Repetitive Perforant-Path Stimulation Induces Epileptiform Bursts in Minislices of Dentate Gyrus from Rats with Kainate-Induced Epilepsy

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The epileptic hippocampus has an enhanced propensity for seizure generation, but how spontaneous seizures start is poorly understood. Using whole-cell and field-potential recordings, this study explored whether repetitive perforant-path stimulation at physiological frequencies could induce epileptiform bursts in dentate gyrus minislices from rats with kainate-induced epilepsy. Control slices from saline-treated rats responded to single perforant-path stimulation with an EPSP and a single population spike in normal medium, and repetitive stimulation at different frequencies (0.1, 1, 2, 5, 10 Hz) did not cause significant increases in the responses. Most minislices (82%) from rats with kainate-induced epilepsy also responded to single perforant-path stimulation with an EPSP and a single population spike/action potential, but some slices (18%) had a more robust response with a prolonged duration and negative DC shift or responses with 2-3 population spikes. Repetitive perforant-path stimulation at 5-10 Hz, however, transformed the single-spike responses into epileptiform bursts with multiple spikes in half (52%) of the slices, while lower frequency (e.g., ≤1 Hz) stimulation failed to produce these changes. The emergence of epileptiform bursts was consistently associated with a negative field-potential DC shift and membrane depolarization. The results suggest that compared to the controls, the “gate” function of the dentate gyrus is compromised in rats with kainate-induced epilepsy, and epileptiform bursts (but not full-length seizure events) can be induced in minislices by repetitive synaptic stimulation at physiological frequencies in the range of hippocampal theta rhythm (i.e., 5-10 Hz).
INTRODUCTION

Epilepsy is characterized by spontaneous, recurrent seizures. Several pathological changes have been reported to occur in the dentate gyrus during epileptogenesis and to contribute to an enhanced propensity for seizure generation. These changes include loss of inhibitory interneurons (Buckmaster and Dudek, 1997; Kobayashi and Buckmaster, 2003; Obenaus et al., 1993), and sprouting of excitatory axons (Molnar and Nadler 1999; Tauck and Nadler, 1985; Wuarin and Dudek, 2001). Similar pathological changes may occur in other regions of the brain. Although these changes in the epileptic brain would favor the generation of seizures, spontaneous seizures in the epileptic brain only occur intermittently, and the onset of seizures is largely unpredictable and poorly understood.

In *in vitro* experiments, epileptiform bursts rarely occur in the dentate gyrus in slices prepared from epileptic animals unless the experimental conditions have been artificially manipulated to alter seizure threshold, such as blocking inhibition and/or increasing \([K^+]_o\) (Hardison et al., 2000; Patrylo and Dudek, 1998; Wuarin and Dudek, 1996). The present study aimed to explore the question of how seizures start and propagate in a “natural” milieu (i.e., without blocking inhibition and manipulation of extracellular ion concentration) in the dentate gyrus. The dentate gyrus is traditionally considered as a “gate,” limiting activity entering hippocampus from entorhinal cortex in normal animals. However, earlier studies have shown that the “gate” function can be compromised by repetitive stimulation (i.e., so-called “maximal dentate activation”, Stringer and Lothman, 1989; Stringer et al., 1989). During epileptogenesis, the dentate gyrus undergoes multiple and consistent pathological changes which favor seizure generation (Dudek et al., 2002). Electrographic seizures in the dentate gyrus of chronically epileptic animals are preceded by increased neuronal firing (Bower and Buckmaster, 2008) or
associated with rhythmic electrographic spikes at 5-12 Hz (Hellier and Dudek, unpublished data). Therefore, we hypothesized that stimulation patterns roughly comparable to normal physiological activity in slices from epileptic brain might cause activity-dependent changes that would induce epileptiform bursts. Using minislices of dentate gyrus (i.e., isolated from adjacent tissues, Fig. 1A) from rats with kainate-induced epilepsy, we tested whether repetitive synaptic activation of the granule cells could trigger epileptiform bursts in this region. Our results suggest that the “gate” function of the dentate gyrus is compromised, and repetitive perforant-path stimulation at physiological frequencies in the range of hippocampal theta rhythm (i.e., 5-10 Hz) can induce epileptiform bursts (but not full-length seizure events) in minislices of dentate gyrus from rats with kainate-induce epilepsy, compared to saline-treated control animals.

METHODS

Animal model of epilepsy. To induce chronic epilepsy in rats, a repeated low-dose kainate-treatment protocol similar to previous studies (Hellier et al., 1998; Shao and Dudek, 2004) was used. Briefly, male Sprague-Dawley rats (Harlan) weighing ~175 g were injected hourly with kainate (5 mg/kg, intraperitoneal). Motor seizures normally occurred after 1-3 injections. Animals had recurring class IV/V seizures (Ben-Ari, 1985; Racine, 1972) for ≥3 h. Control rats received saline injections in parallel with kainate-treated rats. After kainate treatment, rats were monitored for 1-2 h/day, 3-5 days/wk (i.e., 6 h/week) to determine whether they developed spontaneous convulsive seizures. All procedures with animals used in this study were approved by the Colorado State University and University of Utah Animal Care and Use Committees.
Brain slice preparation. Rats were used at least 3 months after kainate or saline treatment, when kainate-treated rats had developed spontaneous seizures. Rats were anesthetized with halothane and decapitated with a guillotine. The brains were quickly dissected out and placed in ice-cold oxygenated artificial cerebrospinal fluid (aCSF) containing (in mM): 124 NaCl, 3 KCl, 26 NaHCO3, 1.4 NaH2PO4, 1.3 CaCl2, 1.3 MgSO4 and 11 glucose. Horizontal hippocampal slices of 450-μm thickness were cut parallel to the base of the brain with a vibroslicer (Campden Instrument, Lafayette, IN). Slices were trimmed and three additional knife cuts were made to isolate the dentate gyrus from entorinal cortex, CA3 and CA1 (i.e., minislices, Fig. 1). Minislices were then transferred to and maintained in a storage chamber filled with aCSF (32–34 °C) and continuously bubbled with 95% O2/5% CO2. Electrophysiological recordings were normally started 2 h after slice preparation.

Recording procedures and data acquisition. Dentate gyrus minislices were mounted onto a heated ramp-type interface chamber (32–34 °C) for electrophysiological recording, and were continuously perfused with gassed aCSF. Simultaneous extracellular field-potential and whole-cell recordings (or extracellular field-potential recording alone) were performed with an Axoprobe-1A amplifier (for field-potential recording, Molecular Device, Foster City, CA) and an Axopatch-1D amplifier (for whole-cell recording, Molecular Device, Foster city, CA). The recording electrodes were made from thick-wall borosilicate glass capillaries (OD 1.65 mm, ID 1.2 mm, Garner Glass, Claremont, CA) with a P-87 Flaming-Brown puller (Sutter Instruments, Novato, CA), and placed in the granule cell layer in either blade of the dentate gyrus (Fig. 1A). A bipolar stimulating electrode composed of two Teflon-coated platinum wires (bare diameter: 25 μm, with coating: 75 μm; separation between wires: ~50 μm [i.e., twice the thickness of...
coating]) was positioned in the lateral perforant path of the dentate gyrus to deliver synaptic stimulation (Fig. 1A). The stimulus intensity was adjusted to evoke a population spike in field-potential recordings (100-600 μA, 200 μs). For extracellular field-potential recordings, pipettes were filled with aCSF. For whole-cell current-clamp recordings, pipettes were filled with intracellular solution containing (in mM): 120 K-gluconate, 1 NaCl, 5 EGTA, 10 HEPES, 1 MgCl₂, 1 CaCl₂, and 2 ATP. The pH was adjusted to 7.2 with 5 M KOH. The calculated liquid junction potential between the intracellular solution and perfusing solution (aCSF) was ~13 mV, and was not corrected in the values reported here. Extracellular recordings were DC-coupled. All signals were sampled at 10 kHz, low-pass filtered at 2 kHz, and recorded online with pClamp 8.0 software (Clampex, Molecular Device, Union City, CA) through a Digidata-1320A digitizer (Clampex, Molecular Device, Union City, CA). Data were analyzed offline with pClamp 8.0 (Clampfit, Molecular Device, Union City, CA). The chi-square ($\chi^2$) test was employed to compare the ratios between groups. The Student’s t-test was used for comparisons between two groups. Data are expressed as means ± SE, and $\alpha = 0.05$ in all tests.

**RESULTS**

* Responses of dentate gyrus minislices to single perforant-path stimulation

In normal aCSF, individual synaptic stimulation at the lateral perforant path evoked an EPSP. An increase in stimulus intensity increased the amplitude of the EPSP and generated a population spike/action potential. A further increase in stimulus intensity increased the amplitude but not the number of population spikes (Fig. 1B). The duration of the response was usually <0.1s. This pattern of response (i.e., EPSP with single population spike/action potential and of short duration) was consistent in slices from control rats in response to perforant-path
stimulation. The majority of the minislices (36 of 44 slices, 82%) from kainate-treated rats also responded to single perforant-path stimulation with responses similar to that in the controls (i.e., EPSP and a single population spike/action potential; Fig. 1C1). However, some slices (8 of 44 slices, 18%) from epileptic rats expressed more robust responses to single perforant-path stimulation. These responses include an initial EPSP followed by a clear negative DC shift lasting for up to 1-2 s (5 of 44 slices, 11%, Fig. 1C2) or responses with 2 or 3 population spikes (3 of 44, 7%, not shown). These prolonged responses in slices from rats with kainate-induced epilepsy are consistent with previous observations (Patrylo and Dudek, 1999), and support the hypothesis that the dentate gyrus undergoes significant pathological changes toward an increased propensity for seizure generation during epileptogenesis.

Induction of epileptiform bursts by repetitive perforant-path stimulation

Next, we tested the hypothesis that repeated physiological activity (i.e., comparatively low-frequency repetitive perforant-path stimulation) might cause epileptiform bursts in minislices from epileptic but not control rats. The stimulus intensity was adjusted to evoke a population spike of ~2-4 mV, and was similar for the control and epileptic groups (231 ± 18 μA, n=36 slices vs. 250 ± 17 μA, n=44 slices; p>0.05, Student t-test). Some dentate minislices appeared healthy (i.e., with large fEPSPs), but it was difficult to generate a population spike of 2-4 mV; these slices were also included in the study. In minislices from control rats, individual synaptic stimulations of the lateral perforant path typically elicited an EPSP with a single population spike/action potential (Fig. 2A, 1B). Repetitive stimulations (0.1-10 Hz, for up to 2 min) sometimes increased the amplitude of the population spike but did not develop multi-spike epileptiform bursts (Fig. 2A, n=35 of 36 slices from 16 rats), except for one slice that developed
multiple-spike burst at 5 Hz (1 of 36 slices, 2.8%; 1 in 16 rats, 6.3%). In addition, some of these slices (n=18) were further tested with 2-4 fold greater stimulus intensities (up to 600 μA) at 5 Hz, but none of them developed epileptiform bursts (data not shown). Thus, the dentate gyrus “gate” in the control rats seemed mostly intact under the current experimental conditions. In contrast, half of the slices from rats with kainate-induced epilepsy (23 of 44 slices, 52%, p<0.001; 15 of 24 rats, 63%, p<0.001, χ² test) developed multi-spike epileptiform bursts during perforant-path repetitive stimulation at 5 Hz. The initial responses with a single spike/action potential (Fig. 2B, upper) were transformed into epileptiform bursts with multiple population spikes/action potentials (Fig. 2B, middle and bottom). The transition from a single-spike response to a multi-spike burst took a variable period of time ranging from a few seconds to a few tens of seconds, and was closely associated with the emergence of a negative shift of the field-potential baseline (see below in Fig. 4). Sixteen of the 21 slices that showed no increase in responses during 5-Hz repetitive stimulation were further tested with greater stimulus intensities. As a result, 5 of them initially showed no change during repetitive stimulation, but then developed epileptiform bursts with two-fold greater stimulus intensity (320 ± 49 pA, from 160 ± 25 pA, n=5), while the rest of the 11 slices remained unchanged with a similar increase in stimulus intensity. In those slices from epileptic rats that responded to individual perforant-path stimulation with a prolonged response, repetitive stimulation further intensified the responses and produced multi-spike bursts (data not shown). These data suggest that the dentate “gate” is significantly comprised in slices from rats with kainate-induced epilepsy, such that epileptiform bursts can be induced by relatively physiological activity, in normal medium.

**Frequency dependence of repetitive stimulation to induce epileptiform bursts**
To determine the most effective frequency to induce the epileptiform bursts, different stimulation frequencies (0.1, 0.5, 1, 2-3, 5 and 10 Hz) were tested. In all but one slice (35 of 36, 97.2%) from control rats, repetitive stimulations at any of the tested frequencies failed to transform a single-spike response into a multiple-spike epileptiform burst (Fig. 3A). In minislices from epileptic rats, only 3 of 32 slices (9.4%) developed epileptiform bursts during repetitive perforant-path stimulation at 1-3 Hz (data not shown). The same slices developed multi-spike, epileptiform bursts when the frequency of repetitive stimulation was increased to 5 Hz (Fig. 3B). A further increase in the frequency to 10 Hz also induced epileptiform bursts (Fig. 3B).

However, the responses tended to decrease or even collapse as 10-Hz stimulation persisted (data not shown). Thus, repetitive stimulation at physiological frequencies in the range of hippocampal theta rhythm (i.e., 5-10 Hz) effectively induced epileptiform bursts in a fraction (~50%) of slices from rats with kainate-induced epilepsy (Fig. 3B).

**Repetitive stimulation induced a significant negative DC shift in field potential and membrane depolarization**

Interestingly, the occurrence of multi-spike epileptiform bursts during repetitive stimulation was consistently accompanied by a negative DC shift in the field-potential (1.4 ± 0.1 mV, n=23 slices; Fig. 4B), a phenomenon similar to that seen during “maximal dentate activation” *in vivo* (Stringer and Lothman, 1989; Stringer et al., 1989). In slices from control rats (and those slices from epileptic rats that failed to induce epileptiform bursts), a negative shift of the field potential was absent or negligible during repetitive stimulation (0.16 ± 0.03 mV, n=54 slices, p<0.001; Fig. 4A). Thus, the negative DC shift in field potential is closely related to and may be important for the development of epileptiform bursts by repetitive stimulation. In
addition, using simultaneous whole-cell recording, we observed membrane potential changes of
the dentate granule cells during the DC shift in the field potential. Repetitive stimulation caused
a modest depolarization in granule cells (Fig. 4A, upper trace) or hyperpolarization (not shown)
in slices from control rats (average membrane potential change: 1.3 ± 1.6 mV, n=5 cells from 5
slices). In slices from rats with kainate-induced epilepsy, repetitive stimulation caused a larger
depolarization in dentate granule cells (8.6 ± 1.6 mV, p<0.01, n=6 cells from 6 slices, Fig. 4B,
upper trace).

DISCUSSION

The main findings in the present study were that in normal medium, repetitive synaptic
stimulation at physiological frequencies in the range of hippocampal theta rhythm (i.e., 5-10 Hz)
induced epileptiform bursts in a fraction (~50%) of the dentate gyrus minislices from rats with
kainate-induced epilepsy but not controls. The induction of epileptiform bursts was closely
associated with a negative DC shift in the field potential and membrane depolarization.

Activity-induced epileptiform bursts and impaired dentate gate function in rats with
kainate-induce epilepsy

Earlier in vitro studies have shown that the dentate gyrus has an enhanced seizure
propensity in slices from the epileptic brain, which can be “unmasked” by blocking GABAergic
inhibition and/or elevating extracellular potassium (Hardison et al., 2000; Patrylo and Dudek,
1998; Wuarin and Dudek, 1996). However, whether or how these conditions may actually occur
in epileptic patients or animal models in vivo is unknown. Earlier in vivo studies in naïve animals
suggest that the dentate gyrus can be maximally activated after trains of high-frequency (10-30
Hz) repetitive stimulation (Stringer and Lothman, 1989; Stringer et al., 1989). Therefore, it is
possible that in the epileptic brain, which has undergone many pathological changes, repetitive
physiological stimuli (which may represent normal signaling in the naïve brain), may cause
exaggerated responses in the epileptic brain, and then lead to the emergence of epileptiform
bursts. The finding that a single episode of repetitive stimulation at physiological frequencies in
the range of hippocampal theta rhythm (i.e., 5-10 Hz), compared to multiple episodes of 10-30
Hz stimulation for the “maximal dentate gyrus activation” in normal animals (Stringer and
Lothman, 1989; Stringer et al., 1989), effectively induced multi-spike bursts implies that the
“gate-keeper” function of the dentate gyrus is impaired in epileptic animals. Although our data
support the hypothesis that the dentate “gate” function is compromised in rats with kainate-
induced epilepsy, about half (48%) of the dentate minislices from epileptic rats did not produce
epileptiform bursts during repetitive stimulation, which might reflect a variable degree of
pathological changes across the dentate gyrus. Another possibility is that the abnormal responses
observed in the present study are not present in all slices from each animal, because some of
them have better preserved local circuitry (depending on the angle of the slice). These variables
may also explain the observation that many minislices showing or not showing bursting were
from the same epileptic animals, which made the correlation of the failure of gate function in
minislices with the severity of epilepsy in the intact animals difficult. Also, because synaptic
reorganization almost certainly occurs in many temporal and limbic structures in addition to the
dentate gyrus, and seizure onsets are variable across brain structures (Bertram, 2009), it seems
quite possible that the changes reported here could be obscured by other alterations in the brain
of kainate-treated rats. It may also be argued that the altered dentate “gate” function is associated
with, but not essential for, epileptogenesis. Nonetheless, our data suggest that repetitive
physiological activity could change the dynamics of the dentate granule cell responses in minislices from the epileptic brain and trigger epileptiform bursts, at least in some of the cases. Interestingly, an earlier study (Finnerty et al., 2001) showed that repetitive stimulation of the perforant pathway at a frequency of 10-15 Hz (i.e., higher than theta frequencies (4-8 Hz)) caused depression in control slices (i.e., the so called “low-pass filtering” function of the dentate gyrus), however, in hippocampal slices prepared from tetanus toxin-injected rats, the responses of dentate granule cells potentiated after an initial depression during 15-Hz stimulation. Their data suggest that the dentate gyrus filtering function is altered in the tetanus toxin-injected rats. Thus, in both the kainate-induced and tetanus toxin-induced epilepsy models, the dentate “gate” function seems to be comprised, such that rhythmic physiological stimuli may trigger epileptiform activity or seizures. More recently, Bower and Buckmaster (2008) have shown that the firing rate of dentate granule cells is increased minutes before the onset of electrographic seizures, suggesting possible activity-dependent induction of seizures in the epileptic brain. However, we were unable to induce full-length seizure events under the current experimental conditions. Possibly, slice preparations (particularly minislices) are less likely to generate prolonged seizure-like bursts, because each minislice only contains a small fraction of the neural circuitry; the same stimulation protocol may cause full seizures in vivo. More in vivo and in vitro experiments are needed to further explore this issue.

Possible mechanisms for the induction of epileptiform bursts by repetitive stimulation

The induction of epileptiform bursts by repetitive stimulation suggests that it requires activity-dependent mechanisms, such as accumulation of extracellular K⁺, facilitation of synaptic excitation and/or depression of synaptic inhibition (see below). Several possible activity-
dependent mechanisms might be involved in the induction of epileptiform bursts by repetitive stimulation. Most notably, the appearance of the epileptiform bursts was closely associated with and potentially resulted from the development of a negative DC shift and membrane depolarization (Fig. 4). Repetitive electrical stimulation is known to cause an accumulation of extracellular K$^+$ (Heinemann et al., 1977; Krnjevic, 1982; Ransom et al., 2000; Stringer and Lothman, 1989; Stringer et al., 1989) and a reduction of extracellular Ca$^{2+}$ (Heinemann et al., 1977; Krnjevic, 1982), both of the changes would excite neurons and cause membrane depolarization and a negative DC shift of the field potential. In addition, repetitive stimulation may cause activity-dependent depression of GABAergic inhibition (McCarren and Alger 1985; Thompson and Gahwiler 1989a, b, c; Mott et al., 1993), which may further enhance and/or accelerate membrane depolarization and negative DC shift of field potentials. Moreover, GABAergic inhibition may be more prone to collapse in epileptic than normal dentate gyrus (Cohen et al., 2003; but see Molnar and Nadler, 2001). Interestingly, however, while all of these changes may occur during repetitive stimulations in normal and epileptic slices, the negative DC shift in the field potential and the epileptiform bursts seldom occurred in controls, but occurred frequently in epileptic rats (sometimes even at lower frequency, i.e., 1-3 Hz, n=3 slices, data not shown). Therefore, the propensity for the occurrence of a negative DC shift in the field potential, the membrane depolarization, and the epileptiform bursts were clearly increased in rats with kainate-induced epilepsy, possibly due to the increased number of recurrent excitatory synapses (Tauck and Nadler, 1985; Wuarin and Dudek, 1996) and enhanced probability of transmitter release (Scimemi et al., 2006) in this region. Moreover, the newly-formed recurrent excitatory circuits during epileptogenesis may well serve as positive-feedback loops, such that the output of granule cells may be reinforced by previous stimulations and thus facilitate the generation of
epileptiform bursts. All of these mechanisms may contribute an increased propensity for activity-dependent epileptiform bursts in slices from rats with kainate-induced epilepsy.

In summary, data from the present study suggest that the “gate” function of the dentate gyrus is significantly compromised in rats with kainate-induced epilepsy. The basis for this interpretation is that epileptiform bursts can be induced in a fraction (~50%) of the dentate gyrus minislices by repetitive stimulation at a relatively physiological frequency, which in turn appears to be associated with membrane depolarization and a negative DC shift in the field potential. Additional experiments are needed to further explore whether or not full-length seizure events can be induced by repetitive stimulation in vivo and in vitro.

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Figure 1. Protocol of the experiments and profile of the responses to individual perforant path stimulations in slices from control and kainate-treated rats. A, diagram showing experimental protocol. Dashed lines represent knife cuts to isolate dentate gyrus from CA3, CA1 and entorhinal cortex. WC: whole-cell recording electrode; FP: field-potential recording electrode; Stim: stimulation electrode. B, typically, a dentate gyrus minislice from control rats responded to single perforant-path stimulation with an EPSP and a single population spike in field-potential recording and an action potential in whole-cell recording. C, in slices from kainate-treated rats, the responses to single perforant path stimulations were more variable and robust. While most minislices showed responses similar to that in the controls (C1), some of the slices displayed responses with a prolonged negative field-potential shift and with or without preceding population spikes (C2). Arrows indicate stimulations and dashed lines represent the baseline potential levels.

Figure 2. Perforant-path repetitive stimulation at 5 Hz induced epileptiform bursts in slices from rats with kainate-induced epilepsy but not control rats. A, simultaneous whole-cell (WC, upper traces) and field-potential (FP, lower traces) recordings showing representative responses to perforant-path stimulations in slices from control rats. The initial response had a single population spike/action potential (i.e., at 1st sec), and did not increase during repetitive stimulation (e.g., at 30th and 60th sec). B, by contrast, 5-Hz repetitive stimulation transformed the initial responses with a single population spike/action potential into epileptiform bursts with multiple population spikes/action potentials in slices from rats with kainate-induced epilepsy. Arrows indicate stimulations and dashed lines represent the baseline potential levels.
**Figure 3.** The most effective frequency to induce epileptiform bursts appeared to be 5 Hz.

A, examples showing responses in slices from control rats to repetitive stimulations at low (i.e., 1 Hz), medium (5 Hz) and high (10 Hz) frequency. Repetitive stimulation failed to induce epileptiform bursts in nearly all slices from control rats, regardless of the frequency of stimulations. B, similar stimulation protocol as above, but in slices from rats with kainate-induced epilepsy. Perforant-path repetitive stimulation-induced epileptiform bursts occurred at a range of frequency from 1-10 Hz, but most often occurred at 5 Hz.

**Figure 4.** Repetitive stimulation-induced epileptiform bursts were associated with a negative DC shift in field-potential and depolarization. A and B, simultaneous whole-cell (WC, upper traces) and field-potential (FP, lower traces) recordings showing changes in membrane potential and the baseline field-potential during 5-Hz perforant-path repetitive stimulation. In slices from rats with kainate-induced epilepsy, repetitive stimulation caused a DC shift in field-potential (B, bottom trace), which was absent or negligible in slices from control rats (A, bottom trace). The initial, middle and later responses (marked by solid circles) to repetitive stimulations in both groups were shown in expanded scale below, as indicated by arrows. Repetitive stimulation caused a modest depolarization in dentate granule cells in slices from control rats (A, upper trace), and appeared to cause a larger depolarization in granule cells in slices from rats with kainate-induced epilepsy (B, upper trace). Dashed lines indicate the baseline voltage levels. Scale bars in A apply to B.
A 5 Hz, Control

B 5 Hz, Kainate-treated

WC 1st sec

FP 30th sec

30th sec

60th sec

1st sec

10th sec

30th sec

30 mV

15 ms

3 mV