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High-frequency Oscillations after Status Epilepticus: Epileptogenesis and Seizure Genesis

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Summary: *Purpose:* To investigate the temporal relation between high-frequency oscillations (HFOs) in the dentate gyrus and recurrent spontaneous seizures after intrahippocampal kainite-induced status epilepticus.

Methods: Recording microelectrodes were implanted bilaterally in different regions of hippocampus and entorhinal cortex. A guide cannula for microinjection of kainic acid (KA) was implanted above the right posterior CA3 area of hippocampus. After recording baseline electrical activity, KA (0.4 μg/0.2 μl) was injected. Beginning on the next day, electrographic activity was recorded with video monitoring for seizures every day for 8 h/day for $\geq$30 days.

Results: Of the 26 rats studied, 19 revealed the appearance of sharp-wave activity and HFOs in the frequency range of 80 to 500 Hz in the dentate gyrus ipsilateral to the KA injection. In the remaining seven rats, no appreciable activity was noted in this frequency range. In some rats with recurrent seizures, HFOs were in the ripple frequency range (100–200 Hz); in others, HFOs were in the fast ripple frequency range (200–500 Hz), or a mixture of both oscillation frequencies was found. The time of detection of the first HFOs after status epilepticus varied between 1 and 30 days, with a mean of 6.3 $\pm$ 2.0 (SEM). Of the 19 rats in which HFO activity appeared, all later developed recurrent spontaneous seizures, whereas none of the rats without HFOs developed seizures. The sooner HFO activity was detected after status epilepticus, the sooner the first spontaneous seizure occurred. A significant inverse relation was found between the time to the first HFO detection and the subsequent rate of spontaneous seizures.

Conclusions: A strong correlation was found between a decreased time to detection of HFOs and an increased rate of spontaneous seizures, as well as with a decrease in the duration of the latent period between KA injection and the detection of spontaneous seizures. Two types of HFOs were found after KA injection, one in the frequency range of 100 to 200 Hz, and the other, in the frequency range of 200 to 500 Hz, and both should be considered pathological, suggesting that both are epileptogenic. **Key Words:** Epileptogenesis—High-frequency oscillations—Dentate gyrus—Kainic acid—Rat.

Processes leading to recurrent spontaneous seizures after an initial precipitating event remain obscure. After status epilepticus induced by intrahippocampal injection of kainic acid (KA), ~50% of rats develop recurrent spontaneous seizures, which appear to arise from the region of the injected hippocampus and adjacent entorhinal cortex (1). The dentate gyrus (DG) is believed to play an important role in the mediation of seizure generation (2,3).

High-frequency oscillations (HFOs) with a frequency range of 100 to 200 Hz, called ripples, occur in the normal rat hippocampus and entorhinal cortex, but not in DG (4–6). Evidence suggests that normal ripples reflect activity of interneurons that facilitate information transfer by synchronizing neuronal activity over wide areas (7–10). In rats with spontaneous seizures after intrahippocampal KA injection, fast ripples (FRs; 200–500 Hz) can be recorded in association with interictal spikes only in areas capable of generating recurrent spontaneous seizures (1). Unlike normal ripples, FRs occur in DG and may reflect synchronously bursting principal neurons (11,12). FRs appear to be a surrogate marker of epileptogenicity, and if they reflect the underlying fundamental mechanisms of epileptogenesis, after KA injection, FRs should appear earlier than spontaneous seizures, and a correlation should appear between certain aspects of FRs and aspects of later seizures (12,13).

In this study we investigated the temporal relation between HFOs and seizure occurrence in the DG during epileptogenesis induced by intrahippocampal injection of KA.

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METHODS

All procedures described in this study were approved by the University of California, Los Angeles, Institutional Animal Care and Use Committee. Twenty-six rats were used for the experiments.

Microelectrode implantation

Adult Wistar rats (300–350 g) were anesthetized with a mixture of ketamine (100 mg/kg), xylazine (5.2 mg/kg), and acepromazine (1.0 mg/kg, administered i.m).

Pairs of tungsten wires (60 μm in diameter) with 0.5-mm vertical tip separation were placed in the right angular bundle to stimulate perforant path afferents to the hippocampus (AP, –7.0 mm from bregma; ML, 3.5 mm, and DV, 2.5 mm from the surface of neocortex). Fixed recording microelectrodes also consisted of pairs of tungsten wires with 1.5-mm vertical tip separation. They were implanted bilaterally at symmetrical points in the DG and CA1 regions of anterior hippocampus (AP, –3.5; ML, 2.0; DV, 3.5–4.5), DG region of the posterior hippocampus (AP, –5.6; ML, 3.5; DV, 5.0), and EC (AP, –8.0; ML, 5.0; DV, 7.0).

The locations of the recording electrodes in the DG were chosen on the basis of the shape of the evoked potentials elicited by perforant-path stimulation. Electrodes with responses consisting of a positive field excitatory postsynaptic potential (fEPSP) with a superimposed negative population spike of 3- to 8-ms latency were considered to be located near the granule cell layer of the DG.

A guide cannula for microinjection of KA was implanted above the right posterior CA3 area of hippocampus (AP, –5.6 mm; ML, 5.5 mm; DV, 4.0 mm).

Baseline data acquisition

One week after surgery, wide-band recordings of electrical activity were performed for 8 to 10 h every day until the day of KA injection. Five 4-channel MOSFET input operational amplifiers mounted in the cable connector, served to eliminate cable movement artifacts. Physiological data were recorded wide-band, 0.1 to 5.0 kHz, and sampled at 10 kHz/channel (16 channels) with 12-bit precision on a Pentium PC by using RC-Electronics (Santa Barbara, CA, U.S.A.) software. During and between electrical recording experiments, rats were subjected to video-monitoring for detection of spontaneous seizures.

Kainic acid injection

After 1 week of recording baseline activity, KA (0.4 μg/0.2 μl normal saline) was injected unilaterally over a period of 5 min in the right posterior hippocampus through the guide cannula in awake rats. The microinjection cannula was designed in such a way that the tip of the cannula was located at a depth of 7.0 mm, which is in the CA3 area of the posterior hippocampus. This coordinate is approximately in the same region as the recording microelectrode in the right posterior DG. Injection was performed at 9 a.m.; status epilepticus began 5 to 20 min after injection and remained during next 4 to 6 h. Electrical activity was recorded continuously for 6 to 8 h after KA injection.

Poststatus data acquisition

Beginning on the next day (24 h after injection), electrographic activity was recorded with video monitoring for seizures every day for 8 h/day for 30 days. Three 3- to 5-min duration samples of electrical activity were selected for further analysis each day. All samples were taken only during periods of slow-wave sleep, as evaluated behaviorally and on the basis of cortical and hippocampal EEG. If seizures were detected, recording continued for $\leq$30 days, at which time the rat was perfused for electrode verification and histologic analysis of the brain. If seizures were not recorded within 30 days after status epilepticus, seizure monitoring continued for an additional 1 to 2 months, after which rats were perfused for histology.

Histologic procedures

At the end of the electrophysiological experiments, rats were deeply anesthetized and perfused with 2.5% paraformaldehyde before Nissl and neo-Timm's staining to verify electrode placements and to evaluate mossy fiber sprouting in the DG (14).

Data analysis

Analysis of behavioral and electrophysiological data were performed by three different individuals who were unaware of the goal of the experiments. For counting behavioral seizures between recording sessions, videotapes were reviewed, and detected seizures were scored on the basis of Racine's scale (15). Analysis of electrophysiological data was carried out off-line on a Pentium computer, by using RC-Electronics and DataPac (Run Technologies, Mission Viejo, CA, U.S.A.) software.

We examined electrical activity of each rat during a baseline period of $\geq$5 days to rule out the presence of HFOs or seizures before KA injection was carried out (HFO? and SZ?, in Fig. 1). After KA injection, the period between status epilepticus and first HFO occurrence was determined (t-HFO; Fig. 1) as well as the period between injection and the first spontaneous seizure

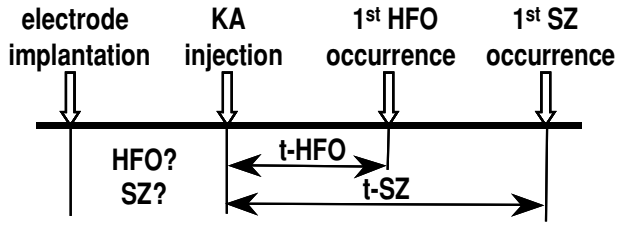

FIG. 1. Scheme of experimental design. t-HFO, the period between kainic acid injection and first high-frequency oscillation (HFO) occurrence; t-SZ, the time between kainic acid injection and first seizure detection. See text for details.

(t-SZ). After these periods, the rates of both HFOs and spontaneous seizures were measured until the end of the electrophysiological experiments.

The limits of the digital bandpass filter (FIR, roll-off, −36 dB) were set at the frequency band 80 to 500 Hz to cover oscillations in the ripple and FR frequency and to exclude any low-frequency events to eliminate any contribution of extracellularly recorded action potentials to the event-triggered averages, and a Hamming window was applied to the bandpass signal. Detected oscillatory events were considered HFOs only if they met a 3:1 signal/background noise criterion and contained at least three full oscillations.

Power spectral analysis of HFOs was performed by using 1,024-point fast Fourier transform (FFT) with zero padding to attain a frequency resolution of 9.7 Hz. During the regression analysis, significance levels also were tested with the Spearman nonparametric test.

Data were analyzed by using analysis of variance (ANOVA) and appropriate individual group tests of significance. Data are expressed as mean ± SD unless otherwise noted, and some statistical comparisons were made by applying Student's t test and χ^2 or Fisher's Exact test when appropriate. The significance level was set at $p < 0.05$.

RESULTS

Of the 26 rats studied, 19 (73%) revealed the appearance of sharp-wave activity and HFOs in the frequency range of 80–500 Hz in the right posterior DG, an area located 3 mm away from the site of injection of the KA in the right posterior CA3 area of the hippocampus. Figure 2 shows an example of the change in EEG pattern recorded from the same rat 1 day before (Fig. 2A) and 3 days after KA injection (Fig. 2B). This HFO activity localized to the injected posterior hippocampus was evident in both the wide-band EEG, the same EEG record when bandpass filtered between 80 and 500 Hz to eliminate low-frequency background, and in the power spectral analysis (Fig. 2C). In the remaining seven (27%) rats, no appreciable activity was seen in this frequency range. Although not visible because of the slow time-base, the interictal spike-like activity in Fig. 2B contained a high proportion of HFOs, often associated with the positive component of the interictal events, and examples of these HFOs are shown in Fig. 3.

In Fig. 3A–C, examples of wide-band and bandpass-filtered HFOs of varying spectral frequency are shown as insets a1, a2, b1, b2, and c1, c2. Examples of population field potentials evoked by stimulation of perforant path are shown in insets a3, b3, and c3. The field potentials revealed that the recording microelectrodes were located in or near the granule cell layer because positive field EPSPs or negative single or multiple population spikes or

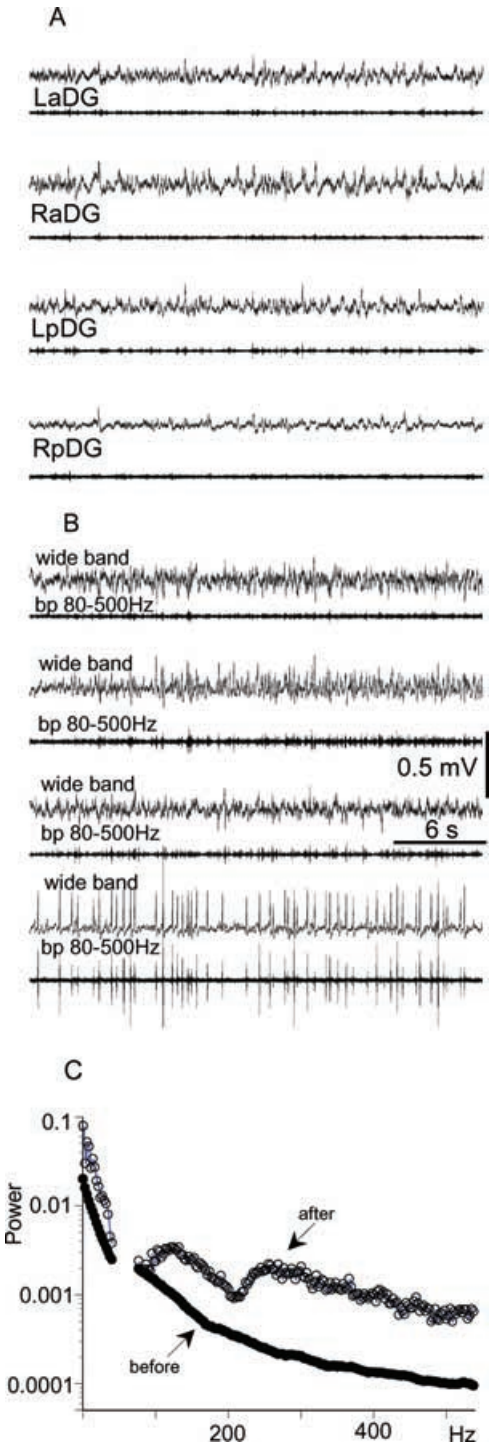

FIG. 2. Examples of wide-band (*top lines*) and 80- to 500-Hz bandpass filtered (*bottom lines*) electrical activity in different areas of dentate gyri before **(A)** and 3 days after **(B)** intrahippocampal kainic acid injection. LaDG and LpDG, left anterior and posterior dentate gyrus; RaDG and RpDG, right anterior and posterior dentate gyrus. **C:** Power spectrograms of wide-band recordings of RpDG before (*solid circles*) and after (*open circles*) status epilepticus. Break in the graph is due to the notch filter used during recordings. Wide band, data recorded and amplified with frequency band 0.1 to 4 kHz; bp 80 to 500 Hz, the same traces but filtered with bandpass filter 80 to 500 Hz.

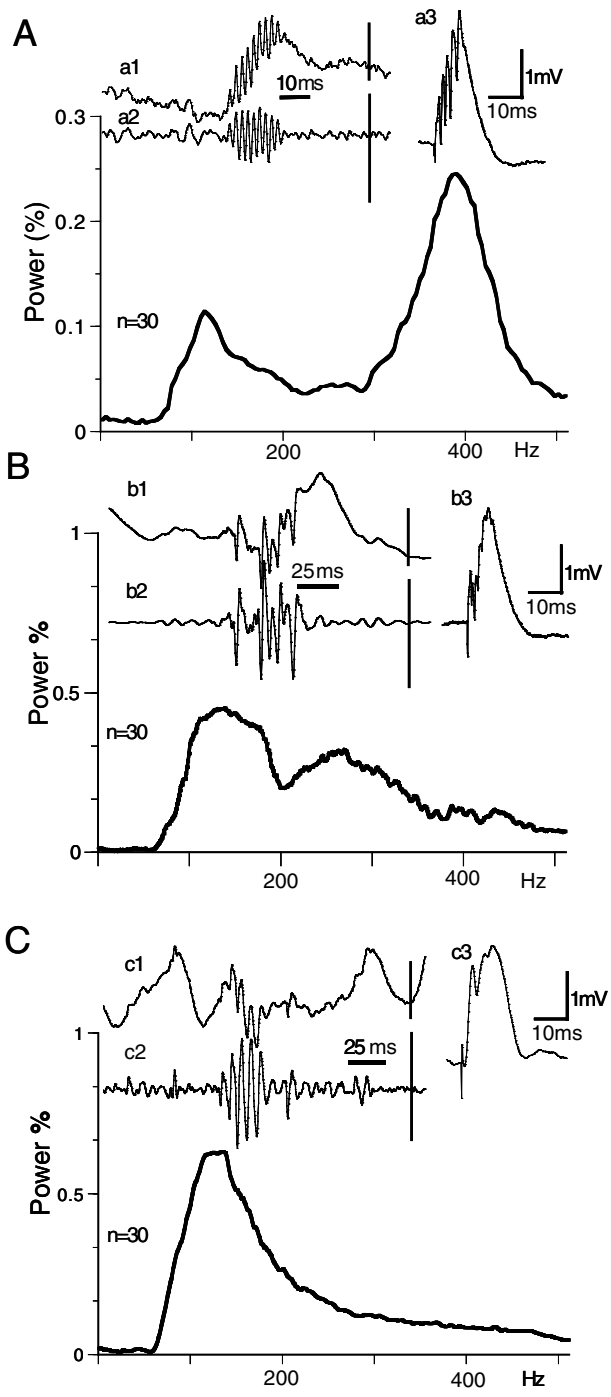

FIG. 3. Power spectrograms and examples of spontaneous and evoked high-frequency oscillations in three groups of rats. **A:** A bimodal spectrogram with dominance of oscillations in the fast-ripple (FR) frequency range, with a peak at 380 Hz. **B:** A bimodal distribution spectrogram with the dominant oscillations in the Ripple frequency range, peak 120 Hz. **C:** A monomodal spectrogram with the peak in the Ripple frequency. (**insets:** a1, b1, c1 are wide-band data; a2, b2, c2 are bandpass filtered 80 to 500 Hz (notice a time-scale difference between a1-2 and b1-2, c1-2); a3, b3, and c3 are examples of evoked potentials from stimulation of perforant path).

both could be recorded in response to electrical stimulation of the perforant path. On the basis of power spectrum analysis (PSA), we found that the 19 animals that generated HFO activity could be separated into two groups. In the first group (n = 12), PSAs had a bimodal shape with peaks in the frequency ranges of 100 to 200 Hz and 200 to 500 Hz (Fig. 3A and B). Analysis of the recording sites in the remaining seven rats with HFOs showed PSAs with a single peak in the frequency range of 100 to 200 Hz (Fig. 3C). Power spectrograms of EEG samples were evaluated every day in a subset of the five rats with the highest rates of HFO occurrence. No significant change was seen in the spectral frequency of HFOs in each specific rat during the latent period between the first HFO detection and spontaneous seizure occurrence.

The time of detection of the first HFO after status epilepticus varied between 1 and 30 days, with a mean of 6.3 ± 2.0 (SEM), but in the majority of rats (11 of 19), the first HFO was recorded within the first 2 days after status. The rate of occurrence of HFOs across all 19 rats at the time of first detection varied between 3 and 58 per minute. HFO rate was at its maximum during the first 3 days after status, with a mean of 19 ± 4.0 per minute, and sharply decreased over the next 2 weeks to rates between one and 15 per minute. During the last 7 days of the 30-day period, the mean HFO rate stabilized at 4.1 ± 0.8 per minute.

Of the 19 rats in which HFO activity appeared, all developed recurrent spontaneous seizures, whereas none of the rats without HFOs developed seizures. Fisher's Exact test indicates that the proportion of rats sharing HFO occurrence and seizure occurrence is highly significant ($p < 0.0001$). The time of the first seizure occurrence varied between 3 and 110 days (mean, 28.7 ± 7.6). The rate of seizures varied between one to nine seizures per month (mean, 3.9 ± 0.5). No significant correlation was found between the rate of HFOs detected on the day of their first appearance and the rate of subsequent spontaneous seizures.

In regard to the sequence of events in animals having spontaneous seizures, HFOs always occurred before the appearance of any seizures. Table 1 shows the relation between the time of first HFO detection and the time of first seizure detection after intrahippocampal KA-induced status epilepticus.

In examining the relation between the time of first detection of HFOs and first detection of spontaneous seizures, we found that the sooner HFO activity was detected after status epilepticus, the sooner the first spontaneous seizure occurred ($p = 0.0003$; Fig. 4A). This relation remains significant if we remove the group of rats with HFOs that occurred on the first day from the analysis ($p = 0.009$) or if we remove the group of rats with HFOs that appeared during the fourth week of experiments ($p = 0.0002$). In

addition, a significant inverse relation occurred between the time to the first HFO detection and the subsequent rate of spontaneous seizures ($p = 0.01$; Fig. 4B; i.e., animals with rapid onset of HFOs had higher seizure rates). Focusing on the interval between the first HFO detection and the first seizure detection, we found that the sooner HFOs were detected, the shorter the interval between the first HFO and the first recorded seizure ($p = 0.03$; Fig. 4C). The shorter the interval between the first HFO and the first recorded seizure, the higher the seizure rate ($r^2 = 0.26$; $p = 0.02$, not shown).

DISCUSSION

This study of the development of HFOs and their relation to chronic seizures in the intrahippocampal KA model of chronic epilepsy demonstrated a strong relation between the appearance of HFOs in the DG after status epilepticus and the subsequent occurrence of recurrent spontaneous seizures. Spontaneous seizures did not occur if no long-term appearance of HFOs occurred after status epilepticus. A strong correlation was found between a decreased time to detection of HFOs and an increased rate of spontaneous seizures, as well as with a decrease in the duration of the latent period between KA injection and the detection of spontaneous seizures.

These observations are consistent with but do not prove a role for HFOs in the process of epileptogenesis. More work is needed to understand the fundamental neuronal mechanisms of HFO generation and the potential for these mechanisms to give rise to spontaneous seizures.

Two types of HFOs were found in the dentate gyrus in these experiments, one in the frequency range of 100 to 200 Hz, and the other in the frequency range of 200 to 500 Hz. The first is in the frequency domain of normal oscillations recorded in the CA1 area, which have been termed *ripples* (4,7), whereas the second is in the frequency domain of pathologic oscillations we have termed *fast ripples* (11,12). Although some ripple-frequency oscillations have been seen in the DG in our previous studies of rats with established spontaneous seizures (16), FR oscillations also were always present. What is unexpected in this study was that, during epileptogenesis, some rats showed only ripples and no FR oscillations in the DG. Power spectral analysis often revealed the existence of oscillations in the frequency band of 100 to 200 Hz (12) in hippocampus, which we did not consider as pathologic, because we were aware that ripples occur in CA1 of the normal rat hippocampus (7) and entorhinal cortex (17,18). In previous studies, however, oscillations >100 Hz have not been described in the DG of the rat under normal conditions (5,6,19,20). In the present study, both ripple and FR frequency oscillations recorded from dentate gyrus after KA injection should be considered pathologic because ripple oscillations do not occur in the normal DG and because either HFO type occurred only in rats with spontaneous seizures. Some of the animals that developed chronic spontaneous seizures in the present study showed

TABLE 1. *Relationship between the time of HFO occurrence and the time of seizure occurrence after intrahippocampal KA status epilepticus*

Rat no.	1st HFO (d)	HFO rate/min	1st SZ (d)	1st HFO–1st SZ (d)	Sz/mo
1	30	4.6	110	80	2
2	1	7.0	4	3	6
3	6	5.6	24	18	3
4	12	3	102	90	1
5	6	4.3	77	71	2
6	2	6.5	7	5	4
7	1	11	2	1	9
8	4	29	5	1	3
9	2	19	4	2	5
10	28	4.6	47	19	1
11	8	5.9	21	12	5
12	1	35	12	11	6
13	2	32	25	23	3
14	1	10	5	4	4
15	1	32	17	16	3
16	1	60	26	25	5
17	1	58	3	2	3
18	1	14	11	10	7
19	10	14	44	14	1
Total	118	361	551	406	75
Mean± SEM(n = 19)	6.2 ± 2.0	18.7 ± 4.0	28.7 ± 7.6	21.4 ± 6.2	3.9 ± 0.5

1st HFO (d), the first day when high-frequency oscillations (HFOs) were detected; HFO rate/min, the HFO rate per minute on the first day of HFO occurrence; 1st SZ (d), the first day when seizure was detected; 1st HFO-1st SZ (d), the period between the first day of HFO appearance and the first seizure occurrence; sz/mo, the rate of spontaneous seizures per month.

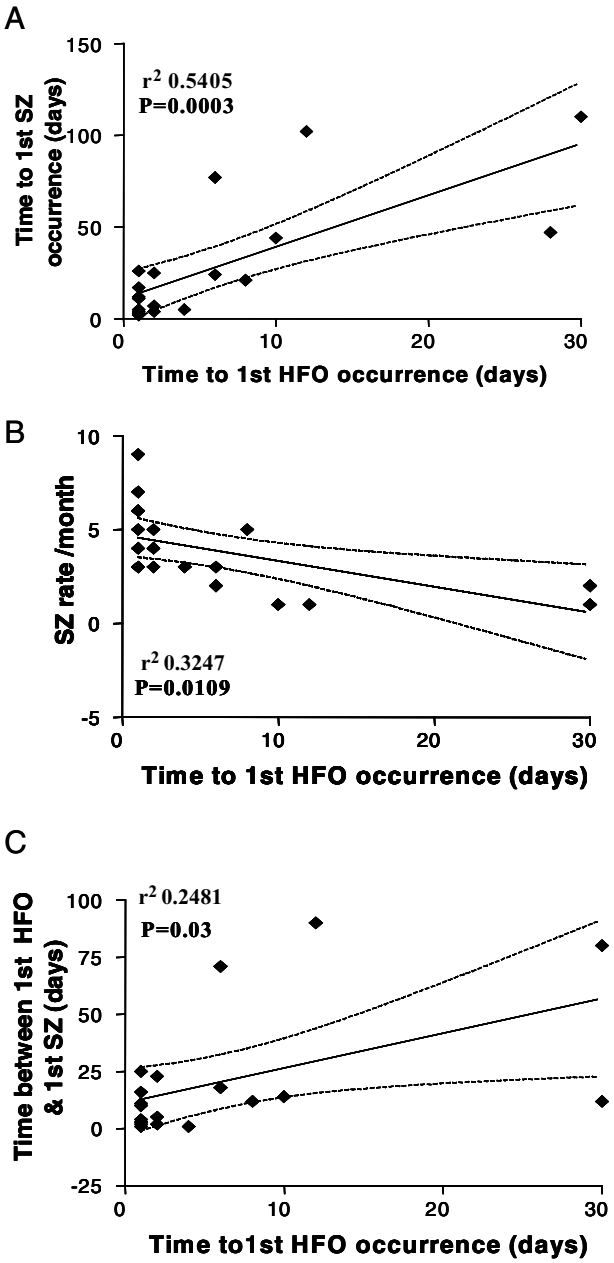

FIG. 4. Correlation between first time of occurrence of high-frequency oscillations (HFOs) and the latent period between status epilepticus and recurrent spontaneous seizures **(A)**, time between first day of HFO occurrence and first day of seizure occurrence **(B)**, and rate of seizures per month **(C)**.

no evidence of early FRs, but only early ripple frequency oscillations in the DG.

It is unclear at this point whether the 100- to 160-Hz oscillations in the DG are generated by the same neuronal network as FRs, but are slower at this early stage, or whether they represent entirely different network events, perhaps similar to normal ripples. Regardless of whether they represent the same or different functional disturbances, for the purpose of this discussion, we refer to both together as pathologic HFOs (pHFO).

The reason for detection of only ripple-frequency oscillations in DG during epileptogenesis, without change in the ratio of ripple-to-FR oscillations over time, is unclear. One explanation for the ripple-frequency oscillations being so prominent in this study could be that we used only fixed microelectrodes. In previous studies, we used movable microelectrodes, which permitted us to localize and selectively record from discrete FR-generating areas. If pathologic ripple-frequency oscillations are generated by a broader network of neurons than are FR oscillations, then the probability for recording ripple oscillations with fixed electrodes could be higher than that for FR oscillations. Thus in the majority of the records, we see ripple oscillations or ripple plus FRs but not pure FRs because the recording electrodes were not in the limited areas capable of FR generation.

Because ripple-frequency oscillations do not normally occur in DG, and because these oscillations are seen only in rats that later develop spontaneous seizures, they are considered to be pathologic and epileptogenic. Several questions are raised by this observation: (a) Are the neuronal mechanisms of pathologic ripple oscillations in DG after KA injection the same as those of normal ripple oscillations in hippocampus and entorhinal cortex (4,7,8,10,21), or are they the same as FRs (11,22)? (b) If they represent the same mechanisms as FRs, does the bimodal frequency distribution during epileptogenesis indicate different neuronal networks? (c) Is there a decrease in pathologic ripple-frequency oscillations and increase in FRs after spontaneous seizures are established, and if so, why? and (d) Do ripple-frequency oscillations recorded in hippocampus, entorhinal cortex, and other parahippocampal structures during epileptogenesis, and after spontaneous seizures are established, represent normal neuronal mechanisms or pathologic ones?

To understand the cellular elements participating in the generation of pHFOs, parallel field ripple and FR oscillations and unit recordings of in vivo experiments followed by labeling and 3D reconstruction of recorded neurons are required.

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