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Dynamic Synapses in the Cortex

Minireview

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Synapses are the specialized connections that allow signals to propagate from one nerve cell to the next. Their privileged position gives them a unique role in neural computation. Synapses are not merely passive relays that faithfully transmit the signal they receive. They are, rather, gatekeepers that actively govern and modulate the flow of information in neuronal circuits. It is the precise pattern of synaptic connectivity and the variable strengths of the individual connections that endow a neural circuit with the capacity to perform specific computations.

Synapses are dynamic: they exhibit use-dependent changes in efficacy on timescales ranging from milliseconds to days, weeks, or longer. Many varieties of short-term synaptic plasticity have been described (reviewed by Magleby, 1987; Zucker, 1989; Fisher et al., 1997), but synapses are often studied under conditions specifically designed to minimize the effect of such plasticity. Thus, we know comparatively little about the functional consequences of short-term plasticity at central synapses. Recent papers by two groups (Abbott et al., 1997; Varela et al., 1997; Markram and Tsodyks, 1996; Tsodyks and Markram, 1997) are beginning to address this question by investigating the synaptic responses to more behaviorally relevant neural stimuli. Their results may have important consequences for our understanding of neural coding in the central nervous system.

Spike Trains In Vivo

In conventional in vitro experiments not specifically designed to study short-term plasticity, physiologists assess synaptic efficacy by stimulating at a low constant frequency (e.g., 0.03–0.1 Hz) that minimizes the interaction between successive pulses. Such protocols are useful because they permit synaptic mechanisms to be dissected under controlled conditions, but they do not reflect the temporal characteristics of the trains of action potentials that typically drive these synapses in vivo.

Figure 1 shows the timing of action potentials recorded in vivo from a neuron in the medial temporal (MT) cortex of an alert macaque monkey. MT cortex is involved in visual motion processing (Albright, 1984). This spike train provides the input to all of the synapses made by this particular neuron onto other cortical neurons. Two characteristics are immediately evident. First, the spike train is highly irregular (see Softky and Koch, 1993). That is, spikes occur apparently at random, like the ticks of a Geiger counter. Most spike trains recorded from both cortical and hippocampal neurons are comparably irregular, and can, to a crude first approximation, be modeled as a Poisson process (the name given to the statistics that govern the random activity of a Geiger counter).

The second striking characteristic of the spike train shown in Figure 1 is that the firing rate is sustained at a high average level (60 Hz) for the duration of the 2 s stimulus. This firing rate is several orders of magnitude higher than the stimuli typically used during in vitro synaptic studies. Transiently, the spike rate can be even higher (or lower); for several 50 ms intervals, the spike rate reached 140 Hz, and some pairs of spikes were separated by as little as 1 ms. During spontaneous activity (when no stimulus was present), interspike intervals were as long as 275 ms. The interstimulus intervals driving the synapses thus ranged over more than 2 orders of magnitude. This range can be even higher for neurons with lower spontaneous rates. It should be noted that the stimulus used in Figure 1 was nearly "optimal," i.e., it was specifically tailored to produce nearly the highest possible spike rate. While less is known about the firing characteristics of neurons in MT cortex in response to more natural stimuli, the irregularity illustrated in Figure 1 is an essentially universal feature of neuronal activity throughout most of the cortex and hippocampus.

Synaptic Response to Irregular Spike Trains

How do central synapses respond to complex patterns of stimuli? Recent studies from two groups have addressed this question (Abbott et al., 1997; Varela et al., 1997; Markram and Tsodyks, 1996; Tsodyks and Markram, 1997). Figure 2 shows the average field potential amplitudes in response to a 2 s random Poisson stimulus train (mean rate = 4 Hz) recorded from layer 2/3 in primary visual cortex (modified from Varela et al., 1997). A striking feature of the response illustrated in Figure 2 is its variability. The response amplitude varies >5-fold, which is larger than the increases in field potential responses typically seen following long-term potentiation (LTP). This variability is not due to random fluctuations, as indicated by the small standard deviations when precisely the same sequence of stimuli was delivered on repeated trials. Rather, it reflects the dynamic nature of synaptic efficacy on short timescales. This experiment illustrates an important general principle: the response of a synapse to a single stimulus or to pairs of stimuli is not sufficient to characterize its efficacy. Depending on the experimental conditions and the particular synapse under investigation, the response to a single pulse can be larger or smaller than the second or subsequent pulses.

The response variability illustrated in Figure 2 arises from the interaction of several distinct mechanisms. Analogous forms of short-term plasticity were first described at the neuromuscular junction (NMJ). Early studies showed that, depending on the recording conditions and stimulation paradigm, the response during a train of pulses could either increase (facilitate) or decrease (depress). In one of the first quantal analyses, del Castillo and Katz (1954) showed that the mechanism underlying the most rapid component of facilitation (called "paired-pulse facilitation") at the NMJ was a presynaptic increase in the probability of vesicular release following stimulation. Subsequent studies have shown that a

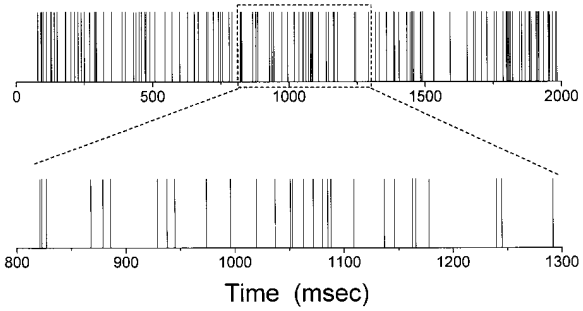

Figure 1. Cortical Neurons In Vivo Fire Rapid and Irregular Trains of Action Potentials

The top panel shows a spike train recorded extracellularly from a neuron in the MT cortex of an awake macaque monkey in response to a 2 s presentation of a nearly optimal visual stimulus. The average spike rate during this trial was 61.5 Hz, and the shortest interspike intervals were 1 ms. The bottom panel shows an expanded view of a region of the same spike train (indicated by the dotted box) to further illustrate details of the timing. (L.J. Croner and T.D. Albright, unpublished data).

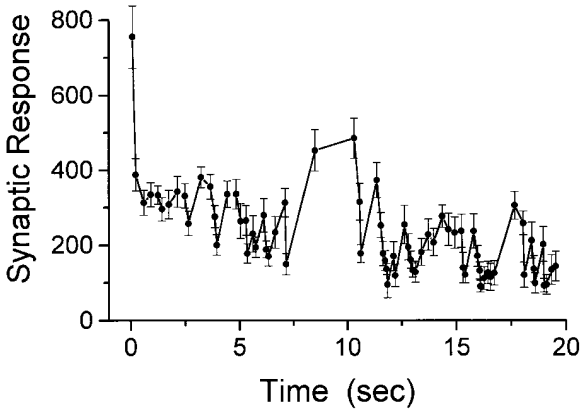

Figure 2. The Synaptic Response during an Irregular Stimulus Is Variable but Repeatable

Field potentials were recorded in layer 2/3 in response to a sequence of extracellular shocks (Poisson distributed stimulus train, mean 4 Hz) delivered through a stimulating electrode placed in layer 4 of a rat cortical slice. The points show the mean ± SD of the synaptic response (field potential amplitude) averaged over five trials. The fluctuations induced by short-term plasticity during the train are much larger than those due to trial-to-trial variability.

change in presynaptic release probability also underlies other forms of facilitation and depression in many other preparations (Magleby, 1987; Zucker, 1989; Fisher et al., 1997).

At the NMJ, at least four distinct components of facilitation have been distinguished on the basis of kinetic and other properties, along with at least one component of depression (Magleby, 1987). Much of the history-dependent variability at central synapses (illustrated in Figure 2) can be accounted for by using models similar to those first developed for the NMJ. Tsodyks and Markram (1997) studied the synapses between pairs of layer 5 neurons in the cortex. They found that they could—for the particular type of spike trains they used—account for most of the response variability at this synapse, particularly during high-frequency stimulation (>10 Hz), with a model that included no facilitation, and a single form of rapid depression. The model proposed by Abbott and colleagues (Abbott et al., 1997; Varela et al., 1997) used as many as three components of depression and zero or one component of facilitation to describe plasticity at layer 2/3 cortical synapses; again, rapid synaptic depression was the dominant feature during high frequency stimulation (Abbott et al., 1997).

The models proposed by both groups are phenomenological: they provide mathematical descriptions that account for their observations. While neither group related the plasticity directly to changes in the underlying molecular machinery, their results are consistent with a presynaptic change in vesicular release probability (as expected from work at the NMJ and previous studies in the cortex, e.g., Thomson et al., 1993). Moreover, their models consider only average activity, i.e., the response averaged across multiple synaptic boutons and multiple trials. Recent studies (e.g., Dobrunz and Stevens, 1997) find heterogeneity across boutons, which introduces further complexity.

Both groups demonstrate that rapid depression is the dominant form of plasticity at moderate to high stimulus frequencies (>10 Hz) at these synapses. This leads to the striking result that at high stimulation frequencies, the response per unit time is a constant, independent of stimulation frequency. At high stimulus frequencies, the steady-state synaptic response per impulse depends inversely on the stimulus frequency, F, as A/F, where A is a proportionality constant. The steady-state response per unit time, R, therefore equals the response per impulse, A/F, times the number of impulses per second. This gives $R = A/F \times F = A$, which shows that the response per unit time is a constant, A, independent of stimulus frequency.

In the hippocampus, depletion of a small pool of readily releasable vesicles underlies a similar form of depression (Dobrunz and Stevens, 1997). If the same mechanism is responsible for the depression seen at these cortical synapses, then the independence of the response rate, R, on stimulation frequency, F, can be readily understood in terms of the underlying mechanism. At high frequencies, the rate at which the depleted vesicle pool is refilled becomes the limiting step. Thus, the steady-state response, A (which might have units of vesicles per second), may be primarily a reflection of the vesicular refilling rate.

Functional Consequences

As suggested by Figure 1, firing frequencies of 10 Hz and above are well within the range observed in vivo. Thus, it is worthwhile to consider some functional implications of the rather surprising independence of the average response amplitude on stimulation frequency. One consequence is that at such high frequencies, the average synaptic output no longer contains information about the input frequency. In this regime, synapses cannot simply be transmitting information about the firing rate. Tsodyks and Markram (1997) discuss possible implications of this for neural coding (also see Stevens and Zador, 1995).

A second consequence of this form of depression is that it renders synapses preferentially sensitive to abrupt changes in firing rate (Abbott et al., 1997). Indeed, in this regime of fast stimulation frequencies, only changes are signaled. If the synapse is in steady-state with an input frequency, F, the steady-state response is $R_{ss} = A/F \times F = A$ (as shown above). If the firing rate, F, changes abruptly by an amount, ΔF, although the eventual steady-state response will be the same, the first few responses will be transmitted as $R_{trans} = (A/F) \times (F + \Delta F) = R_{ss} + A \times (\Delta F/F)$. Thus, the response will initially be changed by an amount proportional to $\Delta F/F$; therefore, the transient response will convey information about the fractional change in the input firing rate. This relationship is analogous to the Weber-Fechner relationship from psychophysics, and may provide a mechanism for neural circuits to process inputs that vary over many orders of magnitude.

A third consequence of this form of depression, not considered by either group, is that it helps enforce a distributed code, i.e., one in which representation involves the activity of a population of input neurons. This can be illustrated by considering the following two hypothetical situations. In the first, one presynaptic neuron fires at 50 Hz, while in the second, 10 presynaptic neurons each fire at 5 Hz. In the absence of depression, the total average postsynaptic response (50 impulses/second) is the same in both cases. In contrast, at synapses where the responses to higher frequency stimuli are greatly attenuated by synaptic depression, the postsynaptic response to the single rapidly firing neuron will be much lower than to the ensemble of more slowly firing neurons. Thus, neuronal responses will be propagated preferentially when the input activity is distributed across many neurons.

Interaction between Short- And Long-Term Plasticity

LTP remains the leading candidate for the cellular basis of learning and memory (Malenka, 1994; Cain and Saucier, 1996). LTP is usually defined as a persistent ($>$30 min) increase in synaptic efficacy. Implicit in this definition is the stimulation protocol used to assess efficacy: isolated pulses delivered at a very low frequency. In fact, the long-lasting changes in the response to stimulus trains are more complex, due to the interaction of LTP with short-term plasticity.

Markram and Tsodyks (1996) tested the connection between pairs of layer 5 pyramidal neurons in slices of rat cortex before and after the induction of LTP. They found that synaptic responses were differentially affected, depending on where they fell during the train of stimuli. The first pulse was always potentiated; indeed, this is the definition of LTP under the conventional stimulation protocol. Surprisingly, the steady-state synaptic response (defined as the average response to the fifth and higher pulses in the train) was unaffected by LTP. The response to the transition pulses 2–4 was variable, so that the net response during the first 4 pulses could be increased, decreased, or unchanged. Thus, the consistent change was not an increase in efficacy, but rather a redistribution of the efficacy toward the first pulse.

These findings have both mechanistic and functional implications. Markram and Tsodyks (1996) argue that the unchanged steady-state response following LTP is hard to reconcile with an expression mechanism in which either silent synapses are unmasked, or postsynaptic receptors are recruited or potentiated. Rather, they favor an increase in presynaptic release probability as the simplest explanation for their observations. Further experiments will be needed to elucidate the implications of this finding on the mechanism of LTP expression.

Most models of the functional role of LTP focus on its requirement for Hebbian (nearly simultaneous pre- and postsynaptic) activity, and can be traced to Hebb's proposal that "When an axon of cell A...repeatedly or consistently takes part in firing [cell B, some] change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased" (Hebb, 1949). A generation of research on artificial neural networks has demonstrated that Hebbian learning can be used to solve some hard computational problems (see, e.g., Hertz et al., 1991). Now it appears that Hebbian pairing leads not simply to an increase in synaptic "efficiency" (efficacy), but instead to a change in synaptic dynamics. If these results hold at other synapses as well, they may well lead to a reevaluation of our current hypotheses regarding the functional role of LTP.

Perspective

Neurons in the hippocampus and cortex fire irregularly, at rates that range from $<$1 Hz to almost 1 KHz. Variability in the interspike interval can exert a powerful effect on synaptic efficacy through the interaction of several forms of short-term plasticity. Recent studies at two intracortical synapses show that at stimulation frequencies well within the range of in vivo firing rates, depression dominates the synaptic response. A particularly intriguing finding is that LTP may double the response to the first impulse in a rapid train, while leaving the response to subsequent impulses almost unaffected. These results suggest that there is much to be learned by using behaviorally relevant patterns of neuronal activity—which need to be determined by in vivo recordings—to probe synaptic physiology. Although synapses in the cortex may get depressed by such high frequency stimulation, the implications for our understanding of the role of synaptic transmission in neural coding are quite exciting.

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