EXPERIMENTAL NEUROLOGY 40, 567-585 (1973)

Spontaneous Firing Patterns of Epileptic Neurons in the Monkey Motor Cortex

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Received January 18, 1972

We recorded the activity of single cells in an alumina-induced epileptogenic focus in precentral cortex of an awake monkey. The firing patterns of 12 units exhibiting the "long first interval" burst pattern were studied in detail. When the monkey was quiescent, the spontaneous activity of these cells consisted of repeated bursts in which the initial spike was followed by a long first interval and then by a high-frequency afterburst. If the interval between the long first interval burst and the preceding activity was less than 100 msec, an inverse relationship between the duration of afterburst and the interburst interval was observed. When cell activity increased sufficiently (sometimes accompanied by overt motor activity) these cells fired at a tonic rate characteristic of normal precentral cells. In all cells, single pyramidal tract shocks elicited a short latency (0.6–1 msec) antidromic spike which could be followed after a long first interval by an afterburst. In most cells the afterburst spikes were slightly larger and longer than the initial spikes (and the spikes occurring during tonic activity). In two cells the afterburst spikes were clearly compounded of two parts, which varied independently as a function of electrode depth and probably represented activation of two regions of the cell. These observations suggest that the afterburst may be triggered by a pacemaker mechanism in a remote region of the same cell.

INTRODUCTION

In 1968 Calvin, Sypert, and Ward (5) reported a highly structured interictal burst pattern recorded from cortical neurons in alumina-gel induced epileptic foci in monkeys. These high-frequency bursts were characterized by a relatively long first interspike interval, followed by considerably shorter interspike intervals. While only a fraction of the

[1] This work was supported in part by PHS Grants NS04053 and NS05211. Dr. Fetz is also associated with the Regional Primate Research Center and Department of Physiology and Biophysics, University of Washington. We thank Dr. William H. Calvin for generous help with computer analysis of burst data and helpful discussions.

cells encountered by them exhibited the long first interval burst pattern, those units which did, did so consistently. We have confirmed the existence of such cells in a subclinical alumina focus and have made further observations on the characteristics of their activity.

Figure 1 illustrates an example of a long first interval burst recorded from a cell in an alumina focus. We will refer to the first spike of the total burst as the initial spike and the high frequency stereotyped portion of the burst following the long first interval as the afterburst. The stereotyped structure of these bursts becomes particularly evident when successive bursts are aligned upon the first spike of the afterburst in a dot raster display. From LINC-8 computer-generated dot raster displays and interval histograms of successive long-first-interval bursts, Calvin, Sypert, and Ward (5) discovered that the short intervals in the afterburst typically showed less variability than the long first interval. Thus, if the dot rasters or time histograms are aligned upon the second spike of the long first interval burst (i.e., the first spike of the afterburst), subsequent afterburst spikes typically showed less variance in their timing than the initial spike. The nature of the variability in the long first interval served to distinguish three different types of long first interval bursts: The distribution of long first intervals in a given cell's bursts was found to be unimodal or bimodal; a further distinction within the unimodal group was made between those with a relatively large variance (10%–20% of the mean) and those with a remarkably low variance (less than 2% of the mean) (5, Fig. 6). The long first interval bursts, recurring every 50–200 msec, were reported to be the exclusive firing pattern of many cells near the center of the alumina focus. Recently, Calvin, Ojemann, and Ward (6) have recorded similar long first interval bursts from cells near epileptic foci in human patients, supporting the possibility that long first interval bursts may represent an abnormal firing pattern characteristic of neurons in epileptic regions of cortex.

To explain the remarkable invariance of long first intervals (interval variability of less than 2%) in several cells, Calvin, Sypert, and Ward (5) proposed a model which invoked axonal conduction velocity as a timing mechanism. Their model assumed that recordings had been from axons which terminated in the focus (2). A spike abnormally initiated at the hyperactive axon terminals passed the electrode antidromically (initial spike) and upon reaching the distal cell body triggered a high-frequency orthodromic burst which was recorded at the electrode as the afterburst. The long first interval was, therefore, explained as the sum of the antidromic and orthodromic conduction time plus the time required to initiate the burst at the distant cell body.

This report describes additional observations made on cells exhibiting the long first interval bursts in an alumina focus. Our observations

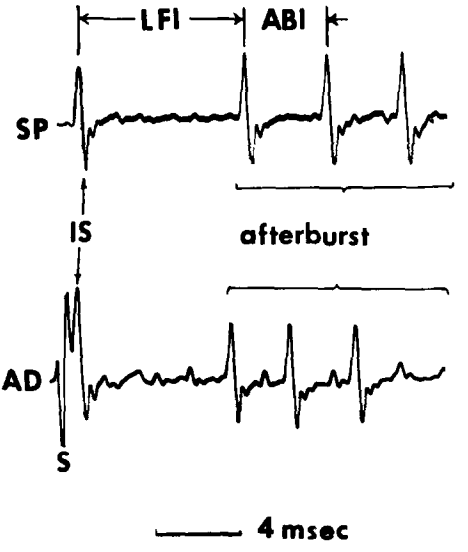

FIG. 1. Spontaneous (SP) and antidromically (AD) evoked long-first-interval bursts in same cell. Initial spike (IS) is followed after a long first interval (LFI) by an afterburst. ABI is first interspike interval of the afterburst. S marks the pyramidal tract stimulus.

significantly modify the possible models which could explain the generation of the long first interval burst pattern.

MATERIALS AND METHODS

All recordings were made from an unanesthetized 3.4-kg *Macaca mulatta* monkey. Four months prior to recordings, the monkey underwent sterile craniotomy with subpial injection of alumina cream (14) in precentral and postcentral cortex of the left hemisphere. One week prior to the first recordings a 25-mm–diameter stainless steel bonefixed adaptor was aseptically implanted over the injection site. The adaptor was sealed with a thin sheet of Silastic rubber to retard infections. During recording sessions it held a Trent Wells hydraulic microdrive which advanced tungsten microelectrodes through the Silastic and dura into the cortex. In addition, a concentric bipolar stimulating electrode was stereotaxically implanted in the ipsilateral pyramidal tract (8). The location of the electrode tip was later verified histologically. The lowest threshold movement evoked by a brief train of stimuli was a twitch of the contralateral fingers. To stabilize the head during recordings, acrylic socket plugs were implanted over the parietal boss of the skull; these received stainless steel bars affixed to the primate chair, thus precluding lateral head movement. This method allowed stable recording of single cells over periods up to 6 hr. During recording sessions the monkey sat in the primate chair

inside an IAC 400 sound-attenuating chamber. Precentral cells were recorded extracellularly with epoxylite coated tungsten microelectrodes with tip capacitances ranging from 2–40 pF. The electrode was connected to a cathode follower in series with a Grass P5 preamplifier set for a bandpass of 350 Hz to 10 kHz. Data was stored on a seven channel Ampex FM tape recorder.

Firing patterns of bursting cells were analyzed and displayed with a LINC-8 computer using programs originally developed by Calvin (3). For this study, Dr. Calvin modified these programs with respect to the criteria used to detect bursts. The previous criteria were a 50-msec interburst interval followed by two successive intervals shorter than 15 msec. Since our cells did not consistently exhibit such long interburst intervals, the criteria were modified to recognize a long first interval followed by two afterburst intervals.

RESULTS

Locus of Recorded Cells. In the first few recording sessions, we sampled cell activity at various points in the accessible cortical area (a 20-mm-diameter circle) to establish the location of the focus and the central sulcus. Most cells in the anterior half of the area were typical of precentral cells in that they exhibited regular firing, responded to passive joint movement and altered their activity during active movements (8, 9). Most units in the posterior half of the area were characteristically postcentral in that they fired more irregularly and usually responded to cutaneous stimulation of the contralateral arm. In the precentral cortex, a small, well-delineated area of relative inactivity was found, containing units with relatively small action potentials; this area correlated with the site of alumina gel injection. On the posterior margin of this area was a well-defined region of cortex exhibiting EEG spikes and containing some cells firing with long first interval bursts. However, most cells in this region exhibited firing patterns typical of normal precentral cells; their activity was regular, often they increased their firing rates in relation to active movements of the contralateral arm, and many responded to passive movements of the contralateral shoulder or elbow. This study concerns an estimated 15% of cells in this region which consistently exhibited long-first-interval bursts as a major part of their firing pattern.

Cell Characteristics. Twelve cells demonstrating long first interval bursts were studied for periods averaging several hours each. The major characteristics of these cells are summarized in Table 1. All units exhibited negative-positive action potentials with peak-to-peak amplitudes greater than 1 mv and were well isolated from background activity. Average firing rates of these cells computed for 5-min intervals ranged between

TABLE 1

CHARACTERISTICS OF LONG FIRST INTERVAL BURSTING CELLS[a]

Cell	PT	LFI	ABI	LFI/ABI	S/B	FR	AP
1	1.0	10.4	4.9	2.2	2–4	11	1.5
2	0.9	6.5	3.1	2.1	4–6	10	1.4
		9.0		2.9			
3	0.8	1.8	1.8	1.0	7–12	18	1.0
		7.0		3.9			
4	0.6	12.3	4.2	2.9	3–4	11	1.2
5	0.9	7.0	3.3	2.1	4–5	11	1.5
		10.2		3.1			
6	1.0	7.8	3.4	2.3	2–4	14	3
		10.2		3.0			
7	1.0	8.0	3.6	2.2	3–4	9.6	1.7
8	0.9	8.2	3.9	2.1	3–4	13	5
9	1.0	5.8	3.0	1.9	2–8	11	1
10	0.9	10.8	3.2	3.4	3–5	15	1.8
11	0.9	3.9	4.0	1.0	4–5	7.5	2
		8.1		2.0			
		12.0		3.0			
12	0.9	5.8	3.9	1.5	2–8	9.0	6.5

[a] Abbreviations: PT, antidromic latency to pyramidal tract stimulation (msec); LFI, duration of modal long first intervals (msec); underlined value represents most common interval; ABI, duration of interspike interval following long first interval (msec); S/B, number of spikes per burst; FR, average firing rate over 5 min period (spikes/sec); AP, maximal peak-to-peak amplitude of cell's action potential (mv).

7.5–18 spikes/sec. All 12 cells responded to pyramidal tract stimulation with an invariant latency of 1 msec or less and followed three stimuli at 500/sec or greater. As shown in Fig. 1 the short-latency antidromic spike evoked by a single pyramidal tract shock was usually followed by a long first interval and afterburst. Thus a single pyramidal tract shock was capable of antidromically evoking a long first interval burst similar to those occurring spontaneously as seen in the trace above. The antidromically evoked long first interval bursts differed from spontaneously occurring long first interval bursts only in having their mean long first interval 15%–30% shorter in duration.

Firing Modes. Cells firing in long first interval bursts were often found to exhibit other modes of firing as well. Most units also showed periods of "regular" tonic firing identical to that seen in normal precentral cells, i.e., interspike intervals were consistently longer than those of the long first interval bursts and the firing rate varied in a continuous fashion.

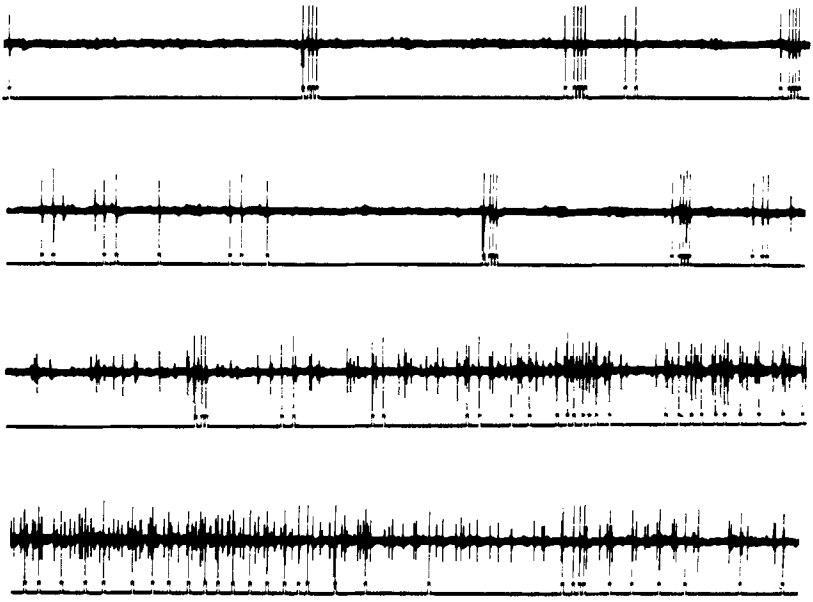

FIG. 2. Continuous record of long-first-interval cell showing bursting and regular modes of activity. Top sweep shows unit activity; bottom sweep shows square pulses triggered from unit. Note that doublets occurred following relatively short interburst intervals and that unit activity changed to a regular firing pattern as the background activity increased. During the period of regular firing the monkey moved the contralateral arm (cell 6).

Such periods of regular activity were sometimes, but not invariably, associated with active movements of the contralateral arm. Figure 2 illustrates a cell whose mode of activity changed (during an active movement) from long first interval bursts to regular firing, concomitant with an increase in activity of adjacent cells.

Several variations of the long first interval burst pattern were seen in these cells. Some of these variations are illustrated in Fig. 3, which shows dot rasters and time histograms of successive long first interval bursts of four different cells. The dot raster displays rows of successive bursts with all second spikes (the first spike of each afterburst) aligned to form a column; thus, the dots to the left of this column represent the initial spike of each long first interval burst and dots to the right represent spikes of the afterburst. The time histograms below each dot raster were computed so that the second spikes of the long first interval bursts were arbitrarily aligned at 20 msec.

The long first interval bursts of cell A (Fig. 3) had a *unimodal* and remarkably invariant long first interval of 8.2 msec, and three to four spikes in the afterburst. The mean first afterburst interval was about

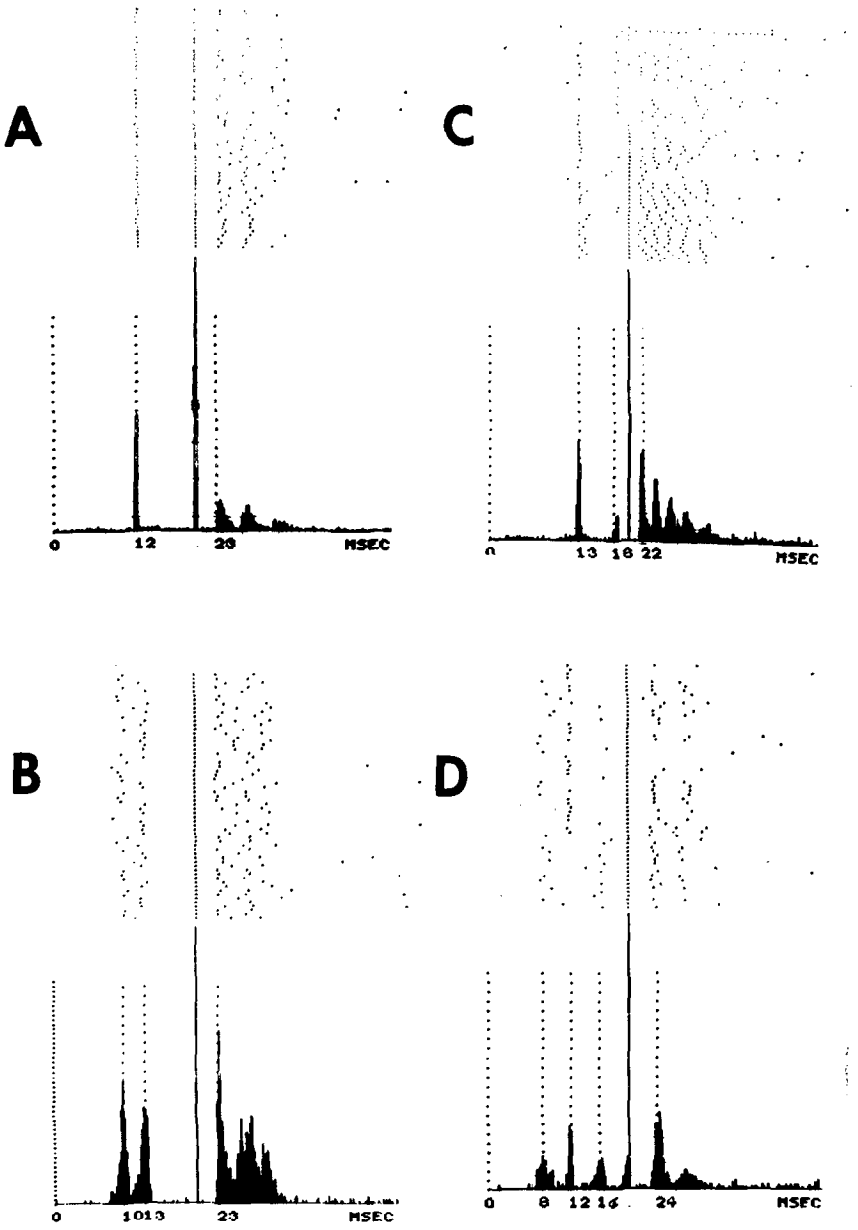

FIG. 3. Dot rasters and time histograms of long-first-interval bursts recorded from four different cells: (A) extremely invariant long first intervals (cell 8). (B) Bimodal long first interval of the type that might be produced if the first spike of the afterburst were absent for some bursts (cell 5). (C) Bimodal long first interval of the type that might be produced if initial spike were absent for some bursts (cell 3). (D) Trimodal long first interval with each modal long first interval an integer multiple of the first ABI (cell 11).

3.9 msec. This cell was atypical in that it showed less variability in the long first interval than in afterburst intervals.

Cell B exhibited a *bimodal* long first interval; some long first interval bursts had a first interval of about 10 msec and others had a first interval of about 7 msec. The dot raster of successive bursts indicates that bursts with the longer first interval occurred intermixed with bursts having the shorter first interval. It is significant that the mean afterburst interval (3 msec) is equal to the difference between the two modal long first intervals. Thus, the fact that the longer first interval (10 msec) equals the shorter first interval (7 msec) plus one afterburst interval (3 msec) suggests that the longer first interval may be obtained from the shorter by deleting the first spike of the afterburst. The implications of this relationship for burst generating mechanisms are discussed below.

A second way in which a bimodal first interval distribution was seen to be generated is illustrated by cell C. In this case, the longer long first interval of 7 msec was the more common as indicated by the large peak at 13 msec. However, a shorter first interval occasionally appeared which was equal in length to the first afterburst interval. Thus, these latter bursts were equivalent in timing to the afterbursts of the former. Inspection of the original data verified the presence of isolated bursts identical in timing to the afterbursts of the 7 msec long first interval bursts, but lacking an initial spike. Note also that the long first interval of 7 msec is approximately four times the length of the mean afterburst interval (1.8 msec).

The long first interval bursts of cell D exhibited a *trimodal* distribution of long first intervals with the remarkable property that each of the three modal first intervals (4, 8, and 12 msec) was an integer multiple of the afterburst interval (4 msec). As shown by the dot raster and confirmed by inspection of the original spike train, these three types of first interval occurred intermixed. This cell dramatically exemplifies a significant relationship between the long first interval and afterburst intervals seen for most of the long first interval cells—namely, that the mean long first interval tended to be an integer multiple of the mean afterburst interval. Table 1 indicates that the ratio of long first interval to afterburst interval was within 0.2 of an integer for nine of the 12 cells observed. In four cases, including cells C and D in Fig. 3, there was more than one modal first interval, and each was close to an integer multiple of the afterburst interval. (This relationship is a statistical one; it holds for mean values, not necessarily for each individual burst.) This relationship suggest that the initial spike may trigger some repetitive pacemaker process in the cell which eventually generates the afterburst. Thus, for cell D the pacemaker could potentially generate an afterburst spike every 4 msec after the initial spike. Whether the first afterburst spike occurs at 4, 8, or 12 msec

would depend on a superimposed process which could suppress the first potential afterburst spikes.

Another mode of firing observed in some cells was a series of doublets, in which the interspike interval corresponded precisely to the long first interval of that particular cell. These cells also exhibited longer afterbursts, but fired in doublets when activity increased (Fig. 2). Such a doublet pattern may be equivalent to a long first interval burst with only one spike in the afterburst.

Recovery of the Afterburst Generation Mechanism. For a given cell the number of spikes in the afterburst varied around a mean value which was typically constant over the 2–6 hr in which the cell was observed. As shown in Table 1 the mean number of spikes in the long first interval burst varied from 3 ± 1 for cell 1 to 10 ± 2 for cell 3. For the 12 cells, there seemed to be no statistically significant correlation between the mean number of spikes in the long first interval burst and the length of the long first interval.

However, for a given cell the actual number of spikes in a burst was significantly related to the length of the preceding interburst interval. When the preceding interburst interval was short, as during rapid firing, the number of afterburst spikes decreased, and in the limiting case of rapid regular firing, the afterbursts disappeared. When the cell was relatively quiescent and the interval preceding a long first interval burst exceeded 80–100 msec, the long first interval burst appeared with its full complement of afterburst spikes. This inverse relation between the preceding interburst interval and number of afterburst spikes held equally true for spontaneous and antidromically evoked bursts. Thus, when the cell fired rapidly in a regular mode, the spontaneous long first interval bursts were absent and pyramidal tract stimulation evoked only one antidromic spike without an afterburst; when the cell was relatively less active, its spontaneous activity consisted of long first interval bursts and pyramidal tract stimulation evoked complete long first interval bursts. These changes for spontaneous bursts are illustrated in Fig. 2; the most complete long first interval bursts occurred when the cell had not fired for at least 80 msec. The extreme of the attenuated afterburst occurred when the cell fired in a rapid series of doublets.

Figure 4 illustrates the attenuation of the afterburst for pairs of long first interval bursts evoked by pyramidal tract shocks at different intervals. When the second long first interval burst was evoked 100 msec after the first (Fig. 4D), it usually contained its full complement of spikes (unless, as shown in the sweep marked sp, a spontaneous burst occurred in the interval, in which case the number of afterburst spikes in the second evoked burst was reduced, as well as those in the spontaneous burst). As the interval between the evoked bursts was reduced, the

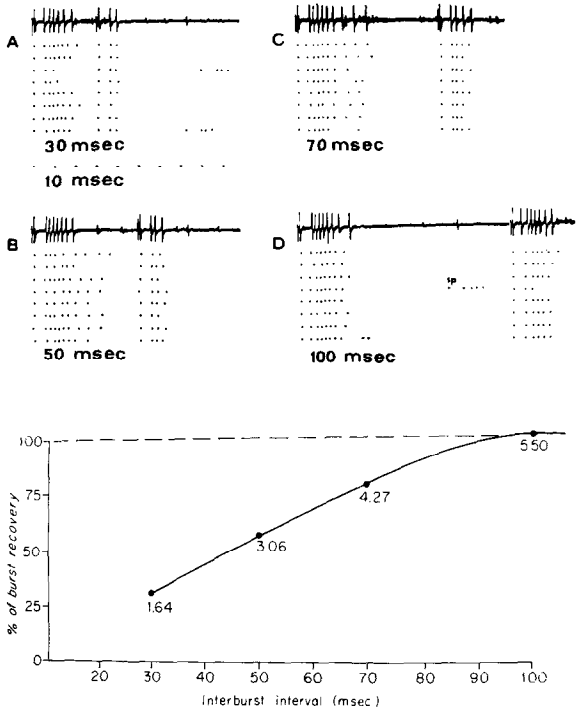

FIG. 4. Top. Action potentials and dot rasters of pairs of long-first-interval bursts evoked by pryamidal tract stimuli separated by specified intervals: (A) 30 msec, (B) 50 msec, (C) 70 msec and (D) 100 msec. Duration of the afterburst is an inverse function of the preceding interburst interval. In D, a spontaneous burst (sp) occurred between evoked bursts and attenuated the number of spikes in the following evoked long first interval burst. Bottom. Number of afterburst spikes in second antidromic long first interval burst plotted as a function of interburst interval (cell 3).

length of the second burst became proportionately attenuated (Fig. 4A, B, C). This inverse relationship between the length of the preceding interval and the length of the long first interval burst would suggest that the burst-generating mechanism requires up to 100 msec to fully recover before a complete afterburst can be generated.

When the interval between pairs of pyramidal tract shocks was further reduced, such that the second antidromically evoked action potential occurred during the long first interval of the first burst, the second stimulus evoked no additional afterburst spikes. In fact, as shown in Fig. 5, the second shock typically suppressed the first expected afterburst spike. Figure 5A shows a typical LFI burst antidromically evoked by one pyramidal tract shock. When a second pyramidal tract shock was introduced 2 msec after the first (Fig. 5B), a normal antidromic spike occurred 1 msec after the second stimulus, but the afterburst began

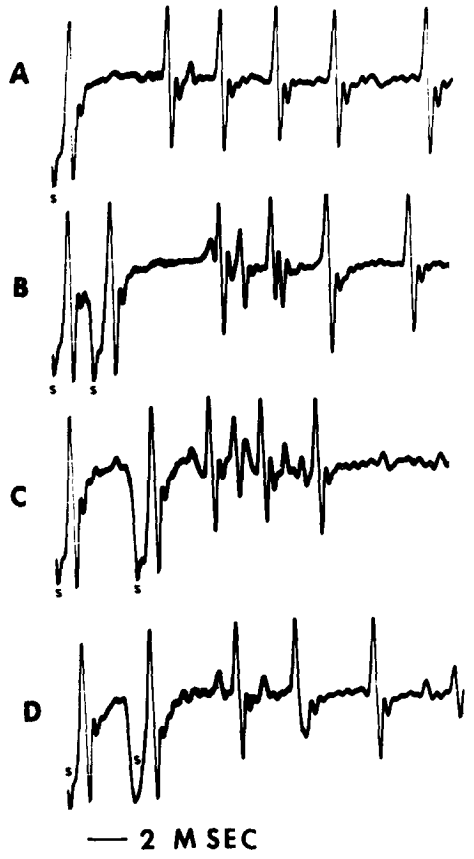

FIG. 5. Long-first-interval bursts evoked antidromically by pyramidal tract stimulation at S. In B-D a second antidromic spike was initiated during the long first interval (cell 5).

later than normally. A similar delay in the afterburst was produced by applying the second pyramidal tract shock 4 msec after the first (Fig. 5C, D).

The second pyramidal tract shock was often introduced during the afterburst itself. Under such conditions an afterburst spike occurring within one antidromic latency of the shock would collide with the antidromic spike before it reached the cell. Since the afterburst interspike intervals were only slightly longer than twice the antidromic latency, this was the most common event. However, even when the antidromic spike did not reach the cell, the pyramidal tract shock briefly suppressed the occurrence of the subsequent afterburst spike (Fig. 6). This observation suggests that collateral effects from the antidromic pyramidal tract

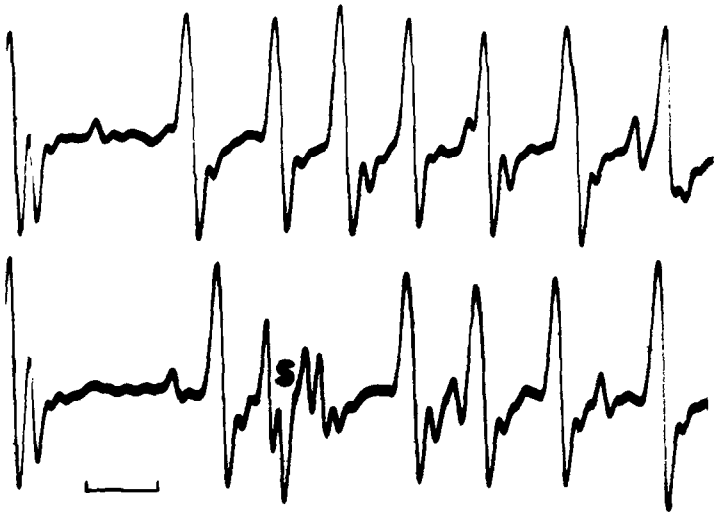

FIG. 6. Top. Antidromically evoked long-first-interval burst. Bottom. Antidromically evoked burst with second pyramidal tract stimulus (S) occurring during afterburst. Calibration 2 msec (cell 3).

volley were effective in briefly suppressing the afterburst spike-generating mechanism.

Compound Structure of the Afterburst Spikes. In most of the cells showing long first interval burst activity, it was clear that the action potentials of the afterburst spikes differed in wave form from the action potentials of the initial spike. This difference was observed both in spontaneous and antidromically elicited long first interval bursts. The afterburst action potentials typically were larger and longer than both the initial spike and spikes occurring during regular activity. In some cells the afterburst action potentials were seen to have a clear inflection near their peak as if composed of two portions. In keeping with the conventional designations, but without implying comparable mechanisms, we shall refer to the first and second portion of the compound afterburst action potential as the A and B portion, respectively (Fig. 7). That these two portions of the compound afterburst spikes represented activation of different parts of the cell was clearly demonstrated by moving the electrode past the cell and observing that these two components of the action potential varied independently and reversibly as a function of electrode position. Figure 7 shows superimposed samples of the action potentials of initial spikes and afterburst spikes recorded from one cell at different electrode depths. At all electrode positions the initial spike (and spikes characteristic of regular activity) exhibited a shape similar to the B portion of the compound afterburst spikes. Superficially, in the

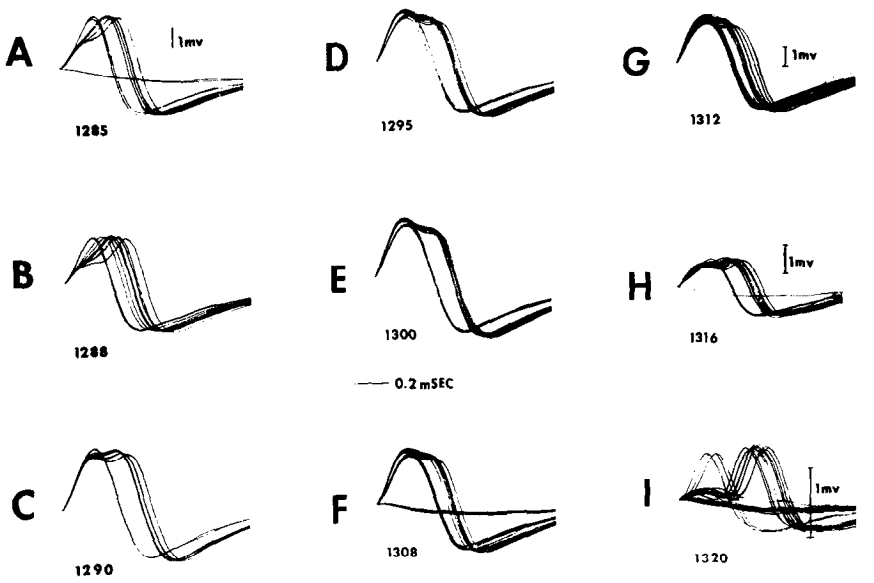

FIG. 7. A-I. Multiple sweeps of expanded action potentials of the same cell at different depths. The briefer action potential corresponds to the initial spike of each burst, the compound action potential corresponds to the spikes of the afterburst. The initial spike was also identical to the action potentials seen during regular activity (cell 10).

cortex (Fig. 7A) the A portion of afterburst spikes was relatively small compared to the B portion and the initial spike. Deeper in the cortex (Fig. 7E) the size of the A spike exceeded that of the B spike and at the deepest levels the A portion dropped rapidly in amplitude (Fig. 7I). The relative heights of the A and B portions as a function of cortical electrode depth are plotted in Fig. 8.

The break in the compound afterburst spike is not simply a result of high frequency firing. When pyramidal tract shocks were separated by 1.5–2 msec the second antidromic spike did not show any comparable break, whereas afterburst spikes following intervals up to 10 msec clearly showed such breaks.

Thus, it would appear that the two portions of the compound afterburst spike reflect two spatially separate events in the cell: The A portion reflects the process which initiates an afterburst spike and precedes the B spike, which is identical to a normal action potential (10, 19).

DISCUSSION

The above observations impose significant restrictions on the possible mechanisms which could produce long first interval bursts. The stereotyped timing pattern of the bursts—with a long interval between the

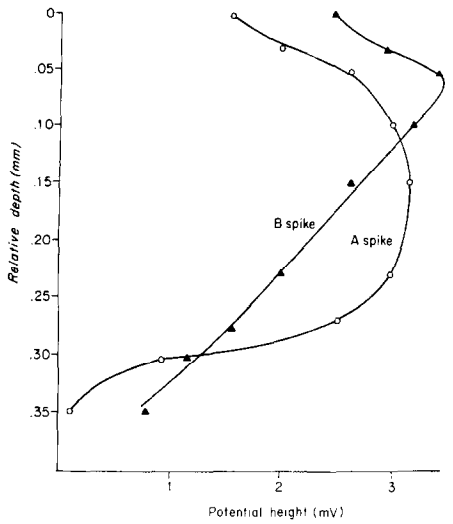

FIG. 8. Depth profile of amplitudes of A and B components of action potentials as a function of electrode depth (cell 10).

initial spike and the afterburst—and the compound structure of the afterburst spikes would indicate that long first interval bursts are not simply the response of a normal cell to an abnormally intense synaptic input (4, 5). Instead, these observations suggest that long first interval bursts probably represent an abnormal spike-generating mechanism intrinsic to the recorded cell which produces the high-frequency afterburst following the initial spike. This conclusion is further strengthened by the fact that an antidromic impulse can trigger a complete afterburst, following the normal initial antidromic spike.

Careful inspection of the action potentials showed that these cells exhibited two types of action potentials. Normal spikes occurred spontaneously both during tonic regular firing and also as the initial spike of the long first interval bursts. These normal spikes were also elicited antidromically by pyramidal tract stimulation. In contrast, the afterburst spikes usually had a greater amplitude and duration, and in several cases clearly consisted of two portions (A and B) separated by an inflection. This suggests that the pacemaker mechanism generating the afterburst spikes may be an abnormally excitable region of the same cell. If the afterburst spikes were simply generated by prolonged synaptic depolarization, the afterburst action potentials should be no different from those occurring during regular activity.

Although high-frequency firing has been known to cause temporal dissociation of action potentials into two components (attributed to an initial segment spike and a subsequent soma-dendritic spike) such a

process does not appear to explain the components of the afterburst spikes. In the long first interval cells the first spike of the afterburst (with preceding interval of 8–12 msec) typically showed as much separation between A and B components as subsequent afterburst spikes (with preceding interval of 3–4 msec). Moreover, Phillips (16, 17) has shown for the baboon and we have confirmed for the rhesus that pyramidal tract cells begin to show clear initial segment–soma-dendritic breaks only if the interval between action potentials becomes less than 1.5 msec. Whereas the first compound afterburst spike exhibited A and B components when the preceding interspike intervals were 10 msec, the short-latency antidromic normal spikes of these same cells exhibited the initial segment–soma-dendritic dissociation only when the interval between pyramidal tract shocks was reduced to less than 2 msec. Thus, the compound structure of the afterburst spikes is not simply an initial segment–soma-dendritic dissociation caused by high-frequency firing.

With two cells which clearly exhibited the compound afterburst spikes we were able to move the microelectrode past the cell and record the two components as a function of electrode position. The A and B portions of the afterburst spikes varied independently as a function of cortical depth, but at each point the B spike was identical in shape to the normal spike (Fig. 7). This would suggest that the B spike and the normal spikes represent activation of the same region of the cell, and that the A portion represents activation at a region spatially separate from the region responsible for the B spike. If the depth at which the B spike (and normal spike) was maximum is taken as the location of the cell soma, the fact that the maximum A spike occurred deeper would suggest that the abnormally excitable region may be in the basal dendrites or an axon bifurcation. The fact that these were pyramidal tract cells indicates that they were morphologically pyramidal shaped cells. There is some evidence that pyramidal shaped cells may sustain active spikes in their apical dendrites (1, 7, 20); this mechanism would predict that the A spike maximum be recorded more superficially than the B spike maximum, contrary to our observations.

The fact that a normal antidromic spike can invade the soma during the long first interval (Fig. 5) implies that the soma membrane is not in cathodal block and further suggests that the afterburst pacemaker is in a separate region of the cell. The occurrence of a second antidromic spike during the long first interval affected the afterburst by delaying its beginning by several msec.

The fact that the length of the afterburst was an inverse function of the duration of the preceding interburst interval (Fig. 4) suggests that the pacemaker mechanism is graded in a manner similar to the prolonged depolarization seen in other epileptic cells. In the penicillin focus,

Matsumoto, Ayala, and Gumnit (15) observed that when two paroxysmal depolarization shifts occurred in succession (either spontaneously or electrically evoked) the duration of the second depolarization shift was inversely related to the interval between them. It is possible that the long first interval cells are sustaining similar prolonged depolarization at some remote region of the cell, which repetitively triggers the afterburst spikes.

In most cells we found a tendency for the mean long first interval to be an integer multiple of the mean first afterburst interval. This was particularly evident in those cells which exhibited bimodal long-first-interval distributions, in which each modal long first interval was an integer multiple of the afterburst interval (Table 1). Such a relation would suggest that the initial spike starts a pacemaker process which could potentially produce afterburst spikes at specific times following the initial spike—namely, at multiples of the afterburst interval. The fact that the first few such possible spikes are absent would suggest an inhibitory or stabilizing process which suppresses the appearance of these spikes and thereby produces a long first interval. Thus, for example, if the first two possible spikes are suppressed, the long first interval would tend to be three times as long as the afterburst interval. If the inhibitory process were to act for a variable time, it might suppress either the first one or two possible spikes and produce long first intervals of either two or three times the afterburst interval, resulting in a bimodal long first interval distribution as seen in Fig. 3B. The existence of such an inhibitory process during the long first interval is supported by the observation that an antidromic spike introduced at variable periods during the long first interval tends to suppress the occurrence of the first afterburst spike (Fig. 5). If such an inhibitory process exists, it must suppress both A and B components of the afterburst spikes since we have found no evidence for partial spikes during the long first interval.

Although some of our observations suggest two regions of spike generation within the same cell, it appears that the firing of these cells can also be modulated by normal synaptic mechanisms. The attenuation of the afterburst duration as a function of the preceding interburst interval follows a time course similar to the recurrent inhibition reported by Stephanis and Jasper (21, 22). The fact that these cells also exhibited periods of normal tonic activity, particularly during overt movements, suggests some degree of normal synaptic influence. We have also found that these modes of firing can be brought under operant control (11), further indicating that the monkey could vary the synaptic input on these cells.

It would therefore appear that the long first interval burst in this animal represents a hybrid of normal and pathological activity. The

normal spikes, which occur during regular firing and also as the initial spikes of the long first interval bursts, may be generated by synaptic potentials. However, when the cell has been relatively quiescent, a normal spike (whether orthodromically or antidromically evoked) may trigger a pacemaker mechanism in some remote region of the cell. This pacemaker may simply be a prolonged depolarization which causes repetitive firing of that region (A spikes) which in turn triggers activity of the axon hillock and soma (B spikes).

Crucial evidence concerning this model could be obtained by intracellular recording from such cells. In a recent study of intracellular potentials in cells in the alumina focus of monkey, Prince and Futamachi (18) found bursts of spike activity generated by prolonged depolarization shifts, which they suggested could readily be interpreted as "augmented synaptic potentials." Interestingly, their cells also showed periods of normal postsynaptic potentials and spikes. However, they found no cells which consistently fired in long first interval bursts. Since long first cells represent a minority of cells in the focus (an estimated 15% of our population), the failure to impale one in a sample of 27 is entirely possible.

It may be that the long-first-interval cells lie on a continuum, between normal cells at one end and cells exhibiting unstructured bursts at the other. At the time these cells were recorded, the monkey's focus was subclinical—i.e., the animal did not exhibit overt seizure activity. Since our monkey had no overt seizure activity during the course of this study, one may question whether its focus was truly epileptogenic. We submit that we were recording from epileptogenic cortex on the basis of the following evidence: (a) EEG recordings over the alumina gel injection region showed epileptic spiking activity both epidurally and subdurally; (b) patterns of cellular activity were abnormally bursty for cells of precentral cortex; and (c) on three separate occasions the monkey was given graded doses of intravenous Metrazol until gross motor seizure activity was elicited; 50 mg reliably precipitated a focal motor clonic seizure involving the contralateral arm (corresponding to the cortical focus); 75 mg produced a focal motor seizure that rapidly progressed to a generalized tonic-clonic seizure. These reproducibly evoked focal seizures corresponded to the monkey's alumina gel focus, as determined by cortical mapping.

Most of the cells recorded showed normal activity and those firing in long first interval bursts also exhibited periods of regular activity. In contrast, the cells described by Calvin, Sypert, and Ward (5) were recorded in monkeys which were clinically very epileptic, undergoing several seizures a day. In that study the majority of cells showed nonstructured bursts, with a few cells firing in long first interval bursts and

hardly any showing normal activity. In that study the long first interval bursts were typically longer than ours and had a shorter long first interval. Furthermore, their long first interval cells showed no periods of regular firing. If such differences are related to the degree of clinical epilepsy, the long-first-interval burst may represent one step in the evolution of a final product: the epileptic, or hyperexcitable cell.

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