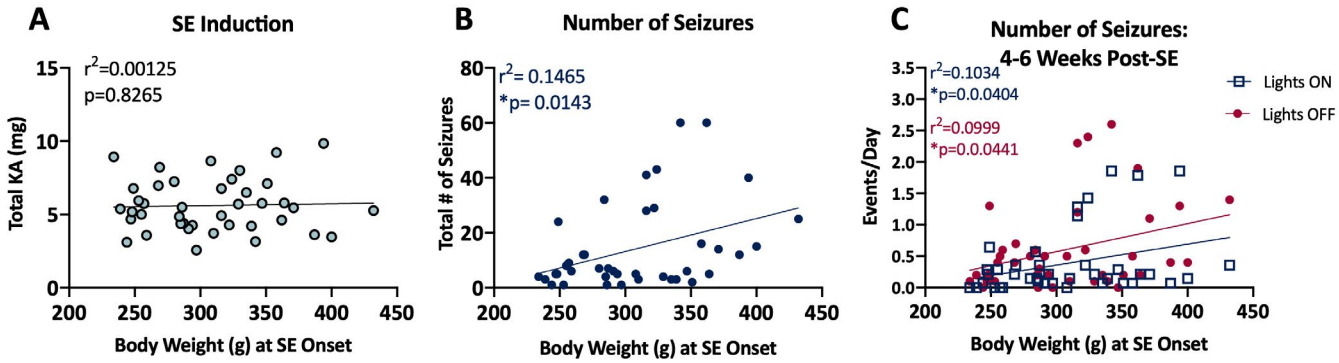

FIGURE 1 The repeated low-dose kainic acid (KA) administration protocol leads to onset of sustained status epilepticus (SE) and spontaneous recurrent seizures (SRS) up to 6 weeks post-SE. (A) There is no correlation between rat body weight at the time of SE induction and the total amount of KA administered by the ip route to male Sprague Dawley rats to induce SE, as defined by the onset of sustained electrographic spiking and at least two-stage 4/5 seizures within a 30-min time period. (B) Rats were then monitored for up to 6 weeks post-SE using an alternating 2-weeks on/2-weeks off/2-weeks on monitoring protocol. There was a significant correlation between the total number of seizures during the 6-week monitoring period and body weight at the time of SE onset. (C) The number of SRS recorded were noted to occur during the lights ON or lights OFF phase in a normal 14:10 light/dark housing conditions in a specific pathogen-free (SPF) vivarium. There was a significant correlation between number of seizures per day during each light phase (ON/OFF) and body weight of rats at the time of SE onset

OFF phases (Figure 1C). Thus, the size of Sprague Dawley rats at the time of SE induction positively correlated to the number of SRS by 6 weeks post-SE, and this correlation was conserved across light phases.

3.2 | Spontaneous seizure burden is more severe in the lights OFF phase

Few seizures were generally detected in the 0-2 weeks post-SE monitoring period, but this time period was included to assess interindividual variability in the onset of SRS in this model. There was no effect of light phase on seizure burden in the 0-2 weeks post-SE monitoring period (Figure 2A; W = 1.0 $P > .9$), but a significantly greater seizure burden was recorded in the lights OFF phase of the 4-6 weeks post-SE period (Figure 2A; W = 544, $P < .0001$). Significantly more SRS events occurred during the lights OFF phases of the 0-2 weeks (Figure 2B; $t = 3.297$, $P = .0021$) and 4-6 weeks post-SE sessions (Figure 2B; $t = 4.637$, $P < .0001$). Further scrutiny within the 4-6 weeks post-SE period revealed that light phase did not markedly influence the Racine seizure severity (Figure 2C; $F_{(1,78)} = 2.133$; $P = .148$), but there were significantly more severe, stage 4/5 seizures than stage 1-3 seizures at this 4- to 6-week time point ($F_{(1,78)} = 36.32$, $P < .0001$).

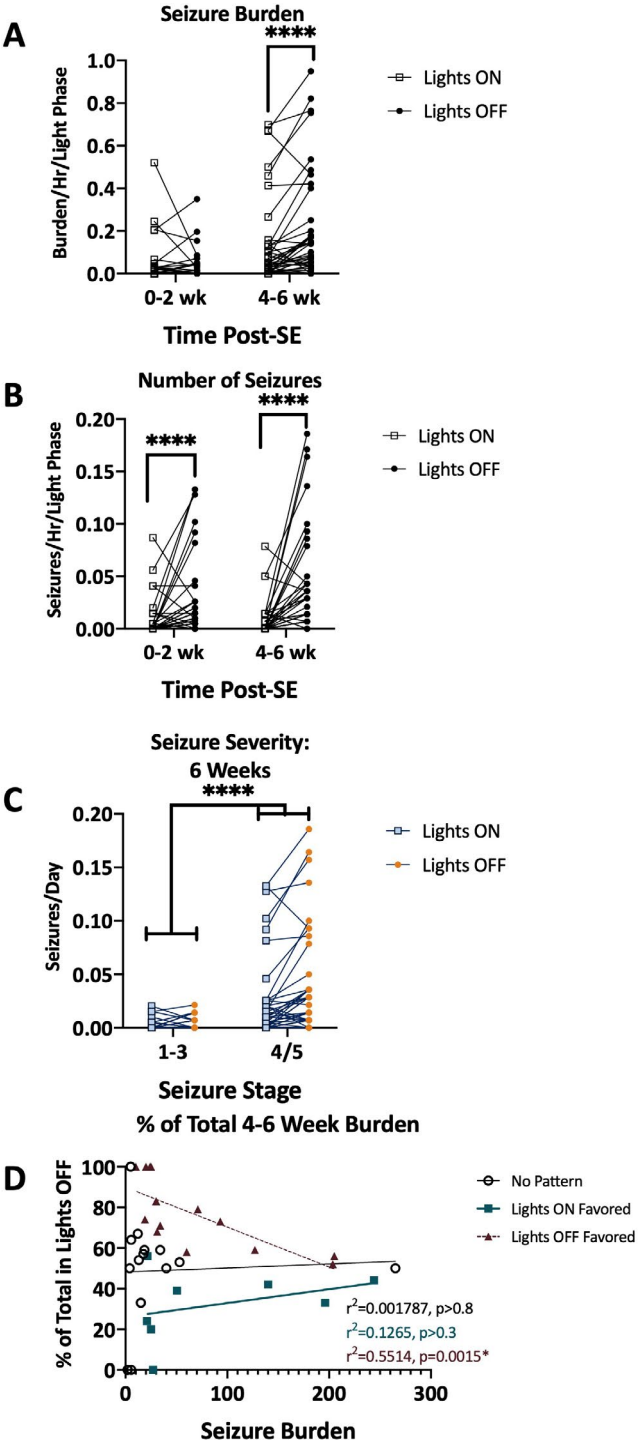

FIGURE 2 The post-kainic acid (KA)-induced status epilepticus (SE) rat model leads to the development of spontaneous recurrent seizures (SRS) within roughly 6 weeks. The distribution of SRS throughout the time post-SE onset was assessed using an alternating 2-weeks on/2-weeks off/2-weeks on monitoring protocol and SRS were tracked to occur during the lights ON and lights OFF phases. Data were analyzed separately for each 2-week monitoring session but presented on a single graph for illustration purposes. (A) There was no significant difference in seizure burden in either the lights ON or OFF phases during the 0-2 weeks post-SE period (Wilcoxon signed-rank test: W = 1.0; $P > .9$). There was a significantly greater average seizure burden in the lights OFF phase of each monitoring day of the 4-6 weeks post-SE monitoring period (Wilcoxon signed-rank test: W = 544; $P < .0001$). (B) Significantly more seizures occurred in the lights OFF phase of each day within the 0-2 week (paired *t* test: $t = 3.297$, $P = .0021$) and 4- to 6-week (paired *t* test: $t = 3.883$, $P = .0004$) monitoring periods. (C) There was no significant effect of light phase on seizure severity in the 4- to 6-week monitoring period (two-factor ANOVA: $F_{(1,78)} = 2.133$, $P = .1482$), but there were generally more stage 4/5 (generalized) seizures than stage 1-3 seizures recorded during all light phases of the 4- to 6-week monitoring epoch ($F_{(1,78)} = 36.32$, $P < .0001$). (D) We grouped rats into three cohorts, representative of the heterogeneity of SRS presentation: Rats that had at least two or more seizure events of their total events in the lights OFF phase (n = 15; 37.5%); rats with at least two or more seizure events of their total events in the lights ON phases (n = 8; 19.5%); and rats without a clear distinction in SRS pattern (n = 17; 41.5%). Within these subgroups, we assessed the correlation between the percentage of total seizure burden that was experienced in lights OFF period vs the total seizure burden in the 4-6 weeks post-SE monitoring period. This was the raw total seizure burden that was not normalized to the hours per monitoring period (lights ON/OFF). There was a significant correlation only between these two outcome measures in rats that had seizures more frequently in the lights OFF period, suggesting that there exists a clear subgroup of rats that more have a strong preference for seizure presentation in early epileptogenesis. *Indicates $P < .01$

3.3 | Marked variability in the spontaneous seizure pattern

Lastly, we assessed whether there were detectable differences in the incidence SRS presentation in these post-SE rats. We identified three distinct cohorts: rats with at least two or more seizures favoring the lights OFF phase (n = 15; 37.5%); rats with at least two or more seizure events favoring the lights ON phases (n = 8; 19.5%); and rats without a clear SRS preference (n = 17; 41.5%). To be consistent with human epilepsy wherein there can be heterogeneity in seizure patterns within a patient population, we then assessed whether the effects of light cycle were more pronounced in any of these cohorts. Rats that experienced seizures in favor of the lights OFF period demonstrated a significant correlation between the percentage of their total events in this period vs total 4- to 6-week seizure burden (Figure 2D). No other subgroup demonstrated any such correlation to total seizure burden during this time period. Thus, there is a subgroup of rats within our large cohort that demonstrated a substantial preference for seizures to occur in the lights OFF phase.

4 | DISCUSSION

Human patients with epilepsy experience seizure periodicity, which may be brain region dependent.[2] For example, the percentage of focal onset seizures that arise during periods of wakefulness is higher in patients with TLE, whereas patients with frontal lobe epilepsy are more likely to experience focal onset seizures during sleep.[3] Relatively few focal seizures are reported by vEEG monitoring during sleep in patients with TLE.[4] In this manner, a rat model of TLE in use for discovery of antiepileptogenic agents should replicate diurnal seizure periodicity. To our knowledge, this is the largest study of the diurnal distribution of SRS in the early phases of epileptogenesis following KA-induced SE in rats using long-duration (2-week) 24/7 vEEG monitoring. Our present analysis adds validity to preclinical disease modification studies with investigational therapies in this intermittent monitoring protocol in a rat model of TLE.

One potentially novel finding is the positive correlation between body weight at time of SE induction and subsequent seizure burden by 6-week post-SE (Figure 1B). While there was no correlation between the amount of KA necessary to induce SE and body weight at this time point (Figure 1A), animals that weighed more at the time of SE insult were more likely to have greater seizure burden during the two, 2-week periods of continuous vEEG monitoring. This correlation was not specific to any one light phase (Figure 1C). The precise mechanisms underlying this correlation clearly require further investigation. Nonetheless, our study confirms that seizure burden is highly variable within a large group of rats with similar SE history.

We herein report that SRS occurred more frequently in the lights OFF phase in early epileptogenesis in the post-KA SE rat model, in contrast to earlier studies. For example, motor seizures have previously been reported to more frequently coincide with periods of inactivity (ie, lights ON phase) in a similarly large cohort of post-KA SE rats (n = 23-32 animals).[11] That study was limited, however, to visual observation of motor seizures over the course of 5-6 days at either 3 or 4 months post-SE.[11] Long-term vEEG recording of post-KA SE rats (30 weeks) more recently suggested that seizures occur more frequently during the lights ON than lights OFF phase.[6] Yet, that study did not differentiate between early vs late epileptogenesis and was limited by a small group size (n = 9 rats).[6] Monitoring of Fischer 344 rats at 5 or 6 months after repeated low-dose KA-induced SE in two small cohorts (n = 6-12 rats/time point) demonstrated a higher frequency and severity of SRS during the lights ON phase.[9] Our findings instead more closely align those of Bajorat and colleagues who demonstrated no significant differences in SRS patterns in the post-pilocarpine SE rat model of TLE using continuous vEEG for up to 300 days (n = 13 rats).[10] Further, a small study of post-pilocarpine and post-KA SE rats (n = 5 rats/TLE model) suggested marked interindividual variability in the multi-day rhythmicity of SRS,[7] for which our present study does certainly support (Figure 2D). In this regard, our study suggests that at least within the early- to mid-epileptogenesis phases, variations in diurnal seizure patterns may be an insufficient outcome measure for disease modification studies due to the significant potential for interindividual heterogeneity in seizure patterns.

The post-KA SE rat model is commonly used for antiseizure drug discovery, and increasingly for antiepileptogenesis and disease modification studies.[12,13] Diurnal patterns of SRS could thus be applied to optimize drug administration for preclinical disease modification studies. One potential limitation of our study is that rats used were single housed throughout the recording period to accommodate chronic tethered vEEG recording. Single-housed rodents exhibit more signs of stress and depressive-like behavior than animals with ample social interaction and enrichment.[20] Single housing can lower the threshold for SE induction and accelerate epileptogenesis.[20] Our present study recorded SRS from over 40 single-housed post-KA SE rats, but we cannot rule out that housing conditions influenced the severity and/or variability of epilepsy in the early epileptogenesis period. However, it is important to note that although the animals used in this study were single housed, they were housed with ample environmental enrichment (Nylabones, corncob bedding, and nest-building materials) in clear Plexiglas holding chambers that allowed them to see, smell, and hear one another. Thus, our housing aimed to minimize social isolation stress while still accommodating

long-term recording capacity to support moderate-throughput preclinical drug discovery. Nonetheless, our study supports the need for more rigorous and frequent evaluation of the rhythmicity of SRS in early epileptogenesis in disease modification studies in the rat post-KA SE model of TLE.

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CONFLICT OF INTERESTS

HSW has served on the Scientific Advisory Board of Otsuka Pharmaceuticals and has served as an advisor to Biogen Pharmaceuticals and Acadia Pharma and is a member of the UCB Speakers Bureau. HSW is a scientific co-founder of NeuroAdjuvants, Inc, Salt Lake City, UT. None of the other authors have any conflict of interest to disclose. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

AUTHOR CONTRIBUTIONS

Experimental design and conception: Mizuno, White, Barker-Haliski; Data acquisition. Mizuno, Koneval, Knox, Zierath, Barker-Haliski; Data analysis: Mizuno, Koneval, Barker-Haliski; Writing of manuscript: All authors.

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