NEURONAL PROCESSES UNDERLYING RHYTHMIC BRAIN ACTIVITY

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The neuroelectric activity of the brain provides a variety of instances of rhythmic events. The periodicity of such events ranges from milliseconds in the case of the firing of individual neurons to circadian in the case of certain aspects of the “sleep” EEG. This paper will be devoted to a discussion of (i) methodological approaches to the detection and description of some of the shorter period rhythmic events, (ii) the nature of the underlying neuronal activity which generates the rhythmicity, and (iii) hints concerning the significance of such rhythmic activity for behavior.

The apparent frequencies of the electrical activity of the brain are often functions of the technical capabilities of the devices which are used to make the recordings. For example, electroencephalograms are usually made with amplifiers which exclude frequencies at both the high and low ends of the spectrum. Slow events (less than 1 Hz) and rapid events (above 50 Hz) are usually not recorded. Direct-coupled amplifiers with high frequency cutoffs in the kilohertz range, together with “non-polarizable” glass micropipette recording electrodes permit a less restricted range of neuronal frequencies to be recorded. In recent years, these more sophisticated techniques have been applied to recordings made in animals during “spontaneous” or trained behavior, as well as in “acute” preparations. (To a very limited extent, some of these techniques have been used in humans, see 1). By the use of microelectrode recordings and DC amplifiers, spontaneous and evoked rhythmic events in the cerebral cortex and in certain subcortical structures have been shown to be related to synaptic processes in individual cerebral neurons. The precise form of
these synaptic events and the presence or absence of neuronal spike discharges depends on several factors. These include (i) the relative level of polarization of the membrane, and (ii) the synaptic input onto the cell from which recordings are made. Figure 1 illustrates the first of these processes (5). The upper traces in this Figure are photographs of potentials recorded inside a cell in the caudate nucleus in response to cortical stimulation. Cells in the caudate nucleus are more often hyperpolarized with respect to the level of polarization necessary to generate action potentials than are neurons in other brain structures (4). In the upper traces of Fig. 1 the cell membrane is hyperpolarized. At the instant indicated by the arrows, a stimulus pulse is applied to the cerebral cortex. The cortical stimulus

![Figure 1. Effect of resting level on PSP. Upper traces: intracellular responses of hyperpolarized caudate neuron to cortical stimulation (arrows). A, "raw" responses; B, averaged synaptic potentials with spikes filtered out. Lower traces: resting membrane potential is depolarized. Note smaller EPSP, deeper IPSP and action potentials. From Hull et al. (5).](image-url)
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evokes an excitatory postsynaptic potential (EPSP) followed by a longer hyperpolarization (IPSP). An action potential does not occur in this hyperpolarized cell. In the lower part of Fig. 1, the cell membrane has been depolarized. Now the cortical stimulus sometimes evokes spike discharges. The EPSP is smaller in amplitude and IPSP is larger in the depolarized than in the hyperpolarized situation. Despite the reduced EPSP amplitude, a spike discharge has occurred because the total membrane potential, including the 5 mv of depolarization, is of sufficient magnitude so as to reach threshold for firing. Recordings made with glass microelectrodes, but utilizing EEG type amplifiers might reveal these differences in postsynaptic potential amplitudes, but would not indicate whether the neurons involved were actually firing. Extracellular unit recordings using classical capacitance-coupled amplifiers would show only that the cell was firing or not firing without indicating anything of the underlying synaptic events.

The second property of neuronal responsiveness is that the timing and appearance of synaptic potentials depends on the nature and location of the synaptic inputs which impinge upon the cell. For example, cortical stimulation produces an immediate firing followed by a long inhibitory period in a caudate neuron, while stimulation of the central median nucleus of the thalamus tends to produce a pure excitatory response (Fig. 2).

The absence of action potentials may be the result of excess depolarization of the neuron, as well as of failure to reach a discharge threshold. For example, as the frequency of stimulation applied to the substantia nigra is increased, the membrane of a recorded caudate neuron first depolarizes and fires more rapidly. As the stimulating frequency is further

Fig. 2. Averaged intracellular responses of caudate neuron to cortical (upper trace, Cx) and central median (lower trace, TH) stimuli. See text for details.
increased the excessively depolarized spike deteriorates and firing ceases. Extracellular recordings made with capacitance-coupled amplifiers would show only the absence of firing. EEG recordings from the same neuronal region might indicate that a long depolarization had occurred but would show neither the time course of this depolarization nor the presence or absence of action potentials (7).

Neuronal rhythmic processes can be analyzed by methods similar to those just discussed. Consider the occurrence of electroencephalographic rhythms at a frequency range of 8–12 Hz, the so-called alpha rhythms in man and “spindle-bursts” (or waves) in animals. Rhythmic activity in this frequency range occurs naturally in humans during drowsiness, during states of inattention and during phases of sleep, and is typical of barbiturate anesthesia. Additionally, 8–12 Hz activity may be induced by single pulse stimulation of particular parts of the brain and under special conditions by sensory stimuli. There is a considerable amount of evidence to indicate that this “spindling” depends for its maintenance on the existence of the thalamus (2). When intracellular d-c recordings are made of responses to single shocks inducing spindling, the synaptic events occurring

Fig. 3. Effect of increasing intensity of cortical stimuli on averaged membrane response of a caudate neuron. Note at 10 v, stimulus (arrow) evokes EPSP-IPSP sequence followed by rhythmic spindling.
are revealed. The stimulus evokes a short depolarizing potential which is succeeded by a long hyperpolarization. This EPSP–IPSP sequence is followed by a rebound depolarization which may, particularly with higher intensity stimuli, consist of a series of rhythmic membrane fluctuations resembling an EEG spindle (Fig. 3).

Another way of inducing brain rhythms is by the application of stimuli at 5–10 Hz to certain thalamic, cortical or striatal regions. Such stimuli evoke so-called “augmenting” or “recruiting” responses in projection areas. These responses are characterized by incrementing amplitudes to successive stimuli which eventually either reach amplitude stability or decrease in such a way that the envelope of the responses may form a spindle. An idea of the neuronal basis of these rhythmic-appearing potentials can be gained by intracellular analysis. Figure 4 illustrates “recruiting” response recorded in a caudate neuron in response to stimulation of the ventral anterior nucleus of the thalamus. At low repetition rates (2.5/sec) each stimulus produces an EPSP out of which spikes fire. This is followed by a longer IPSP and then by a “rebond” depolarization. As the frequency of thalamic stimulation is increased, two events occur. The first is that action potentials no longer follow the IPSPs (6/sec) because a second pulse is delivered before the IPSP is terminated. The second is that the cell membrane is hyperpolarized as a succeeding pulse is applied.
closer and closer to the deepest part of the IPSP. This results in larger EPSPs from each of which one or two spikes fire. With faster frequencies of stimulation the membrane is hyperpolarized to such an extent that even though each individual stimulus produces a depolarization, firing threshold is generally not reached (not illustrated). An EEG recording made from the region of such a neuron would show the classical “augmenting” or “recruiting” responses.

The data discussed to this point came from “acute” experiments. Similar observations can be made with difficulty in freely moving behaving animals, and, rarely, in humans. It is necessary to devise a metric by which the contributions of individual neurons to macroelectrode responses recorded with conventional EEG techniques in the human can be assessed. Initial attempts to approximate such a metric are under way. When completed, it is expected that a quantitative statement of peak latency and the relative proportion of certain components will permit the recreation

\[ REC: \text{L. MED. ANT. SIG. GYR.} \]

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\begin{align*}
&\text{L. Cd. ALONE} \\
&\text{L. Cd. - 70 - L. LG.} \\
&\text{1st PAIRING} \\
&\text{L. LG.} \\
&\text{AFTER PAIRING} \\
&\text{BEFORE AROUSAL} \\
&\text{AFTER AROUSAL} \\
&\text{100 \u{u}V} \\
&\text{500 \u{u}V} \\
&\text{200 msec}
\end{align*}
\]

Fig. 5. Cortical responses to inhibitory and afferent inputs in behaving cat. Upper of each pair of traces is “multiple unit” activity. Lower is evoked potential response. Both are recorded from the same cortical electrode. See text for details. From Buchwald et al. (3).
of any d-c-recorded evoked postsynaptic potential and with certain qualifications concerning the method of recording, the recreation of "EEG-type" recorded evoked potentials as well.

Finally, it is worthwhile to discuss the recording of rhythmic activities from the brains of free moving animals. Such recordings often can be correlated with the animals' performance. Figure 5, for example, shows the response of a cortical neuron to a pulse applied to the caudate nucleus in a cat which has learned to press a bar for milk reinforcement. This stimulus induces an inhibition of firing of extracellularly recorded units and a concomitant rhythmic spindling activity (S L. Cd. alone). Such stimuli, applied at the rates of 2–3 Hz and at intensities sufficient to evoke the unit inhibition and spindling, stop an animal's bar-pressing. If the cat being stimulated in this way is subjected simultaneously to a sensory input (L. Cd.-70-L. LG.; 1st pairing), it tends to alert and resume pressing. At the same time, the inhibition of unit activity is released and the rhythmic spindling no longer occurs. If pairing of the inhibitory and sensory stimuli is continued (23rd pairing), however, the animal again stops pressing and the rhythmic spindling resumes. In fact, with repetition, the sensory input itself is often sufficient to induce rhythmic spindling activity (S L. LG. — before arousal). Introduction of a sensory stimulus in another modality (after arousal) returns the animal to action and stops the spindling (3).

In intracellular recordings, the cellular bases of these phenomena have been explored. In such experiments the inhibitory period preceding the spindle was found to consist of a long IPSP which was curtailed by pairing the inhibitory stimulus with a sensory input (6). Analysis of this intracellular response and others like it can provide basic information concerning rhythmicities which appear under certain conditions in human brain in response to repetitive sensory stimuli and the relationship of such rhythmicities to observed behavior.

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REFERENCES


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