

Research article

## Gamma oscillation underlies hyperthermia-induced epileptiform-like spikes in immature rat hippocampal slices

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Published: 28 November 2001

Received: 24 September 2001

BMC Neuroscience 2001, 2:18

Accepted: 28 November 2001

This article is available from: <http://www.biomedcentral.com/1471-2202/2/18>

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### Abstract

**Background:** Recently a hyperthermic rat hippocampal slice model system has been used to investigate febrile seizure pathophysiology. Our previous data indicates that heating immature rat hippocampal slices from 34 to 41°C in an interface chamber induced epileptiform-like population spikes accompanied by a spreading depression (SD). This may serve as an *in vitro* model of febrile seizures.

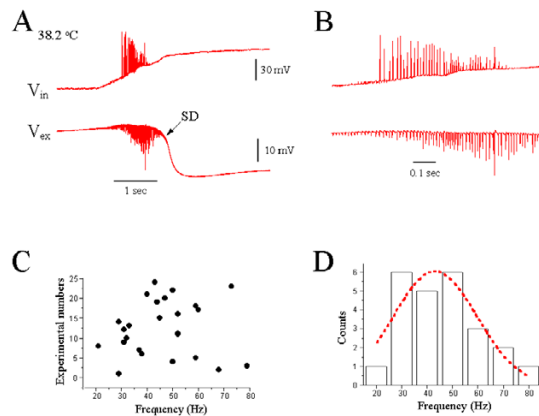
**Results:** In this study, we further investigate cellular mechanisms of hyperthermia-induced initial population spike activity. We hypothesized that GABA<sub>A</sub> receptor-mediated 30–100 Hz  $\gamma$  oscillations underlie some aspects of the hyperthermic population spike activity. In 24 rat hippocampal slices, the hyperthermic population spike activity occurred at an average frequency of  $45.9 \pm 14.9$  Hz (Mean  $\pm$  SE, range = 21–79 Hz, n = 24), which does not differ significantly from the frequency of post-tetanic  $\gamma$  oscillations ( $47.1 \pm 14.9$  Hz, n = 34) in the same system. High intensity tetanic stimulation induces hippocampal neuronal discharges followed by a slow SD that has the magnitude and time course of the SD, which resembles hyperthermic responses. Both post-tetanic  $\gamma$  oscillations and hyperthermic population spike activity can be blocked completely by a specific GABA<sub>A</sub> receptor blocker, bicuculline (5–20  $\mu$ M). Bath-apply kynurenic acid (7 mM) blocks synaptic transmission, but fails to prevent hyperthermic population spikes, while intracellular diffusion of QX-314 (30 mM) abolishes spikes and produces a smooth depolarization in intracellular recording.

**Conclusion:** These results suggest that the GABA<sub>A</sub> receptor-governed  $\gamma$  oscillations underlie the hyperthermic population spike activity in immature hippocampal slices.

### Background

Febrile seizures are the most prevalent type of seizures experienced by children, affecting up to 5% of the world's population [1]. Although most febrile seizures are benign

and do not require treatment, they are distressing to parents, and in a few circumstances, can increase the risk of subsequent epilepsy [2]. In clinical practice, therapy for febrile seizures presently is unsatisfactory, since clinical



**Figure 1**  
Hyperthermia-induced  $\gamma$  oscillation. (A): Heating hippocampal slice to 38.2°C induced epileptiform-like spikes, followed by a slow spreading depression (SD) recorded by intracellular ( $V_{in}$ ) and extracellular ( $V_{ex}$ ) electrodes simultaneously. (B): Expanded time scale from (A) to show initial epileptiform-like spikes. (C): Distribution of frequency of initial epileptiform spikes in 24 experimental cases. (D): Gaussian-fitting shows a  $\gamma$  band frequency (30–80 Hz) distribution of hyperthermia-induced epileptiform spikes.

data are insufficient to document efficacy of most anti-epileptic drugs [3]. The most commonly used drug, phenobarbital, has significant deleterious effects on learning and behavior.

A better understanding of the underlying mechanisms of febrile seizures might lead to new strategies of prevention or treatment [4]. Recent work has identified several genes associated with familial febrile seizure tendencies [5–7]. Some of these genes code for ion channels that govern excitability of nerve tissue. We recently published a study of the characteristic hyperthermic responses represented as epileptiform-like population spike activity accompanied by spreading depression (SD) in a rat hippocampal slice, which may serve as an *in vitro* model of febrile seizures [8]. The hyperthermic response was age-dependent, occurring almost exclusively in young, but not newborn, rats. The primary underlying abnormality in this model was inability of neuronal tissue properly to regulate extracellular potassium concentrations. During heating of the slice, extracellular potassium concentrations rose transiently from the normal 5 mM to as high as 40 mM and extracellular field potential shifted about 20 mV negative, a reversible condition known as SD. During the early phases of SD, neurons burst synchronously in a pattern analogous to seizures. Since hyperthermic epileptiform-like population bursts exhibited the frequency

of  $\gamma$  oscillations (30–100 Hz), we hypothesized that GABA<sub>A</sub> receptor-governed  $\gamma$  oscillations might underlie the cellular basis of hyperthermic epileptiform-like population spike activity.

The  $\gamma$  frequency oscillations (30–100 Hz) are characteristic of responses to sensory input measured by cortical EEG [9]. In the hippocampal slice preparation,  $\gamma$  oscillations can be evoked by brief, high frequency tetanic stimuli to region CA1 [10–13]. The extracellular field potential response during these oscillations takes the form of a train of population spikes in stratum pyramidale at  $\gamma$  and  $\beta$  (15–30 Hz) frequencies [14]. Intracellular recordings during  $\gamma$  oscillations induced by tetanic stimulation reveal a slow membrane depolarization in conjunction with GABA<sub>A</sub> receptor-mediated inhibitory postsynaptic potentials [11,15]. This synaptic inhibition-based  $\gamma$  activity entrains action potential generation in pyramidal neurons, leading to the population spikes at  $\gamma$  band frequencies. The specific GABA<sub>A</sub> receptor antagonist, bicuculline, blocks the  $\gamma$  oscillations [14,16], an action that can be modeled by simulated neuronal networks [17]. The  $\gamma$  band oscillations appear to play an important role in generation of ictal epileptiform activity in hippocampal slices [18]. This study explores the role of  $\gamma$  oscillations in epileptiform activity in the hyperthermic rat hippocampal slice.

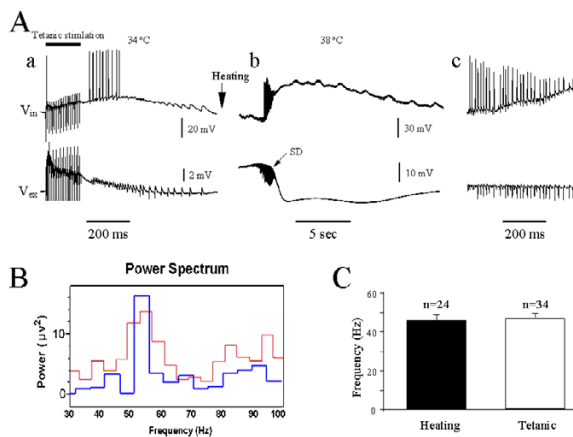
## Results

### Hyperthermia-induced epileptiform-like population spike activity

More than 90% of slices heated to 40°C showed a "febrile-seizure like event," represented as initial epileptiform-like population bursts, followed by SDs. Figure 1A shows a typical "febrile seizure-like event" elicited by heating a hippocampal slice from 33.9 to 38.2°C. The epileptiform discharges demonstrated a frequency of 80 Hz (Fig. 1B), within the 30–100 Hz  $\gamma$  oscillation range. Summary of data from 24 slices showed that 71% (17/24) of hyperthermic epileptiform-like population spike activity fired at a frequency range between 30–50 Hz (Fig. 1C,D), with a mean oscillation frequency of  $45.9 \pm 3.0$  (mean  $\pm$  SE,  $n = 24$ ).

### Comparison of post-tetanic $\gamma$ oscillation and hyperthermic population spike activity

Figure 2 shows the comparison between hyperthermic population spike activity and post-tetanic  $\gamma$  oscillations. In standard artificial cerebrospinal fluid (ACSF), a tetanic stimulation at 100 Hz, 100  $\mu$ sec, 2 mA, for 200 ms (20 trains) elicited  $\gamma$  and  $\beta$  frequency population spikes, visible both with intracellular and extracellular recordings. In the same slice, heating to 38°C (2Ab) evoked population oscillation very similar to those of post-tetanic  $\gamma$  oscillations. Power spectrum analysis of the population of

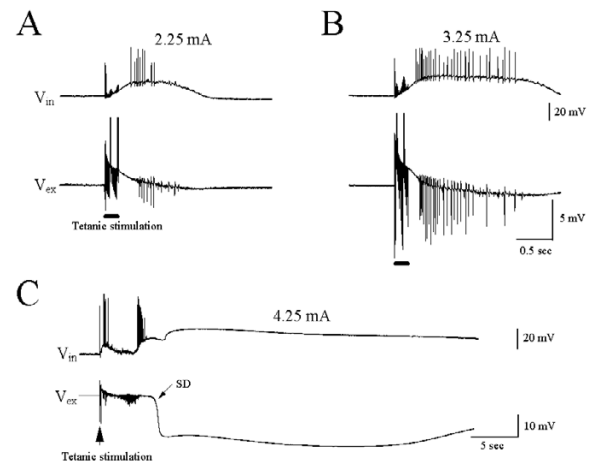


**Figure 2**  
Comparison of hyperthermic and post-tetanic  $\gamma$  oscillations. (A): **a.** Post-tetanic stimulation (100 Hz, 20 trains, 2 mA, 100  $\mu$ s) induced  $\gamma$  oscillation at 34°C. **b.** Heating the same recorded slice to 38°C induced an initial  $\gamma$  oscillation accompanied by a slow SD. **c.** Expanded time scale shows the similar frequency ranges of post-tetanic and hyperthermic oscillations. (B): Comparison of frequency power by power spectrum analysis between Aa and Ab. (C) There is no significant difference of average frequency between post-tetanic and hyperthermic oscillations.

responses among all slices, showed similar frequency peak of hyperthermic and post-tetanic gamma oscillations (Fig. 2B). Among all slices, hyperthermic oscillations occurred at a frequency of  $45.9 \pm 3.0$  Hz (mean  $\pm$  SE,  $n = 24$ ) and post-tetanic gamma oscillations at  $47.1 \pm 2.6$  (mean  $\pm$  SE,  $n = 34$ ). These two frequencies do not significantly differ (Fig. 2C).

#### Effects of high intensity tetanic stimulation

Results from this and our previous study showed that the SD always followed hyperthermic bursts [8], but tetanic stimulation induced only  $\gamma$  oscillations in the absence of SD (Fig. 2). Therefore, we investigated whether high-intensity tetanic stimulation could induce  $\gamma$  oscillations followed by SD. Fig. 3A illustrates a weak  $\gamma$  oscillation of field potential in response to tetanic stimulation at 2.25 mA. Tetanic stimulation at 3.25 mA induced a strong  $\gamma$  oscillation with a large field burst amplitude and long-lasting depolarization (Fig. 3B). In 6 of 7 tested slices, tetanic stimulation at 4.25 mA induced, not only prominent  $\gamma$  oscillations, but also SDs (Fig. 3C). These post-tetanic depolarizations had duration and time course very similar to those of hyperthermic SDs (Fig. 1A,2Ab).

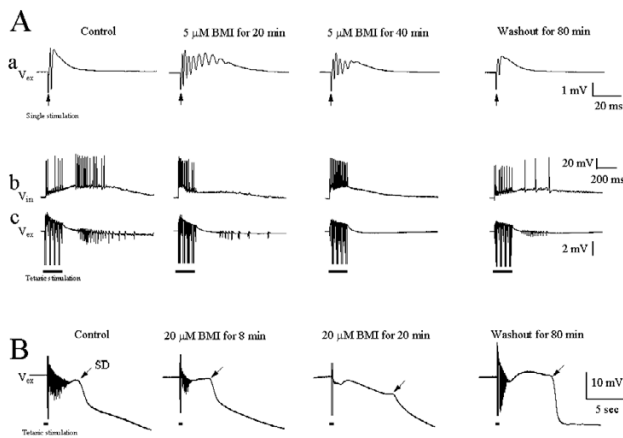


**Figure 3**  
Post-tetanic stimulation at high intensity induced  $\gamma$  oscillations followed by a slow SD. (A): Post-tetanic stimulation at 2.25 mA elicited a rudimentary  $\gamma$  oscillation. (B): Post-tetanic stimulation at 3.25 mA induced a typical  $\gamma$  oscillation with large amplitude and long duration. (C): Post-tetanic stimulation at 4.25 mA induced a  $\gamma$  oscillation followed by a slow SD. Traces A-C are recorded from the same slice, which is a typical representative of five experiments.

#### Effects of bicuculline

We utilized the specific GABA<sub>A</sub> receptor antagonist, bicuculline methiodide (BMI), to ascertain whether  $\gamma$  oscillations were dependent upon GABAergic mechanisms. The effect of BMI on the field potential in region CA1 is shown in Fig. 4. Bath-applied BMI (5  $\mu$ M) changed the single evoked population spike to multiple spikes, in a reversible manner. In the same slice, tetanic stimulation delivered in control artificial cerebrospinal fluid (ACSF) induced typical  $\gamma$  oscillations, and these  $\gamma$  oscillations were abolished by addition of BMI to the perfusate.  $\gamma$  oscillations recovered partially by 80 minutes of wash in ACSF. Figure 4B shows another case in which high intensity of tetanic stimulation was applied to elicit  $\gamma$  oscillations and SDs. Addition of 20  $\mu$ M BMI reversibly blocked  $\gamma$  oscillations, but not the SD.

In a second set of experiments using five slices (Fig. 5), we examined the effects of BMI on hyperthermic epileptiform-like population bursts. Bath-application of 10  $\mu$ M BMI for 20 min abolished post-tetanic  $\gamma$  oscillations. After several minutes of exposure to BMI, slices demonstrated rhythmic spontaneous bursts of population spikes (Fig. 5B), indicating that GABA<sub>A</sub> receptors have been blocked by BMI. Under these conditions, heating of the slice only evoked the SD without the initial population spikes (Fig. 5C).



**Figure 4**  
The GABA<sub>A</sub> receptor antagonist, bicuculline (BMI), blocks post-tetanic  $\gamma$  oscillations. (A): **a.** BMI (5  $\mu$ M) induced multiple field potential spikes to a single stimulation, **b** and **c.** BMI reversibly blocked post-tetanic  $\gamma$  oscillations. (B) BMI (20  $\mu$ M) blocked high intensity (4 mA) tetanic stimulation-induced  $\gamma$  oscillation, but not the slow SD. The traces in (A) were recorded from the same neuron ( $n = 6$  experiments) and in (B) from another neuron ( $n = 4$  experiments).

#### Effects of kynurenic acid and QX 314

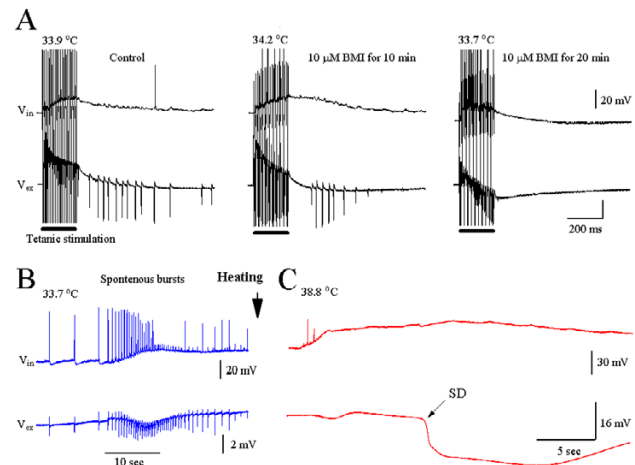
Figure 6A shows the effect of the ionotropic glutamate receptor antagonist, kynurenic acid (Kyn-A, 7 mM), on  $\gamma$  oscillations. Kyn-A dramatically attenuated evoked synaptic transmission, but failed to prevent hyperthermia-induced  $\gamma$  oscillations and slow SDs, suggesting that excitatory synaptic transmission is not necessary for hyperthermic  $\gamma$  oscillations and SDs. In Fig. 6B, 30 mM QX-314 was incorporated into the recording electrode. The action potentials were blocked by intracellular QX-314 diffusion. Heating the slice to 37°C elicited a  $\gamma$  oscillation followed by a slow SD in the extracellular field recording. However, the intracellularly-recorded hyperthermic  $\gamma$  oscillation disappeared and was replaced by a smooth depolarization (Fig. 6B).

#### Discussion

This study suggests that GABA<sub>A</sub> receptor-governed  $\gamma$  oscillations underlie the hyperthermic population spike activity in immature hippocampal slices.

#### Gamma oscillations underlie hyperthermic epileptiform-like population spikes

Gamma oscillations are defined as coherent cortical oscillations at  $\gamma$  (30–100 Hz) band frequency frequencies in *in vivo* and *in vitro* models. In hippocampal slice preparations,  $\gamma$  oscillations can be triggered by high frequency tetanic stimuli, called post-tetanic  $\gamma$  oscillations

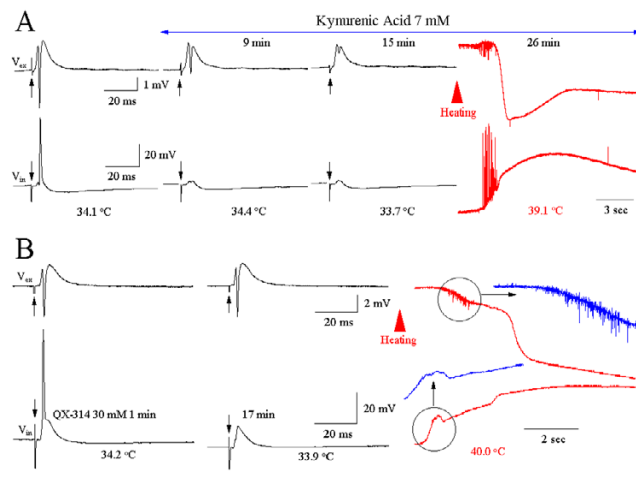


**Figure 5**  
(A): BMI (10  $\mu$ M) blocked post-tetanic  $\gamma$  oscillations. (B): Persistence of spontaneous spikes and bursts after BMI block of  $\gamma$  oscillation. (C): In the presence of BMI, heating the slice to 38.8°C induced a slow SD without initial  $\gamma$  oscillations. Traces A-C were recorded from the same neuron ( $n = 6$  experiments).

[10–13]. In addition to post-tetanic  $\gamma$  oscillations, the  $\gamma$  oscillations also can be elicited by metabotropic glutamate receptor agonists, carbacol, or free extracellular Mg<sup>2+</sup>[18,19]. In this study, we report that  $\gamma$  oscillations can occur in a model of a clinical disorder, namely hyperthermia. Hyperthermic epileptiform-like population spikes occur within the band of  $\gamma$  frequencies (30–100 Hz). Post-tetanic  $\gamma$  oscillations can be mimicked by hyperthermic stimulation in the same slice. Tetanic stimulation at high intensity induces initial  $\gamma$  oscillations followed by a slow SD which resembles hyperthermic epileptiform-like population spikes followed by a slow SD. Finally, both post-tetanic  $\gamma$  oscillations and hyperthermic epileptiform-like population spikes were completely blocked by a GABA<sub>A</sub> receptor antagonist, BMI. This experimental evidence suggests that the GABA<sub>A</sub> receptor-governed  $\gamma$  oscillations underlie the hyperthermic population spikes in our *in vitro* model system.

#### Possible mechanisms of hyperthermic $\gamma$ oscillation

Accumulating lines of evidence demonstrate that the genesis mechanisms for post-tetanic  $\gamma$  oscillations involve slow GABA<sub>A</sub> receptor-mediated depolarization, extracellular K<sup>+</sup> elevation and field effects [10–13]. The present study showed that these three major factors also underlie hyperthermic  $\gamma$  oscillations. As shown in Fig. 1A and 2A, the hyperthermic  $\gamma$  oscillations always overlaid the slow membrane depolarizations. For post-tetanic  $\gamma$  oscillations, the slow depolarizations were mediated by tetanic stimulation-induced GABAergic depolarizing ac-



**Figure 6**  
 (A): Kynurenic acid (Kyn, 7 mM) blocked evoked synaptic transmission, but failed to prevent  $\gamma$  oscillations and SDs elicited by heating the slice. Traces illustrate four slice recordings. (B): QX-314 blocks hyperthermia-induced  $\gamma$  oscillation in the intracellular recording from three slices.

tion [20–23]. This GABAergic depolarization is attributed to the tetanic stimulation-induced accumulation of intracellular chloride [24] and extracellular potassium [22]. For hyperthermic  $\gamma$  oscillations, heating causes a  $\text{Na}^+/\text{K}^+$  pump failure [8], in turn resulting in the accumulation of intracellular  $\text{Na}^+$  and  $\text{Cl}^-$ , as well as extracellular  $\text{K}^+$ , finally causing a slow membrane depolarization. In our previous report, the extracellular  $\text{K}^+$  indeed elevated dramatically during hyperthermia-induced epileptiform-like population spikes and SDs [8]. Field effects further contribute to post-tetanic  $\gamma$  oscillations [25,26]. High Frequency tetanic stimuli leads to cellular swelling [27,28], increasing extracellular resistance. According to Ohm's law, this increases the voltage deflection recorded for a given current flowing through this extracellular resistance. Current generated by the active population travels through the resistances of the extracellular space and of the nearby inactive cells, therefore producing the extracellular population spikes and meanwhile depolarizing the inactive cells. In this manner, inactive cells are brought closer to threshold, enhancing their opportunity to firing together [29–31]. The extracellular resistance is the major determinant of field-effect strength [32]. Since the extracellular volume fraction in CA1 stratum pyramidale is only 12% compared with approximately 18% in CA3 and granule cells [33], the CA1 pyramidal cells are particularly susceptible to field effects. The accumulation of extracellular  $\text{K}^+$  during hyperthermic SDs depolarizes membrane potential, which triggers initial  $\gamma$  oscillations. Cell swelling reduces the extracellular space, which triggers slow SDs [8], (Fig.

1A and 2A). In Fig. 6A, after blockade of synaptic transmission by kynurenic acid (7 mM), heating the slice still induced  $\gamma$ -oscillation followed by SD, suggesting that a non-synaptic mechanism (local field effect) may be involved in the generation of hyperthermic  $\gamma$ -oscillations and SDs. Figure 6B demonstrated that hyperthermic  $\gamma$ -oscillations disappear in the presence of an intracellularly delivered  $\text{Na}^+$  channel blocker (QX 314, 30 mM).

### Gamma oscillations and seizures

Epileptic activity can result from an imbalance between glutamatergic excitation and GABAergic inhibition. However, this simple balance model has been challenged by findings that GABAergic transmission remains effective in some epilepsy models, in epileptogenic human tissue [34–40], and by current findings of the excitatory effects of GABA [18,22,23]. Therefore, the GABA excitatory effects may work as a possible ictogenic mechanism under some special condition such as tetanic stimulation. Indeed, recently Köhling et al. reported that under epileptogenic condition (free  $\text{Mg}^{2+}$  in ACSF),  $\gamma$  band oscillations arise from GABAergic depolarizations and that this activity may lead to the generation of ictal discharges [18]. It has been reported that prolonged periods of  $\gamma$  oscillations are associated with temporal lobe seizures in *in vivo* rats [41]. Furthermore, human EEG studies with subdural recording electrodes showed that a  $\gamma$  band oscillation could be recorded at the start of typical seizure activity [42]. In this respect, the hyperthermic  $\gamma$  oscillations may also play a critical role in generation of neuronal epileptiform activity. The extent to which the hyperthermic slice serves as a model of febrile seizures remains to be determined. If  $\gamma$  oscillations do prove to be important in clinical febrile seizures, then future work might profitably examine the therapeutic potential of mild disinhibition to disrupt inhibitory GABA-mediated synchrony at the start of ictal activity.

### Conclusions

In the *in vitro* hippocampal slice preparation, hyperthermia-induced epileptiform-like population spikes are at  $\gamma$  band frequencies, and can be blocked by BMI. Therefore, the  $\text{GABA}_A$  receptor-governed  $\gamma$  oscillations underlie the hyperthermic population spikes in immature hippocampal slices.

### Materials and methods

Experiments were performed on transverse hippocampal slices prepared from Sprague-Dawley rats, ages 17 to 29 days. Rats were anesthetized with halothane and decapitated. The brain tissue was removed rapidly and placed in iced artificial cerebrospinal fluid (ACSF). Brain tissue was then glued to a cryotome, and a few 450–500  $\mu$  transverse slices were cut through the hippocampal formations. Slices were allowed to incubate and recover

for at least an hour in room temperature ACSF comprised of the following composition (mM): NaCl 117; KCl 5.4; NaHCO<sub>3</sub> 26; MgSO<sub>4</sub> 1.3; NaH<sub>2</sub>PO<sub>4</sub> 1.2; CaCl<sub>2</sub> 2.5; glucose 10, continuously bubbled with 95% O<sub>2</sub> plus 5% CO<sub>2</sub>.

Slices were transferred one at a time to the recording chamber (FST, air-liquid interface chamber), and suspended on nylon net at the interface. Carbogen (95% O<sub>2</sub> plus 5% CO<sub>2</sub>) was bubbled across the upper surface of the slice. Temperature was regulated by a feedback circuit, accurate to 0.5 ± 0.2°C. Baseline temperature was 34°C. After verification of evoked population spike stability for three consecutive stimuli over a time course of 15–30 minutes, bath temperature set-point was increased to 41°C and notation was made of actual temperature measured by a thermistor probe.

Extracellular field potentials were recorded with a borosilicate glass micropipette pulled to a tip diameter of 1 μm, filled with 2 M sodium chloride and with resistance approximately 1–10 MΩ. Intracellular recordings were performed with a pulled-glass fine tip micropipette (< 1 μm), with resistance approximately 80–110 MΩ, filled with 4 M potassium acetate. Hyperthermic spreading depressions (SDs) were considered to have occurred when all of the following conditions were met: 1. At least 10 mV extracellular negativity; 2. Duration of extracellular negativity at the half-height of at least 10 seconds; 3. Loss of evoked field in CA1; and recovery of field to at least 50% of control amplitude within 30 minutes of cooling to baseline temperature. Electrophysiological data were stored on a computer (Axon scope), and played back on a laser printer. Slow potentials, including extracellular field during SD also were recorded on a continuous rectilinear chart recorder. To measure oscillation frequency, we chose a slice oscillation range beginning at 200 ms, then used the "frequency count" function of the Origin program to get average frequency from each slice. Chemicals used in the experiment consisted of bicuculline methiodide (BMI), kynurenic acid (Sigma, St. Louis, MO) and QX-314 (Tocris). All animal experiments were in accord with Institutional animal welfare committee guidelines.

## Acknowledgements

All authors were supported by the Marjorie Newsome and Sandra Solheim Aiken Funds for Epilepsy and the Women's Board of the Barrow Neurological Institute. RSF was supported by the Maslah Saul Chair and the James and Carrie Anderson Laboratory fund for epilepsy research.

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