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# Depolarization Block of Neurons During Maintenance of Electrographic Seizures

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**Bikson, Marom, Philip J. Hahn, John E. Fox, and John G.R. Jefferys.** Depolarization block of neurons during maintenance of electrographic seizures. *J Neurophysiol* 90: 2402–2408, 2003. First published June 10, 2003; 10.1152/jn.00467.2003. Epileptic seizures are associated with neuronal hyperactivity. Here, however, we investigated whether continuous neuronal firing is necessary to maintain electrographic seizures. We studied a class of "low-$Ca^{2+}$" ictal epileptiform bursts, induced in rat hippocampal slices, that are characterized by prolonged (2–15 s) interruptions in population spike generation. We found that, during these interruptions, neuronal firing was suppressed rather than desynchronized. Intracellular current injection, application of extracellular uniform electric fields, and antidromic stimulation showed that the source of action potential disruption was depolarization block. The duration of the extracellular potassium transients associated with each ictal burst was not affected by disruptions in neuronal firing. Application of phenytoin or veratridine indicated a critical role for the persistent sodium current in maintaining depolarization block. Our results show that continuous neuronal firing is not necessary for the maintenance of experimental electrographic seizures.

## INTRODUCTION

Epileptic seizures are generally assumed to result from excessive synchronized firing of large neuronal aggregates. During experimental seizures, tightly synchronized neuronal firing is manifest by the generation of extracellular population spikes (Andersen et al. 1971; Haas and Jefferys 1984); however, transient interruptions in population spike activity can be observed during the prolonged extracellular negativities that characterize ictal electrographic seizures (Durand 1993; Jefferys 1994). These interruptions could result from a reduction in synchrony or a complete interruption in neuronal firing.

It is well established that electrographic seizures are associated with large increases in interstitial potassium concentration (Sykova 1983). It has been proposed that interstitial potassium ($[K^+]_o$) accumulation could play a causal role in seizure development (Dichter et al. 1972; Fertziger and Ranck 1970; Somjen 1979). It is generally held that intense neuronal firing contributes, in a feed-forward manner, to each potassium wave (Fertziger and Ranck 1970; Fisher et al. 1976; Patrylo et al. 1996; Yaari et al. 1986a).

In this report, we tested the hypotheses that during ictal epileptiform events, $[K^+]_o$ can increase sufficiently to induce depolarization block, that this (rather than neuronal desynchronization) accounts for the loss of population spikes, and that $[K^+]_o$ transients can be sustained in the *absence* of neuronal firing. In addition, we investigated the role of persistent sodium currents in the generation of depolarization block during electrographic seizures. We used the low-$Ca^{2+}$ model of epilepsy (Jefferys and Haas 1982; Taylor and Dudek 1982; Yaari et al. 1983) in which ictal events include periods of population spike disruption and in which synaptic transmission is blocked (Jones and Heinemann 1987).

Some of the results in this paper have been reported in abstract form (Fox et al. 2002).

## METHODS

Transverse hippocampal slices (400 $\mu$m) were prepared from male Sprague-Dawley rats (160–225 g; anesthetized with ketamine and medetomidine). Experiments were performed under the UK "Animals (Scientific Procedures) Act, 1986." The slices were submerged in a holding chamber filled with "normal" artificial cerebro-spinal fluid (ACSF) consisting of (in mM) 125 NaCl, 26 $NaHCO_3$, 3 KCl, 2 $CaCl_2$, 1.0 $MgCl_2$, 1.25 $NaH_2PO_4$, and 10 glucose. After >60 min, slices were transferred to an interface recording chamber.

Spontaneous activity was induced by perfusion of slices for >60 min with "low-$Ca^{2+}$" ACSF (35°C) consisting of (in mM) 125 NaCl, 26 $NaHCO_3$, 5 KCl, 0.2 $CaCl_2$, 1.0 $MgCl_2$, 1.25 $NaH_2PO_4$, and 10 glucose. Only slices with spontaneous "ictal" bursts >3 mV amplitude and >10 s duration were accepted as electrographic seizures in this study (shorter duration events have more variable characteristics; Bikson et al. 1999; Patrylo et al. 1996).

Antidromic stimulation (200 $\mu$s) was applied via a bipolar Nichrome wire (50 $\mu$m) electrode using a constant-current stimulator (DS-3, Digitimer, Hertfordshire, UK). Tetrodotoxin (TTX) was obtained from Alomone Labs (Jerusalem, Israel). Phenytoin and veratridine were obtained from Sigma (Dorset, UK). The stock solution of veratridine (0.1 mM) was made with 0.1 mM HCl.

"Uniform" extracellular DC electric fields were applied parallel to the somatic-dendritic axis of the CA1 region as described previously (Durand and Bikson 2001; Jefferys 1981). The waveforms applied to parallel Ag/AgCl wires were generated by a voltage stimulator (Digitimer, DS-2, Hertfordshire, UK), and converted to a constant current by a stimulus isolation unit (BAK Electronics BSI-1, Mount Airy, MD). The electric field (mV/mm) in the chamber was calibrated using two recording electrodes separated by 0.5 mm and depended linearly

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on the applied current. Anodic or cathodic stimulation on the alveus side of the CA1 region is defined as positive and negative fields, respectively.

All recordings were made from the CA1 pyramidal cell layer. Extracellular field potentials were recorded with glass micropipettes (2–8 MΩ) filled with low-$Ca^{2+}$ ACSF. In applied field experiments, the potential from a second electrode, placed in the bath near an isopotential line, was subtracted (Bikson et al. 2001). Intracellular glass micropipettes were filled with 2 M potassium methylsulphate and had resistances of 60–120 MΩ. Pyramidal neurons had an average resting membrane potential of −58 ± 11 (SD) mV and average action potential amplitude of 64 ± 10 mV.

Recordings of extracellular concentration of potassium ions ($[K^+]_o$) were performed using double-barreled ion-sensitive microelectrodes. One channel was backfilled with low-$Ca^{2+}$ ACSF as the reference channel. The ion-sensing channel was backfilled with 100 mM KCl solution, and its tip was silanized and loaded with a valinomycin ion exchanger (FLUKA 60398). Calibrations against 1, 10, and 100 mM $[K^+]$ (fixed 152.25 mM $[Na^+]$ background) were used to calculate $[K^+]_o$ on a linear scale.

All signals were amplified and low-pass filtered (1–10 kHz) with an Axoclamp-2B or 2A (Axon Instruments) and Neurolog NL-106 and NL-125 amplifiers (Digitimer) and digitized using a Power 1401 and Signal software (Cambridge Electronic Design, Cambridge, UK). Results are reported as mean ± SD ($n$ = number of slices or cells); changes were considered significant if $P < 0.05$ using Student's $t$-test.

## RESULTS

### *Low-$Ca^{2+}$ burst waveform and associated potassium transients*

Low-$Ca^{2+}$ bursts are characterized by a slow extracellular field shift often with superimposed fast population spikes (due to synchronized neuronal firing). While previous data have indicated variability in the amplitude of these superimposed population spikes (Jefferys and Haas 1982; Patrylo et al. 1996; Yaari et al. 1983), the source and significance of this variability has not previously been determined. We classified events in which population spikes were disrupted (<0.7 mV) continuously for 2–15 s as "intermittent-spiking" bursts and the remainder as "persistent-spiking" bursts (all bursts >10 s, see METHODS); in 59% of cases, bursts were intermittent spiking, and in 41%, persistent spiking.

Consistent with previous studies (Haas and Jefferys 1984; Jefferys and Haas 1982; Yaari et al. 1983), each low-$Ca^{2+}$ field burst was associated with a transient increase in $[K^+]_o$ that persisted for the entire duration of the slow extracellular field shift (Fig. 1, *A* and *B*). We found no significant difference in the average $[K^+]_o$ peak or duration of the $[K^+]_o$ transient "plateau" (>8 mM) recorded during persistent-spike bursts versus intermittent-spike bursts (12.4 ± 1.1 vs. 12.2 ± 0.9 mM and 11.2 ± 4.0 vs. 13.5 ± 3.2 s; 5 slices for each burst type). Burst termination was characterized by a relatively rapid (approximately 3 s) decrease in $[K^+]_o$ (Fig. 1, *A* and *B*, *).

### *Simultaneous field and intracellular recording during ictal bursting*

The interruption of population spikes during ictal bursting could reflect either the desynchronized firing of neurons or a complete lack of action potential generation. To differentiate between these possibilities, we determined the intracellular correlate of each burst type. Only intracellular activity >500 ms after burst initiation was analyzed (Bikson et al. 2003).

Persistent-spiking bursts were associated with a neuronal depolarization surmounted by action potentials ($n$ = 7, Fig. 1*C*;

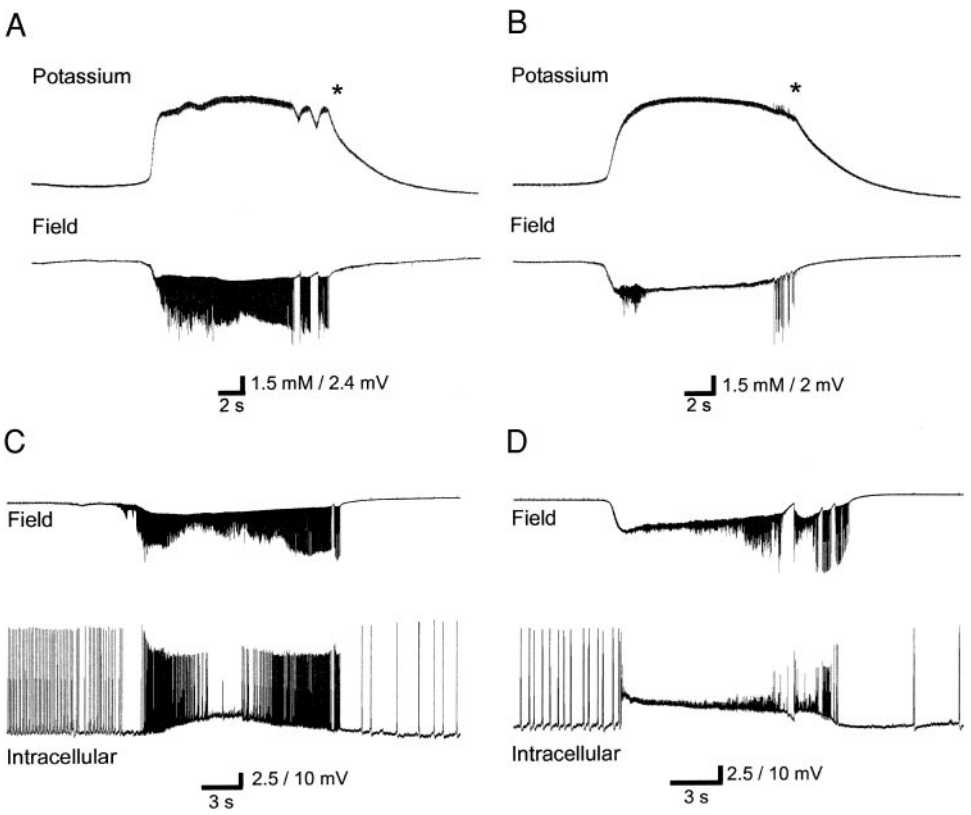


FIG. 1. Extracellular potassium and intracellular correlates of intermittent- and persistent-spiking bursts. Spontaneous activity was recorded in the CA1 hippocampal region after a 60-min exposure to low-$Ca^{2+}$ artificial cerebrospinal fluid (ACSF). Simultaneous field and extracellular potassium recording during a persistent-spiking (*A*) and an intermittent-spiking burst (*B*). Note that extracellular potassium transients persisted for the entire duration of the event, even while population spikes stopped. Extracellular potassium decreased rapidly at burst termination (star). Extracellular potassium is plotted on a linear scale; baseline potassium = 5 mM. *C* and *D*: simultaneous field and intracellular recording from the pyramidal cell layer during a persistent-spiking (*C*) and an intermittent-spiking burst (*D*).

Agopyan and Avoli 1988; Albrecht et al. 1989; Haas and Jefferys 1984; Jefferys and Haas 1982). Individual neurons fired in phase with a majority of large (>2 mV) population spikes. Neurons fired irregularly, but still in phase, with small population spikes. During persistent-spike bursts, brief (<2 s) interruptions in population spike generation were associated with a cessation in cell firing.

Pyramidal neurons were also depolarized for the entire duration of intermittent-spiking field bursts. All neurons stopped firing during interruptions in population spike generation ($n$ = 23, Figs. 1*D* and 2*A*); stoppages in neuronal firing occurred during the maximal cell depolarization. Small aborted action potentials appeared as the membrane potential recovered from its peak depolarization and full-size action potentials re-appeared if large population spikes resumed.

The source of prolonged action potential disruption during intermittent-spiking bursts was investigated. Changes in membrane resistance during bursts were monitored with brief hyperpolarizing steps (Fig. 2*B*). Depolarization was associated with a significant decrease in input resistance (from 31.2 ± 11.7 to 20.2 ± 12 MΩ; $n$ = 9). The peak transmembrane (intracellular minus extracellular) depolarization during intermittent-spiking bursts (15.1 ± 5.7 mV) was significantly higher than during persistent-spiking (10.3 ± 3.7 mV). To determine whether depolarization block contributed to action potential suppression during intermittent-spiking bursts, cells were hyperpolarized with tonic current injection. Hyperpolarization induced action potential generation during intermittent-spiking field bursts in 10 of 15 neurons tested (Fig. 2, *C* and *D*); in the remaining 5 neurons, spontaneous action potentials were not completely suppressed at any of the current injections tested, suggesting poor space clamp.

To confirm that during prolonged population spike interruption neurons were inactivated (incapable of generating action potentials) rather than "at rest," neurons were excited by antidromic stimulation. During the inter-burst (control) period, antidromic stimulation triggered large population spikes and could develop into an ictal burst (Haas and Jefferys 1984). Stimulation *during* a burst when population spikes were interrupted triggered a dramatically reduced population spike (minimum amplitude 11.7 ± 7.4% of control, $n$ = 4, data not shown), indicating that a majority of neurons were in a nonexcitable state.

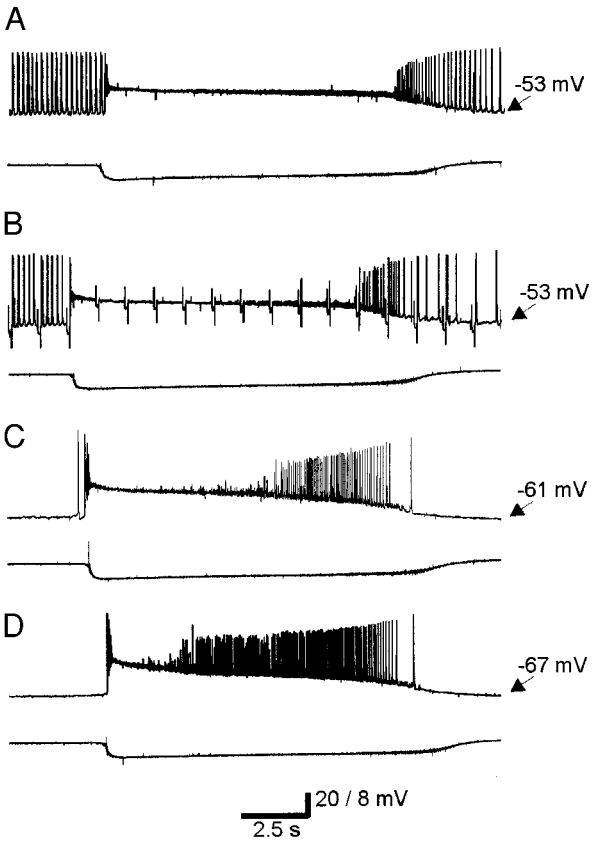


FIG. 2. Intracellular current injection during intermittent-spiking bursts. Simultaneous field and intracellular recording from the CA1 hippocampal region during intermittent-spiking bursting induced by low-$Ca^{2+}$ perfusion. *A*: no current injection. *B*: brief hyperpolarizing pulses were applied every 1 s to measure cell input resistance before, during, and after a field burst. *C* and *D*: constant current was injected to hyperpolarize the cell.

### *Effect of uniform electric fields on burst waveform*

Application of uniform extracellular electric fields produces a rapid membrane polarization in all CA1 pyramidal cells. Positive (anode on alveus side) fields produce hyperpolarization of the normal spike initiation zone (soma and proximal axon), while negative fields induce somatic/axonal depolarization (Durand and Bikson 2001).

Application of positive fields during persistent-spiking bursts reduced the slow field shift amplitude and could suppress population spike generation ($n$ = 3 slices; Fig. 3*A*, *middle*). After termination of polarization, population spikes resumed as the slow field shift returned to prefield levels. Application of negative (depolarizing at the soma) fields during persistent-spiking bursting also *suppressed* population spike generation (Fig. 3*A*, *bottom*) but did not affect the average duration of each burst (106.4 ± 9.1% control), indicating that excessive neuronal depolarization during ictal bursts can suppress population spike generation without necessarily interfering with burst maintenance.

Application of positive fields during intermittent-spiking bursts induced a gradual decay in the slow field shift amplitude ($n$ = 6; Fig. 3*B*, *middle*). In three of six slices, population spikes were *induced* during positive (hyperpolarizing at the soma) field application. In all slices, after termination of the polarization, population spikes were observed until the slow field shift returned to prepolarization levels. Application of negative fields during intermittent-spiking bursts either slightly increased or did not affect the amplitude of the slow extracellular field shift (Fig. 3*B*, *bottom*) and failed to elicit population spikes.

### *Role of persistent sodium currents*

Extracellular [$Ca^{2+}$] reduction enhances persistent sodium currents (Su et al. 2001). Previous studies have shown that anticonvulsants known to block persistent sodium currents can suppress low-$Ca^{2+}$ burst initiation (Heinemann et al. 1985; Rose et al. 1986). Here we tested the effects of modulating persistent sodium currents in shaping the ictal burst waveform.

Veratridine, which enhances the persistent sodium current (Alkadhi and Tian 1996), was added to slices exhibiting persistent-spiking bursts. Veratridine (0.2–0.3 μM, approximately

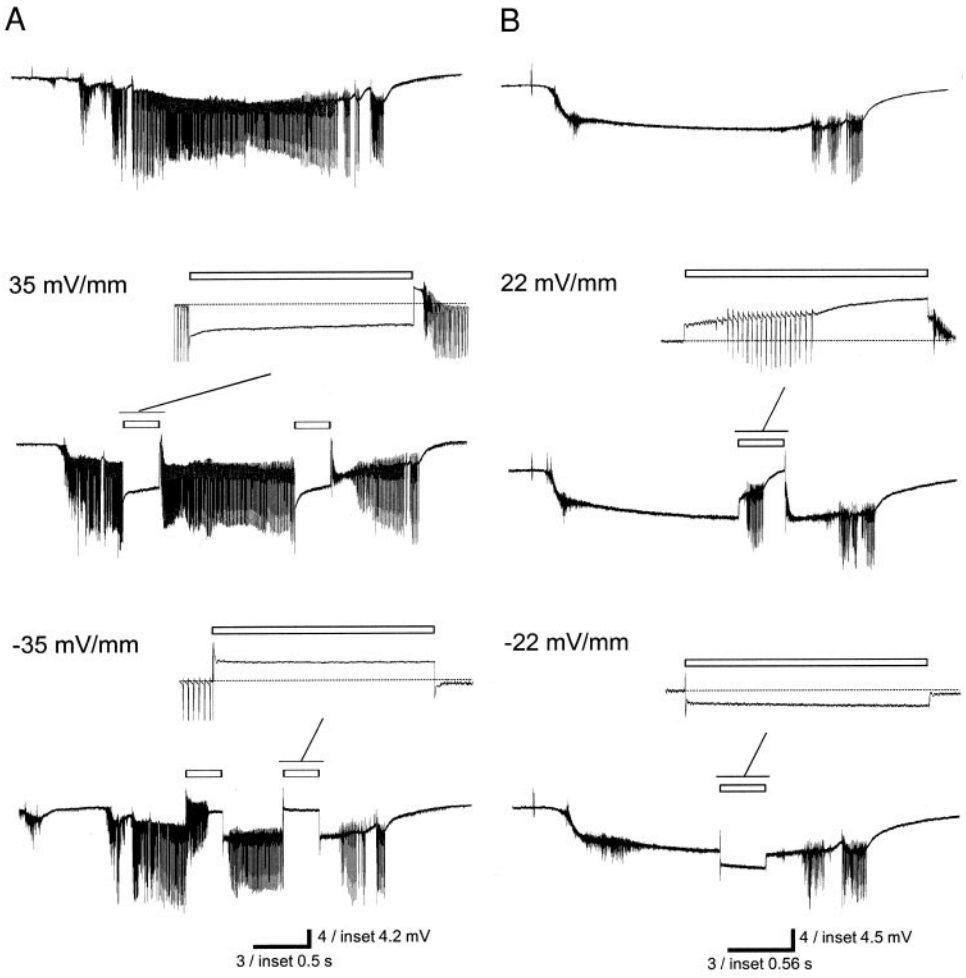


FIG. 3. Effect of applied uniform electric fields on low-$Ca^{2+}$ burst waveform. Control persistent-spiking burst (*A, top*) and intermittent-spiking bursting (*B, top*). Positive (*middle*) or negative (*bottom*) fields were applied (2-s pulses at open bars) during each burst type. Application of fields results in a square wave stimulus artifact (whose direction depends on the isopotential electrode position) for the duration of stimulation on which endogenous slow voltage shifts and population spikes, when present, can still be measured.

20 min, $n = 5$) resulted in increases in the amplitude (to 128 ± 28% of control) and duration (to 158 ± 53% of control) of the slow field shift and a transition to intermittent-spiking bursts (Fig. 4*A*). In four of five slices, this was followed by spreading depression (Fig. 4*A*, *).

Under reduced-$[Ca^{2+}]_o$ conditions, in acute hippocampal slices, phenytoin (<100 μM) preferentially blocks the persistent sodium current (Su et al. 2001; Tunnicliff 1996; Yaari et al. 1986b). Phenytoin was added to slices exhibiting intermittent-spiking bursts. After 20 min, phenytoin (25–50 μM) caused a decrease in the amplitude (73 ± 16% control) and duration (78 ± 10% control) of the slow field shift and a transition to persistent-spiking bursts in five of six slices tested (Fig. 4), in the remaining slice burst duration decreased below 10 s. This *enhancement* of population spikes by the anticonvulsant, phenytoin, is consistent with a role for depolarization block in suppressing action potential generation.

Acute application of low concentrations of TTX can block the persistent sodium current without markedly decreasing action potential amplitude (Su et al. 2001). TTX was added to slices exhibiting intermittent-spiking bursts. After 20–40 min, TTX (50 nM) caused a transition to persistent-spiking bursts in three of nine slices tested; in the remaining slices, burst type was not changed or burst duration decreased below 10 s. This variability may reflect the narrow concentration "window" in which TTX will depress the persistent sodium conductance in a population of neurons without affecting action potential generation. The transition to persistent-spike bursting (Fig. 4; $n = 3$) was not associated with a consistent change in slow field shift amplitude (106 ± 20% control) or duration (83 ± 12% control); however, peak population spike amplitude was significantly *increased* (120 ± 15% control). Application of higher (100–150 nM) TTX concentrations caused a decrease in burst duration below 10 s and could completely suppress epileptiform activity ($n = 7$; data not shown).

## DISCUSSION

Our results show that the prolonged interruptions in population spike generation during (>10 s) low-$Ca^{2+}$ electrographic seizures result from the depolarization block of neurons. Moderate decreases in population spike amplitude are likely to reflect *1*) a decreased likelihood that any individual pyramidal cell will fire at all (rather than fire out of phase with other neurons) and/or *2*) a decrease in average action potential size.

### *Potassium release in the absence of neuronal firing*

The main conclusion of this study is that neuronal firing is not required for the maintenance of in vitro ictal events; the duration of ictal bursts (Figs. 3*A*, *bottom*, and 4) and the associated $[K^+]_o$ transients were not necessarily dependent on continued neuronal firing. Extracellular potassium concentra-

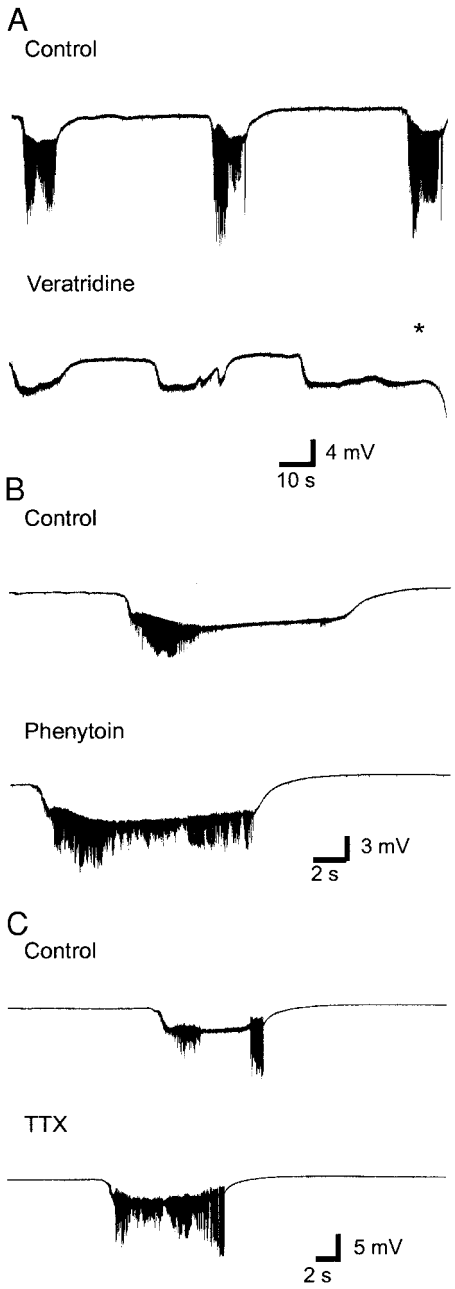


FIG. 4. Effect of veratridine, phenytoin, and tetrodotoxin (TTX) on epileptiform burst waveform. During perfusion with low-$Ca^{2+}$ media, spontaneous field bursts were monitored with an electrode in the CA1 pyramidal cell layer. *A*: effect of addition of veratridine (200 nM) to the perfusate. Note that addition of veratridine eventually led to spreading depression (*). *B*: effect of addition of phenytoin (25 $\mu$M, 20 min) to the perfusate. *C*: effect of addition of TTX (50 nM) to the perfusate.

tion remained elevated during neuronal firing interruptions (Fig. 1) that lasted much longer than the time needed for $[K^+]_o$ clearance (Fig. 1, *A* and *B*, *; Lux et al. 1986); this indicates that potassium must be released by an action potential-independent mechanism. The continued release of potassium during neuronal depolarization block requires both open potassium channels and a driving force for potassium efflux; persistent inward currents would depolarize the membrane providing the driving force and helping maintain open potassium channels. This is consistent with the decrease in membrane resistance during ictal bursts (Fig. 2*B*). In the experimental conditions used in this study (i.e., in the absence of neurotransmitter release or electrical stimulation), it is unlikely that glial cells contribute to the elevated $[K^+]_o$ (Bikson et al. 2001; Somjen 1979; Sykova 1983).

The prolonged $[K^+]_o$ "plateau" during some bursts (Fig. 1, *A* and *B*) and insensitivity of peak $[K^+]_o$ to burst type suggest potassium clearance mechanisms, probably with a major contribution from glia, maintain $[K^+]_o$ at a "ceiling" (Somjen 1979; Sykova 1983) level over a range of neuronal potassium release rates.

### *Persistent sodium currents and depolarization block*

Since no relationship was found between $[K^+]_o$ measured in stratum pyramidale and population spike disruption, other factors must also contribute to the generation of the larger membrane depolarization (depolarization block) observed during intermittent-spiking events. Our results suggest that activation of persistent inward currents promoted the generation of depolarization block (Fig. 4). In addition, the spatial distribution of $[K^+]_o$ transients outside the pyramidal cell layer (Yaari et al. 1986a) or reductions in $[K^+]_i$ (Kager et al. 2000) may contribute to membrane depolarization.

The persistent sodium current is depressed by several clinically useful anticonvulsants (Bialer et al. 1999). Moreover, enhancement of persistent sodium currents has been linked to seizure generation in several animal models and with specific human epilepsy phenotypes (Bikson et al. 2002; Kearney et al. 2001; Meisler et al. 2001). Persistent sodium current dependent bursting of individual neurons (Jensen and Yaari 1997; Segal 1994) has been suggested to underlie these correlations. We propose that the persistent-sodium current may also facilitate the generation of electrographic seizures by promoting potassium release from both spiking neurons and neurons in depolarization block (Fox et al. 2002).

### *General relevance*

Cases of depolarization and disruption of individual neuronal firing have been reported in several animal epilepsy models in vitro (Albrecht et al. 1989; Avoli et al. 1990; Konnerth et al. 1986; Somjen et al. 1985; Traynelis and Dingledine 1988) and in vivo (Bragin et al. 1997; Dichter et al. 1972; Kandel and Spencer 1961) and in human tissue (Avoli et al. 1999; Babb et al. 1987). Our results suggest that, when electrographic seizures continue through periods of severely reduced population spike activity, the majority of neurons, at the focus, are in depolarization block. Regions to which this focus projects may experience increased afferent input, depending on axonal responses to tonic depolarization and elevated $[K]_o$, but any such input will be asynchronous and would result in a more widespread reduction in synchronized neuronal activity (Alarcon et al. 1995; Netoff and Schiff 2002).

If depolarization block occurs during human epileptic seizures, its most extreme manifestation would be the suppression of rhythmic EEG activity. Meyer et al. (1966) describe focal clinical seizures that were accompanied by a diminution in the amplitude of EEG activity; despite the lack of large repetitive spikes in the EEG, they observed a net loss of potassium from the brain. Ikeda et al. (1999a) have also shown that the tonic

phase of a focal seizure can be accompanied by an electrodecremental pattern in the EEG. Focal electrodecremental events can also be seen in some EEG (Alarcon et al. 1995; Blume et al. 1984) and subdural recordings immediately prior to a clinical seizure; these events can be associated with negative DC shifts, which could result from potassium accumulation (Ikeda et al. 1996; Ikeda et al. 1999b). The results of this study raise the possibility that reductions in activity at an epileptic focus might result, not from desynchronization or inhibition of neuronal activity, but from the development of depolarization block, during which potassium release would continue.

## DISCLOSURES

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