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Research report

Nonlinear dynamic properties of low calcium-induced epileptiform activity

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Abstract

The analysis of the dynamic properties of epileptiform activity in vitro has led to a better understanding of the time course of neural synchronization and seizure states. Nonlinear analysis is thus potentially useful for the prediction of seizure onset. We have used nonlinear analysis methods to investigate the development of activity in the low calcium model of epilepsy in brain slices. This model is particularly interesting since neurons synchronize in the absence of synaptic transmission. The dynamic properties calculated from extracellular recordings of activity were used to analyze the transition to synchronous firing and their relation to neuronal excitability. The global embedding dimension, local dimension and the Lyapunov exponent were calculated from time segments corresponding to the onset, transition and fully developed stages of activity. The analysis was repeated for recordings made in the presence of various levels of DC electric fields to modulate neuronal excitability. The global and local dimensions did not change once activity was first initiated, even in the presence of the electric field. The maximum Lyapunov exponents increased during the onset of activity but decreased when the applied hyperpolarizing electric field was large enough to partially suppress the activity. These findings establish a relationship between neuronal excitability and the maximum Lyapunov exponent, and suggest that the Lyapunov exponent may be used to distinguish between various states of the neural network and might be important in seizure prediction and control. © 2001 Elsevier Science B.V. All rights reserved.

Theme: Disorders of the nervous system

Topic: Epilepsy: human studies and animal models

Keywords: Electric field; Dimension; Lyapunov exponent; Excitability

1. Introduction

Epilepsy is a central nervous system disorder characterized by a sudden, synchronized, and excessive discharge in a population of neurons. The mechanisms involved in triggering the initiation, spread and termination of epileptic seizures in vivo are not well understood. The use of nonlinear measures to characterize epileptiform activity has led to a better understanding of basic mechanisms both in animal experiments and in humans. Spontaneous epileptiform bursts induced in high K^+ and zero Mg^{2+} have been characterized as chaotic [23]. Chaos control and anticontrol theory have been creatively applied to the control of electrical discharges in brain slices perfused with a high potassium solution to induce epileptiform activity [21]. Nonlinear analysis methods promise to be important tools for clinical practice [19,20].

Reducing extracellular calcium ($[Ca^{2+}]_o$) is a method of inducing epileptiform activity in rat hippocampal brain slices that effectively blocks all chemical synaptic transmission [13,14,27]. The low $[Ca^{2+}]_o$ model retains many characteristics of focal hippocampal seizures in vivo, including a focal origin and local spread, a gradual increase in synchronicity and post-event refractoriness [6,17]. However its dynamical properties have not yet been studied. In this paper, we calculated the global embedding dimension, the local dimension and the Lyapunov exponent for extracellular recordings of low $[Ca^{2+}]_o$ activity. Values calculated at various stages were compared in an effort to detect the development of generation of activity.

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In order to test the hypothesis that there is a direct correlation between some dynamic parameters and neuronal excitability, the dynamic properties of the activity were studied as a function of neuronal excitability. The levels of excitability of hippocampal pyramidal cells can be determined from the duration of afterdischarges generated by antidromic stimulation [28]. Electric fields in the central nervous system are known to play a significant role in modulating neuronal excitability [8,17,24]. Low-amplitude DC fields can suppress events in the low $[Ca^{2+}]_o$ model of epileptiform activity by reducing excitability [9]. In order to further establish the relationship between excitability and nonlinear dynamic properties, external DC electric fields were applied to modulate low $[Ca^{2+}]_o$ activity. We calculated and analyzed nonlinear dynamic parameters from field recordings taken in the presence of electric fields, which were normalized as a fraction of the field required for total block.

2. Materials and methods

2.1. Experimental protocols

All experiments were performed in the CA1 pyramidal cell region of hippocampal brain slices prepared from Sprague–Dawley rats (125–175 g). Rats were anesthetized using ethyl ether and decapitated. The brain was rapidly removed and one hemisphere glued to the stage of a tissue slicer (Vibroslicer, Campden). Slicing was carried out in cold (3–4°C) oxygenated sucrose-based artificial cerebrospinal fluid (ACSF) consisting of (in mM): Sucrose 220, KCl 3, NaH_2PO_4 1.25, $MgSO_4$ 2, $NaHCO_3$ 26, $CaCl_2$ 2, and dextrose 10. Sucrose-based slicing medium has been shown to increase cell viability in vitro [4]. The resulting 350-μm slices were maintained in a holding chamber filled with artificial cerebrospinal fluid (ACSF) at room temperature and bubbled with 95% O_2–5% CO_2. ACSF has the following composition (in mM): NaCl 124, KCl 3.75, KH_2PO_4 1.25, $CaCl_2$ 2.0, $MgSO_4$ 2.0, $NaHCO_3$ 26, and dextrose 10. After at least 1 h of recovery, slices were transferred to a standard interface recording chamber perfused with normal ACSF at 35±0.5°C, and exposed to a warmed, humidified 95% O_2–5% CO_2 vapor maintained over the surface of the slice. After testing for viability, the solution was switched to low $[Ca^{2+}]_o$ ACSF with the following composition (in mM): NaCl 124, KCl 4.75, KH_2PO_4 1.25, $CaCl_2$ 0.2, $MgSO_4$ 1.5, $NaHCO_3$ 26, and dextrose 10. Prolonged incubation (20–30 min) in this 'low $[Ca^{2+}]_o$' ACSF resulted in spontaneous epileptiform activity in the CA1 region. Extracellular recordings were made with 150 mM NaCl-filled glass microelectrodes (5–10 MΩ). All recordings were obtained from the stratum pyramidale in the CA1 area. Two parallel Ag/AgCl wire electrodes were placed on opposite sides of the interface chamber. Uniform electric fields (1–5 mV/mm) were generated across individual slices through a waveform generator (Wavetek) and a current converter (Grass Instrument Co.) (Fig. 1). The recorded signals were amplified and low-pass filtered (100 Hz) with an Axoprobe-1A amplifier (Axon Instruments), an FLA-01 amplifier (Cygnus Technology Inc.) and finally stored on videotape. The stored data was transferred with a sampling rate of 300 Hz to a personal computer using National Instruments NB-MIO-16L board and LabView software. For experiments using antidromic stimulation to measure neuronal excitability, a GRASS-S 88 (Grass Instrument Co.) was used to stimulate the alveus and evoke population spikes. The response was sampled at 3 kHz and low-pass filtered at 1 kHz.

2.2. Data analysis

The dynamic features of low $[Ca^{2+}]_o$-induced seizure-like activity were analyzed using recently developed nonlinear dynamics tools [1]. The global embedding dimension d_E, local dimension d_L and the Lyapunov exponent λ are estimated in this paper using cspW (Contemporary Processor for Windows 95, Applied Nonlinear Sciences, LLC/Randle Inc.). The accuracy of the software has been checked on well characterized oscillators such as Lorenz equations. The dynamic dimensions and the Lyapunov exponent are computed in sequence after the time delay is determined with the AMI (average mutual information) algorithm. The computation is performed on data segments of length 5 min and 10 min long in Sections 3.1 and 3.2, respectively.

From a set of observations $\{x(n)\}$, a set of vectors defined as $Y = \{y(n) \in R^d: y(n) = x(n), x(n+T), \ldots, x(n+(d-1)T)\}$ are used to trace out an orbit of the system, where d is the number of observations in the vector and T is the sample interval. The minimum dimension that unfolds the attractor so that there is no overlap in unfolding an observed orbit is the global dimension d_E. Though the minimum embedding dimension d_E or any larger dimension can be used for analysis, dimensions larger than d_E lead to excessive computation in subsequent calculations, e.g. the Lyapunov exponent [15]. The calculation of d_E is based on the differentiation of 'true' neighbors and 'false' neighbors in orbits $y(n)$ when the dimension is increased from d to $d+1$ [2].

After obtaining the global embedding dimension, a fixed number of neighbors of reference point y_0 are chosen. The points in this neighborhood are projected to the trial dimension d and if the computed nearest neighbor can pass the 'local false neighbor' test, we call this dimension local dimension, d_L [3]. The local geometry and dynamics of an attractor are described in a space with dimension d_L. When $d_L < d_E$, it should be possible to apply a smooth state–space transformation to the data to further unfold the attractor from a set in R^{d_E} to one in R^{d_L} without losing any important dynamical features [3]. The local dimension d_L

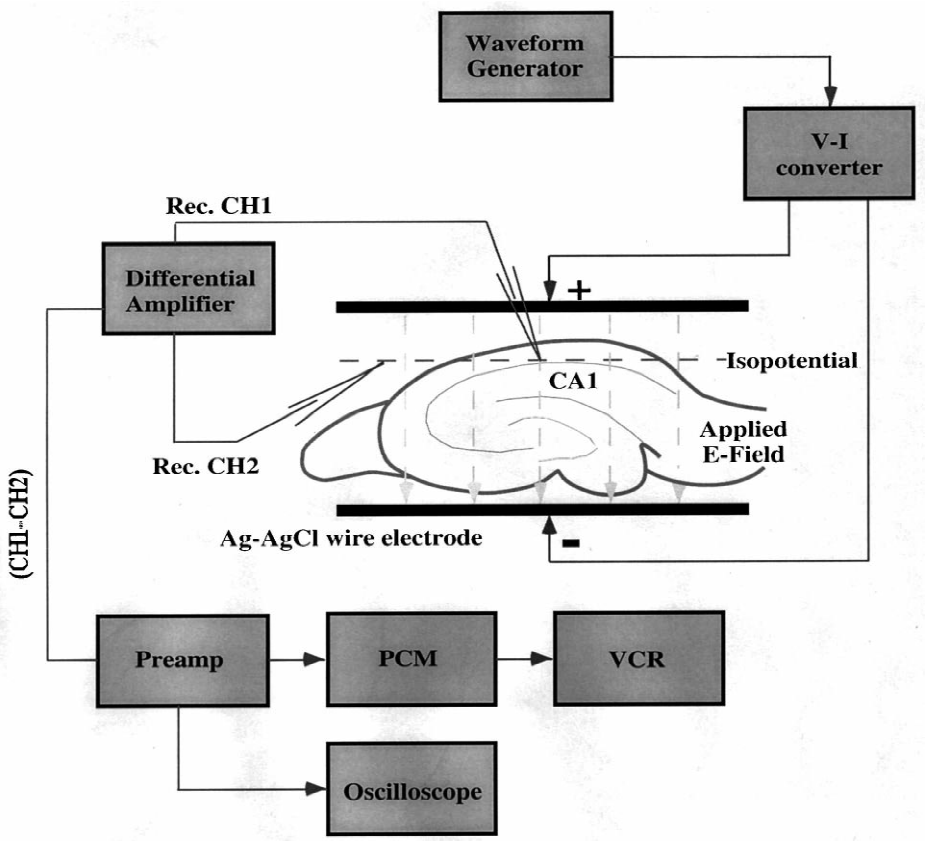

Fig. 1. Experimental setup for the application of uniform fields across hippocampal slices. The fields were generated by passing current between two parallel AgCl-coated silver wires. Spontaneous epileptiform activity was monitored with a field electrode (CH1) positioned in the stratum pyramidale. The stimulus artifact was removed from the field recording by subtraction of the voltage recorded at an isopotential (CH2).

is invariant under state–space coordinate transformations which are of smooth diffeomorphisms and thus is useful in classifying dynamic states.

The Lyapunov or characteristic exponents are an indication of the rate of convergence or divergence in phase space of the trajectories of a dynamical system [7]. If one or more of them is positive, then trajectories that are initially nearby will diverge over time. cspW was used to calculate the Lyapunov exponent according to the following algorithm. First, local neighborhood-to-neighborhood mappings are approximated by a third-order Taylor series. The linear term of the series is the Jacobian of this system. Following the reconstructed trajectory, the Jacobian matrices are multiplied together. The log of eigenvalues of this matrix give the Lyapunov exponents λ_i. In this analysis, only the maximum exponent λ_{max} was used to characterize various states of the system.

3. Results

3.1. Dynamic properties of low calcium activity during its development

In rat hippocampal slices synaptic transmission was blocked within 5–10 min following perfusion with low $[Ca^{2+}]_o$ (<0.2 mM) solution [12] and this effect was confirmed by the method of orthodromic stimulation. Negative field shifts, characteristic of this activity, began to appear after the slice had been in solution for ~15 min. The development of low $[Ca^{2+}]_o$ events was monitored by recording 5-min data windows during the onset, transition and fully developed stages of activity. These windows were recorded when the slice was exposed to low $[Ca^{2+}]_o$ solution for 20 min, 35 min and 50 min respectively.

Fig. 2A–C shows representative field bursts from each of the three sample windows (Onset: 20-min group; Transition: 35-min group; Fully developed: 50-min group). The average frequency of the events ($\pm$S.D.) for each window ($n=7$ slices) is 14.80 ± 8.32, 10.23 ± 4.26, and 6.92 ± 3.41 (Events/100 s) respectively; the average amplitude ($\pm$S.D.) measured from the baseline to the most negative point of the event is 0.21 ± 0.05, 1.12 ± 0.33, and 1.56 ± 0.70 (mV), respectively. The three windows have significantly different frequencies and amplitudes as determined by an analysis of variance (ANOVA) test ($P<0.05$) [25]. Though the amplitude of the fully developed activity (50-min group) is significantly larger than that in the onset stage (20-min group), the frequency is significantly reduced as several small events merge to become single large potential shift.

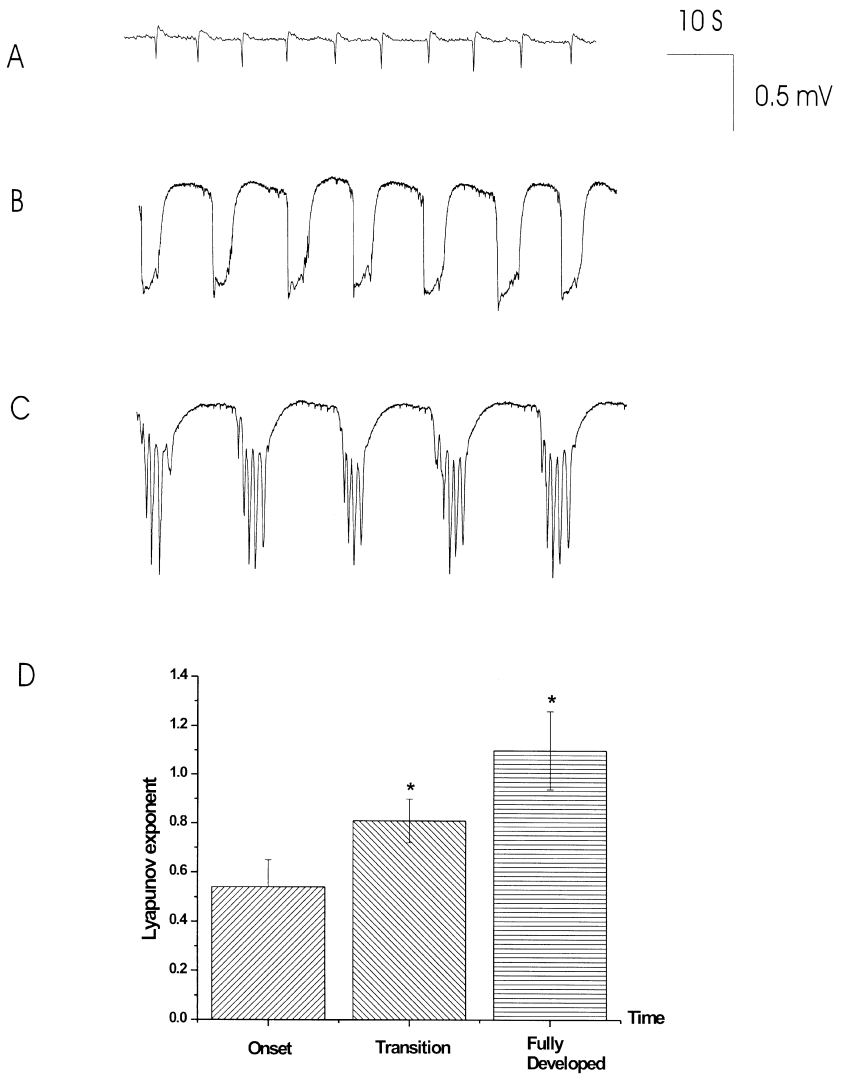

Fig. 2. Development of low $[Ca^{2+}]_o$-induced epileptiform activity. The extracellular recordings indicate the onset (A), transition (B), and fully developed (C) stages of activity. Recordings were made 20, 35 and 50 min respectively following perfusion with low $[Ca^{2+}]_o$ solution. Note that amplitude increases but frequency decreases in each progressive stage. (D) The maximum Lyapunov exponents calculated for 5-min windows at each stage.

The level of neuronal excitability was quantified by measuring the duration (D) (Fig. 3A) of the response to antidromic stimulation [28]. In separate experiments, slices ($n=4$) were exposed to low $[Ca^{2+}]_o$ solution and excitability was measured during the three windows. As activity developed, the response duration gradually increased (Fig. 3B, 40 trials for each group), indicating increased excitability.

The global dimension, local dimension and λ_{max} of the activity were calculated for the three time windows ($n=7$ slices). Once activity began, the local and global dimensions remained constant at 5 and 6, respectively, from the early developing period throughout the fully developed stage. This suggests that the dynamics of the activity may be captured in a model of low dimension. Invariance of dynamic dimensions implies that the governing dynamics during the development of low $[Ca^{2+}]_o$ are stable with respect to the number of degrees of freedom.

λ_{max} of the activity for the three windows were 0.54 ± 0.11 (Onset), 0.81 ± 0.09 (Transition) and 1.10 ± 0.16 (Fully developed) (Fig. 2D). Although the global and local dimensions of the three groups were the same, their Lyapunov exponents differed significantly ($P<0.05$). These results suggest that the system becomes more unpredictable as activity develops.

Measurement of Lyapunov exponent is currently considered the most efficient method for distinguishing chaotic from nonchaotic behavior. For a chaotic system at least one Lyapunov exponent must be positive. We found at least one positive Lyapunov exponent in all samples ($n=16$ slices) with fully developed spontaneous activity. The power spectrum of these samples (Fig. 4A) resembles wide band noise and is another characteristic of chaotic systems [16]. Fig. 4B shows a reconstructed two-dimension attractor using a time delay of 0.5s. The reconstructed attractor has fuzzy boundaries compared to the simple closed loop expected for a limit cycle. This is the further evidence of the chaotic nature of the system [26].

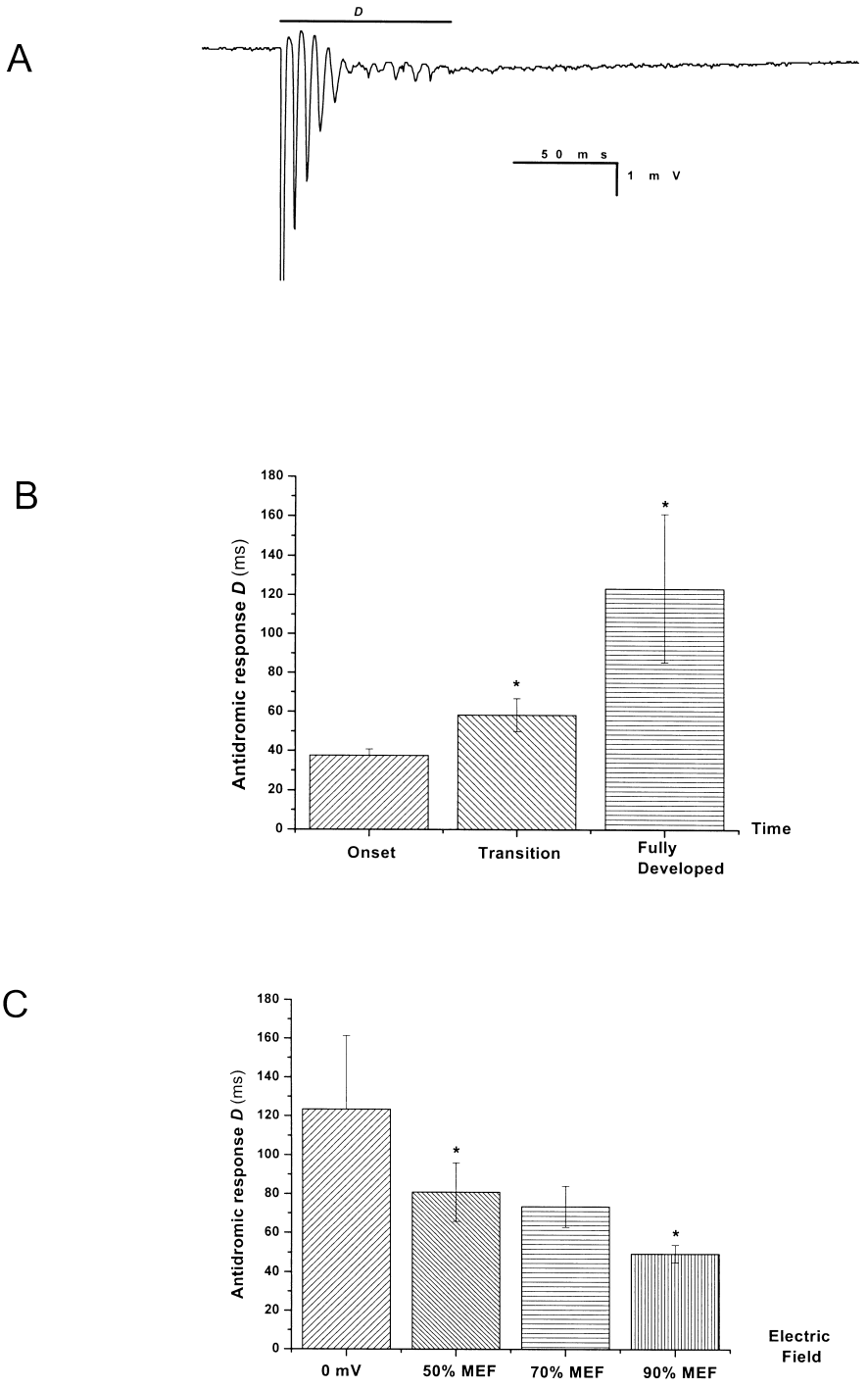

Fig. 3. Antidromic response of hippocampal neuron. Two hundred μA 200-μs pulses were delivered at alveus. (A) The duration (*D*) of the afterdischarge, which was recorded in CA1 layer, is the indicator of neuronal excitability. (B) The duration of the afterdischarge of onset, transition, and fully developed stages of the activity. (C) The duration of the afterdischarge in the presence of electric fields. MEF is defined in Fig. 5.

3.2. Effects of applied electric fields on the dynamic properties of low calcium activity

The effect of long duration DC electric fields on the dynamic properties of low $[Ca^{2+}]_o$ activity was studied ($n=9$ slices) using a hyperpolarizing orientation. After activity was fully developed, the minimum electric field (MEF) required to block a single event was determined and used as a reference value. Any electric field with the amplitude over this threshold has been shown effective to annihilate events and superimposed population spikes [9,29]. Electric fields with amplitude of 0 mV, 50% MEF,

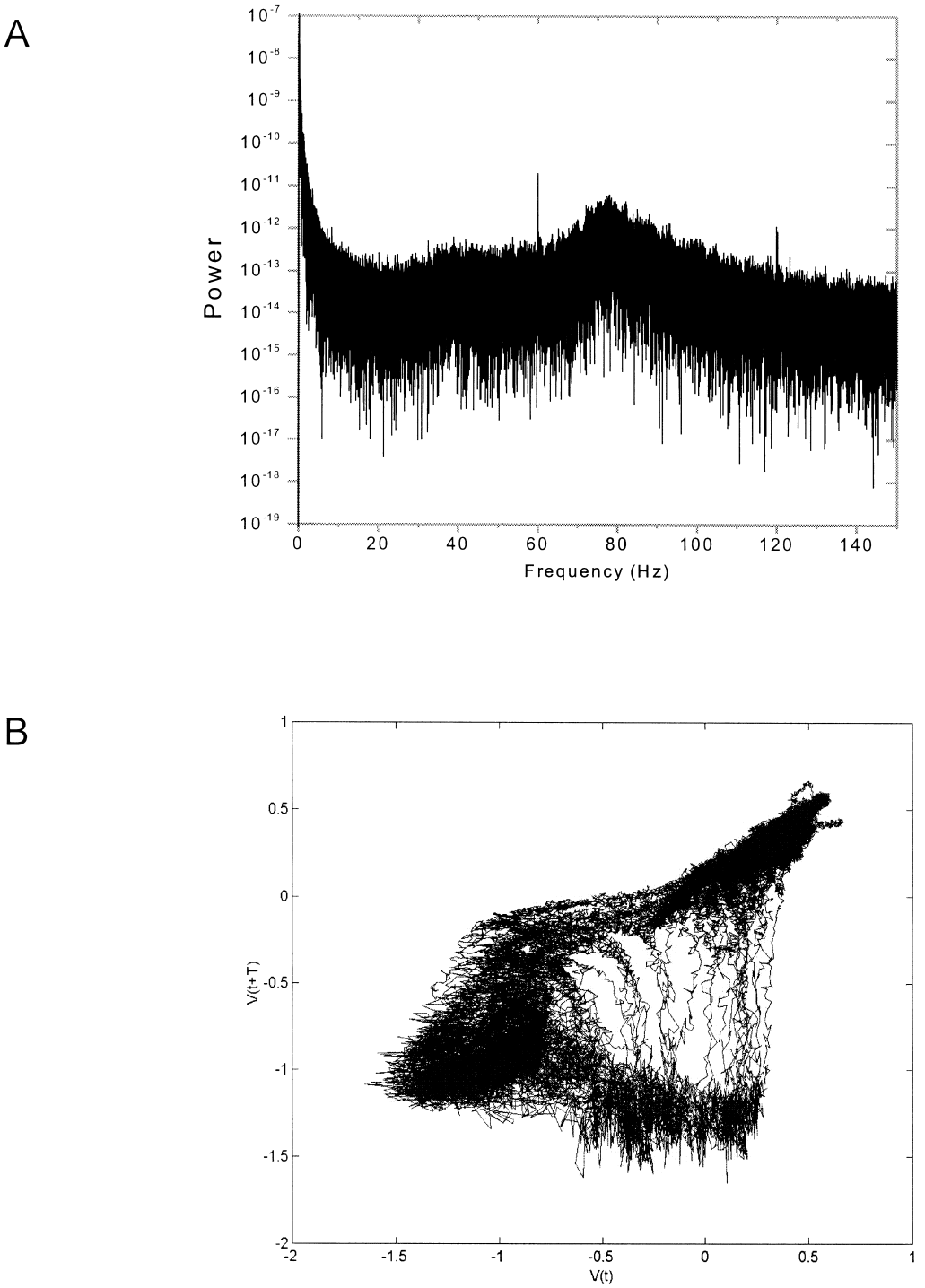

Fig. 4. Power spectrum and reconstructed attractor of low $[Ca^{2+}]_o$-induced epileptiform activity. Sampling rate is 300 Hz. Time delay T is selected as 0.5 s for reconstructing. (A) Power spectrum. (B) Reconstructed attractor.

70% MEF and 90% MEF were then applied to the slice for 10 min, with at least 5 min rest interval between each trial. Fig. 5A–D shows an example of the activity recorded from one slice for each field strength tested. Average frequency and amplitude data from nine slices are shown in Table 1. The frequency between two adjacent groups decreases significantly ($P<0.05$) as the electric field amplitude is increased. Further increases in field strength fully annihilated the activity (not shown). However, the field has no significant effect of the amplitude of events.

As for part A, the neuronal excitability of hippocampal pyramidal cells for different values of applied electric field

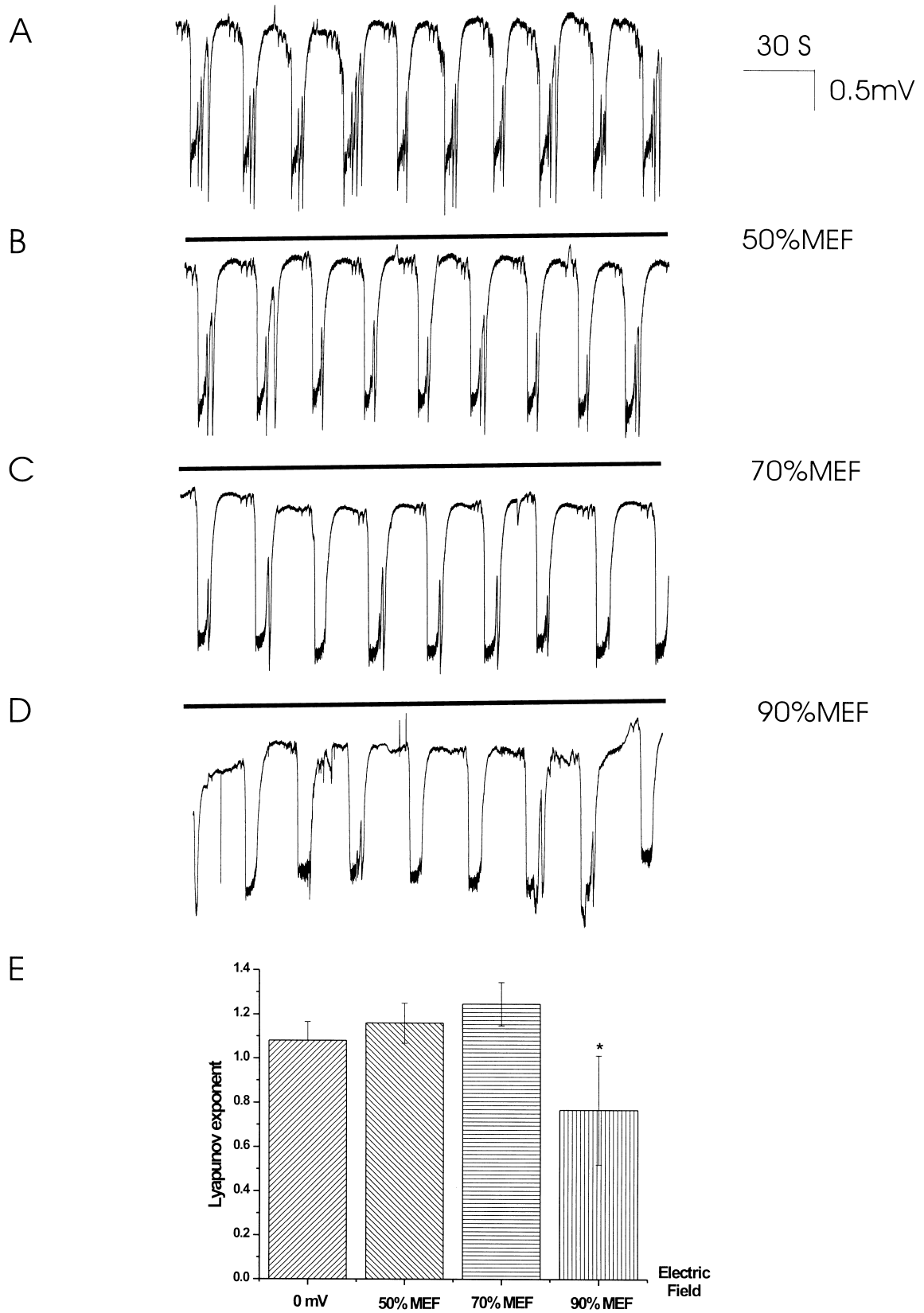

Fig. 5. Low $[Ca^{2+}]_o$-induced epileptiform activity in various levels of electric fields. Minimum electric field (MEF) that can block activity was first determined then set as a reference. 50%, 70% and 90% of this field were later applied on the slice. The activity in the absence of electric field (A), in the presence of 50% MEF (B), in the presence of 70% MEF (C) and in the presence of 90% MEF (D). (E) The maximum Lyapunov exponents of the activity in different electric fields.

Table 1
Average frequency and amplitude of low $[Ca^{2+}]_o$-induced epileptiform activity in different levels of electric fields[a]

	0 mV	50% MEF	70% MEF	90% MEF
Frequency (events/100 s)	7.26±1.42	5.90±1.05	5.13±1.25	4.02±0.75
Amplitude (mV)	2.17±0.99	2.11±1.04	2.00±0.93	1.87±0.71

[a] MEF is defined in Fig. 5. When the hyperpolarizing electric fields were increased, the frequency of the activity decreased significantly between adjacent groups while amplitude did not.

was studied by measuring the duration of an antidromic response. The response duration decreased as the strength of the hyperpolarizing electric field increased (Fig. 3C, 40 trials for each group.). This indicates a trend of decreasing neuronal excitability leading up to full block of events at 100% MEF.

Local and global embedding dimensions are estimated by the same method as before. Calculated values of 5 and 6, respectively, suggest that these parameters are not affected by the presence of the electrical field. Since the dimensions can be regarded as an estimation of the number of degree of freedom of the system, this result provides further evidence of stable governing dynamics in low $[Ca^{2+}]_o$ activity, even under the influence of external electric fields.

λ_{max} was not affected by electric fields applied at levels of 50% MEF and 70% MEF (Fig. 5E), but decreased significantly when the fields strength was further raised to 90% MEF. ANOVA tests showed that λ_{max} for the 90% MEF group is significantly smaller than those for onset or transition. The reduction of λ_{max} indicates that the activity becomes less complex as part of each event (such as the population spikes superimposed on the negative field shift) is suppressed by the large electric field.

4. Discussion

Although a precise measurement of the Lyapunov exponent is difficult to obtain with experimental data from biological systems, our results, especially where $\lambda_{max} >> 0$, strongly suggest that low $[Ca^{2+}]_o$ activity is chaotic. However, our aim is not to provide an exact value of λ_{max} for low $[Ca^{2+}]_o$-induced epileptic activity, but rather we take it as a relative measure for the nonlinear characterization of seizure-like activity during its initiation and during the application of electric fields. The prediction of epileptic seizures by measurement of nonlinear parameters has recently been shown to be effective [22]. Maritinerie et al. [20] used correlation density D and Lehnertz and Elger [19] used effective correlation dimension D^{eff} as tools to anticipate the onset of seizure. They demonstrated that in most cases epileptic seizure could be predicted as much as 2–6 min prior to onset. For low $[Ca^{2+}]_o$-induced epileptiform activity, the amplitude of λ_{max} can be used to detect a change in activity from the onset to the transition state and from transition to the fully developed state. A positive Lyapunov exponent was detected long before the activity was fully developed, although during this time, the activity appeared to be periodic. The Lyapunov exponent can be regarded as an informal measure of complexity [26]. The increasing trend of λ_{max} in the sliding time windows after the slice is exposed to low $[Ca^{2+}]_o$ solution clearly represents a route from simple to complex behavior. However, the estimated dimensions of the system do not increase in our low $[Ca^{2+}]_o$ experimental model following the initiation of activity. cspW did not give a valid cross-correlation because the linear range needed to calculate the correlation dimension could not be found in the cross integral [11]. This suggests that dimension methods may be not always suitable for the purpose of prediction. However, our results support the possibility of using λ_{max}, at least in the low $[Ca^{2+}]_o$ model, to predict the impending onset of seizure states. The early identification of a seizure state using nonlinear parameters is of special interest since it provides a key for studying synchronization mechanisms as activity makes a transition from a normal to a pathological state. Furthermore, prediction of approaching seizures with sufficient warning makes it possible to abort seizure generation by specific pharmacological or other interventions such as electrical stimulation [5].

One reason that λ_{max} is a useful predictor is probably its relationship with neural excitability: the higher the level of neural excitability, the higher the exponent. Nonlinear dynamic analysis methods have been applied in a number of scientific disciplines including neurophysiology in the past two decades [10,18]. Neural systems are nonlinear, and our results suggest that nonlinear dynamic methods, as the complement of normal simple linear methods, can be profitably applied for studying underlying mechanisms. In our case, frequency and amplitude can also be used to differentiate between stages of activity in some instances. But neither property alone is directly related with neuronal excitability. For instance, frequency decreases when neurons are more excitable during the initiation of the activity, but decreases when the excitability is reduced by a hyperpolarizing electric field. However, nonlinear measures like the Lyapunov exponent are better indicators of the underlying mechanisms of a nonlinear system.

In conclusion, we found that λ_{max} but not the dynamic dimensions can be used to differentiate between various states of low $[Ca^{2+}]_o$ activity and therefore predict the onset of synchronization. λ_{max}, but not the dimensions of

the activity, is related to neuronal excitability. This relationship between λ_{max} and excitability could explain its ability to predict the onset of epileptiform activity in the low $[Ca^{2+}]_o$ model.

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