Basic mechanisms of epileptic seizures[1]

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The results of recent experimental studies continue to enhance the understanding of basic mechanisms involved in epileptogenesis. Intracellular recordings from both in vivo and in vitro preparations have defined essential elements that underlie the pathologic firing patterns characteristic of "epileptic neurons." Generation of epileptogenic discharges depends on the interplay of three major factors: (1) the inherent capacity of some neurons to elaborate active responses that lead to paroxysmal bursting; (2) the breakdown of normal inhibitory mechanisms and the augmentation of excitatory synaptic activities; and (3) the biasing effect on these processes of modulating neurotransmitter substances which help to maintain pathologic discharges. Differences between acute and chronic foci probably depend more on the degree and intensity of these factors than on fundamentally different mechanisms.

Index terms: Epilepsy • Neuroregulators • Seizures

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Epileptiform activity is characterized by paroxysmal discharges occurring synchronously in a large population of cortical neurons, characterized on the electroencephalogram (EEG) as a sharp wave or "spike." The cellular correlates of clinical and EEG paroxysmal activity have been studied in a variety of experimental preparations, including intact animals, sections of the neocortex and hippocampus, and neuronal cell cultures. The availability of micropipettes suitable for intracellular recording has been critical in elucidating the essential cellular characteristics of experimental epileptogenesis. We wish to emphasize current de-

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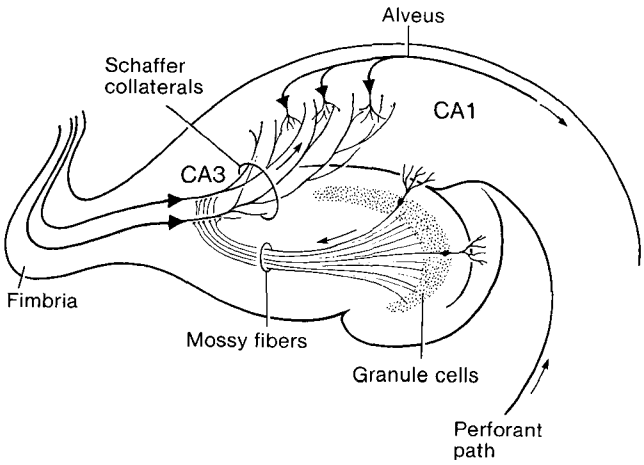

Fig. 1. Diagram of a section of the hippocampus, showing the major cellular areas (CA1, CA3, and granule cells of the dentate gyrus) and synaptic connections (mossy fibers connecting granule cells to CA3 pyramidal neurons, and Schaffer collaterals going from CA3 to CA1 cells). The path of an incoming signal as it enters the hippocampus from the entorhinal cortex via the perforant path is indicated by the arrows.

velopments based largely on intracellular recordings made in hippocampal brain slices maintained in vitro following application of convulsant drugs.

The hippocampal slice model

The brain slice preparation has a number of technical advantages that permit acquisition of data about the physiological and biophysical properties of different cell types, their synaptic interconnections, and changes in the extracellular environment that influence epileptogenesis.[1-4] The hippocampus, shown diagrammatically in *Figure 1*, has been a particularly suitable model for basic studies because its comparatively simple and laminated structure preserves many important neuronal connections even in thin slices and allows easy identification of major cell regions using a dissecting microscope.[5] Lorente de Nó[6] divided the hippocampus into a superior region, containing fields CA1, CA2, and CA3, and an inferior region which includes CA4 and the dentate gyrus. The superior region is one of the most seizure-prone areas of the brain; thus its cells must have properties and connectivities that have special significance for epileptogenesis.

Studies of the hippocampus have demonstrated that generation of an epileptogenic discharge depends upon the interplay of three major factors: (*a*) the inherent capacity of certain normal neurons to elaborate active responses, leading to sustained depolarization and paroxysmal bursting; (*b*) the breakdown of normal inhibitory mechanisms and the augmentation of excitatory synaptic mechanisms, thereby facilitating synchronous neuronal interactions; and (*c*) the effect of modulating neurotransmitter substances which may serve to trigger and help maintain the discharge.

Active responses

An understanding of hippocampal (and probably neocortical) epileptogenesis requires a thorough comprehension of the complex intrinsic membrane properties of pyramidal neurons. Hippocampal pyramidal cells are capable of generating both a single action potential (cellular spike) and a burst of two or more superimposed on a slow depolarizing wave. This wave typically lasts 30–50 msec and is followed by a hyperpolarizing potential lasting up to several seconds. This firing pattern is typical of normal CA3 neurons, but is usually seen only during epileptogenesis in CA1 cells.

Wong and Prince[7,8] described the normal spontaneous activity of a CA3 pyramidal neuron as consisting of depolarizing bursts which occur rhythmically with a repetition rate of about 1/sec. Bursting occurs regularly both in the cell body and in apical dendrites. Under normal conditions, neurons in CA3 burst asynchronously. In contrast, normal CA1 neurons only rarely exhibit burst firing at the soma.[9-11] Brief pulses (under 5 msec) of current to the cell body will reliably elicit bursting in CA3 cells,[10] but even sustained intrasomatic application of current to CA1 neurons will only produce trains of single action potentials[9,11-13] (*Fig. 2*). While the usual orthodromic, synaptically mediated stimulus evokes only single action potentials at dendrites of CA1 neurons, these same dendrites have a latent capacity for burst firing, since injection of current will produce burst discharges (*Fig. 3*). Furthermore, CA1 bursting in response to orthodromic stimuli can be induced by application of convulsant drugs that block post-synaptic inhibition mediated by gamma-aminobutyric acid (GABA)[7,10] (*Fig. 3*). During epileptogenesis, spontaneous bursting occurs in both CA3 and CA1 regions, but CA1 bursting is dependent upon input from CA3 cells via Schaffer collaterals. When the stratum radiatum is cut, interrupting Schaffer collateral input, spontaneous bursting ceases in CA1, but continues in CA3 (*Fig. 4*).

These observations demonstrate that there are marked differences in the functional characteristics of hippocampal pyramidal cells which cor-

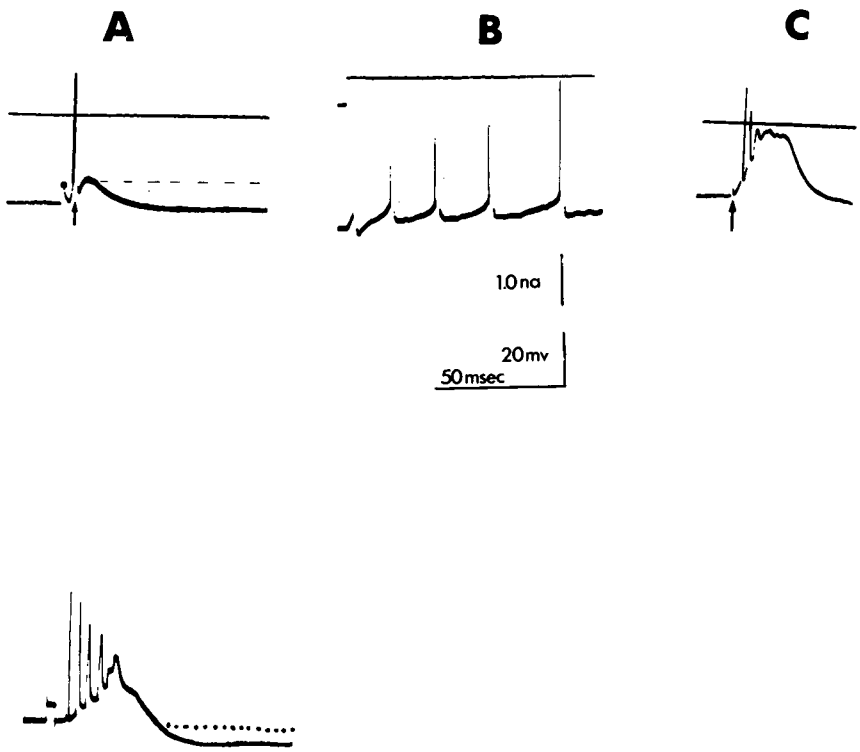

Fig. 2. *Top trace:* Intracellular recordings from a CA1 pyramidal neuron. The position of the bar above each recording indicates the magnitude and direction of injected current. **A.** Synaptic activation by stimulation of the stratum radiatum (*dot*) produces an excitatory post-synaptic potential (EPSP), which is sufficient to generate a single action potential (*arrow*). **B.** Even intense depolarization of the cell body with applied current elicits only a train of action potentials. **C.** With addition of penicillin to the bathing medium, synaptic activation (as in **A**) elicits a depolarizing burst.

Bottom trace: Intracellular recording from a CA3 neuron. Even in the absence of convulsant drugs, orthodromic stimulation produces depolarizing bursts. [Modified from Schwartzkroin[11] and reproduced with permission of the author and publishers]

respond to their topographic segregation. They also show that the hippocampal pyramidal neurons in CA3 normally fire in depolarizing bursts, but the firing among different neurons is asynchronous. Synchronous population bursting occurs during epileptogenesis. Moreover, the inherent capacity of CA1 neurons to fire in bursts is ordinarily suppressed or aborted by post-synaptic inhibition, which in turn can be uncovered by convulsant drugs that alter the normal balance between excitation and inhibition. From this, one may infer that under certain circumstances, normal neurons are potential "epileptic neurons." Finally, CA3 cells act as pacemakers for bursting in CA1 neurons during hippocampal epileptogenesis.

The major ion species involved in burst discharges appears to be calcium. If calcium conductance is blocked by manganese, bursting no longer occurs in CA3 neurons even though the capacity to generate trains of single action potentials remains; the depolarizing after-potential which normally follows single action potentials in hippocampal neurons is also eliminated by calcium blockade.[14] In contrast, blocking inward sodium current with tetrodotoxin does not eliminate a depolarizing envelope similar to the slow depolarization that underlies burst firing.[15] Thus the generator potential for burst activity appears to be largely calcium-mediated and may actually represent summation of consecutive depolarizing after-potentials.[8]

A long-lasting after-hyperpolarization (AHP) terminates burst discharge in CA3 cells,[14,16,17] the repetitive firing of CA1 cells,[18,19] and epileptiform bursting of CA1 cells.[20] The most important underlying ionic mechanism is a calcium-dependent potassium-mediated current similar to that described in connection with spinal mononeurons.[21,22] As expected, no AHP can be elicited in

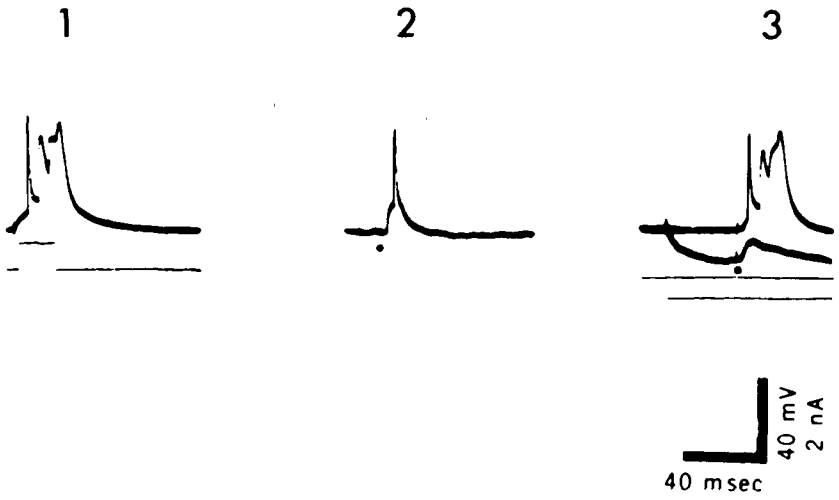

Fig. 3. Intradendritic recordings from CA1 pyramidal neurons. (*1*) Direct stimulation by intracellular depolarizing current (*lower line*) produces a spike burst. (*2*) Orthodromic synaptic activation (*dot*) normally produces only an EPSP which may generate a single action potential. A burst response in the dendrite is suppressed by inhibition. (*3*) In the presence of penicillin, orthodromic stimuli (*dot*) are now effective in triggering burst firing in post-synaptic dendrites because penicillin blocks GABA-mediated post-synaptic inhibition. [Modified from Wong and Prince[7] and reproduced with permission of the authors and *Science*]

most circumstances when calcium entry is blocked.[18,20] An additional event may be implicated in the special situation of hyperpolarizations seen following epileptiform bursting. In this case, calcium chelation by ethylene-bis-oxyethylene-nitrilo-tetracetic acid (EGTA) only partially antagonizes AHP.[16] Thus there may be a delicate balance between inflow of calcium ions and outward currents carried by potassium.

Synaptic interactions

The active responses described above relate to burst phenomena in single cells. However, additional mechanisms are required to account for the population behavior typical of epilepsy, whereby large neuronal aggregates burst in near synchrony. Recent experiments demonstrate that penicillin, a powerful convulsant, does not affect passive membrane properties or the active cellular responses of hippocampal pyramidal cells.[23,24] The relevant action of penicillin as a convulsant agent seems to be its specific antagonism of GABA-mediated post-synaptic inhibition.[7,23,25] Other GABA antagonists such as bicuculline and picrotoxin undoubtedly exert their epileptogenic effects by a similar mechanism.[16,20]

Our understanding of acute focal epileptogenesis derives largely from observations made in experimental preparations involving blockage of inhibition. Past arguments concerning the relative importance of "synaptic" vs. "intrinsic" mechanisms may be viewed as artifical and of value only as a historical curiosity.[26–29] Both mechanisms must be involved, and each contributes significantly to different aspects of the epileptogenic process. Cells must be capable of depolarizing in paroxysmal bursts, but at the same time, synaptic events are essential for promoting the synchronous discharge of many neurons and sustaining epileptic activity. Traub and Wong[30–33] have combined experimental observations with computer models to formulate an explanation of synchronous discharge. Their model is based on experimental data which show that (*a*) individual neurons have the capacity to burst in response to a sufficient stimulus; (*b*) penicillin at least partially blocks synaptic inhibition so that the remaining synaptic input onto pyramidal cells is predominantly excitatory; and (*c*) CA3 cells excite one another by chemical synapses, although it is unlikely that one CA3 neuron will randomly interact with another.[34] In this model, neurons are categorized as "initiators" or "followers" (*Fig. 5*). Initiators are neurons capable of spontaneous bursting, e.g, pyramidal cells in CA2 and CA3, and must have widespread synaptic connections with follower neurons. Following a local stimulus to the initiating or pacemaker aggregate, or perhaps only a single cell, bursts are triggered, providing an intense dis-

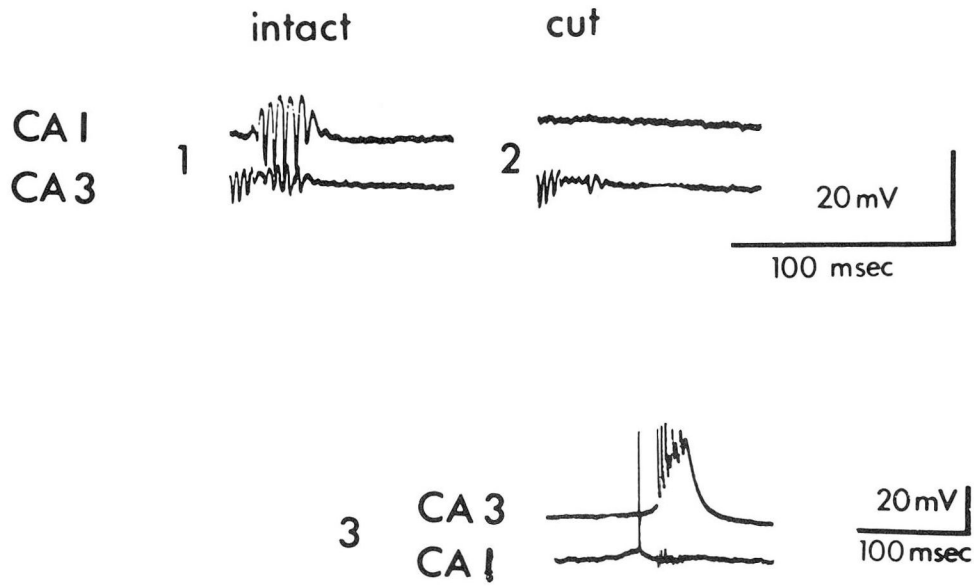

Fig. 4. *Top trace:* (*1*) Spontaneous epileptogenic field potentials recorded simultaneously from the CA1 and CA3 regions, corresponding to EEG spikes. Note that the burst in CA3 leads that in CA1. (*2*) After a cut is made between CA3 and CA1, spontaneous epileptogenic field potentials continue to be recorded in CA3, but are now absent in CA1. (*3*) Simultaneous intracellular recordings from CA3 and CA1 neurons after the cut show that bursting is no longer present in CA1 cells. [Modified from Schwartzkroin and Prince[12] and reproduced with permission of the authors and publisher]

charge that propagates throughout the extensive axonal ramifications of the initiator cell pool. Follower cells receive a synchronous volley and in turn become initiators for a new group of follower neurons. This process continues, resulting in the involvement of more and more cells until the entire population bursts. This model effectively explains the latency shifts characteristic of epileptiform activity within cellular networks. Such shifts vary with the location of the stimulus because of the essentially random interconnections and the changes that occur from

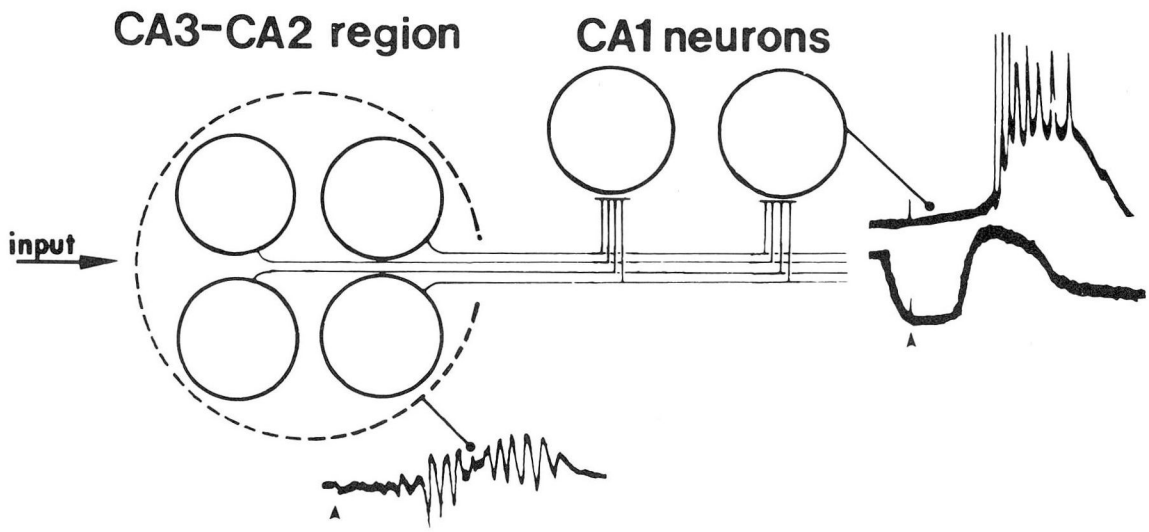

Fig. 5. Schematic representation of the generation of long-latency bursts in CA1 pyramidal cells. An input stimulus to the CA2–CA3 "pacemaker" region triggers synchronized bursting of epileptogenic neurons, which propagates along axonal collaterals of CA2–CA3 pyramidal cells to elicit large-amplitude EPSPs in CA1 neurons. These EPSPs in turn trigger burst firing in the epileptogenic cell populations of CA1. [Reproduced from Wong and Traub[31] with permission of the authors and publisher]

burst to burst due to alterations in synaptic efficacy and the relatively refractory nature of single cells.[33] It is also important to note that even when recurrent synaptic inhibition is reduced enough to allow synchronization to develop, other inhibitory processes such as the calcium-activated hyperpolarizing potassium current ensure termination of the interictal event.

Recent work with neocortical brain slices seems to confirm the general applicability of this model to other areas involved in focal epileptogenesis. A small population of neurons with intrinsic burst properties has been observed in layers 4 and 5 of the neocortex[35,36]; and it has been proposed that these cells may act as initiators of cortical epileptogenic discharges, much like CA3 cells in the hippocampus.[37] Experiments examining the responsiveness of bicuculline-disinhibited neocortical neurons to the excitatory neurotransmitter glutamate[38] support this hypothesis: epileptogenic discharges are most easily produced when glutamate is applied to layer 4, the location of the spontaneously bursting cells. Chatt and Ebersole's observations on the visual cortex of cats also suggest a pacing role for the pyramidal cells of layer 4.[39]

Cholinergic modulation of neuronal excitability

By themselves, neither active responses nor synaptic interactions clarify the nature of the trigger for focal epileptogenic discharges in the intact animal, nor do they suggest a physiological equivalent for the convulsant-induced condition of reduced inhibition required in the experimental model. Recent in vitro experiments suggest that cholinergic modulation of neuronal excitability may be an important factor in inducing interictal activity and promoting transition from an interictal to an ictal state. Acetylcholine acts on hippocampal neurons in a number of ways: it produces initial hyperpolarization, followed by a long-lasting depolarization with decreased conductance which leads to prolonged bursting[40,41] (*Fig. 6*). The initial hyperpolarization is a presynaptic effect, presumably due to excitation of inhibitory interneurons.[41,42] Other investigators have reported that acetylcholine decreases the effectiveness of inhibitory post-synaptic potentials (IPSP).[43,44] These two observations are not incompatible, since an initial increase in inhibition (hyperpolarization) might be the result of depolarization of inhibitory interneurons or their terminals followed by diminished IPSP effectiveness due to either loss of transmitter sensitivity (desensitization) or presynaptic inhibition. Regardless of the mechanism, the disinhibition (depolarization) caused by acetylcholine might be sufficient to drive cells toward interictal activity. Acetylcholine also augments inward sodium and calcium currents by decreasing conductance of a voltage-sensitive potassium current, the M current,[45] which is most prominent at resting and threshold membrane potentials; this action is similar to that produced by barium, which acts on the same ionophore as acetylcholine.[42] Concurrently, acetylcholine decreases conductance to the calcium-activated potassium current. The net result is that any excitatory drive onto the affected cells is favorably biased. Thus both the amplitude and duration of depolarizing potentials such as EPSPs are preferentially enhanced, which may be viewed as an amplification of their effect. This probably accounts at least in part for the prolonged bursting seen following application of acetylcholine. Acetylcholine-mediated disinhibition is associated with multiphasic field potentials (equivalent to the EEG spike) similar to those seen following conventional convulsant drugs such as penicillin.

The cholinergic actions cited above can be blocked by atropine. Studies of normal hippocampal pyramidal cells in the presence of atropine suggest that acetylcholine normally exerts a tonic effect that results in increased resistance.[40,46] Physiologically, one may speculate that increases in actylcholine, due to either increased release or a decrease in acetylcholinesterase activity, may play an important role in initiating epileptogenic discharges. Acetylcholine released during any type of interictal activity would increase the effectiveness of other excitatory inputs and promote transition to the ictal state.

Acute vs. chronic epileptogenic foci

Humans with localized epilepsy typically have chronic foci that are characterized neuropathologically by distortions in neuronal morphology (loss of dendritic spines, simplification of the arborization pattern, and shrinkage of the entire neuron), neuronal dropout, and gliosis. The experimental situation that most closely resembles that in humans is the use of alumina gel to produce a chronic focus in other primates. The cellular characteristics of chronic foci have not been characterized as completely as those produced by application of convulsant drugs, but a number of features distinguish chronic from

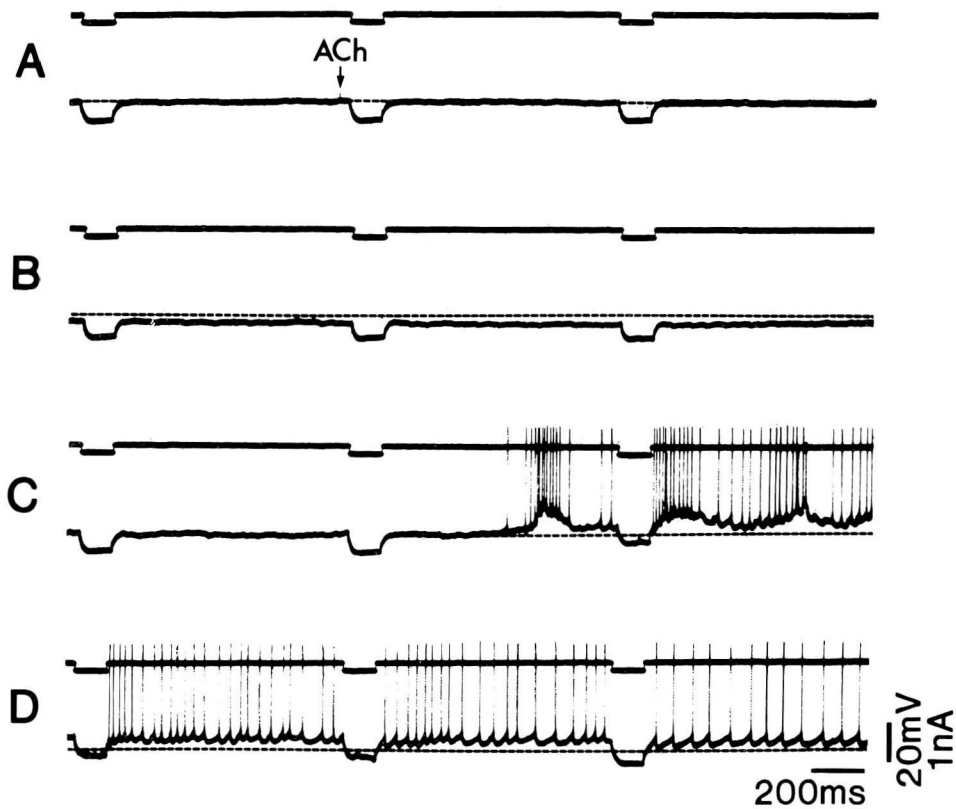

Fig. 6. Response of a hippocampal pyramidal neuron to acetylcholine. **A** and **B**. When a drop of acetylcholine is applied at the point indicated by the arrow, there is progressive hyperpolarization of the cell (shown in **B**) below the resting membrane potential of −65 mV (*dotted line*), lasting about 9 sec.

C and **D**. The cell has become depolarized above the resting membrane potential (about 10 mV in this example). Depolarizing responses are associated with increased firing rates and intermittent bursting. The top traces in each drawing represent the application of electric current pulses in order to monitor the input resistance of the membrane. [From Benardo and Prince[10] and reproduced with permission of the publisher]

acute foci. In general, the manifestations of cellular excitability are more subtle,[27,47,48] there is a significantly higher incidence of non-bursting cells, the cellular discharges themselves are of lower voltage and shorter duration, and cellular interactions exhibit far less synchrony. In addition, there is an extremely variable relationship between the firing patterns of individual cellular elements and the surface-recorded electrocorticogram. Extracellular studies of firing patterns in human epileptogenic cortex during surgery reveal that cell bursts correlate with surface spikes only about 50% of the time.[49]

One important factor that may account for many of these differences is that epileptogenic mechanisms in the intact brain are unlikely to be uniform throughout the focus; large numbers of neurons may be only partially or even selectively affected by the pathologic process. Furthermore, in the intact animal, external inputs from ascending brain stem projections, the thalamus, and other cortical neurons are constantly changing. Given the diverse causes of focal epilepsy in man, it is likely that a number of different pathophysiologic routes may lead to a common final pathway expressed as cellular bursting. For example, selective loss of GABAergic interneurons[50–52] may lead to loss of effective post-synaptic inhibition on dendrites, thus permitting "release" of latent bursts. Alterations in neuronal morphology may result in changes in the density of different ion channels, adversely affecting the relative intensity of excitatory and inhibitory conductances. Finally, ill-defined genetic factors may play a role.

While it is essential to characterize the full range of differences that exist between chronic and acute foci experimentally, it is likely that the

basic mechanisms will be found to vary more in degree than in type. The synaptic events that produce neuronal synchronization within the chronic epileptogenic focus are probably qualitatively similar to those occurring in vitro.

Generalized seizures

Generalized seizures are those which involve large parts of both cerebral hemispheres from the outset: typical examples are tonic–clonic ("grand mal") and absence seizures ("petit mal"). Interictally, the EEG shows various patterns of generalized spikes or spike–wave complexes. Many features of absence epilepsy have been reproduced experimentally in cats given large doses of parenteral penicillin.[53] Over the last 15 years, Gloor et al have successfully exploited this model of spike–wave epilepsy to clarify a number of mechanisms that account for the distinct clinical and EEG characteristics of generalized seizures. Gloor's corticoreticular theory emphasizes critical interactions at three levels of the neuraxis: the cortex, the thalamus, and the reticular activating system. The essential abnormality appears to be pathologically heightened excitability or reactivity of the cortex to thalamic inputs. Ascending projections of the reticular system contribute to modulating the overall excitability level of the cortex. The interhemispheric synchrony of the spike–wave paroxysms requires that the corpus callosum be intact,[54] but this synchrony is always approximate at best. Precise analysis of temporal relationships using an oscilloscope demonstrates that at any point in time a given cortical area may lead one generalized spike–wave burst, but then follow another area which leads the next.[54] Cortical spiking always precedes epileptiform discharges in deep structures[55] so that older concepts of a subcortical pacemaker must be discarded. Nonetheless, the thalamus and intact thalamocortical projections are essential for the elaboration of typical generalized spike–wave paroxysms.[56,57] What few cellular studies have been conducted indicate that most cortical neurons increase their firing rates or exhibit low voltage bursting simultaneously with the cortical or EEG spike;[58] during the aftergoing EEG slow wave, cortical cells show hyperpolarizing (inhibitory) potentials.

A complete understanding of generalized epilepsy requires integration of experimental and clinical observations, which is not presently possible. Nonetheless, the wide clinical spectrum between absence seizures on the one hand and tonic–clonic seizures on the other implies important pathophysiologic considerations. It is likely that the detailed manifestations of individual clinical seizures are determined by the extent of either diminished inhibition or excessive excitation. In experimental penicillin spike–wave epilepsy, the fundamental disturbance appears to be a laminar profile of concentration-dependent inhibitory blockade across the cortex. In human absence epilepsy, the analogous situation might be a genetic alteration of cortical inhibition. Since absence seizures primarily affect perception, cognition, and memory, with almost instantaneous return of normal activity upon cessation of the abnormal discharge, we speculate that the pathologic process, while diffuse, probably affects cortical elements differentially or even selectively, perhaps in a laminar or topographic fashion. The extent and severity of the basic disturbance may well determine whether a patient has absence seizures, tonic–clonic seizures, or a mixture of the two.

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