EXPERIMENTAL NEUROLOGY 43, 59–74 (1974)

Antidromic and Orthodromic Activation of Epileptic Neurons in Neocortex of Awake Monkey

ALLEN R. WYLER, EBERHARD E. FETZ, AND ARTHUR A. WARD, JR. [1]

Departments of Neurological Surgery, Physiology and Biophysics and Regional Primate Research Center, University of Washington School of Medicine, Seattle, Washington 98195

Received October 30, 1973; revision received December 6, 1973

One hundred forty normal and epileptic precentral neurons recorded from two awake monkeys with chronic experimental (alumina gel) epileptic foci were orthodromically and antidromically activated by thalamic and pyramidal tract stimulation. The response of normal neurons to single stimuli from either site was a single action potential, whereas epileptic neurons responded with a burst. Epileptic neurons firing in long-first-interval bursts responded antidromically to pyramidal tract stimulation with a long-first-interval burst, and orthodromically to thalamic stimulation with a burst whose timing coincided with the afterburst of the long-first-interval burst. Repetitive thalamic stimulation at critical frequencies of 4–5 Hz were particularly effective in evoking synchronized burst activity.

INTRODUCTION

The mechanisms responsible for generating bursts of high-frequency firing characteristic of epileptic neurons are of considerable experimental and clinical interest. Although many cells within an epileptic focus may simply be responding to massive synaptic input (22), others exhibit burst patterns not easily explained by such a mechanism. One such burst pattern is that of the long-first-interval burst, originally reported by Calvin *et al.* (4). This burst pattern was of interest because of its peculiar timing sequence, and theories which could account for the striking invariance observed within some bursts were difficult to postulate. Since the initial report, their findings have been confirmed in alumina gel foci (25) and

[1] This study was supported by U. S. Public Health Service Grants NS 05211, NS 04053, and NS 11027. We thank Mr. Ronald Barensten for help with electronic instrumentation, Mr. Jerrold Maddocks and Ms. Elizabeth Goodfellow for assistance with the illustrations, and Mr. William Congdon for electrode manufacturing.

tungstic acid foci (manuscript in preparation) as well as in human epileptic cortex (5). Therefore, further investigations into variables that influence such bursts may help clarify repetitive firing mechanisms of other types of epileptic neurons. More recent studies (6, 25) reported several salient observations on long-first-interval bursts: (i) Cortical cells with long-first-interval discharges were all pyramidal tract neurons; (ii) Antidromic stimulation of these neurons evoked long-first-interval bursts identical to spontaneous bursts; (iii) Indirect evidence indicated that bursts were initiated at a spatially separate location from the site of initiation of the normal action potential. (25, 28).

Although Westrum, White, and Ward (24) have shown pathologic dendrites in epileptic foci, there has been no convincing physiologic data to support the notion that such dendrites are responsible for epileptic burst discharges. Since 1949, Lorente de Nó (14) and others (1, 2, 8, 9, 11, 16, 17) presented anatomic and physiologic evidence that axons from the nucleus ventralis lateralis and nonspecific thalamic nuclei synapse on the apical dendrite of pyramidal tract neurons in sensorimotor cortex. The physiologic evidence was based primarily on the rise times and durations of postsynaptic potentials correlated with augmenting and recruiting responses, suggestive of electrotonic spread along distant regions rather than a direct invasion from axosomatic synapses. Although such conclusions are tenuous, the data suggest that the majority of excitatory synapses from thalamus onto pyramidal tract neurons do occur on the apical dendritic regions rather than the immediate proximity of the axon hillock. Therefore, the focal, chronic alumina gel epileptic focus in motor cortex provides a model of epileptic pyramidal tract neurons which may be activated either orthodromically or antidromically—thereby initially exciting two anatomically different regions of the same cell. This study was undertaken to determine if differences existed between the timing structure of bursts so evoked.

METHODS

The long-first-interval burst (Fig. 2C) is made up of an initial spike, followed by a relatively long interspike interval which is terminated by a stereotyped high-frequency burst (the afterburst) (4, 25).

Production of Epilepsy. Two *Macaca mulatta* monkeys (2.5 and 3.7 kg) that had a verified normal EEG underwent trephination over left precentral gyrus (at the hand region) for subpial injection of aluminum hydroxide using the protocol recently reviewed by Ward (23). Postoperative EEGs showed EEG correlates of epilepsy, and in the next 4 months the monkey underwent continuous 24-hr monitoring with the methods described by Lockard and Barensten (13). Both monkeys developed frequent general-

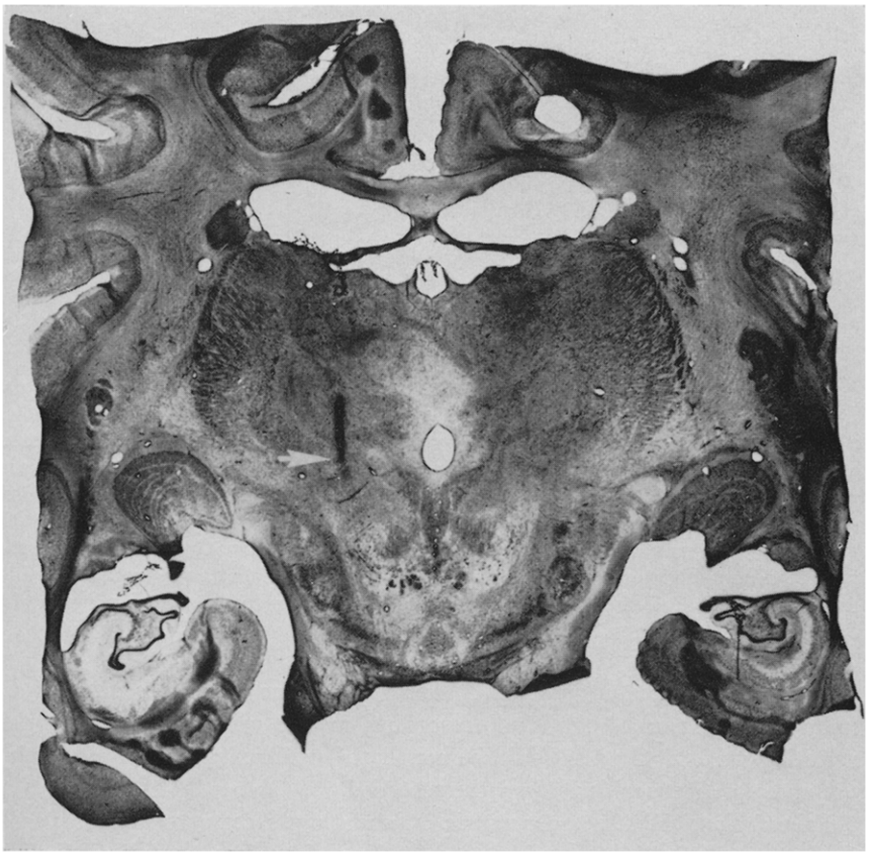

FIG. 1. Coronal section through the thalamus to demonstrate the location of the tip of the thalamic-stimulating electrode (marked by the white arrow) in the inferior portion of central-median nucleus of thalamus (Luxol Fast Blue-Nissl stain).

ized clinical seizures, and one had an intermittent epilepsia partialis continuans involving the contralateral arm.

Recording. Extracellular tungsten electrode recording techniques were used (6, 25). The monkeys were undrugged and alert (as confirmed by monitoring scalp EEG) during recording. On-line PDP-8/e computer analysis gave consecutive 15-sec totals of normal and unit burst activity, and burst index for each epoch. (The burst index is the ratio of abnormal unit activity to total unit activity per 15 sec; abnormal activity, is defined for the computer, as consecutive interspike intervals less than 5 msec.) All action potentials were negative–positive (biphasic) and distinctly isolated from surrounding activity. All data were recorded on a 6-channel Ampex FM tape recorder. A PDP-8/e computer was used for compiling post-

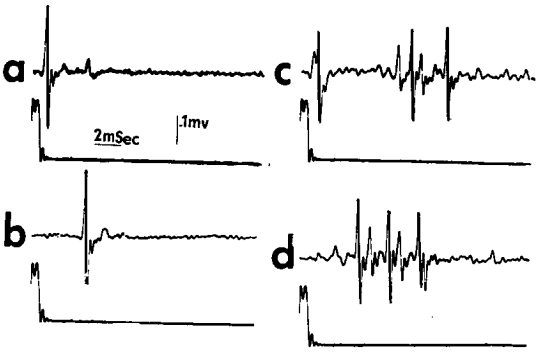

FIG. 2. Upper sweeps are triggered from stimulus marker (bottom of each trace). Sweep "a" and "b" are from a normal pyramidal tract neuron; sweep "a" shows a short latency (0.9-msec) response to pyramidal tract stimulation, sweep "b" shows a 4-msec, orthodromic response to thalamic stimulation. Sweep "c" and "d" are from two abnormal pyramidal tract neurons recorded simultaneously. Sweep "c" shows that both neurons fired in long-first-interval bursts (with two spikes per each afterburst) to pyramidal tract stimulation. "d" shows the same two neurons responding orthodromically to thalamic stimulation. Note that the burst produced by orthodromic activation resulted in interspike intervals similar to those appearing in the afterburst of antidromically induced bursts.

stimulus histograms using LAB-8/e programs. The relative location of all units with respect to the skull recording mount was noted so that the resulting map of all units could be correlated with exact brain typography (at autopsy) from which they were recorded.

Stimulation. Bipolar, concentric stimulating electrodes were placed stereotaxically in the pyramidal tract (19) and nucleus central median of thalamus (AP 8.5, L3, H + 4 (19)) ipsilateral to the focus. Electrode placements were confirmed histologically, and Fig. 1 demonstrates the location of the tip of a thalamic electrode.

Pyramidal tract cells were identified by a response with an invariant latency to at least three stimuli at 2-msec intervals to the pyramidal tract. Short latency cortical responses to thalamic stimulation were considered orthodromic if they did not collide with a spontaneously occurring action potential from which stimuli were triggered. Stimulus durations ranged from 0.1–0.3 msec, were symmetrically biphasic, and of less than 12 v intensity for thalamus and 6 v for the pyramidal tract. All stimuli used were at threshold for evoking a response; suprathreshold stimulation was not used in procuring data. To determine the percentage of stimuli which evoked neuronal responses, a series of 50 sham stimuli (no voltage applied) were given and the number of action potentials that fell within the 8-msec poststimulus period were counted. Then stimulating current was delivered and the number of responses within the 8-msec poststimulus period counted.

If a burst with a duration exceeding the 8-msec poststimulus period was elicited, all action potentials within the burst were included, but each burst was counted as one poststimulus event, so that responses to thalamic stimuli could not exceed 100% for any one cell.

RESULTS

A stereotaxically produced map of all recorded units was correlated with the cortex that lay under the recording mount and it was confirmed that all units were from the precentral gyrus within 1–2 mm of the alumina gel injection sites.

Cell Characteristics. A total of 140 cells were recorded. Ninety-two cells were judged normal and 48 cells abnormal (epileptic) on the basis of their burst indices; i.e., normal cells demonstrated burst indices less than 10, whereas abnormal cells showed individually variable burst indices ranging from 15–81. Of the 92 normal cells, 55 were pyramidal tract neurons; of the 48 abnormal cells, 21 were pyramidal tract neurons. All cells were recorded with the animal fully awake.

Normal Cells. Of the 55 normal pyramidal tract neurons, all responded antidromically to single pyramidal tract stimulation with a single action potential (Fig. 2) after a latency of 0.7–1.2 msec. Eighteen of these cells (35%) followed single thalamic stimuli with individually variable latencies between 2.0 and 7.1 msec. Of the 47 non-pyramidal tract cells, two responded antidromically to thalamic stimuli (followed 500/sec repetitive stimuli) with single action potentials after a latency of 0.6 and 1.1 msec. Of the remaining 45 non-pyramidal tract neurons, 28 responded orthodromically to thalamic stimulation with a single spike of variable latency

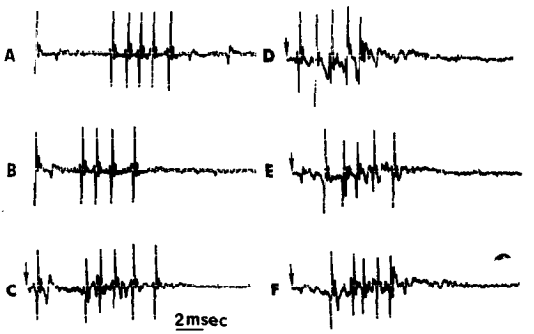

FIG. 3. Sweeps "A" and "B" demonstrate spontaneous long-first-interval bursts of a (1-mv action potential) pyramidal tract neuron. Sweep "C" shows an antidromically evoked long-first-interval burst. (Arrow marks stimulus occurrence). Sweeps "D–F" show variable latency response to thalamic stimulation; these bursts correspond to the afterbursts of spontaneous and antidromically evoked afterbursts.

(2.0–8 msec). None of the normal cells responded to either orthodromic or antidromic activation with a burst.

Abnormal Pyramidal Tract Neurons. The 21 abnormal pyramidal tract neurons demonstrated burst indices ranging between 20 and 53. During periods of spontaneous bursting, all of these cells showed mostly unstructured bursts, but they often showed variable long-first-interval burst as well (Fig. 3) (25). When antidromically stimulated (during relative quiescent periods), abnormal pyramidal tract cells often responded with long-first-interval bursts (Fig. 3D). As previously reported, attenuation of the afterburst was present (25) if the stimulus occurred within 100 msec of a previous burst that had been either antidromically induced or spontaneously occurring. If cell silence of 100 msec preceded pyramidal tract stimulation, a positive correlation existed between the burst index and the probability of antidromically evoking a stereotyped long-first-interval burst. Only the two cells with burst indices greater than 50 followed antidromic activation with full afterbursts 100% of the time, the others responded with full long-first-interval bursts a varying percentage of time.

Nineteen of 21 abnormal pyramidal tract neurons responded orthodromically to thalamic stimuli; 50–73% of these responses were bursts, the remainder were single spikes with comparable latencies (2–8 msec). Evoked bursts demonstrated interspike intervals which usually corresponded to the afterburst of spontaneously and antidromically evoked long-first-interval bursts. An example of this may be seen in Figs. 2 and 3 in which two pyramidal tract cells responded to antidromic stimulation with long-first-interval bursts, but which responded to orthodromic (thalamic) stimulation with bursts similar in timing structure to the antidromically elicited afterburst. The latency from thalamic stimulus to initiation of the burst had no consistent correlation with the duration of the long first-interval of spontaneously occurring bursts, as might be expected if the first interval was dependent on a corticothalamic conduction pathway. Whether repetitive firing could be provoked by single thalamic stimulation seemed to be in part related to the presence or absence of immediately preceding neuronal firing and to the magnitude of the cell's burst index. Orthodromically elicited bursts could be most consistently evoked after periods of 10 msec after single spikes, and 100 msec after bursts. Occasionally an orthodromic response consisted of a full long-first-interval burst, but this was rare and occurred only in those cells with burst indices greater than 40. The magnitude of the burst index was positively correlated with the percentage of orthodromically evoked burst responses.

Two abnormal pyramidal tract cells responded antidromically to thalamic stimulation with long-first-interval bursts which were indistinguishable from those elecited by pyramidal tract stimulation. In both cells, variability of the long-first-intervals was too great for comparison between bursts

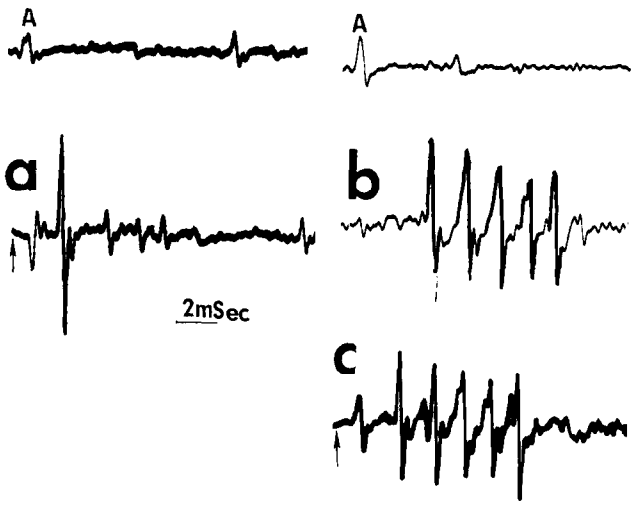

FIG. 4. Comparisons between one normal and two abnormal non-pyramidal tract neurons (from the same area of cortex) in response to single thalamic stimulation. The top sweep of each column shows the "A wave" response to pyramidal tract stimulation without antidromic activation of the neurons pictured below them. Trace "a" is a normal, non-pyramidal tract cell response, with a slightly variable 2-msec latency to thalamic stimulation. Neurons "b" and "c" were abnormal (from the same electrode tract). Single thalamic stimulation resulted in high-frequency bursts of unit activity for each cell. (Such bursts correspond in timing and structure to spontaneously occurring bursts). All sweeps were triggered from the stimulus marker. Action potential amplitudes were 1 mv, 500 and 400 μv for cells a, b, and c, respectively.

occurring spontaneously and those elicited from the two antidromic sites.

Non-Pyramidal Tract Abnormal Cells. Of the 27 abnormal non-pyramidal tract cells, 23 responded orthodromically to thalamic stimulation with bursts as shown in Fig. 4; none responded antidromically. The latencies of orthodromic burst responses were 2.0–7.3 msec, which is not significantly different from orthodromic latencies of normal cells. As in the pyramidal tract cells, the probability of thalamic stimulation evoking a burst was dependent on immediately preceding activity—especially if a spontaneous burst occurred within 200 msec prior to stimulation. As shown in Fig. 4, orthodromically evoked bursts often corresponded precisely in timing to spontaneously occurring bursts. Cells with high burst indices were more likely to respond to thalamic stimulation with a burst.

Ten non-pyramidal tract cells responded orthodromically to 51–78% of pyramidal tract stimuli with variable mean latencies (1.8–15.5 msec) and with bursts indistinguishable from spontaneously occurring bursts. All of these cells also responded to thalamic stimulation with bursts having less

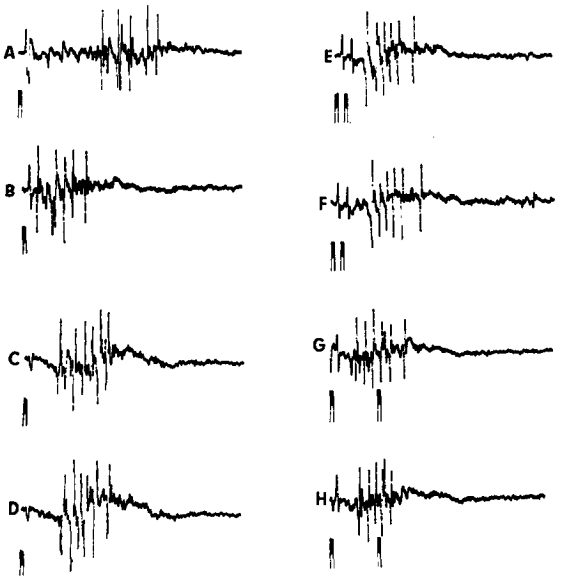

FIG. 5. All sweeps are triggered from stimulus marker. Sweep "A" and "B" demonstrate a variable latency response of an epileptic non-pyramidal tract neuron to thalamic stimulation. Sweep "C" and "D" are the same cell's response to pyramidal tract stimulation. Sweep "E" and "F" show response to paired thalamic stimuli 2 msec apart, whereas "G" and "F" demonstrate paired thalamic stimuli 10 msec apart. Note short-latency antidromic response of smaller unit in background. Action potentials were 600 μv.

variable, and shorter mean latencies (1.1–5.8 msec). It may be assumed that such short-latency responses to pyramidal tract stimulation could be accounted for by excitation via pyramidal tract axon collaterals or through lemniscal pathways. These cells were not "slow pyramidal tract neurons" because they had variable latencies and failed to follow trains of stimuli. One such cell is shown in Fig. 5. Two examples are given for pyramidal tract-induced and thalamic-induced bursts. These did not differ in duration or mean interspike interval from spontaneously occurring bursts.

Paired Stimuli. In all abnormal neurons which responded to thalamic stimulation, paired stimuli separated by 2–180 msec were given. For pyramidal tract and non-pyramidal tract cells, a second stimulus immediately before or during an orthodromically evoked burst did not attenuate or augment the resulting burst (Fig. 5). When the first stimulus failed to elicit a response, the second stimulus almost invariably evoked a burst. Therefore, the only consistent influence of shocks paired from 2–10 msec was to increase the percentage of following, if the pair was considered a single event.

If a second stimulus occurred from immediately after a burst until 180 msec after the burst, the second stimulus was ineffective in evoking a second burst. If the first stimulus did not evoke a burst, and a spontaneous burst did not occur between stimuli, then the second stimulus was more successful than random shocks. Therefore, the first stimulus, if ineffective, appeared to enhance the ability for the second to produce a burst (Fig. 6). It should be noted that in this figure all bursts are in response to the first stimulus. The ineffectiveness of the second stimulus is likely due to cortical mechanisms since, as seen in Fig. 6, a cortical field response (at arrows) resulted from the second thalamic stimulus. An exception to the above were the abnormal pyramidal tract neurons which did not show a well-defined postburst refractory period of 180 msec. These neurons could respond with a second burst for paired stimuli as close as 100 msec; but at intervals below this, the second stimulus often failed to produce a burst.

Repetitive Stimulation. All of the above non-pyramidal tract neurons were subjected to 15- to 30-sec periods of repetitive thalamic stimulation beginning at a frequency of 1 Hz and progressing in 0.5-Hz increments to a frequency of 10 Hz. Normal cells waxed and waned with respect to percentage following and also poststimulus latency, typical of recruiting

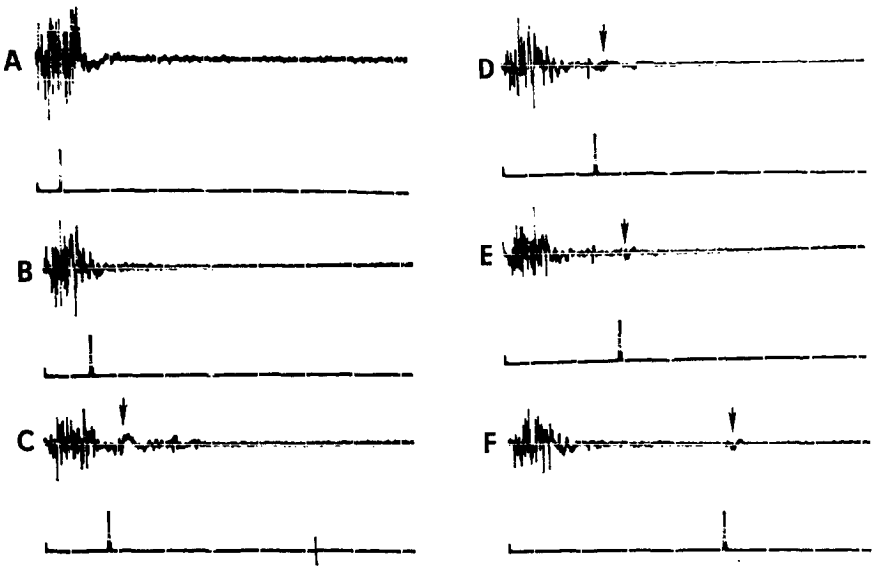

FIG. 6. Response of two neurons to paired thalamic stimulation. Top line is unit activity, and lower line shows stimulus marker (sweeps triggered off first stimulus marker). Paired stimuli are separated by 20, 40, 50, 70, 100, and 180 msec, respectively, for sweeps A–F. The arrows in C–F show the field response resulting from thalamic stimulations.

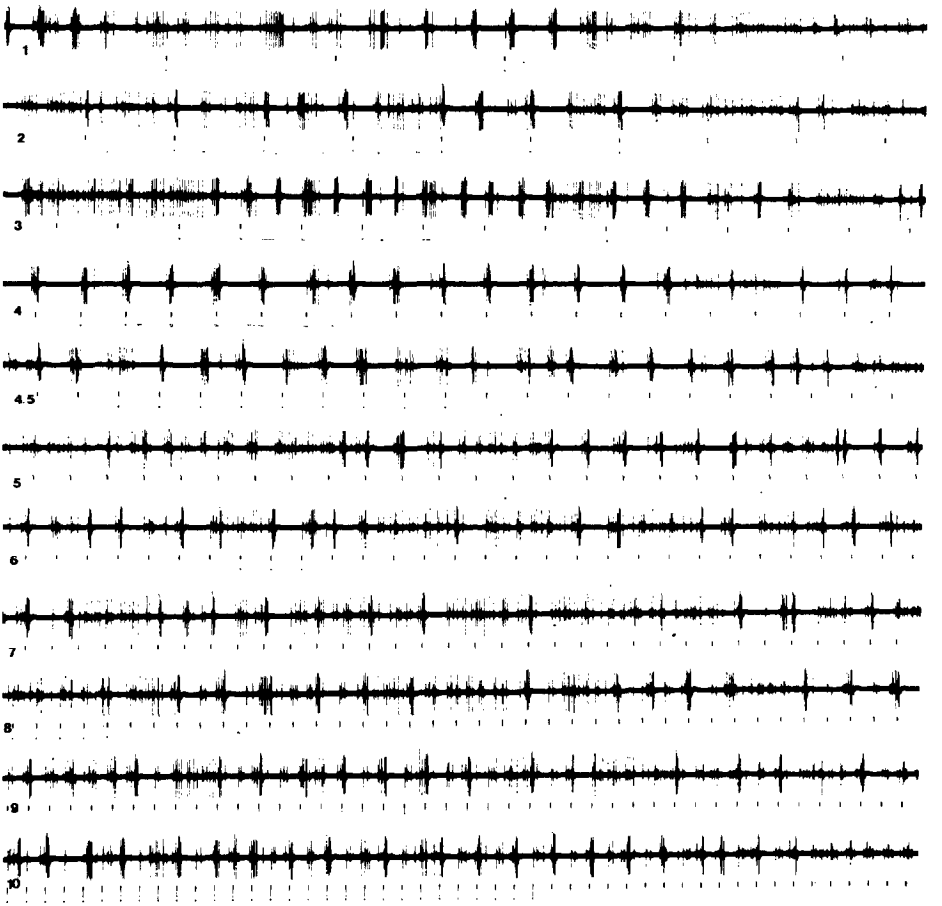

FIG. 7. Repetitive thalamic stimulation at frequencies from 1–10/sec. The numbers immediately below each trace is the stimulation frequency, and the stimulus markers are directly below the unit activity. Note that for this neuron stimulation of the thalamus at 4/sec evoked the longest continuous trains of bursts with concomitant synchronization of the small, normal background unit.

responses (9, 16, 17). Generally, abnormal cells followed frequencies from 1–1.5 Hz with similar percentages as produced by random shocks, but at frequencies of 2–2.5 Hz and 4.5 Hz, cyclic periods of 100% following with full bursts occurred. Each cell had a "critical" frequency at which the longest periods of 100% burst following was produced and these critical frequencies ranged between 4 and 5 Hz (Fig. 7). For each cell, the harmonic of this frequency also produced periods of rhythmic following, but with a limiting interburst interval of approximately 200–250 msec; i.e., a cell responding to the "critical" stimulation frequency of 4.5 Hz with 100% following, would follow 50% (every other stimulus) of stimuli presented

at 9 Hz. At frequencies above or below these "critical frequencies" the percentage of following fell (Fig. 8). It should be noted that at times when more than one cell was simultaneously observed, repetitive stimulation at the "critical frequency," or its harmonic, synchronized the firing of other cells (regardless of whether the other cell was normal) such that the cells fired together. During these periods of repetitive stimulation, the epilepsia partialis continuans of one monkey was markedly augmented, but in no instance was a generalized seizure precipitated by this method. For 10–20 sec after the repetitive stimuli the cells fired in normal patterns.

DISCUSSION

In a previous report (26) we defined two groups of epileptic neurons on the basis of the variability of the cell's burst index during periods in which the animal was not moving, but was alert by behavioral and EEG criteria. The burst indices of normal neurons were not significant (less than 10), whereas group 2 neurons showed burst indices greater than 10 with an index variability of greater than ±10. Group I neurons had higher mean burst indices but, more significantly, their variability was less than ±10 during constant behavioral conditions. The abnormal neurons comprising the present study were all classified as group 2 epileptic neurons; and the

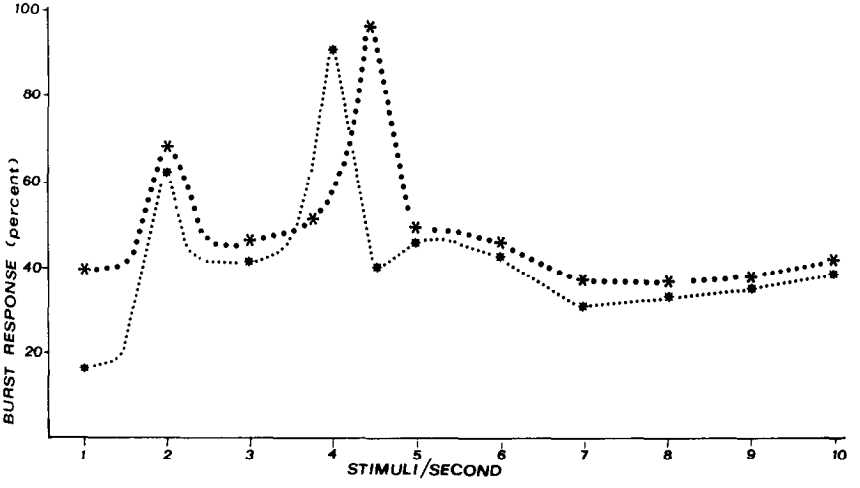

FIG. 8. Response of two representative group 2 non-pyramidal tract neurons to repetitive thalamic stimulation. The percentage of poststimulus high-frequency unit burst responses is plotted as a function of stimulus frequency. Fifty consecutive responses during periods of maximal following were selected for this graph. Both neurons demonstrated initial burst indices between 30 and 42, with a variance of greater than ±10.

abnormal burst response to thalamic stimulation further supports the concept that group 2 neurons are indeed pathological when compared to normal neurons encountered along the same electrode tracts within abnormal cortex. Moreover, it appears that the burst index and its variability is a useful measure of the degree of pathologic neuronal activity. Although the existence of intrinsically "epileptic neurons" is still controversial, it is our belief that such neurons not only exist, but they fall on a continuum; the burst index and variability defines a relative position of each epileptic neuron on a continuous spectrum from normal neurons on one end to exclusively bursting neurons on the other.

The location of the thalamic stimulating electrode was in the anterior, lateral, inferior region of nucleus central median and very near medial limits of nucleus ventralis lateralis. Therefore, with stimulation, a mixture of specific and nonspecific nuclei were probably activated, resulting in neither a pure augmenting nor a pure recruiting response. Nevertheless, this report was not intended to study the specific effects of pure augmenting or recruiting responses upon epileptic neurons but rather to provide a means of orthodromically activating neocortical cells with as little contamination from antidromic pathways as possible. Thus, the electrode seems appropriately located for this purpose. Unfortunately, many reports concerning effects of thalamic stimulation upon neocortical neurons have utilized cats which may or may not have similar synpatic projections to neocortex compared to monkeys. Moreover, many of the studies were undertaken with gallamine paralysis which introduces several variables which might influence the data: (i) Gallamine has been shown to have a minor central effect (*7*); (ii) Paralyzed and/or encéphale isolé preparations tend to produce EEG and pupillary signs of sleep; (iii) A paralyzed and/or encéphale isolé preparation has greatly diminished sensory input to thalamic, reticular, and sensorimotor neurons. In total, such preparations, although essential for documenting specific synaptic relay systems, do not provide a realistic example of neuronal activity in awake, undrugged animals. An example is the differences in responsiveness of pyramidal tract neurons to stimulation of the nucleus ventralis lateralis during wakefulness and sleep recently reported by Steriade, *et al.* (20, 21). It is, therefore, difficult to compare our results which were obtained from awake and undrugged monkeys to other studies on drugged and paralyzed cats with respect to latencies and the percentage each cell followed thalamic stimulation.

Although discrete thalamocortical pathways have not been documented between the central-median complex and sensorimotor cortex in monkey, Bowsher (2) has given evidence that such fibers may exist. Albe-Fessard *et al.* (1) reported cortical latencies of 2–4 msec in cat (slightly longer in monkeys), and Blum *et al.* (3) documented a surprisingly invariant 3.0

msec latency in cat sensorimotor neurons to single stimulation of the central-median nucleus. These latencies would indicate polysynaptic pathways, but their lower limits (2 msec) could be accounted for by monosynaptic conduction. In the awake monkey we observed response latencies to thalamic stimulation more closely approximating those reported by Albe-Fessard.

The salient difference between normal and abnormal neurons was in the response to orthodromic stimulation. All normal neurons responded to a single thalamic stimulus with a single action potential, whereas abnormal neurons responded with a burst. In Blum's study (3), neurons in sensorimotor cortex always responded to orthodromic activation (from a variety of sites) with a single action potential. Purpura *et al.* (16, 17) and Jasper and Stefanis (8) reported that repetitive stimulation of either specific (ventralis lateralis) or nonspecific (central-median) nuclei could evoke bursts; but such bursts were comprised of longer interspike intervals than those observed in epileptic bursts and also the primary response (the response to the first stimulus of repetitive stimuli) never induced a burst in pyramidal or non-pyramidal cells. Therefore, clear distinctions should be drawn between the effects of single and repetitive thalamic stimuli upon cortical cells in precentral gyrus.

It is of particular interest that in those pyramidal cells which initially appeared abnormal (burst index above 10), antidromic stimulation evoked variable long-first-interval bursts after periods of neuronal inactivity greater than 100 msec. In such cases, bursts evoked by orthodromic thalamic stimulation appeared essentially similar to the afterburst of the long-first-interval bursts. Occasionally, in those cells with high burst indices (greater than 50), orthodromic stimulation also evoked a long-first-interval burst, but this was uncommon. Purpura *et al.* (16, 17), and Klee (11) have speculated, based on the time course of PSPs in pyramidal tract neurons, that specific and nonspecific thalamocortical afferents terminate upon the cell's dendrites. If this is the case, then dendritic excitation by converging afferents may be sufficient to evoke only the afterburst without allowing the initial spike of the full long-first-interval burst to develop. This would be compatible with earlier data (6, 25, 26, 28) which indicated that the burst generator for pyramidal tract neurons may be in the neuron's soma-dendritic region. A model of the long-first-interval burst could be proposed as follows: the initial spike of the burst may occur as a result of normal activation of the axon hillock with resulting propagation of depolarization toward the dendrite(s). Regardless of whether dendritic potential changes are actively or electrotonically maintained, as discussed by Purpura (18), depolarization of a pathologic (deafferented) dendrite (24) might produce a sufficient current sink such that the afterburst could be initiated. Additional evidence supporting this hypothesis is obtained by

observation of changes in burst structure which such cells demonstrate during sleep (27). Klee (11) has confirmed previous documentation that, in pyramidal tract neurons, reticular inactivity results in a slight depolarization in the neuron's resting membrane potential; if such is the case, then the long-first-interval should shorten during sleep which, in fact, it does (27). Termination of the afterburst could result from summating recurrent inhibition (25).

Since those cells characterized as non-pyramidal tract neurons represent a heterogeneous group in which cell morphology and synaptic relationships remain somewhat ambiguous, the above model may not be as easily applied. The fact that these cells do not demonstrate a proclivity to fire in long-first-interval bursts may depend partly upon the ratio of dendrite to soma membrane area and the relative degree to which each region may effect action potential initiation at the axon hillock. The continuum of burst indices (pathologic neuronal activity) in the cells we have studied in this and other reports (6, 25, 26) parallels the continuum of dendritic abnormalities Westrum (24) described for experimental foci.

Finally, it should be pointed out that, in those cases in which pyramidal tract and non-pyramidal tract neurons were tested with paired thalamic stimuli at varying intervals, the pyramidal tract neurons' response recovered to a full burst within 100 msec, whereas the non-pyramidal tract neurons usually were refractory to evoked burst activity for 200 msec after a burst. This time course for recurrence of a burst was also illustrated by repetitive stimulation. Repetitive stimulation with frequencies from 4–10 Hz, resulted in EEG waveforms most closely resembling those of a recruiting response. But, unlike recruiting or augmenting responses which show maximal amplitudes at rhythms of 6–12 Hz (9), epileptic neurons demonstrated the most reliable bursting (and also the largest amplitude EEG spiking) at frequencies between 4 and 5 Hz (median of 4.5 Hz). This "critical frequency" not only produced the longest periods of consecutive epileptic bursts, but was also the most effective for synchronizing surrounding neurons to fire during the bursts. This "critical frequency" approximates the frequency of spontaneously occurring bursts, pathologic cortical slow waves, and the limiting interval for which paired shocks could evoke two complete bursts.

It has been postulated that the thalamus may play a role in synchronizing epileptic cortex into a "critical mass" capable of propagating a seizure. Mullans *et al.* (15) reported beneficial effects from lesions within the region of ventralis lateralis, and Kusske *et al.* (12) and Jelsma *et al.* (10), demonstrated reduction of focal and generalized epilepsy in cats, monkeys, and man with more anterior thalamic lesions. Our data would suggest that the anterior, lateral region of central median might be another subcortical region to investigate in the control of epilepsy.

REFERENCES

1. ALBE-FESSARD, D. C., KOCKA-MIRANDA, and E. OSWALDO-CRUZ. 1959. Activités d'origines somesthésiques évoqueés au niveau du cortex non specifique et du centre médian du thalamus chez le singe anesthésié au cloralose. *Electroencephalogr. Clin. Neurophysiol.* **11**: 777–787.
2. BOWSHER, D. 1966. Some afferent and efferent connections of the parafasicular-center-median complex, pp. 99–108. *In* "The Thalamus." D. P. Purpura and M. D. Yahr [Eds.]. Columbia University Press, New York.
3. BLUM, B., L. M. HALPERN, and A. A. WARD, JR. 1968. Microelectrode studies of the afferent connections and efferent projection of neurons in the sensorimotor cortex of the cat. *Exp. Neurol.* **20**: 156–173.
4. CALVIN, W. H., G. W. SYPERT, and A. A. WARD, JR. (1968). Structured timing patterns within bursts from epileptic neurons in undrugged monkey cortex. *Exp. Neurol.* **21**: 535–542.
5. CALVIN, W. H., G. A. OJEMANN, and A. A. WARD, JR. 1973. Human cortical neurons in epileptogenic foci: comparison of interictal firing patterns to those of "epileptic" neurons in animals. *Electroencephalogr. Clin. Neurophysiol.* **34**: 337–351.
6. FETZ, E. E., and A. R. WYLER. 1973. Operantly conditioned firing patterns of epileptic neurons in motor cortex of chronic monkey. *Exp. Neurol.* **40**: 586–607.
7. HALPERN, L. M., and R. G. BLACK. 1967. Flaxedil (gallamine triethiodide): evidence for central action. *Science* **155**: 1685–1687.
8. JASPER, H., and C. STEFANIS. 1965. Intracellular oscillatory rhythms in pyramidal tract neurons in the cat. *Electrocncephalogr. Clin. Neurophysiol.* **18**: 541–553.
9. JASPER, H. H. 1960. Unspecific thalamocortical relations, pp. 1307–1321. *In* "Handbook of Physiology, Sec. I, Vol. II, Neurophysiology." J. Field, H. W. Magoun, and V. E. Hall [Eds.]. American Physiological Society, Washington, DC.
10. JELSMA, R. K., C. M. BERTRAND, S. N. MARTINEZ, and P. MOLINA-NEGRO. 1973. Stereotaxic treatment of frontal-lobe and centrencephalic epiliepsy. *J. Neurosurg.* **39**: 42–51.
11. KLEE, M. R. 1966. Differentt effects on the membrane potential of motor cortex units after thalamic and reticular stimulation, pp. 287–322. *In* "The Thalamus." D. P. Purpura and M. D. Yahr [Eds.]. Columbia University Press, New York.
12. KUSSKE, J. A., G. A. OJEMANN, and A. A. WARD, JR. 1972. Effects of lesions in ventral anterior thalamus on experimental focal epilepsy. *Exp. Neurol.* **34**: 279–290.
13. LOCKARD, J. S., and R. I. BARENSTEN. 1967. Behavioral experimental epilepsy in monkeys. I. Clinical seizure recording apparatus and initial data. *Electroencephalogr. Clin. Neurophysiol.* **22**: 482–491.
14. LORENTE, DE NÓ, R. 1949. Cerebral cortex: architecture, intracortical connections, motor projections, pp. 288–312. *In* "Physiology of the Nervous System." J. P. Fulton [Ed.]. Oxford University Press, New York.
15. MULLANS, S., G. VAILATI, J. KARASICK, and M. MAILIS. 1967. Thalamic lesions for control of epilepsy. *Arch. Neurol.* **16**: 277–285.
16. PURPURA, D. P., and R. J. SHAFER. 1964. Cortical intracellular potentials during augmenting and recruiting responses. I. Effects of injected hyperpolarizing currents on evoked membrane potential changes. *J. Neurophysiol.* **27**: 117–132.

17. PURPURA, D. P., R. J. SHAFER, and F. S. MUSGRAVE. 1964. Cortical intracellular potentials during augmenting and recruiting responses II: patterns of synaptic activities in pyramidal and non-pyramidal tract neurons. *J. Neurophysiol.* **27**: 132–150.
18. PURPURA, D. P. 1967. Comparative physiology of dendrites, pp. 372–393. *In* "The Neurosciences." G. C. Quarton, T. Melnechuk, F. O. Schmitt [Eds.]. The Rockefeller University Press, New York.
19. SNIDER, R. S., and J. C. LEE. 1961. "A Stereotaxic, Atlas of the Monkey Brain (Macaca mulatta)." University of Chicago Press, Chicago.
20. STERIADE, M., P. WYZINSKI, and V. APOSTOL. 1973. Differential synaptic reactivity of simple and complex pyramidal tract neurons at various levels of vigilance. *Exp. Brain Res.* **17**: 87–110.
21. STERIADE, M., P. WYZINSKI, and V. APOSTOL. 1972. Corticofugal projections governing rhythmic thalamic activity. pp. 221–273. *In* "Corticothalamic Projections and Sensorimotor Activities." T. L. Frigyesi, E. Rinvik, and M. D. Yahr [Eds.]. Raven Press, New York.
22. WARD, A. A., JR. 1969. The epileptic neuron: chronic foci in animals and man. pp. 263–289. *In* "The Basic Mechanisms of the Epilepsies." H. H. Jasper, A. A. Ward, Jr., and A. Pope (Eds.). Little, Brown, Boston.
23. WARD, A. A., JR. 1972. Topical convulsant metals. pp. 13–36. *In* "Experimental Models of Epilepsy." J. K. Penry, D. P. Pupura, J. Woodbury, A. Tower, and R. D. Walter [Eds.]. Raven Press, New York.
24. WESTRUM, L. E., L. E. WHITE, and A. A. WARD, JR. 1965. Morphology of the experimental epileptic focus. *J. Neurosurg.* **21**: 1033–1046.
25. WYLER, A. R., E. E. FETZ, and A. A. WARD, JR. 1973. Spontaneous firing patterns of epileptic neurons in motor cortex of chronic monkey. *Exp. Neurol.* **40**: 567–585.
26. WYLER, A. R., and E. E. FETZ. 1974. Behavioral control of firing patterns of normal and abnormal neurons in chronic epileptic cortex. *Exp. Neurol.* **42**: 448–464.
27. WYLER, A. R. 1974. Epileptic neurons during sleep and wakefulness. *Exp. Neurol.* **42**: 593–608.
28. WYLER, A. R., E. E. FETZ, and A. A. WARD, JR. 1973. Injury-induced long-first-interval burst in neocortex of monkey. *Exp. Neurol.* **41**: 773–776.