"Epileptic Neurons" in Temporal Lobe Epilepsy

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Introduction

Epilepsy is a devastating chronic neurological disorder that affects about 0.8% of the population worldwide. The clinical hallmark of epilepsy is recurrent seizures, which consist of synchronised discharges of large groups of neurons. Several lines of evidence suggest that the hippocampal formation is critically involved in TLE. Firstly, recordings from intracerebrally implanted electrodes demonstrate that the first electrographic abnormalities in temporal lobe seizures often appear within this structure (18). Secondly, surgical removal of the amygdala and hippocampal formation considerably diminishes or abolishes seizures in most TLE patients (54). Thirdly, in a large group of TLE patients, the hippocampal formation shows a characteristic and stereotypical pattern of damage, known as Ammon's horn sclerosis, consisting of segmental neuron loss in the CA1, CA3, and CA4 subfields of the Ammon's horn, synaptic reorganization of surviving neuronal populations and severe astrogliosis (6, 9, 36). For all these reasons, research on the mechanisms leading to increased seizure suceptibility in TLE has focused on functional and structural alterations in the hippocampus proper and its most important input and output regions, ie, the entorhinal cortex and the amygdala. Because an epileptic seizure is the manifestation of a sustained and highly synchronized discharge of a large group of neurons, a fundamental issue in TLE research is the identification of the functional changes that are responsible for abnormal neuronal recruitment and synchronization.

Hitherto, most studies in experimental and clinical TLE have focused on the analysis of epilepsy-related changes in synaptic connections between neurons. A striking structural change found in hippocampi of both epileptic animals and humans is sprouting of excitatory axons and formation of new synaptic contacts on surviving neurons (5, 28, 34). A number of in vitro studies have provided preliminary evidence that such abnormal recurrent sprouting may contribute to the hyperexcitability seen in TLE (41, 51). Yet, others maintain that sprouting is not a crucial factor in epileptogenesis (30, 31). In addition to these structural changes, alterations in the density and subunit composition of neurotransmitter receptors have been reported, such as upregulation of synaptic *N*-methyl-D-aspartate (NMDA) receptor function (16, 27, 32, 38, 47) or changes in γ-amino-butyric $acid_A$ ($GABA_A$) receptor-mediated inhibition (8, 11, 12, 14, 19, 34). These changes also are candidate mechanisms for the hippocampal hyperexcitability seen in TLE.

Intrinsically Bursting Neurons and Neuronal Synchronization

In contrast to the multitude of well-documented changes in excitatory and inhibitory synaptic function, the possibility that persistent changes in intrinsic neuronal properties may also contribute to hippocampal epileptogenesis in TLE has received only minor attention (40, 53). This holds true despite the fact that the intrinsic discharge behavior of hippocampal neurons has been thought important in synchronization processes. In modeling studies, neurons that generate a high-frequency burst of action potentials as their minimal response to threshold stimulation, and particularly those that burst-fire spontaneously, were deemed critically important in entraining additional neurons into a synchronized population discharge (45, 47). Such neurons, designated bursting neurons, constitute a minority within the normal mammalian cortex. In the CA1 region, for example, virtually all pyramidal cells are regular firing cells in ordinary conditions (about 20% can be driven to burst-fire, but only in response to very strong depolarizing current pulses; ref 23). However, regular firing neurons can be readily converted to burst-firing mode by changing the ionic composition of the extracellular fluid (21, 41). This phenomenon is illustrated in Figure 1. It can be seen that either raising the extracellular K^+ concentration ($[K^+]$; Figure 1A) or lowering the extracellular Ca^{2+} concentration ($[Ca^{2+}]_o$; Figure 1B), transforms a regular firing cell into a low-threshold burster. Similar actions are exerted by modest increases in extracellular pH (17) or decreases in extracellular osmotic pressure (4). Interestingly, although these changes differ in their effects on synaptic activity, they all lead to the generation of epileptiform events both in

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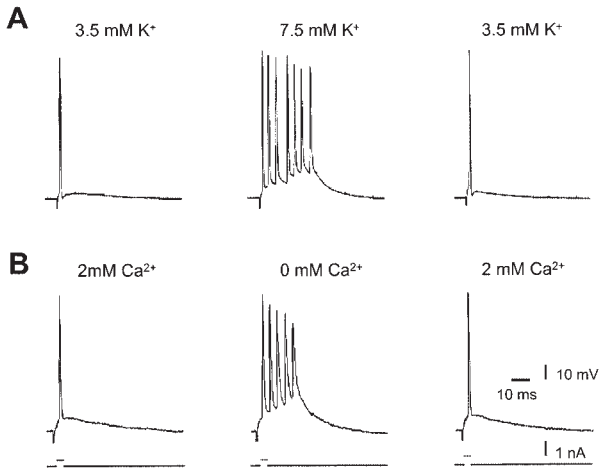

Figure 1. Regular firing neurons are converted to burst-firing neurons in acute models of epilepsy. The vast majority of CA1 pyramidal cells generate only one spike in response to intracellular injection of a brief (ca. 3-5 ms) depolarizing current pulse in ordinary conditions (leftmost panels). **A.** Elevating $[K^+]_o$ or **B.** reducing $[Ca^{2+}]_o$ all led to a marked increase in the proportion of intrinsically bursting neurons (middle panels), that was reversible upon perfusion with normal extracellular solution (rightmost panels). In each panel, uppermost traces are membrane voltage, lowermost traces are current pulses.

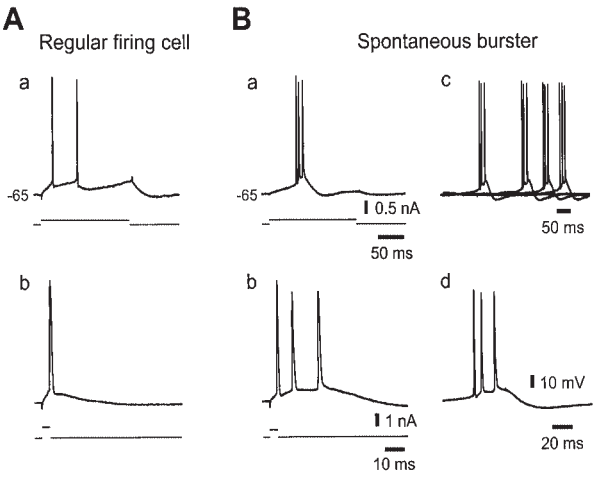

Figure 2. Different firing patterns of CA1 pyramidal cells in the pilocarpine model of TLE. **A.** Representative example of a regular firing cell (nonburster) which responds to a depolarizing current injection with a series of independent action potentials (panel a) and to a brief (4 ms) current injection with a single action potential (panel b). **B.** Example of a low-threshold burster which displays a burst of action potentials to long and brief stimulation (panels a and b), and also generates burst discharges spontaneously (panels c, four overlaid traces, one of which is expanded in panel d). In panels a and b, uppermost traces are membrane voltage, lowermost traces are current pulses.

vitro and in vivo (eg, 1, 2, 20, 52). Cumulatively, these data suggest that the epileptogenicity of hippocampal tissue is tightly linked to the propensity of principal neurons to burst-fire intrinsically.

Intrinsically Burst-firing Neurons in Chronic TLE

The above findings have prompted us to investigate the possible participation of intrinsically bursting neurons in animal models of TLE, which show spontaneous seizures. We have recently addressed this question in the widely studied pilocarpine model of TLE (40). In this model, a chronic epileptic condition resembling human TLE is produced in rats by a single episode of pilocarpine-induced status epilepticus (29). Interestingly, we observed a dramatic increase (>90%) in the fraction of burst-firing CA1 pyramidal cells in slices from epileptic rats (Figure 2). Of these, many neurons burst-fired in response to threshold depolarizations, with some of these neurons (about 10% of all pyramidal cells) generating spontaneous burst discharges (Figure 2B). A similar increase in the fraction of bursters was found also in the subiculum of pilocarpine-treated rats (49).

Role of Intrinsic Bursters in the Initiation of Epileptiform Discharges

Given that intrinsically bursting neurons prevail in epileptic tissue, in what ways do they instigate the generation of epileptiform discharges? We proposed that burst-firing pyramidal cells that are spontaneously active serve as pacemakers for the rest of the neuronal population, bursters and nonbursters alike. Therefore, we predicted that such neurons should discharge prior to the general neuronal population. We have examined this idea in hippocampal slices sectioned from pilocarpine-treated epileptic rats (40). Some of these slices manifest spontaneous epileptiform activity. In these slices we found that the discharge of spontaneous bursters preceded the recruitment of the remaining neuronal population by a few milliseconds or tens of milliseconds, as if they were the initiators of the epileptiform discharge (25, 40). Examples of a representative spontaneously bursting CA1 pyramidal neuron are shown in Figure 3B (panel a, 1-3: examples of different burst discharges from the same neuron). The relation of the intrinsic burst discharge to the discharge of the general neuronal population recorded with field electrodes is depicted in Figure 3B, panel b (uppermost traces: membrane voltage, lower traces, field potential). In contrast, regular firing neurons invariably discharged simultaneously either with or after the population discharge. This is illustrated in Figure 3A, panels a and b. A similar analysis of the role of bursters versus regular firing cells in the initia-

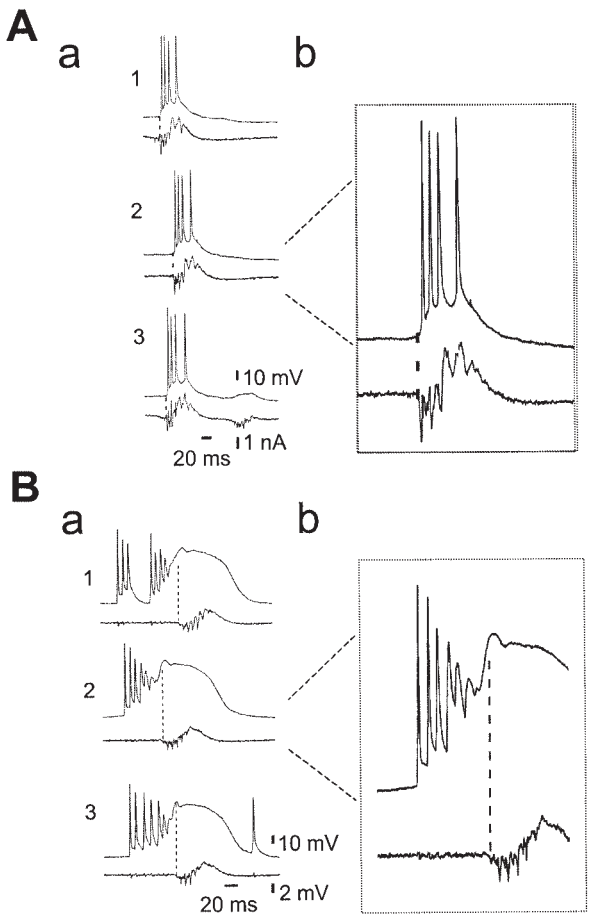

Figure 3. The discharge of spontaneous bursters, but not of other pyramidal cells, precedes the recruitment of the remaining neuronal population during epileptiform discharges. **A.** Relation of the firing of a nonburster (recorded with an intracellular microelectrode, uppermost traces in each pair) to the discharge of the nearby neuronal population (recorded with an extracellular microelectrode, lowermost traces in each pair) during three epileptiform events (a, 1-3; the second event is enlarged in part b). Regular firing neurons invariably discharged simultaneously with, or after the beginning of population discharge. **B.** Relation of the firing of a spontaneous burster to the discharge of the nearby neuronal population (during three epileptiform events (a, 1-3; the second event is enlarged in part b). The discharge of spontaneous bursters always preceded the population discharge.

tion of epileptiform events was performed previously in the high $(K^+)_o$ model of hippocampal epilepsy, yielding similar results (25). These data strongly suggest that spontaneous bursters may be the pacemakers of epileptiform events in the acute and chronic epileptic hippocampus.

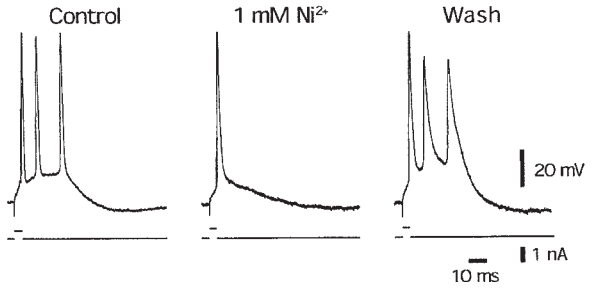

Figure 4. Intrinsic bursting in a CA1 pyramidal cell from epileptic tissue is suppressed by blocking voltage-sensitive Ca^{2+} channels. Burst discharges elicited by brief depolarizing current pulses were reversibly suppressed by 1 mM Ni^{2+}. In each panel, uppermost traces are membrane voltage, lowermost traces are current pulses.

Ionic Basis of Intrinsic Bursting in Epileptic Tissue

What is the ionic mechanism of intrinsic bursting in acute and chronic epileptic tissue? In general, the generation of a spike burst is a complex process that depends on the activation of slow inward currents by the first spike. These currents, in turn, produce a spike afterdepolarization that, when sufficiently large, triggers additional spikes, each of which reinforces the afterdepolarization (24). In most cases, the slow inward current mediating the spike afterdepolarization is thought to be either a Ca^{2+} current (I_{Ca}) or a persistent Na^+ current (I_{NaP}), or both. Thus, bursts in Purkinje cells (39) and supragranular cortical neurons (13) seem to be generated by I_{NaP}. In subicular and neocortical neurons, the mechanism of burst generation is controversial, some authors favoring either an I_{Ca}- (26) or a I_{NaP}-dependent mechanism (37). Expectedly, procedures which enhance I_{NaP}, such as exposure to sea anemone toxin (35) can convert native nonbursting neurons into bursting neurons. Likewise, suppression of outward K^+ currents activated during action potentials, which counteract the spike afterdepolarizations, also may induce bursting (3, 33, 42).

In CA1 pyramidal cells, intrinsic bursting has been shown to rely on I_{NaP} under ordinary ionic conditions, as well as following increases in $[K^+]_o$ or decreases in $[Ca^{2+}]_o$ (3, 43). Intrinsic bursting in these acute epilepsy models are not blocked by reducing I_{Ca}, either by removing Ca^{2+} from, or by adding 0.5 mM Cd^{2+} to, the perfusion solution. In contrast, burst discharges are blocked by low concentrations of tetrodotoxin, before the amplitudes of the fast action potentials are reduced. These and other findings indicate that I_{NaP} most likely fur-

nishes the depolarizing drive for intrinsic bursting in these acute models of hippocampal epilepsy.

Suprisingly, we found that intrinsic bursting in chronic epileptic hippocampal tissue may also depend on I_{Ca} (40). Thus, blocking I_{Ca} by adding 1 mM Ni^{2+} to the perfusing solution, suppressed intrinsic bursting in ~70% of the CA1 pyramidal cells in pilocapine-treated epileptic rats (Figure 4). Furthermore, intracellular application of the Ca^{2+} chelater BAPTA did not affect this activity, indicating that intrinsic bursting is driven directly by I_{Ca}, rather than by a Ca^{2+}-activated cationic current (40). Our findings therefore suggest that the burst mechanism in chronically epileptic tissue may rely primarily on long-term up-regulation of an I_{Ca}, which in turn plays an important role in initiating epileptiform discharges.

Concluding remarks

The studies described above cumulatively suggest that enhanced intrinsic bursting may be an important factor in the neuronal hyperexcitability seen in both acute and chronic epilepsy models. The demonstration of the de novo appearance of Ca^{2+}-dependent intrinsic bursting in the pilocarpine model of TLE is intriguing. It would be of utmost importance to identify the molecular basis of this alteration. Several molecular changes might possibly underlie the development of Ca^{2+}-dependent bursting. There might be a genuine increase in the density of one or more types of voltage-dependent Ca^{2+} channels due to enhanced transcription or altered regulation of Ca^{2+} channel subunits. Alternatively, existing Ca^{2+} channels may become more efficient in initiating burst discharges due to down-regulation of opposing K^+ currents, such as transient K^+ currents (33) or the noninactivating M-type K^+ current that is activated at near-threshold membrane potentials (21).

Available data suggests that I_{Ca}s in hippocampal neurons may be increased in chronic epilepsy. In the kindling model, the enhancement of I_{Ca}s in CA1 pyramidal cells (48) may be a consequence of increased transcription of voltage-sensitive Ca^{2+} channel subunits. However, only transient increases of the α_{1A}, α_{1D} and α_{1E} subunit mRNA have been observed so far in kindled CA1 pyramidal cells (22). In the kainate model, I_{Ca}s in dentate granule cells are also augmented (7), but the molecular basis for this change has not been explored. Despite the upregulation of voltage-sensitive Ca^{2+} channels on the functional and mRNA level, no change in the distribution of $\alpha_{1A\text{-}D}$ channel proteins could be detected in hippocampal neurons of kainate-treated animals. Instead, L-type Ca^{2+} channel immunoreactivity seemed to be selectively augmented in reactive astrocytes (50). Thus, the question of whether and which neuronal voltage-sensitive Ca^{2+} channel subunits are regulated in TLE is presently controversial. Clearly, further analyses are necessary to pinpoint the molecular changes that might underlie the switch in firing mode observed in chronic epilepsy. A determination of the exact nature of these changes could allow the generation of novel antiepileptic drugs aimed specifically at blocking the initiation of epileptic seizures.

Acknowledgments

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