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Cellular Mechanisms in Experimental Epileptic Seizures

Abstract. *Action potentials of single cells, recorded by means of extracellular microelectrodes from the cat's cerebral cortex after topical application of penicillin, undergo characteristic changes in the course of seizure episodes. In individual neurons, these changes in spike configuration are fully reversible and are repeatedly observed with each of such episodes. Two alternative interpretations offered for these findings appear to be critically dependent upon the relationship between the position of the microelectrode and the cell itself: there might be a transitory failure of the spike to invade part of the neuronal membrane or transitory neuronal swelling.*

A series of experiments was recently conducted for the purpose of analyzing the basic features of the epileptiform activity in the cerebral cortex (*1–3*). These experiments were performed on cats (*cerveau isolé* or light barbiturate anesthesia, or both) after discrete, topical cortical application of penicillin. The epileptogenic properties of this drug and other technical details were described previously (*1, 4, 5*). Both intra- and extracellular recording were obtained from the population of cortical elements in the affected area.

Here we report an interesting aspect of findings which was not included in the main account of our study (*1, 2*). Several interpretations are possible, and two of these are discussed in relation to the mechanisms for the development of the rhythmical self-sustained discharge which characterizes the epileptic seizure.

Soon after cortical application of penicillin, isolated paroxysmal events (Fig. 1, *A, E*) began to appear, consisting of typical electroencephalographic and single cell behavior patterns (*1, 5*). These, which can be considered the experimental equivalent of interictal (subclinical) events of human epilepsy, kept recurring spontaneously for many hours or could be "triggered" by various types of electrical stimuli (direct cortical or callosal stimulation, or stimulation of the specific projection pathways) at critical frequencies (*3, 6*). On occasions, the gross and unitary activity underwent characteristic changes (Fig. 1, *B–D*) and assumed the form of long lasting, ictal episodes (*2*).

The behavior of 56 cortical units could be studied repeatedly in the course of several of such ictal episodes by means of extracellular electrodes. This study was carried out either by photographing on moving film the cathode ray oscilloscope tracing of both gross surface cortical and unitary changes (Fig. 1), or with photographs of single sweeps of the oscilloscope. By this second method, the same changes could be analyzed in detail as shown by the samples selected at given intervals before, during, and after the course of the ictal episode, the entire episode being monitored, in parallel from the same input, in inkwriting tracings (Fig. 2). When this method was used, it was convenient to trigger the sweeps (and the epileptiform events) with brief electrical pulses applied locally or to the contralateral homologous region of the cortical surface. The phenomena to be described, however, did not seem to be altered by, or depend upon such stimulation and were repeatedly observed also in its absence (for example, see Fig. 1).

In 29 of these 56 cells it was found that, in the bursts of spikes of modulated (Fig. 1*A*) or of progressively decreasing amplitude (Fig. 2*A*), which characterize the inter-ictal behavior of the "epileptic" neuron, the action potentials consisted of a diphasic (positive-negative) deflection. In the course of the ictal episode, however, these same spikes would undergo a relatively constant modification, losing their diphasic character, due to a partial (Fig. 1, *C, D*) or total (Fig. 2, *B, C*) disappearance of the second, negative phase. In addition, during the episode a slow positive potential would appear in coincidence with the spike firing (Fig. 1, *C, D*); if already present this potential would become more prominent (Fig. 2) or, if a similar, negative potential was appreciable before the ictal episode, its polarity would reverse. These and other changes (shortening of latency when the spikes were activated by electrical pulses; increase in the duration of individual spikes), which are not taken into consideration here, were reproducible in the course of different ictal episodes for any given one of the 29

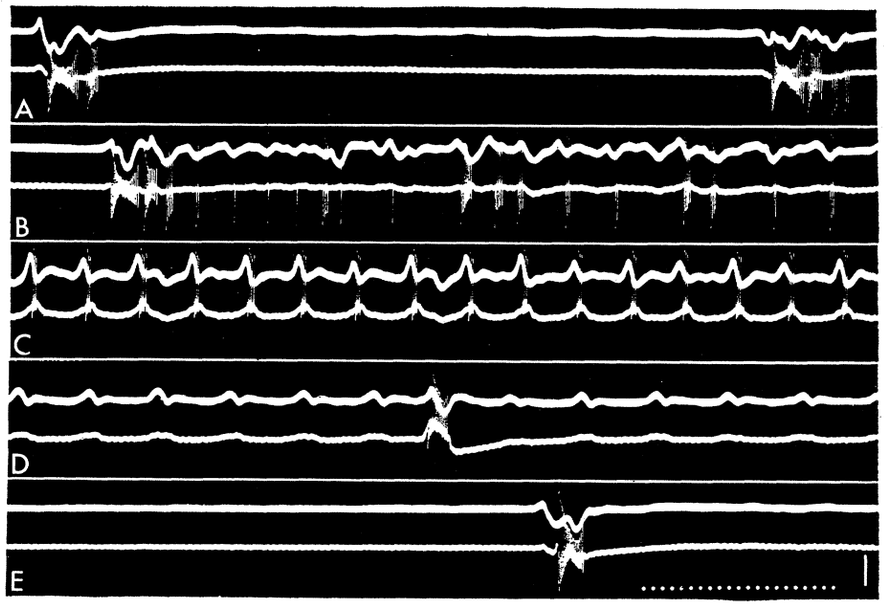

Fig. 1. Records from gyrus sigmoideus posterior close to site of penicillin application. In each pair of tracings the upper one is from gross surface electrodes (a-c amplification), the lower one from an extracellular micropipette (d-c amplification). The five sections are separated by the following intervals in seconds: *A–B* (0.5); *B–C* (11); *C–D* (8); *D–E* (23). *A,E*: "inter-ictal" manifestations; *B–D*: "ictal episode." Positivity is indicated by upward deflection. Calibrations: 1.5 mv (upper tracing) and 3 mv (lower tracing); 25 msec.

cells, and were completely reversible (compare *A* with *E* in Fig. 1 and *A* with *D* in Fig. 2).

Since these characteristic changes in activity were found only while recording with extracellular electrodes from a certain number of elements in the course of all the numerous, rather stereotyped ictal episodes which have been observed, it seems reasonable to assume that they depend on a critical position of the microelectrode tip (see also *7*) and, specifically, on a critical relationship between this and the body of the cell under examination. This assumption is supported by the finding that in the case of a few units in which the aforementioned changes were absent in the course of one ictal episode, these would appear with subsequent ictal episodes after the microelectrode had been manually moved slightly nearer to that cell. The fact that these changes, when present, would occur in close coincidence with the ictal episode, that they were fully reversible at its end, and that the whole sequence of changes in the activity of a given cell would be repeated in the course of several ictal episodes suggests that they are not a capricious finding or a simply curious "artifact". We therefore propose two alternative explanations.

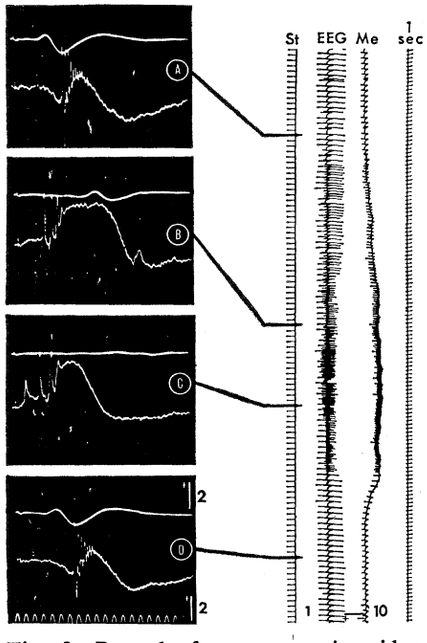

Fig. 2. Records from gyrus sigmoideus posterior close to site of penicillin application (different animal from that used for Fig. 1). Parallel input to oscilloscope (left) and to inkwriting apparatus (displayed vertically on the right) from surface electrode (*EEG*, upper channel, a-c amplification) and an extracellular micropipette (*Me*, lower channel, d-c amplification). Stimuli (*St*) are applied to the contralateral homologous area (0.1 msec square pulses, 5 v, 0.7/sec). Each of these "triggers" a paroxysmal discharge (see inkwriting tracing), four of which are displayed in the oscilloscope sweeps: before (*A*), during (*B*, *C*) and after (*D*) an "ictal episode." Calibrations (in millivolts) and polarity as indicated. Time (oscilloscope): 100 cy/sec.

During the development of an ictal episode, the spikes fail to invade part of the cell. The spike, which is supposed to originate relatively far away from the electrode tip, can no longer spread to that portion of the cell membrane which the electrode tip happens to be near. This interpretation not only requires a critical electrode-cell relationship in each case but also a rather constant position of the electrode tip at a certain distance from the site of origin of the spike. Furthermore, it does not provide an immediately convincing explanation for the other spike changes (besides the disappearance of diphasicity) and it might require additional assumptions to account for the slow changes in potential which accompany the spike(s).

In our alternative interpretation it is assumed that these modifications in unitary activity are actually due to a transitory, reversible change in the relationship between electrode tip and cell body and, specifically, to a nearing of the two. The expected increase in spike amplitude, in this situation, would not take place due to the excessive membrane depolarization which characterizes the cellular behavior during the ictal episode (*2, 8*). The d-c changes usually noted during an ictal episode (see Fig. 2, *Me* tracing on right side) are suggestive of some "movement," and analogous modifications in spike pattern could be observed when the conditions were optimal—in the absence of an ictal episode—and when the cell was approached under voluntary control of the micromanipulator (in which case, however, the spike would also show an increase in its amplitude). Since, in the present situation, it is reasonable to consider the position of the electrode tip as fixed, the change could result only from some displacement of the surrounding tissue. In this case, if such displacement were mainly one of extrinsic (that is, nonneuronal) structures, one would expect in each individual situation a random change, the cell body being pushed either close to, or away from, the electrode tip, depending on the location of that portion of tissue undergoing displacement and on the direction of the movement. But our observations were consistently similar—that is, suggestive of a uniform direction of the presumed movement. It would thus appear that it is the cell itself which "approaches" the electrode tip; this could take place through an increase in the cell volume. If this interpretation is correct, one should conclude that the nervous elements undergo a transitory swelling in the course of a seizure.

It is not possible to state which of these two hypotheses correctly represents the events underlying the described findings: both phenomena might even contribute to their appearance but alternative and more convincing explanations are probably available. In any case it seems worth pointing out that these rather puzzling yet repeatedly reproducible changes in cellular activity were unnoticed in intracellular records and could be detected only with extracellular leads.

Of the two suggested interpretations, the first would provide a pathophysiological substrate for the development of long lasting, repetitive activity which characterizes the epileptic seizure: the occurrence of the seizure should then be possible because of the spike failure to invade the neuronal soma (see *2, 9*). The second interpretation would indirectly confirm some of Van Harreveld's (*10*) views and emphasize the pathogenetic role of (cellular) hydration in epileptic processes.

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