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SHORT-TERM SYNAPTIC PLASTICITY

Robert S. Zucker
Department of Molecular and Cell Biology, University of California, Berkeley, California 94720; e-mail: zucker@socrates.berkeley.edu

Wade G. Regehr
Department of Neurobiology, Harvard Medical School, Boston, Massachusetts 02115; e-mail: wregehr@hms.harvard.edu

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■ **Abstract** Synaptic transmission is a dynamic process. Postsynaptic responses wax and wane as presynaptic activity evolves. This prominent characteristic of chemical synaptic transmission is a crucial determinant of the response properties of synapses and, in turn, of the stimulus properties selected by neural networks and of the patterns of activity generated by those networks. This review focuses on synaptic changes that result from prior activity in the synapse under study, and is restricted to short-term effects that last for at most a few minutes. Forms of synaptic enhancement, such as facilitation, augmentation, and post-tetanic potentiation, are usually attributed to effects of a residual elevation in presynaptic $[Ca^{2+}]_i$, acting on one or more molecular targets that appear to be distinct from the secretory trigger responsible for fast exocytosis and phasic release of transmitter to single action potentials. We discuss the evidence for this hypothesis, and the origins of the different kinetic phases of synaptic enhancement, as well as the interpretation of statistical changes in transmitter release and roles played by other factors such as alterations in presynaptic Ca^{2+} influx or postsynaptic levels of $[Ca^{2+}]_i$. Synaptic depression dominates enhancement at many synapses. Depression is usually attributed to depletion of some pool of readily releasable vesicles, and various forms of the depletion model are discussed. Depression can also arise from feedback activation of presynaptic receptors and from postsynaptic processes such as receptor desensitization. In addition, glial-neuronal interactions can contribute to short-term synaptic plasticity. Finally, we summarize the recent literature on putative molecular players in synaptic plasticity and the effects of genetic manipulations and other modulatory influences.

INTRODUCTION

Neurons communicate with each other primarily through fast chemical synapses. At such synapses an action potential generated near the cell body propagates down the axon where it opens voltage-gated Ca^{2+} channels. Ca^{2+} ions entering nerve terminals trigger the rapid release of vesicles containing neurotransmitter, which is ultimately detected by receptors on the postsynaptic cell. A dynamic

enhancement of such synaptic transmission has been recognized for over 60 years (1, 2). Virtually all types of synapses are regulated by a variety of short-lived and long-lasting processes, some of which lead to a decrease in synaptic strength and others that lead to synaptic enhancement. At some synapses with repeated use, synaptic enhancement occurs and facilitatory processes dominate; at others the result is a decrease in synaptic strength and depression prevails. In most cases, it is apparent that multiple processes are present, and the result can be a combination of facilitation and depression in which synaptic strength is highly dependent on the details of the timing of synaptic activation (3–6). Here we are concerned with the properties and mechanisms of use-dependent plasticity on the tens of milliseconds to several minutes time scale.

ENHANCEMENT OF TRANSMISSION

Many chemical synapses show a multi-component increase in synaptic efficacy or a growth in the amplitude of individual postsynaptic potentials (PSPs) or postsynaptic currents (PSCs) on repetitive activation. This enhancement of transmission comes in several flavors, with quite distinct lifetimes (7).

Facilitation

Synaptic enhancement that is prominent on the hundreds of milliseconds time scale is referred to as facilitation. It can be seen with pairs of stimuli, in which the second PSP can be up to five times the size of the first (Figure 1). During brief trains of action potentials (APs), successive PSPs grow within about a second to a size that can easily reach several times—and in some synapses several dozen times—the original PSP. Facilitation often builds and decays with a time course that can be approximated with an exponential of ~100 ms. At some synapses, facilitation can be further subdivided into a rapid phase lasting tens of milliseconds (F1) and a slower phase lasting hundreds of milliseconds (F2).

Post-Tetanic Potentiation

There are also processes that become increasingly important as the number of stimuli in a train is increased. For these processes, each AP enhances synaptic strength by 1–15%, but because they last for five seconds to several minutes, the integrated effect of a train of hundreds of pulses can lead to a many-fold enhancement (Figure 2). There is considerable variability in synaptic plasticity exhibited by synapses on these time scales. Sometimes processes such as augmentation, which grows and decays with a time constant of ~5–10 s, can be distinguished from post-tetanic potentiation (PTP), which lasts for 30 s to several minutes. At other synapses, these components are not easily separable, and they are often lumped together and referred to as PTP. During realistic stimulus trains, multiple processes are often present. This is illustrated in Figure 2 where both facilitation and PTP are important during the prolonged train. This is further complicated by the fact that

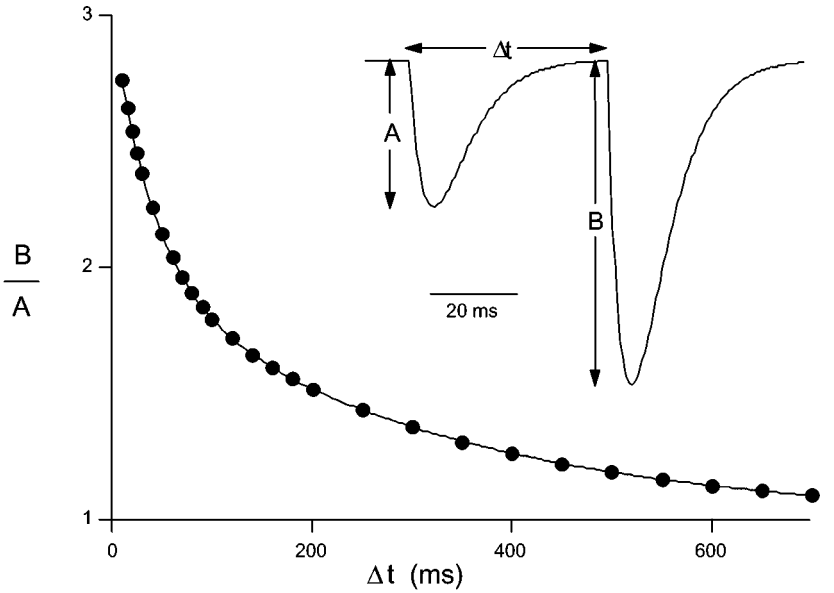


Figure 1 Simulated experiment showing paired-pulse facilitation of the sort that occurs at many synapses. As shown in the inset, activation with pairs of stimuli separated by time Δt evokes synaptic currents with the second response (B) larger than the first (A). As shown in the plot of B/A versus Δt, the magnitude of facilitation decreases as the interpulse interval is increased. In this experiment the amplitude of facilitation can be approximated by a double exponential decay of the form $1 + C_1\exp(-t/\tau_1) + C_2\exp(-t/\tau_2)$ (*solid line*). Based on this fit, this synapse would have two components of facilitation: F1 facilitation with $\tau_1 = 40$ ms, and F2 facilitation with $\tau_2 = 300$ ms. At many synapses the distinction between F1 and F2 is not clear, and the duration of facilitation is well approximated by a single exponential fit.

prolonged stimulation is usually accompanied by depression, and potentiation is often only observed after a tetanus, following recovery from depression.

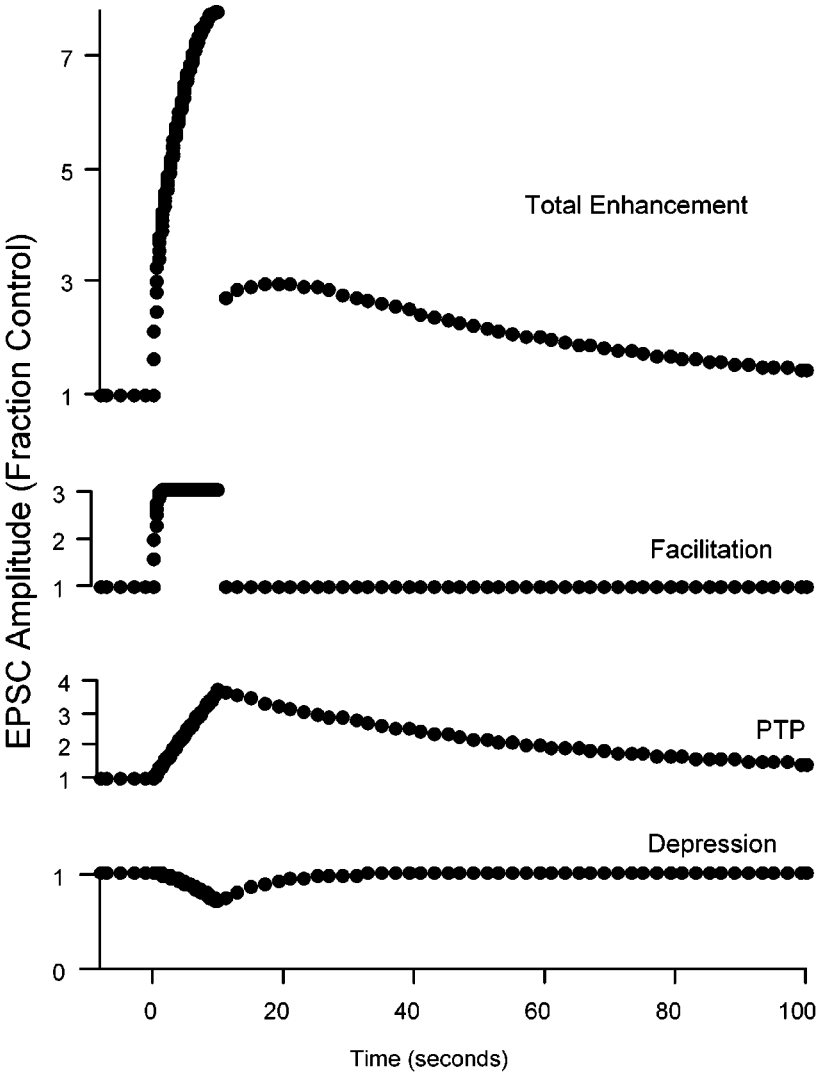
MECHANISMS OF ENHANCEMENT

Statistics of Release Indicate Changes are Presynaptic

In all synapses studied, facilitation, augmentation, and PTP have all been shown by quantal analysis to be presynaptic in origin—to involve specifically an increase in the number of transmitter quanta released by an AP without any change in quantal size or postsynaptic effectiveness (reviewed in 7). Much additional effort has gone into analysis of the changes in statistics of transmitter release using a binomial model of release from a pool of available quanta *n*, with release probability *p*. Enhanced release is accompanied by increases in *p*, *n* or both (8, 9). The parameter

n corresponds most closely to the number of release sites or active zones that contain clusters of vesicles, some of which appear docked near the presynaptic membrane immediately opposing postsynaptic receptors (10). Interpretation of these results is complicated by the fact that a simple binomial model, assuming uniform *p* at all release sites, ignores the likely variability in *p* (9, 11). This can lead to underestimation of changes in *p* and spurious increases in *n*.

It seems clear, then, that short-term synaptic enhancement reflects an increase in the probability of release of available quanta, with perhaps also an increase in the



number of release sites capable of releasing a quantum. Either statistical change could be due in turn to an increase in the probability of activating exocytosis of a docked vesicle or an increase in the probability that a release site is occupied by a docked vesicle ready for release (12). The latter could occur if the pool of vesicles available to rapidly occupy release sites is increased. This pool, often called the readily releasable pool, is released within a few seconds by hyperosmotic shock (13, 14), which provides a measure of its size similar to that obtained by measures of synaptic depression (see below). Augmentation in hippocampal synapses is unaccompanied by an increase in the size of this readily releasable pool, suggesting instead an increase in the probability of release from this pool (15).

In correlated ultrastructural and statistical studies (16), control values of *n* appear to correspond to active zones with multiple dense bodies, whereas the increased *n* in PTP seems to include the number of active zones with single dense bodies. Thus increase in *n* may reflect a real recruitment of release from previously dormant or silent active zones with fewer dense bodies.

THE CRUCIAL ROLE OF Ca^{2+} IONS

Early attempts at explaining short-term synaptic enhancement focused on electrical events in presynaptic terminals. Possibilities such as increased invasion of nerve terminals by APs, or broadening APs, or effects of afterpotentials, or increased

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Figure 2 Simulated experiment showing synaptic plasticity during and following high-frequency stimulation. In this experiment, a synaptic input was stimulated at 0.5 Hz and the amplitude of the PSC remained constant. Tetanic stimulation at 10 Hz for 10 s resulted in an eight-fold synaptic enhancement by the end of the train (*top, closed circles*). Some synaptic enhancement persisted upon returning to 0.5 Hz stimulation. In this example, the total synaptic enhancement (*top, closed circles*) was a result of facilitation, PTP, and depression. Facilitation, which is relatively short-lived with a time constant of 400 ms, built up rapidly during tetanic stimulation, but did not persist after commencing low-frequency stimulation. A slower process resulted in enhancement that increased gradually during the train. After returning to low-frequency stimulation this form of enhancement persists and is known as post-tetanic potentiation (PTP). At many synapses, a form of enhancement (augmentation) intermediate between facilitation and potentiation also exists. This experiment illustrates that at most synapses multiple processes contribute to synaptic enhancement. It also shows that PTP can be studied in isolation from facilitation following a train, but that during the train, both slow and fast forms of enhancement contribute to enhancement. Because longer-lasting forms of enhancement typically result in a small enhancement per pulse, paired-pulse experiments as in Figure 1 are suited to studying facilitation with little contamination from PTP.

Ca^{2+} influx due to facilitation of Ca^{2+} channels, were eliminated in a variety of preparations (8, 17, 18, although see below). Facilitation can even be evoked by constant depolarizing pulses under voltage clamp that activates an invariant Ca^{2+} influx and constant presynaptic $[Ca^{2+}]_i$ change (19). Although, as described below, facilitation of Ca^{2+} influx can contribute to synaptic facilitation, in most cases other mechanisms make more prominent contributions.

The Residual Ca^{2+} Hypothesis

At neuromuscular junctions, an AP can cause facilitation equally well, even if transmitter release does not occur (20, 21); therefore, facilitation seems to arise from some process following AP invasion but preceding secretion. This led naturally to the possibility that facilitation was somehow a consequence of the influx of Ca^{2+} ions during conditioning stimulation. Strong evidence for this idea came from the seminal experiments of Katz & Miledi (22). They used a focal extracellular pipette to provide Ca^{2+} ions to neuromuscular junctions in a Ca^{2+}-free medium and showed that a conditioning impulse not only failed to release transmitter in the absence of external Ca^{2+}, it also failed to facilitate release. Subsequently it was shown that augmentation and potentiation also depend, at least in part, on the presence of external Ca^{2+} during conditioning stimulation (23–25). Such results led to the "residual Ca^{2+} hypothesis": Facilitation is caused by an action of Ca^{2+} remaining in the nerve terminals after the conditioning stimulus. In the past 25 years, substantial evidence has accumulated in support of the residual Ca^{2+} hypothesis: There is a correlation between elevations in $[Ca^{2+}]_i$ and synaptic enhancement; elevating $[Ca^{2+}]_i$ enhances synaptic strength, and preventing increases in $[Ca^{2+}]_i$ eliminates short-term enhancement.

PRESYNAPTIC $[Ca^{2+}]_i$ CORRELATES WITH FACILITATION, AUGMENTATION, AND POTENTIATION The first attempts to correlate $[Ca^{2+}]_i$ with synaptic plasticity compared post-tetanic Ca^{2+}-activated K^+ current in the cell body of a presynaptic neuron in *Aplysia* to the decay of PTP in a postsynaptic cell (26). It can be difficult to determine the time course of $[Ca^{2+}]_i$ with Ca^{2+}-dependent K^+ channels (27) because of the voltage- and Ca^{2+} dependence of these channels and their degree of colocalization with voltage-gated Ca^{2+} channels (28–30). Subsequently the kinetics of presynaptic post-tetanic $[Ca^{2+}]_i$ changes were measured with the Ca^{2+}-sensitive metallochromic dye arsenazo III and compared with PTP (31). With the advent of fluorescent dyes allowing ratiometric measurement of $[Ca^{2+}]_i$ without knowledge of dye concentration, more accurate estimation of $[Ca^{2+}]_i$ became possible. Numerous studies have demonstrated an apparently linear relationship between magnitude of potentiation, augmentation, or F2 facilitation, and residual $[Ca^{2+}]_i$ concentration in vertebrate and invertebrate neuromuscular junctions and mammalian central and peripheral synapses (18, 32–42). Facilitation triggered by conditioning pulses under voltage clamp also correlates linearly with the measured (43) or inferred (44) magnitude of Ca^{2+} influx during those pulses. That this residual

Ca^{2+} is capable of influencing transmitter release is suggested by the fact that all phases of enhancement of evoked release are accompanied by an increase in the frequency of spontaneously released quanta (miniature PSPs or mPSPs) (42, 45–54).

ELEVATING PRESYNAPTIC $[Ca^{2+}]_i$ ENHANCES AP-EVOKED RELEASE Various manipulations have been used to mimic the effect of residual Ca^{2+}: fusion of Ca^{2+}-containing liposomes with nerve terminals (55), exposure to Ca^{2+} ionophores (56, 57), release of Ca^{2+} from poisoned mitochondria (58), presynaptic Ca^{2+} injection by iontophoresis (19), or release of Ca^{2+} by photolysis of presynaptic caged Ca^{2+} chelators (59–62). In all cases, AP-induced PSPs were dramatically increased. At calyx of Held synapses, small conditioning Ca^{2+} influx could facilitate release to a later influx (63).

BUFFERING PRESYNAPTIC $[Ca^{2+}]_i$ REDUCES SHORT-TERM ENHANCEMENT The Ca^{2+} chelators EGTA and BAPTA can be loaded into nerve terminals in the acetoxymethylester form, where they can be de-esterified by endogenous esterases. The de-esterified buffer can accumulate to millimolar levels (as opposed to the micromolar concentration of the AM-ester used to bathe the preparation). In many studies, presynaptic loading of such exogenous Ca^{2+} buffers strongly reduced both components of facilitation (34–36, 40, 41, 45, 52, 64–69) and augmentation (15, 69). Facilitation and augmentation have also been reduced by presynaptic injection of Ca^{2+} buffers into squid and crayfish terminals (66, 70–72), and PTP is reduced in hippocampal synapses expressing excess amounts of the native Ca^{2+}-binding protein calbindin (73), whereas deletion of the gene for the Ca^{2+}-binding protein parvalbumin increases facilitation at cerebellar synapses (74). The finding that the slowly acting buffer EGTA is effective in reducing synaptic enhancement suggests that the target(s) of Ca^{2+} action cannot be very close to Ca^{2+} channels and affected only by the transient local micro-domains of high $[Ca^{2+}]_i$ because these would be affected little by EGTA. In a few instances, authors have reported difficulty in reducing facilitation or augmentation by use of exogenous buffers (65, 75, 76), which may be due to inadequate buffer concentrations or saturation of the buffer by repeated activity.

Another way of rapidly reducing Ca^{2+} concentrations is to use caged Ca^{2+} chelators that increase their affinity for Ca^{2+} upon exposure to ultraviolet light. Zucker and colleagues (61, 77) injected the caged BAPTA diazo-2 or diazo-4 into *Aplysia* central nerve terminals and crayfish peripheral nerve terminals and photolyzed it to increase presynaptic Ca^{2+} buffering after conditioning stimuli and post-tetanic waiting periods designed to select only facilitation, augmentation, or potentiation. All three forms of enhancement were reduced on diazo photolysis and reduction of residual $[Ca^{2+}]_i$.

REDUCING Ca^{2+} INFLUX REDUCES SHORT-TERM ENHANCEMENT Another way to probe the role of $[Ca^{2+}]_i$ in synaptic enhancement is to assess the effects of altering Ca^{2+} influx. This is done by changing extracellular Ca^{2+}, blocking Ca^{2+} channels

with toxins or divalent ions, or by altering the presynaptic waveform, which changes Ca^{2+} entry. Experiments of this sort are, however, difficult to interpret. At most synapses, reducing Ca^{2+} entry not only decreases $[Ca^{2+}]_i$ but also reduces depression by decreasing the initial release of neurotransmitter (see below), which can resemble an increase in facilitation. Facilitation can also be genuinely increased by a desaturation of the release process. In studies of synapses under conditions of little depression and far from saturation of release, it was shown that reducing Ca^{2+} influx decreased facilitation and augmentation phases of enhanced release (78–81). Elevating external $[Ca^{2+}]$ was often, but not always, able to reverse the effects of Ca^{2+} channel blockers.

Facilitation is sometimes stronger following a successful conditioning stimulus than a failure (82, 83). This may reflect the fact that the number of Ca^{2+} channels opening and the amount of Ca^{2+} entry in an active zone are stochastic processes, and both the probability of secretion and the magnitude of residual Ca^{2+} and, consequently, of facilitation depend on this random variable.

PSEUDOFACILITATION In some counterintuitive experiments, it was found that presynaptic perfusion of the Ca^{2+} buffer BAPTA not only reduced transmission, but concurrently increased facilitation, at some cortical synapses (64). The additional facilitation was shown not to reflect a reduction in depression, but rather an artificial saturation of BAPTA by the first AP, leaving less buffer to capture Ca^{2+} in a conditioned response. Unlike genuine facilitation, this pseudofacilitation could not be blocked by EGTA perfusion because slow-binding EGTA cannot steal entering Ca^{2+} from fast-binding BAPTA. Moreover, pseudofacilitation increased with elevation of external $[Ca^{2+}]$, unlike real facilitation. Although the results suggest that natural facilitation does not work in the same way as pseudofacilitation, they emphasize the possibility of modulating facilitation by altering the Ca^{2+} buffering properties of cytoplasm.

The Single-Site Hypothesis

In the original formulation of the residual Ca^{2+} hypothesis (22), it was proposed that the peak incremental $[Ca^{2+}]_i$ elevation following an AP acts at some presynaptic site to trigger phasic release, while residual Ca^{2+} from that event summates with the incremental Ca^{2+} rise in a subsequent test AP to produce short-term synaptic enhancement. It is now recognized that neurotransmitter release is triggered by an increase in Ca^{2+} levels near open voltage-gated Ca^{2+} channels (Ca_{local}). Within tens of milliseconds, Ca^{2+} then diffuses and equilibrates throughout the presynaptic bouton giving rise to a residual Ca^{2+} signal (Ca_{res}). Thus for a bouton with a resting Ca^{2+} level of Ca_{rest}, the Ca^{2+} level available to trigger release in response to the first stimulus is ($Ca_{rest} + Ca_{local}$) and for a second closely spaced stimulus is ($Ca_{rest} + Ca_{local} + Ca_{res}$).

Independent estimates of the relative magnitudes of $[Ca^{2+}]_i$ triggering phasic secretion and synaptic enhancement suggest that a single type of Ca^{2+}-binding

site cannot account for both phasic transmitter release and short-term plasticity. Ca_{rest} is ~100 nM, Ca_{local} is tens of micromolar or higher (84–89), whereas Ca_{res} at times of substantial facilitation, augmentation, or potentiation reaches only ~1 μM (32–34, 41). For PSC $\propto Ca^4$ (90), $Ca_{rest} = 100$ nM, and $Ca_{local} = 20$ μM, a Ca_{res} of 1 μM would produce a synaptic enhancement of only ~20% if there were a single type of Ca^{2+} binding site, far smaller than the observed enhancement, which can be 10-fold.

Another test of this model is whether short-term synaptic enhancement accumulates as predicted if each AP in a train adds a constant increment to residual Ca^{2+}, which decays according to kinetics necessary to account for the phases of enhancement following a single AP. These sorts of calculations have almost always failed to account for the accumulation of facilitation, augmentation, and potentiation of evoked and spontaneous release (48, 91–97; but see 40). Instead, augmentation and potentiation appear to multiply the effects of facilitation (48, 98), and the effect of Ca^{2+} on facilitation appears to multiply its effect on secretion (52). These quantitative studies thus suggest that facilitation is a separate process from both phasic secretion and the slower processes of augmentation and potentiation.

A comparison of the enhancement of evoked synaptic responses and spontaneous neurotransmitter release provides another test of the single-site hypothesis. A conditioning stimulus also increases mPSP frequency, a phenomenon often called delayed release and also thought to reflect increases in $[Ca^{2+}]_i$ (49). According to the single-site model, if $Ca_{res}(t)$, expressed as a fraction of Ca_{local}, is represented as $\varepsilon(t)$, where t is time from the end of the conditioning stimulus and Ca_{rest} is ignored, then the fourth power dependence of transmitter release on $[Ca^{2+}]_i$ (90) predicts that enhanced mPSP frequency decays as $\varepsilon^4(t)$, while facilitation, $f(t)$ (the fractional increase in enhanced evoked release compared with un-enhanced release), should decay as $f(t) = (1 + \varepsilon(t))^4 - 1 \approx 4\varepsilon(t)$, for small $\varepsilon(t)$. Comparison of post-tetanic decays in mPSP frequency and evoked PSP seemed roughly consistent with this prediction, at least for facilitation, in some preparations (46, 53, 99). Elevation of presynaptic Ca^{2+} at crayfish neuromuscular junctions by photolysis of caged Ca^{2+} also increased evoked release and mPSP frequency in ways reasonably consistent with predictions (60). However, other studies have found serious discrepancies between observations and quantitative predictions of the single-site hypothesis. The enhancement of evoked release was much smaller then predicted by the single-site hypothesis from the rate of spontaneous release for facilitation at the mouse neuromuscular junctions (52); for facilitation, augmentation, and potentiation at frog neuromuscular junctions (47); and for facilitation at parallel fiber synapses onto stellate cells in the cerebellum (95, 100).

Facilitation seems to reach a peak immediately after each AP at normal temperature (48). However, near 0°C a delay of a few milliseconds appears (101), so that facilitation is maximal long after phasic secretion has terminated. If this apparent delay in facilitation is real, and not because of a superimposed very fast phase of depression (82), it is further evidence that facilitation and phasic secretion result from distinct Ca^{2+} actions.

A different clue that short-term enhancement involves one or more processes distinct from phasic release is its diversity. Different synapses in the same species, and even different terminals from the same presynaptic neuron, can show vastly different magnitudes of facilitation (64, 69, 102–107). Normally, synapses with a high output to low-frequency stimulation show less facilitation than low-output synapses, which could result from a saturation of release (93) from high-output synapses or from a concurrent depression masking facilitation (see below). Either action would be alleviated by reducing external [Ca^{2+}]. However, in one study it was found that reducing [Ca^{2+}] did not erase the differences in amount of facilitation expressed by different types of synapses (108). Synaptic enhancement is also separable from baseline transmission in *Aplysia* neurons, where heterosynaptic activity was found to specifically reduce augmentation and PTP (109). A use-dependent reduction of paired-pulse facilitation has also been reported at *Aplysia* synapses (72). Thus facilitation and augmentation/PTP appear to be independently regulated properties of synaptic transmission.

Multiple Site Hypotheses

These considerations force the notion that synaptic enhancement is due to Ca^{2+} acting at a site or sites different from the fast low-affinity site triggering secretion (32–35, 45, 48, 52, 89, 97, 110–112). There are many unresolved questions regarding the properties of the Ca^{2+}-binding sites and the factors governing the time course and magnitude of synaptic enhancement.

WHAT DETERMINES THE TIME COURSE OF ENHANCEMENT? Does enhancement arise from the continuing action of residual Ca^{2+} due to the extended presence of free Ca^{2+} ions acting in equilibrium with the sites causing enhancement? If so, the kinetics (accumulation and decay) of facilitation, augmentation, and potentiation depend on the kinetics of residual Ca^{2+}. Alternatively, enhancement may decay with its own intrinsic kinetics, reflecting slow unbinding of Ca^{2+} from enhancement sites or, alternatively, aftereffects of Ca^{2+} binding owing to subsequent reactions.

Initially, the bound Ca^{2+} idea was favored, especially for facilitation, which seemed to last longer than would be expected from calculations of diffusion of Ca^{2+} away from the region where secretion is triggered near Ca^{2+} channel mouths (89). Also, a lower apparent Ca^{2+} cooperativity in triggering facilitated release (110) was interpreted as meaning that some Ca^{2+} ions were already bound, although the results could be explained by effects of depression and saturation. Persistent binding was also suggested by measures of residual Ca^{2+} based on Ca^{2+}-dependent K^+ current (27), but these results were confounded by the voltage dependence of the K^+ channels, and bound Ca^{2+} models were favored by investigators who could not block enhancement with exogenous Ca^{2+} buffers (see above).

Many studies indicate that the time course of residual Ca^{2+} contributes to the duration of synaptic enhancement. Recent Ca^{2+} diffusion simulations suggest sluggish residual Ca^{2+} kinetics at a diffusional distance of $\sim$100 nm from Ca^{2+} channels

where facilitation could be activated (70). Ca^{2+} accumulation at such sites can account roughly, but with some significant imperfections, for accumulation of facilitation in a train. At many synapses there is a close correlation between the time course of residual Ca^{2+} and the durations of facilitation, augmentation, and potentiation (18, 32–42). At crayfish neuromuscular junctions and *Aplysia* central synapses, elimination of all phases of enhancement by flash photolysis of diazo supports a causal relation between residual Ca^{2+} and these forms of plasticity (61, 77). Further support for facilitation arising from residual Ca^{2+} comes from studies of cerebellar parallel fiber synapses onto Purkinje cells (35). Buffering presynaptic residual Ca^{2+} with EGTA reduces both the magnitude and the duration of facilitation from 200 ms to a process decaying with a 40-ms time constant. The remaining facilitation appears to reflect the intrinsic kinetics of facilitation, when chelation of residual Ca^{2+} allows Ca^{2+} ions to bind to the facilitation site only during the AP.

HOW MANY SITES OF Ca^{2+} ACTION? Although there is strong evidence in support of at least one high-affinity Ca^{2+} binding site responsible for synaptic enhancement, it is not clear how many types of Ca^{2+} binding sites are involved in synaptic enhancement. The existence of four phases of enhancement—F1, F2, augmentation and PTP—suggests that four distinct processes are involved, each, perhaps, with its own unique binding site. But all of these phases could in principle arise from Ca^{2+} acting at one site but decaying (and accumulating) with multiple phases controlled by diffusion, buffering, extrusion, and uptake. Numerous studies have examined the issue of the number of Ca^{2+} binding sites involved in enhancement, but no consensus has been reached.

The effects of rapid reductions in $[Ca^{2+}]_i$ with flash photolysis of diazo suggest that there are two distinct sites involved in synaptic enhancement at the crayfish neuromuscular junction (61). F1 and F2 facilitation were eliminated within 10 ms. Only part of augmentation and potentiation disappeared this rapidly; most decayed with a time constant of $\sim$0.4 s after photolysis. Augmentation and potentiation also show similar dependence on residual $[Ca^{2+}]_i$, increasing transmission about 10-fold per micromolar (33). These results are consistent with three types of Ca^{2+} binding sites: a low-affinity rapid site involved in phasic release, a moderate-affinity site with relatively rapid kinetics involved in the F1 and F2 components of facilitation, and a high-affinity site with slow kinetics that contributes to PTP and augmentation.

A multiplicative relationship between augmentation and potentiation on the one hand, and facilitation on the other (48, 98), suggests that at vertebrate neuromuscular junctions there are at least two distinct processes governing short-term synaptic enhancement. As argued previously, these two sites are separate from the site triggering phasic secretion. However, at lobster neuromuscular junctions, a model in which fast and slow facilitation components and augmentation summate in accordance with Ca^{2+} accumulating at a single site, describes the accumulation of synaptic enhancement better than multiplicative models (40).

Differential effects of Sr^{2+} or Ba^{2+} ions on synaptic enhancement suggest multiple sites of enhancement. Ba^{2+} selectively increases augmentation, whereas Sr^{2+} selectively increases and prolongs F2 facilitation of both evoked and post-tetanic delayed release (47, 113–115). However, measurements of presynaptic Sr^{2+} dynamics show that the effects of Sr^{2+} are due to differences in buffering and removal between presynaptic Sr^{2+} and Ca^{2+} (100, 116), leading specifically to an increase in $[Sr^{2+}]_i$ during the F2 facilitation phase. Thus the Sr^{2+} results do not necessarily imply different sites of action.

Thus further experiments are required to determine how many types of Ca^{2+}-binding sites are involved in synaptic enhancement at different synapses. Based on the evidence above, it seems likely that for some synapses synaptic enhancement is best described by at least a fast site involved in facilitation and a slower site in augmentation and potentiation.

KINETICS OF POTENTIATION AND AUGMENTATION Augmentation arises from the phase of $[Ca^{2+}]_i$ decay that follows diffusional equilibration in nerve boutons and appears to be regulated by two plasma membrane extrusion pumps—a Ca^{2+}-ATPase and Na^+/Ca^{2+} exchange (117–119). Prolonged stimulation loads nerve terminals with both Na^+ and Ca^{2+}. The reduction in the Na^+ gradient reduces removal of Ca^{2+} by Na^+/Ca^{2+} exchange and can even reverse this process, which results in influx through this system during and after a long tetanus (118, 119). This results in amplification of residual $[Ca^{2+}]_i$ and prolongation of its removal, contributing to PTP, the slowest phase of synaptic enhancement (120–124). Prolonged stimulation also results in Ca^{2+}-loading of presynaptic mitochondria at crayfish and lizard neuromuscular junctions; leakage of this stored Ca^{2+} provides a major source of the long-lasting residual Ca^{2+} underlying PTP (39, 125–127). A similar role is played by endoplasmic reticulum at frog neuromuscular junctions (128), while both mitochondria and endoplasmic reticulum appear to be involved in the regulation of residual Ca^{2+} at peptidergic nerve terminals (129–131). Thus augmentation and potentiation result from the different dynamics of Ca^{2+} removal, dependent on extrusion and uptake processes, that dominate, respectively, after short and long tetani. Residual Ca^{2+} acts on both rapid ($<$10 to 40 ms) and somewhat slower-acting ($\sim$0.4 s) targets to regulate transmission.

KINETICS OF FACILITATION Facilitation appears to arise from Ca^{2+} acting at a site with intrinsic kinetics of $<$10 ms at crayfish neuromuscular junctions (61) and $\sim$40 ms at cerebellar synapses (35). The longer duration of normal facilitation apparently reflects the duration of $[Ca^{2+}]_i$ at its site(s) of generation. The two components of facilitation observed at some synapses may reflect two separate sites of action in F1 and F2 facilitation. Alternatively, $[Ca^{2+}]_i$ may decay non-exponentially, for example by diffusion away from active zones or clusters of active zones, with non-exponential kinetics (70, 132, 133). At hippocampal synapses, residual Ca^{2+} underlying facilitation can also be affected by release from intracellular stores such as the endoplasmic reticulum (134), although this contribution

of release from internal stores to facilitation is controversial (135). Treatments such as Sr^{2+} may affect the two sites differentially (47, 113), or may have different effects on the processes controlling diffusion, such as buffer mobility or saturation (100, 116). The number of sites involved in facilitation remains unclear.

The quantitative relationship between decay of mPSP frequency and enhanced evoked release is not simple (95). However, it is possible that the two processes may be controlled by Ca^{2+} acting at two sites, the facilitation site and the secretory trigger, in ways that reflect different degrees of saturation and interaction in controlling spontaneous release and evoked release.

SYNAPTIC ENHANCEMENT, SLOW RELEASE, AND MOBILIZATION When presynaptic $[Ca^{2+}]_i$ is suddenly elevated, either by strong depolarization or photolysis of caged Ca^{2+}, transmitter release often exhibits a biphasic time course: an initial intense rapid phase of secretion, called the secretory burst, followed by a slower phase with a time constant of hundreds of milliseconds to seconds (136–142). This phase is intermediate in duration between F2 facilitation and augmentation and shares with them a Ca^{2+} dependence that is easily blocked by intracellular EGTA. It is usually interpreted as a Ca^{2+}-dependent mobilization of vesicles from a reserve to a readily releasable pool. After exhaustion of the readily releasable pool, recovery also proceeds with time constants of hundreds of milliseconds to seconds, and this process can also be Ca^{2+} dependent (138, 140, 142–145). Finally, recovery of secreted vesicles can occur by slow and fast pathways, and Ca^{2+} can favor a fast pathway occurring within seconds (146, 147, but see 148) or a fraction of a second (137).

It is tempting to suppose that one or both of these processes (mobilization and Ca^{2+}-dependent recovery of released vesicles) are related to enhancement of synaptic transmission on repetitive stimulation. This is not likely, however, especially for facilitation. The reason is that facilitation has intrinsic kinetics of tens of milliseconds or less (35, 61), much faster than mobilization of vesicles into or recovery from depletion of the releasable pool.

Augmentation may resemble a seconds-long component of recovery from depletion of the readily releasable pool (138, 142, 145). However, augmentation's intrinsic rate constant is $\sim$0.4 sec (61) and could only be related to the fastest forms of replenishment of the readily releasable pool. But augmentation appears to occur without any increase in the size of that pool (15). PTP is certainly long enough that it could involve slow recovery and mobilization processes. However, its intrinsic time constant is also a fraction of a second (61) and normally PTP is governed by the slow removal of residual Ca^{2+}. Any relationship between synaptic enhancement and vesicle recovery processes is therefore unlikely.

USE-DEPENDENT CHANGES IN Ca^{2+} ENTRY

The picture painted here of residual Ca^{2+}-dependent short-term plasticity describes the situation at the great majority of chemical synapses. However, a few examples have arisen where there is a change during repetitive activation in the Ca^{2+} influx

evoked by an AP. In most cases the contributions of such changes in Ca^{2+} entry make a relatively small contribution to the overall plasticity of the synapse.

Ca^{2+} influx during a train can change by virtue of the properties of the Ca^{2+} channels. At the brainstem calyx of Held giant synapse, a form of Ca^{2+} channel facilitation to repeated depolarizations dependent on the build-up of presynaptic Ca^{2+} has been observed (149, 150). For other experimental conditions there can be a reduction in presynaptic Ca^{2+} current (151). It is possible that this behavior contributes to synaptic facilitation or depression at some synapses. In hippocampal neurons, facilitation was attributable partly to a potential-dependent relief of G-protein–mediated Ca^{2+} channel inhibition, resulting in increased influx through P/Q-type Ca^{2+} channels in repeated APs (152).

Another possibility is that during trains of activity Ca^{2+} entry into cells is sufficient to reduce $[Ca^{2+}]$ in extracellular space. At the calyx of Held, depolarization of the postsynaptic cell to 0 mV for 100 ms resulted in a 35% reduction in the PSC (153). This depression recovered within half a second and was accompanied by an inhibition of postsynaptic Ca^{2+} entry. Such a decrease in Ca^{2+} entry is consistent with the small volume of extracellular space and the magnitude of Ca^{2+} influx that can occur during prolonged depolarization (154). For typical levels of activity, the depletion of extracellular Ca^{2+} and its contribution to short-term plasticity are likely to be small.

At a few synapses, presynaptic spike broadening owing to cumulative K^+ channel inactivation contributes to facilitation by increasing Ca^{2+} entry during later APs in a train. Whole-cell recording from pituitary terminals reveals that repeated stimulation produces presynaptic APs that broaden, which in turn produces more Ca^{2+} influx per spike and facilitation of hormone release (155). Similarly, whole-cell voltage clamping of hippocampal mossy fibers revealed that spike broadening occurs during trains of presynaptic activity and that this broadening results in increased Ca^{2+} entry evoked by APs late in a train (156). This broadening arises from rapid inactivation of a K^+ channel involved in AP repolarization.

At some synapses, reductions in spike amplitude or duration, or failures of spike invasion of terminals seem to play a role in synaptic depression, especially to long trains of stimuli (157–160). In one instance, AP failure was attributable to the gradual activation of Ca^{2+}-dependent K^+ current (161).

Consideration of the magnitude of synaptic plasticity present at synapses where changes in Ca^{2+} entry has been observed suggests that often other mechanisms dominate the overall plasticity of the synapse. For example, at the calyx of Held, facilitation of Ca^{2+} entry occurs even while depression dominates the overall behavior of the synapse (150). The inaccessibility of presynaptic terminals has made it difficult to assess the importance of changes in Ca^{2+} entry to plasticity at synapses where the presynaptic terminal cannot be voltage clamped. Sometimes it is possible to use optical techniques to measure presynaptic AP waveforms or Ca^{2+} influx. Such an approach at the parallel fiber synapses in the cerebellum suggests that neither waveform changes nor changes in Ca^{2+} entry make important contributions to plasticity during trains of presynaptic APs (18, 162–164).

DEPRESSION OF TRANSMITTER RELEASE

At many synapses, periods of elevated activity lead to a decrease in synaptic strength. Multiple mechanisms can contribute to such synaptic plasticity. The most widespread mechanism appears to be a presynaptic decrease in the release of neurotransmitter that likely reflects a depletion of a release-ready pool of vesicles. In addition, a decrease in synaptic strength can arise from the release of modulatory substances from the activated presynaptic terminals, postsynaptic cells, or neighboring cells. Finally, postsynaptic properties such as desensitization of ligand-gated receptors can make the target neuron less sensitive to neurotransmitter.

Often a presynaptic mechanism contributes to a decline in PSC amplitude during repeated stimulation and takes seconds to minutes to recover after stimulation (4, 20, 165, 166). Although such synaptic depression was described nearly 60 years ago (1, 2), the mechanisms responsible for it are still poorly understood.

Statistical analysis of changes in quantal parameters during depression almost always reveals a reduction in the average number of quanta released, but binomial models of release may indicate reductions either in p, the probability of release of releasable quanta, or n, the number of releasable quanta, or both (reviewed in 8). Both changes could result from a reduction in AP effectiveness or Ca^{2+} influx, from feedback inhibitory actions of released transmitter on presynaptic autoreceptors, or from a reduction in the occupation of release sites by docked vesicles.

Depletion Models of Depression

A key characteristic of depression at many synapses is use dependence. Higher levels of transmission are associated with larger depression, and reduction of baseline transmission (for example by reducing external $[Ca^{2+}]$), relieves depression. Sometimes there is even a negative correlation between statistical fluctuations in the first of paired responses and the magnitude of the second (166, 167). Most models of short-term synaptic depression are based on the idea that it reflects depletion of a pool of vesicles that are poised and release ready. A number of such depletion models exist that vary in their assumptions and level of complexity.

According to the depletion model in its simplest form (165, 168), a synaptic connection contains a store of S releasable vesicles, and an AP releases a fraction, F, of this store. If each vesicle released produces a synaptic current i, stimulation produces a response equal to FSi. In this model, the store is transiently depleted of FS vesicles, so immediately following a stimulation, only S-FS vesicles are available for release. If the fraction of available vesicles released by an AP remains unchanged, then a second stimulus will produce a response that is proportional to the number of remaining release-competent vesicles. The amplitude of the second response is then $S(1\text{-}F)Fi$, and the ratio of the amplitude of two closely spaced responses is $(1\text{-}F)$. It is usually assumed that there is a mono-exponential recovery of the release-ready store or pool of vesicles.

This model provides a simple explanation of some basic features of depression that are apparent at many synapses. For example, the larger the initial probability of release, the more pronounced is depression for two closely spaced stimuli. If F is very low initially, there is no depression, if F is 0.5, the second PSC is half as large as the first, and if F is 1, the second stimulus evokes no response at all because no releasable vesicles are available. This dependence of the magnitude of depression on the baseline probability of release has been described at many synapses. The exponential recovery from depression has also been observed at many synapses for a variety of experimental conditions.

It is important to distinguish measures of store size S and fraction of release F, estimated from the magnitude of depression, from measures of the statistical parameters of transmitter release n and p, estimated from a statistical quantal analysis of the variance of transmitter release (8, 10, 169). Typically, F is greater than p and S is less than n (170). This is because the statistical parameter n apparently corresponds to the total number of release sites, each of which may be able to release only one quantum (vesicle) to an AP (see below). The statistical parameter p has two components, one (p_{occ}) corresponding to the probability that a release site is occupied by a docked and releasable vesicle, and one (p_{eff}) the probability that an AP releases docked vesicles. The pool of immediately releasable vesicles (S) then corresponds to $p_{occ}n$, which is less than n, and the fraction of this pool released by an AP (F) corresponds to p_{eff}, which is greater than $p = p_{occ}\, p_{eff}$.

In spite of its success, this form of the depletion model is inadequate in several ways. Some of the basic assumptions are likely incorrect, such as F being constant. For example, different release sites are likely to release quanta with different initial probabilities, p_{eff} (107): The sites with highest release probability are depleted of more "willing" vesicles first, and the sites containing more "reluctant" docked vesicles after some stimulation have a lower probability of release. This results in a reduction in the average value of F, as well as in S during depression (63, 165, 171, 172). The simple model can also either underpredict or overpredict steady-state depression produced by trains of activity, and the assumption of a mono-exponential recovery has been questioned (4, 173–177).

In trying to improve upon such a model it is instructive to consider the anatomy of synapses. Studies at the electron microscope level reveal that synapses usually contain hundreds of vesicles in the vicinity of release sites, but only a small number of these vesicles are in contact with the membrane. These docked vesicles are thought to be poised and nearly ready to fuse in response to AP invasion of the presynaptic bouton or are at least available for immediate replenishment of release sites that are vacated by exocytosis. These vesicles are referred to as the readily releasable pool, whereas the more distant vesicles that are unable to respond rapidly are referred to as the reserve pool. In some synapses, the immediately releasable vesicles may be restricted to a fraction of the apparently docked and release-ready vesicles, with perhaps only one per active zone (see below). These immediately releasable vesicles are sometimes referred to conceptually as docked and primed for release. Following exocytosis of docked vesicles, recovery appears to occur by

multiple processes into both reserve and readily releasable pools (Figure 3) (146, 178–180).

The concept of pools of vesicles in different states has provided a useful framework for thinking about synaptic depression (3, 4, 171, 175–177, 181–185). Repeated stimulation would result in the depletion of the readily releasable pool, which in turn would lead to a decrease in the number of vesicles that could be released by an AP and depression. According to depletion models that consider pools of vesicles, the extent of depression will depend on the number of vesicles in the reserve and release-ready pools and the transition rates between these pools. Other factors such as maximum sizes of the immediately releasable pool (limited by number of active zones), the release-ready pool (limited by the number of docking sites), the reserve pool (limited by the availability of vesicle membrane recoverable by endocytosis from recently secreted vesicles), and use-dependent changes in the movements of vesicles between pools impose additional restrictions not envisioned in the classical depletion models that treated vesicle movements between pools as a simple mass action without any limits on pool size. The mathematical description of such models can be quite complex, and several unanswered questions remain that are important to developing and assessing such models.

A curious aspect of synaptic depression is that it is not accompanied by a reduction in frequency of spontaneous release of quanta (186–188). This is hard to reconcile with depletion models of depression unless spontaneous release comes from a different pool of vesicles than evoked release or is subject to different limitations.

In a few instances, deep depression on extensive stimulation is accompanied by a presynaptic reduction in quantal amplitude (189–191). This may reflect the release of newly recovered and incompletely filled vesicles.

HOW BIG IS THE READILY RELEASABLE POOL AT INDIVIDUAL RELEASE SITES? A number of approaches have been taken to measure the size of this pool of vesicles, including a large depolarizing pulse in the presynaptic terminal, caged Ca^{2+} in the presynaptic terminal, application of high-osmolarity solution, and integration of fully depressing responses to brief stimulus trains (13, 14, 107, 171). The challenge with all of these approaches is to measure the full size of the release-ready pool without it being replenished from the reserve pool. Failure to release all of the vesicles will lead to an underestimation of the size of the pool, whereas contributions from the reserve pool can lead to an overestimation (192). Serial electron microcopy has also been used to determine the number of morphologically docked vesicles, which may correspond to the readily releasable pool. Estimates of the functional size of the readily releasable pool per active zone are 7–8 at the parallel fiber and climbing fiber synapses, 22 in goldfish bipolar neurons (193), 32 in frog saccular hair cells (194), 130 in cat rod photoreceptors (195), an average of about 10 for the CA1 region of the hippocampus (196, 197), and in layers 1a and 1b of pyriform cortex, the average number of docked vesicles is 16 and 27, respectively (198). There is considerable variability in the number of docked vesicles at individual synapses, even for the same type of synapse.

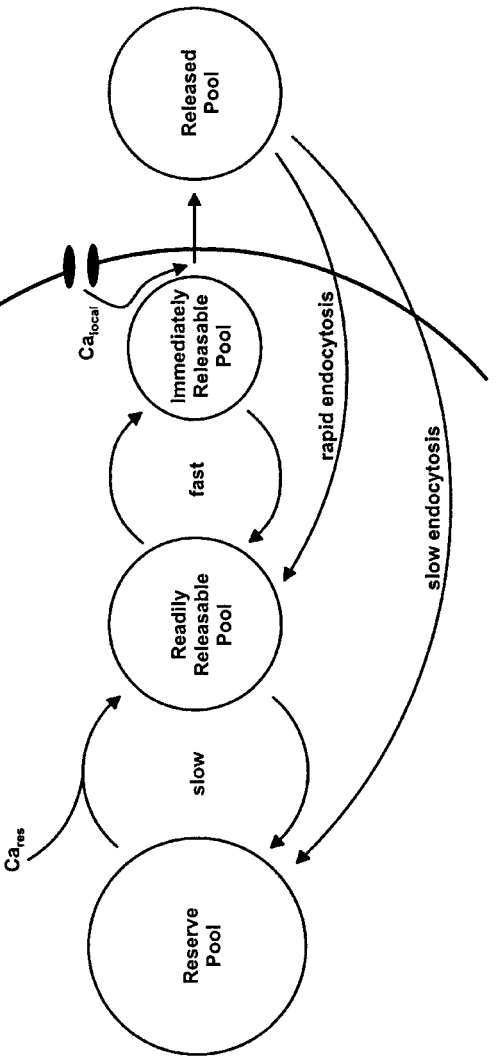

Figure 3 Functional anatomy of an active zone. Each active zone contains one, or at most a very few, vesicles attached to release sites, docked and primed at the plasma membrane, and immediately releasable by the local high $[Ca^{2+}]_i$ near Ca^{2+} channels opened by APs. These vesicles are rapidly replaced by other docked vesicles in a readily releasable pool. Most vesicles are stored in a large reserve cluster behind the plasma membrane. These can be used to refill the readily releasable pool after it is depleted in depression by a Ca^{2+}-dependent mobilization process. Released vesicles are recovered by fast and slow endocytic processes into readily releasable and reserve pools.

AT A SINGLE RELEASE SITE, CAN ONLY A SINGLE VESICLE BE RELEASED IN RESPONSE TO AN AP, OR IS IT POSSIBLE TO HAVE MULTIVESICULAR RELEASE? The observation that the number of release sites determined by quantal analysis is very similar to the number of active zones or synaptic contacts gives rise to the idea that some mechanism restricts the number of vesicle fusions to a single one per synaptic contact per impulse, so that a single release site is a single active zone (10, 197, 199, 200). More recent experiments support this hypothesis and also propose that following neurotransmitter release at an individual release site the inability to trigger additional release events persists for ~10 ms (13). However, other studies at hippocampal synapses (201) and inhibitory (202) and excitatory (203) cerebellar synapses suggest that individual release sites may release multiple vesicles.

The issue has important implications for the mechanisms that give rise to depression. This is illustrated by considering the cerebellar climbing fiber synapse, which is depressed to 50% of control amplitudes by a single conditioning pulse. If depression reflects a depletion of the readily releasable pool, and there is an average of 7–8 morphologically docked vesicles at each release site (204), how can a single conditioning pulse result in so much depression? This suggests that either each morphological docked vesicle is not release ready, or that multivesicular release must occur (203).

Ca^{2+}-DEPENDENT RECOVERY FROM DEPRESSION Recent studies have provided new insight into depression and recovery from depression. Whereas recovery from depression usually can be approximated by an exponential with a time constant of several seconds, for some experimental conditions an elevation of presynaptic Ca^{2+} levels accelerates the recovery from depression (143–145). At the climbing fiber synapse, when external $[Ca^{2+}]$ is elevated to 4 mM, significant recovery from depression occurs in less than 100 ms. This finding suggested the hypothesis that high levels of residual Ca^{2+} accelerate recovery from depression. To test the involvement of residual Ca^{2+}, EGTA was introduced into the presynaptic terminal to accelerate the decay of residual Ca^{2+}, which did not affect the initial probability of release but eliminated rapid recovery from depression. Residual Ca^{2+} also accelerated recovery from depression at the calyx of Held.

These studies help to resolve a long-standing deficiency of depletion models of depression in that they failed to predict the magnitude of synaptic responses during high-frequency presynaptic activity. Based on the magnitude and time course of depression evoked by a brief conditioning train, depletion models greatly underestimated synaptic efficacy during prolonged trains of activity. This led to the hypothesis that the rate of recovery from depression is accelerated during trains. This can now be understood in terms of the build-up of presynaptic Ca^{2+} levels accelerating recovery from depression, and allowing the presynaptic terminal to meet the increased demand for neurotransmitter during a train.

One way of accounting for Ca^{2+}-dependent recovery from depression is to update the depletion model such that increases in residual $[Ca^{2+}]_i$ accelerate the mobilization of vesicles from a reserve pool (143–145). Another possibility, put

forth by Wu & Borst (171), suggests that "during repetitive firing, accumulation of intracellular calcium may facilitate release of the rapidly replenished but reluctant vesicles, making them available for sustaining synaptic transmission." This study suggests that recovery from depression at the calyx of Held does not result from the Ca^{2+} dependence of recruitment of vesicles from a reserve pool to a ready releasable pool.

Other studies have also questioned a role for residual Ca^{2+} in the acceleration of recovery from depression. Weis et al. (205) manipulated presynaptic levels at the calyx of Held with the rapid Ca^{2+} chelator fura-2 and observed the effects on presynaptic $[Ca^{2+}]_i$ and on synaptic transmission. Based on these experiments and the behavior of several models, they concluded that at the calyx of Held "$[Ca^{2+}]_i$ in the range 50–500 nM does not significantly affect the rate of vesicle filling at this synapse," and that recovery from synaptic depression is "governed by localized, near membrane Ca^{2+} signals not visible to the indicator dye, or else by an altogether different mechanism."

A recent study by Sakaba & Neher of the calyx of Held (206) resolves some of the questions regarding Ca^{2+}-dependent recovery from depression. They manipulated resting presynaptic $[Ca^{2+}]_i$ levels and found that higher initial $[Ca^{2+}]_i$ accelerates recovery from depression. These findings argue against the study by Weis et al. (205) and confirm the importance of residual Ca^{2+} (143–145).

WHY DO SOME SYNAPSES SHOW NO DEPRESSION? Some synapses, for example at crayfish opener muscles (207) and chick ciliary ganglion (208), show virtually no sign of synaptic depression. Prolonged high-frequency activity eventually depletes the entire or reserve pool of transmitter, but no immediately releasable and rapidly depletable pool is evident. Presumably, this is because at such synapses the readily releasable pool is very rapidly replenished between APs and thus is effectively never depleted.

DEPRESSION INCONSISTENT WITH DEPLETION MODELS At crayfish fast flexor neuromuscular junctions (209), locust motor neuron synapses (160), and at *Aplysia* synapses between sensory and motor neurons (210–212), depression arising presynaptically occurs independently of changes in the initial level of transmission, and the steady-state degree of depression is nearly independent of stimulation frequency. At the *Aplysia* synapses, buildup of residual $[Ca^{2+}]_i$ and Ca^{2+} channel inactivation also play no roles in depression (212), which is probably caused by switching off of release sites (213). Similarly, for both an excitatory synapse in the goldfish (214) and inhibitory synapses in the rat (164), the extent of depression does not depend on the magnitude of the first release, and at giant cochlear nucleus synapses, a Ca^{2+}-dependent form of depression appears to occur independently of changes in initial release level (215). Strangely, cyclothiazide (normally a blocker of glutamate receptor desensitization) appears to eliminate this depression by some presynaptic action. These studies argue for a mechanism of presynaptic depression that does not reflect depletion of neurotransmitter-containing vesicles. One possible

explanation is that there is an activity-dependent gating mechanism limiting vesicle fusion through a refractory process and that this actually prevents vesicle depletion. At the crayfish synapse, depression is largely relieved by inhibition of NO synthase (216), suggesting that at this synapse NO generation is somehow responsible for synaptic depression.

At the squid giant synapse, a step elevation in $[Ca^{2+}]_i$ by caged Ca^{2+} photolysis activated secretion that decayed with a 30-ms time constant (217). Although resembling depletion of a readily releasable store, this explanation appears inconsistent with the property that further step increases in $[Ca^{2+}]_i$ evoked additional bouts of secretion and that the rate of fatigue is independent of $[Ca^{2+}]_i$ step magnitude. The authors characterized this behavior as a form of adaptation in Ca^{2+} sensitivity of release that could contribute to depression, although its kinetics seem too slow to be involved in AP-evoked release. Some of these properties could be explained by the existence of multiple pools of vesicles with different Ca^{2+} sensitivities, as has been shown for secretion of cortical granules by sea urchin eggs (218, 219). Other properties can be explained by invoking a Ca^{2+}-sensitive mobilization of vesicles from reserve to readily releasable pools (R. S. Zucker, unpublished calculations).

SYNAPTIC DEPRESSION VIA ACTIVATION OF METABOTROPIC RECEPTORS

Many presynaptic terminals in the mammalian CNS possess high-affinity metabotropic receptors that can be activated by chemical messengers such as GABA, glutamate or adenosine. Synaptic strength is controlled in part by the occupancy of these receptors, which in turn is set by the extracellular concentrations of their agonists. In some cases, tonic levels are sufficient to partially activate the receptors, but synaptic activity can further increase receptor occupancy by transiently elevating neuromodulator concentration. Following release, transmitter molecules can act either homosynaptically and bind to presynaptic autoreceptors or heterosynaptically by diffusing to nearby terminals. Examples of such signaling are given below and reviews of such modulation (220, 221) should be consulted for a more comprehensive treatment of synaptic modulation by activation of metabotropic receptors.

Homosynaptic Inhibition

The contents of a vesicle can act on the presynaptic terminal from which they were released. This is called homosynaptic modulation, and it is usually inhibitory. In most cases, when neurotransmitter builds up sufficiently to activate presynaptic receptors, the end result is negative feedback and a reduction in the future release of neurotransmitter. For example, vesicles contain ATP at relatively high concentrations, and when a vesicle fuses, ATP is released (222). In extracellular space, ATP is broken down into adenosine, which can activate presynaptic adenosine receptors

and lead to homosynaptic inhibition (223). At neuromuscular junctions, this process contributes to depression to prolonged stimulation, but it is not responsible for the major part of synaptic depression (224). At some GABAergic synapses (225, 226), but not at others (227, 228), depression arises partly from a retrograde action of GABA on presynaptic $GABA_B$ receptors, presumably reducing Ca^{2+} influx to subsequent APs. A similar process involving presynaptic metabotropic glutamate receptors appears responsible for only a very tiny proportion of synaptic depression at calyx of Held synapses (229).

Heterosynaptic Inhibition

Activation of synaptic inputs can also affect neighboring synapses. For example, activation of excitatory inputs to a region can activate GABAergic interneurons causing a widespread increase in extracellular GABA levels (230–232). This can activate presynaptic $GABA_B$ receptors and inhibit synaptic strength for seconds following periods of elevated activity. Presynaptic boutons contain many types of receptors that sense a variety of extracellular chemical messengers, all potentially involved in heterosynaptic depression.

Retrograde Control of Neurotransmitter Release

It is also possible for the postsynaptic cell to influence release from the presynaptic terminal. Different types of dendrites can release a variety of messengers that can act through G-protein–coupled receptors located on presynaptic terminals to influence neurotransmitter release. Neuromodulators such as dopamine, dynorphin, glutamate, GABA, and oxytocin are released by fusion of vesicles that are located within the dendrites and cell bodies (233–239). Retrograde messengers are also released by non-vesicular mechanisms. Endogenous cannabinoids such as anandimide and 2-AG are produced by cleavage of phospholipids and are sensed by CB1 receptors on presynaptic terminals. Retrograde signaling by endogenous non-vesicular release of cannabinoids has been shown to suppress inhibitory synapses in the hippocampus and both excitatory and inhibitory synapses in the cerebellum (240–244). Vesicular and non-vesicular release of retrograde messengers are both Ca^{2+} dependent and provide a way for activity of the postsynaptic cell to influence release from its synaptic inputs.

PRESYNAPTIC IONOTROPIC RECEPTORS

Many presynaptic terminals contain ionotropic receptors that can also contribute to short-term synaptic plasticity (245). A variety of ionotropic receptors can be present, although the extent to which these receptors contribute to synaptic plasticity is not known. These receptors include Ca^{2+} permeable receptors such as NMDA receptors and $\alpha 7$ nicotinic receptors, as well as Ca^{2+} impermeable receptors such as $GABA_A$ and glycine receptors, which are coupled to Cl^--permeable channels.

Activation of presynaptic ionotropic receptors can either increase or decrease neurotransmitter release by several mechanisms.

At brain stem synapses, glycine opens presynaptic Cl^- channels, which in turn depolarizes the terminal, opens voltage-gated Ca^{2+} channels, elevates presynaptic $[Ca^{2+}]_i$, and facilitates subsequent release of neurotransmitter (246). At the mossy fiber synapse on hippocampal CA3 pyramidal cells, glutamate activation of presynaptic kainate autoreceptors can contribute to synaptic enhancement (247). Blockade of these autoreceptors, as well as their genetic deletion (248), reduces the magnitude of synaptic enhancement during trains. It is hypothesized that this synaptic enhancement is caused by presynaptic depolarization induced by kainate receptor activation by previously released glutamate. High levels of kainate can also contribute to synaptic depression at this synapse (249); thus it appears that a bi-directional short-term regulation of synaptic transmission by autoreceptors is possible.

INVOLVEMENT OF GLIA IN SHORT-TERM PLASTICITY

There is growing realization that glia may be involved in some forms of short-term plasticity (250, 251). With their intimate association with synapses, astrocytes and perisynaptic Schwann cells are well positioned to regulate synapses. They have an established role in clearance of neurotransmitter and may participate in synaptic plasticity by controlling the speed and extent of such clearance (252, 253). This can in turn impact the degree of postsynaptic receptor activation and desensitization.

Another way that glia may be involved in synaptic plasticity is by sensing extracellular messengers and then releasing substances that can affect synaptic efficacy (250, 251). Glia have receptors for many neurotransmitters such as glutamate, GABA, acetylcholine, and ATP. Appropriate signaling molecules elevate glial $[Ca^{2+}]_i$ levels either through Ca^{2+}-permeable channels or by release from internal stores. The resulting increases in $[Ca^{2+}]_i$ can trigger vesicular release of substances from astrocytes, which can then act on presynaptic terminals to regulate neurotransmitter release. This signaling system provides a way for glia to sense release from presynaptic terminals and provide feedback to that terminal.

This interaction between neurons and glia and a potential role for glia in short-term synaptic plasticity have been observed at several synapses. In hippocampal cell culture, stimulation of astrocytes can depress the strength of synaptic contacts between neurons (254). This is the result of Ca^{2+}-evoked glutamate release that inhibits release by activating presynaptic metabotropic glutamate receptors (254–256). At the frog neuromuscular junction, perisynaptic Schwann cells can either potentiate or depress transmission. During prolonged repetitive stimulation of motor neurons, perisynaptic Schwann cells show a rise in $[Ca^{2+}]_i$ levels owing to ATP- and acetylcholine-activated IP_3-dependent release from endoplasmic reticulum (257–259). This increase in $[Ca^{2+}]_i$ can enhance the release of

neurotransmitter from the presynaptic terminal (260). In addition, disruption of G protein and NO signaling reduced the extent of depression induced by high frequency stimulation, suggesting that glia can also contribute to depression at this synapse (261, 262). In hippocampal slices, glia are involved in the enhancement of transmission between interneurons and pyramidal cells (263). During repetitive stimulation, inhibitory neurons activate $GABA_B$ receptors on astrocytes, which raises their internal $[Ca^{2+}]_i$ and somehow feeds back to the presynaptic terminal to enhance transmission.

These studies suggest that astrocytes contribute to multiple forms of synaptic plasticity at many synapses in the brain. Clarification of the role of glia in short-term plasticity is in its early stages and promises to remain an exciting area of research in coming years.

POSTSYNAPTIC MECHANISMS OF SYNAPTIC DEPRESSION

Desensitization

Another mechanism that can lead to use-dependent decreases in synaptic strength is through desensitization of postsynaptic receptors (reviewed in 264). Ligand-gated channels undergo a process called desensitization that is analogous to inactivation of voltage-gated channels. Exposure of ligand-gated channels to an agonist can lead to channel opening and can also put some of the channels into a nonresponsive state. It can take tens of milliseconds or even minutes for channels to recover from such a desensitized state.

In *Aplysia*, early work revealed cholinergic excitatory and inhibitory synapses in which desensitization of postsynaptic receptors is the major process responsible for depression of a component of the postsynaptic potential (265, 266). Desensitization of AMPA receptors has been shown to play a role in synaptic transmission at a number of synapses. Desensitization contributes to plasticity at the calyceal synapse between the auditory nerve and the nucleus magnocellularis of the chick (267, 268). At this synapse, inhibitors of desensitization partially relieve synaptic depression to pairs of pulses and trains (269). Blockade of glutamate transporters enhanced depression (270), suggesting that they normally limit depression by reducing the extracellular accumulation of glutamate. Desensitization also occurs at the synapses between cones and bipolar cells in the retina (271), at giant cochlear nucleus synapses (272), and at retinogeniculate synapses, where AMPA receptor desensitization contributes to a reduction in AMPA receptor ePSCs during realistic patterns of activity (C. Chen, D.M. Blitz & W.G. Regehr, in review). Desensitization also contributes to depression of NMDA receptor responses in hippocampal cultures, where the amount of desensitization is regulated by postsynaptic potential (274). Desensitization may also play a role in the apparent reduction in quantal amplitude inferred at hippocampal glutamatergic synapses (275).

The extent of AMPA receptor desensitization to short-term plasticity is likely dictated by the structure of the synapse, the probability of release, and the time course of transmitter clearance. Receptor desensitization does not play a widespread role in short-term plasticity (162, 276, 277). The chick calyceal synapse and the retinogeniculate synapse both have many closely spaced release sites that are not well isolated from one another. This allows glutamate release at one site to diffuse, bind to, and desensitize nearby receptors. The glial sheath that encompasses aggregates of synaptic contacts onto the geniculate neuron may allow glutamate to pool and may contribute to the occurrence of AMPA receptor desensitization. In contrast, even though climbing fibers make hundreds of synaptic contacts with Purkinje cells, because each synapse is ensheathed by glia, the release sites are well isolated from one another, and there is no opportunity for glutamate released from one site to desensitize AMPA receptors at nearby release sites (204, 278). Another consideration is that if vesicle fusion occurs at a given release site and leads to receptor desensitization of the corresponding receptors, presynaptic depression could prevent the release of transmitter at that site and obscure receptor desensitization. Desensitization occurs at other types of receptors where it may contribute to synaptic plasticity (279). Low concentrations of GABA reduce synaptic currents at GABAergic hippocampal synapses, and it has been proposed that desensitization can regulate the availability of GABA receptors (280). NMDA receptors can also be desensitized by a variety of mechanisms (264, 281–283) that may contribute to synaptic plasticity of the NMDA responses. For acetylcholine receptors, although they can also desensitize, at the neuromuscular junction desensitization has little effect on the amplitude of synaptic responses during trains of activity (284).

Relief of Polyamine Block

Another postsynaptic mechanism leading to short-term synaptic plasticity was revealed at synaptic connections between pyramidal neurons and postsynaptic multipolar interneurons in layer 2/3 of rat neocortex (285). Synaptic currents at this synapse are mediated by AMPA receptors, which are blocked by endogenous intracellular polyamines that are present in almost all cells. In excised patches, this polyamine block is relieved by depolarization (286). At the synapses onto layer 2/3 interneurons, this relief of polyamine block enhances the responses of AMPA receptors and helps to offset a synaptic depression produced by another mechanism. Thus a facilitation of AMPA receptors due to potential-dependent relief of polyamine block can lead to a postsynaptic form of facilitation.

MOLECULAR TARGETS IN SYNAPTIC ENHANCEMENT

The search for molecular mediators of short-term synaptic plasticity has been intense. In the case of postsynaptic mechanisms, presynaptic ionotropic receptors, and metabotropic receptors, there has been good success in identification of the

molecules involved in synaptic plasticity. It has proven to be more difficult to identify the molecules responsible for facilitation, PTP, and depression, but many possibilities remain to be explored.

Difficulties In Identifying Specific Effects on Short-Term Plasticity

One of the primary difficulties in the identification of molecules directly involved in short-term plasticity is that manipulations affecting the baseline level of transmission indirectly influence the magnitude of short-term plasticity. At most synapses, an increase in the initial probability of transmitter release decreases the magnitude of synaptic enhancement, and, conversely, a decrease in the probability of release results in larger synaptic enhancement or reduced synaptic depression. This is such a widely recognized relationship that it has become a standard means of gauging whether a neuromodulator has a presynaptic or postsynaptic site of action.

Thus the interpretation of effects on short-term plasticity often requires a measure of the effects on the baseline level of transmission. There are several possible ways of making such measurements: (*a*) Ideally, an analysis of quantal content should be performed. Often neurons are connected by a large number of synaptic contacts and determining the quantal content of baseline recordings is not straightforward. In that case, measures of PSP or PSC amplitude should be made, along with tests for postsynaptic effects such as measuring miniature PSP or PSC amplitudes. (*b*) At synapses where NMDA receptors are present, use-dependent block of NMDA receptors by MK801 can be used to detect changes in the probability of release. (*c*) With use of styryl dyes such as FM1-43, vesicle turnover rates to low-frequency stimulation can be assessed.

Often it is experimentally difficult to measure the baseline level of synaptic transmission. For example, transmission may be examined in brain slices where extracellular stimulation is used to evoke responses that are detected with extracellular electrodes. The amplitude of the evoked response does not provide a measure of baseline transmission because it reflects the activation of many presynaptic fibers and depends upon the positioning of the stimulus and recording electrodes, the intensity of stimulation, and the overall health of the slice. Although NMDA receptors may be present, they are difficult to measure with extracellular methods because of their slow time course. Thus it is difficult to quantify the initial magnitude of release with extracellular methods, and many studies do not determine whether changes in plasticity are direct effects on facilitation or depression, or if they are secondary consequences of changes in the initial probability of release.

Another potential complication arises in situations where synapses are manipulated for a prolonged time before the effects on plasticity are assessed. Particularly in the case of genetic mutations, a variety of homeostatic mechanisms allow neuronal systems to respond to the initial effect of a manipulation with secondary changes. This makes it difficult to exclude the possibility that changes in short-term plasticity arise as a secondary consequence through a homeostatic mechanism.

Despite these potential complications, important advances have been made both in the elimination of certain molecular schemes and in the identification of molecules with potential roles in synaptic transmission.

Ca^{2+}-Binding Proteins

An early hypothesis (287) for longer forms of enhancement, particularly PTP, posed that it was caused by Ca^{2+} acting via calmodulin and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) to phosphorylate synapsin I, a vesicle-associated protein that binds actin filaments. Phosphorylation was shown to reduce synapsin I cross-linking to actin, and this could liberate vesicles and make them more available for release.

TESTS OF THE SYNAPSIN HYPOTHESIS Unfortunately, most data from genetic mutants of CaMKII and synapsin I failed to corroborate predictions of this elegant hypothesis. Synapsin I null mutants display normal PTP in hippocampal CA1 neurons, as do CaMKII heterozygotes expressing reduced CaMKII (288–291). PTP was reduced in synapsin II mouse knockouts (292), but this form of the protein is not phosphorylated by CaMKII. CaMKII inhibitors failed to block PTP in hippocampal neurons (293), augmentation at CA3 association/commissural synapses (69), or any form of short-term enhancement at crayfish neuromuscular junctions (61). In contrast, at *Aplysia* synapses PTP was reduced by presynaptic injection of synapsin I/II antibodies and was enhanced by synapsin I injection (294).

Synapsins do appear to play an important role in the maintenance of a reserve pool of vesicles and the mobilization of vesicles from that pool to the readily releasable pool (292, 295–297). Genetic disruption of synapsins leads to a deepening of synaptic depression and loss of undocked vesicles from active zone clusters. The association of vesicle-associated synapsin with actin filaments may also explain why actin depolymerization deepened synaptic depression and slowed its recovery in snake motor neurons (298) and disrupted the reserve pool of vesicles and deepened depression at *Drosophila* motor neurons (299).

CaMKII also seems to influence synaptic plasticity at some synapses. CaMKII inhibition reduced PTP at several fish electroreceptor lateral line synapses, but not others (300), and it reduced augmentation at CA3 mossy fiber synapses (69). Mutations in CaMKII targeted to *Drosophila* presynaptic sensory terminals reduced depression without necessarily affecting baseline transmission (301). Facilitation was increased in the synapsin I null mutants and decreased in CaMKII mutants (290), but unaffected in *Aplysia* synapses (72); these effects occurred in the absence of effects on baseline transmission. It seems likely that synaptic plasticity can be regulated by, if not mediated by, the phosphorylation state of presynaptic proteins.

OTHER SECRETORY PROTEINS A lot of attention is focused now on a number of Ca^{2+}-binding proteins found in synaptic terminals, especially proteins associated with the secretory apparatus. The discovery that facilitation is accompanied by a reduction in synaptic delay or speeding of release kinetics (302, 303) encourages

interest in such proteins. So does the inference from modeling studies that facilitation is caused by Ca^{2+} acting fairly close to Ca^{2+} channel mouths, although not as close as the secretory trigger (70).

Synaptotagmin III and VII are isoforms of synaptotagmin I, the low-affinity Ca^{2+}-binding vesicle protein that is the most popular candidate for the Ca^{2+} trigger of phasic exocytosis (304, 305). These plasma membrane isoforms (306) have higher Ca^{2+}-binding affinity to their C2 domains (307), and interfering with their Ca^{2+} binding blocked exocytosis (308). Because a high-affinity Ca^{2+} receptor involved in generating facilitation could also be required for normal baseline secretion (70), these synaptotagmins are good candidates as Ca^{2+} targets involved in facilitation.

Doc2α (for double C2 domain) is a presynaptic Ca^{2+}-binding protein involved in synaptic transmission (57). Overexpression of Doc2 enhanced growth hormone secretion from PC12 cells, and peptides disrupting its interaction with Munc13 (another presynaptic protein; see below) inhibited transmitter release from sympathetic neurons (309). Doc2 was a good candidate Ca^{2+} target in synaptic enhancement until recently, when it was found that in Doc2α null mutants paired-pulse facilitation and PTP were normal (310). Steady stimulation for 30 s resulted in even more enhancement in Doc2α null mutants, possibly reflecting an enhancement in augmentation. These results suggest that Doc2α may under some circumstances modulate synaptic enhancement, but it is unlikely to mediate its activation by Ca^{2+}.

RIM (for rab-3 interacting molecule) is a third Ca^{2+}-binding protein localized to the plasma membrane (311), which binds to rab-3, a vesicle protein thought to be involved in vesicle trafficking and targeting. Transfection of PC12 cells with RIM enhances secretion, so this protein remains another putative Ca^{2+} target for activating synaptic enhancement.

An additional rab-3 and Ca^{2+}-binding protein called rabphilin is located in synaptic vesicle membranes. Reducing normal rabphilin expression inhibited secretion in PC12 cells (312), while injecting rabphilin into squid giant presynaptic terminals also inhibited secretion (313). Rabphilin knockout mice, on the other hand, showed normal hippocampal baseline synaptic transmission, as well as normal facilitation and augmentation (314). Thus rabphilin is a less-favored candidate as a Ca^{2+} sensor mediating short-term synaptic enhancement.

Munc13-1 is a syntaxin-binding presynaptic protein containing C2 domains, although its Ca^{2+} binding could not be established (315). In mouse knockouts, most hippocampal excitatory synapses were defective, apparently due to interference with a vesicle priming step (316), but in the few synapses where transmission remained, augmentation was enhanced by increase in the store of readily releasable vesicles (A. Sigler, J.-S. Rhee, I. Augustin, N. Brose & C. Rosenmund, in review). This contrasts with normal augmentation where no increase in store size is observed (15). Thus rather than mediating normal synaptic enhancement, this protein may modulate its expression.

CAPS (Ca^{2+}-dependent activator protein for secretion), a protein restricted to dense core vesicles, binds Ca^{2+} with low affinity (270 μM) (318). CAPS antibodies

inhibit norepinephrine release from synaptosomes, which suggests a role in triggering phasic secretion. But in melanotrophs, CAPS antibodies specifically block a phase of secretion that is highly sensitive to $[Ca^{2+}]_i$ levels below 10 μM, leaving open the possibility that this site may play a role in synaptic enhancement (319).

Another presynaptic protein with Ca^{2+}-binding C2 domains is called piccolo or aczonin (320, 321). This protein binds Ca^{2+} with low affinity, more consistent with a role in triggering phasic vesicle fusion than in mediating synaptic enhancement (322). At present, physiological evidence for any role of this protein in synaptic transmission is lacking.

Scinderin is a Ca^{2+}-dependent actin-binding protein that appears to regulate exocytosis in chromaffin cells (323). Although no neuronal homologue is known, such a protein could easily mediate Ca^{2+}-dependent changes in the size of the readily releasable store or the probability of release of quanta by APs.

Frequenin is a presynaptic Ca^{2+}-binding protein whose overexpression can greatly enhance synaptic facilitation (324). However, depolarizing pulses without Na^+ influx (in tetrodotoxin) do not exhibit excessive facilitation. Frequenin may therefore affect the accumulation of $[Na^+]_i$, and consequently of $[Ca^{2+}]_i$ under regulation of Na^+/Ca^{2+} exchange and lead to an increase in synaptic enhancement.

There are two other Ca^{2+}-dependent presynaptic protein interactions. Ca^{2+} acting at low micromolar concentrations can trigger binding of the presynaptic Ca^{2+} channels to the plasma membrane SNARE proteins syntaxin and SNAP-25 (325). A potential cation-binding site coordinated with synaptobrevin and syntaxin within the SNARE assembly has also been inferred from structural studies (326). Effects of Ca^{2+} binding to either of these sites on synaptic transmission remain to be studied.

Other Genetic Manipulations

In addition to Ca^{2+}-binding proteins, a number of other presynaptic proteins have been identified that play important roles in synaptic transmission. Mutations or knockouts of genes encoding such proteins have been used to probe their roles in synaptic plasticity, particularly in mice and fruit flies.

MOUSE MUTANTS Rab-3A is a GTP-binding protein found in synaptic vesicle membranes, believed to function in the targeting of vesicles to active zones. Mouse knockouts of this gene show enhanced facilitation, even in the presence of increased baseline transmission (327); PTP was unaffected (304). Synapses showed an unusual ability to release more than one vesicle per active zone, suggesting that a limit on secretion had been removed, thereby allowing more facilitation to be expressed. Curiously, presynaptic injection of rab-3 into *Aplysia* neurons also increased facilitation (but not PTP), but now baseline transmission was reduced (81); thus in these experiments release could have been desaturated. It appears that Rab-3A can modulate synaptic transmission in a way that indirectly affects facilitation.

Synaptogyrin I and synaptophysin I are synaptic vesicle membrane proteins of unknown function. Double knockouts of both genes showed modest reductions in facilitation and PTP, whereas facilitation was normal in single knockouts of either gene, and PTP was only slightly depressed in synaptogyrin mutants (328). Baseline transmission was unaffected. These proteins can influence, especially in concert, the magnitude of short-term enhancement.

Facilitation was impaired in null mutants of the gene encoding neurotrophin-3, a nerve growth factor expressed mainly in the hippocampal dentate gyrus (329). Baseline transmission was normal. Application of exogenous neutrophilin-3 also reduces facilitation in normal rat hippocampal CA1 cells, but this is probably a consequence of a strengthening of synaptic transmission (330).

Mutations in the gene encoding the brain protein ataxin-1 showed a modest impairment in paired-pulse facilitation, although PTP remained normal (331). However, reduced facilitation could be an indirect consequence of altered baseline transmission, which was not recorded.

Mouse knockouts of the mGluR4 subtype of metabotropic glutamate receptor show reduced facilitation and PTP (332). The results suggest a role for glutamatergic feedback via presynaptic metabotropic receptors in enhancing transmitter release. However, effects on baseline transmission were not assessed, so effects of saturation or countervailing depression cannot be excluded.

DROSOPHILA MUTANTS A number of genetic manipulations in *Drosophila* have interesting effects on short-term synaptic enhancement. *Rutabaga* and *dunce* are mutants defective in an adenylyl cyclase and phosphodiesterase, respectively. The former has reduced capability for cAMP synthesis; the latter has enhanced levels of cAMP owing to diminished degradative activity. Both mutants displayed remarkably diminished facilitation and PTP under low-$[Ca^{2+}]$ conditions in which basal transmission was also reduced in *rutabaga* but was normal in the *dunce* mutants (333). The latter also showed reduced Ca^{2+} cooperativity in triggering secretion. Surprisingly, some boutons showed enhanced augmentation. Without knowledge of possible changes in presynaptic $[Ca^{2+}]_i$ regulation, the results are difficult to interpret. In a different study, *rutabaga* mutants and inhibitors of adenylate cyclase and protein kinase A showed a diminished mobilization of vesicles from reserve to readily releasable pools (334). Certainly a role or roles, although perhaps indirect, are implicated for cAMP in the regulation of synaptic plasticity.

Shibire is a temperature-sensitive mutant of the gene for dynamin, a protein essential for vesicle endocytosis. At non-permissive temperatures, in addition to the expected gradual decline in transmission owing to the inability to restore vesicles to the reserve pool, a rapid form of depression is seen that is inconsistent with the delays involved in recovering vesicles by endocytosis, which suggests an additional role for dynamin in maintaining an intact readily releasable pool (335).

Leonardo is a *Drosophila* cytosolic protein also located in synaptic vesicles and involved in regulation of a number of second messenger pathways. Null mutants displayed enhanced facilitation but reduced augmentation and PTP (336).

However, baseline transmission was reduced, which could account for the effect on facilitation, whereas excessive depression could have been mistaken for effects on augmentation and PTP.

Latheo is a DNA-regulating protein in *Drosophila* also concentrated presynaptically and able to affect synaptic transmission. Null mutants of the *latheo* gene show seriously impaired facilitation, augmentation, and PTP at neuromuscular junctions (337). Although transmission is strongly increased, the effects on synaptic plasticity persist even when baseline transmission is restored to normal in low-[Ca^{2+}] medium. Transgenic overexpression of latheo rescues synaptic enhancement in the mutants. Not known to be a Ca^{2+}-binding protein, latheo may not be the target of Ca^{2+} action in regulating synaptic transmission, but it certainly seems to play important roles in short-term synaptic enhancement.

Finally, αPS3-integrin is a *Drosophila* cell adhesion protein localized to presynaptic boutons. Its genetic inactivation results in enlarged presynaptic arborizations, enhanced transmission, and reduced facilitation and PTP (338). Integrin inhibitory peptides have similar effects. Compensating the effect on baseline transmission by reducing [Ca^{2+}] leaves PTP impaired, but surprisingly restores augmentation to greater than control levels (facilitation was not tested under these conditions). Deficits in synaptic enhancement are conditionally rescued by heat shock when mutants are transfected with an integrin gene under control of a heat shock promoter. Integrins thus also appear capable of strongly influencing the expression of short-term synaptic enhancement.

SUMMARY OF MOLECULAR MEDIATORS There are indications that the presynaptic proteins synapsin I and II, synaptogyrin, synaptophysin, munc13-1, latheo, integrin, and native Ca^{2+}-binding proteins all influence the expression of facilitation, augmentation, and/or potentiation. Neutrophilin-3 and metabotropic glutamate receptors can also influence synaptic plasticity. However, present evidence does not point to any of these as the Ca^{2+} target in activating any particular phase of short-term synaptic plasticity.

Other Modulatory Influences

Many factors can influence synaptic plasticity, but the effects may be indirect, merely a consequence of changes in strength of synaptic transmission. For example, numerous aminergic and peptidergic neuromodulators either enhance or reduce facilitation at crustacean neuromuscular junctions, but the reported effects are always inversely related to effects on baseline transmission (339). At crayfish neuromuscular junctions, serotonin enhances synaptic transmission and prolongs facilitation without prolonging the time course of residual Ca^{2+} (340). This curious result is hard to reconcile with the evidence that the duration of facilitation reflects that of residual Ca^{2+}.

The identity of postsynaptic targets can influence the magnitude or dominance of facilitation or depression (341, 342), as can developmental age (343) and the

removal of synaptic competition by sensory deprivation (344, 345). These findings support the possibility of independent developmental regulation of short-term synaptic plasticity.

Disruption of the tight association of presynaptic Ca^{2+} channels with the SNARE complex can be achieved by injecting peptides that compete with this binding. This increases synaptic facilitation, but also decreases baseline transmission (346). A low-[Ca^{2+}] medium had similar effects, so the modulation of facilitation is probably a consequence of the reduction in basal transmission.

Perfusion of calyx of Held terminals with inhibitors of G proteins increased synaptic depression and slowed its recovery (347). It is not clear what proteins were affected by this treatment, but because rab3 mutants show increased facilitation (327), they may not be the only targets affected by G protein inhibitors.

Calmodulin inhibition slowed recovery from depression at the calyx of Held and prevented refilling of the readily releasable pool of vesicles (206). It is possible that calmodulin is required for the Ca^{2+}-dependent mobilization of transmitter.

The phosphatase inhibitor okadaic acid depressed facilitation at frog neuromuscular junctions (45). But effects on basal transmission and depression were not reported, so the effect may be only indirect or apparent. Another phosphatase inhibitor with a similar spectrum of action, calyculin A, was without effect.

Overexpression of synaptotagmin I or II and treatment with cytochalasin (an actin depolymerizer) can appear to increase facilitation at neuromuscular junctions, but this may be a consequence of reduced short-term depression (348, 349).

Brain-derived neurotrophic factor reduced facilitation at these junctions as well as at cortical synapses, but this could be a consequence of increased basal transmission (330, 350).

Induction of status epilepticus by kainate reduces facilitation and PTP, probably by increasing the basal probability of transmitter release (351).

Deletion of the gene for the Ca^{2+}-binding protein calbindin-D_{28k} reduced facilitation and PTP (352), a surprising result because overexpression of calbindin has similar effects (73); however, the effects on synaptic plasticity in the deletion mutants might have been caused by effects on basal transmission levels, which were not monitored.

Bacterial lipopolysaccharide endotoxin increased paired-pulse facilitation without affecting baseline transmission (353), but a possible reduction in concurrent depression was not eliminated.

Finally, tetanic stimulation of cortical synapses has been found to reduce post-tetanic paired-pulse facilitation in a way dependent upon a postsynaptic $[Ca^{2+}]_i$ elevation and protein kinase activation (354, 355). The apparent reduction in facilitation was actually caused, however, by a concurrent desensitization in postsynaptic AMPA-type glutamate receptors and so was really a modulation of depression (see below).

A rise in postsynaptic $[Ca^{2+}]_i$ has been reported to be essential for PTP in some *Aplysia* central synapses (356). However, it appears that it is a particularly long-lasting component of PTP that is affected (357); therefore this may more

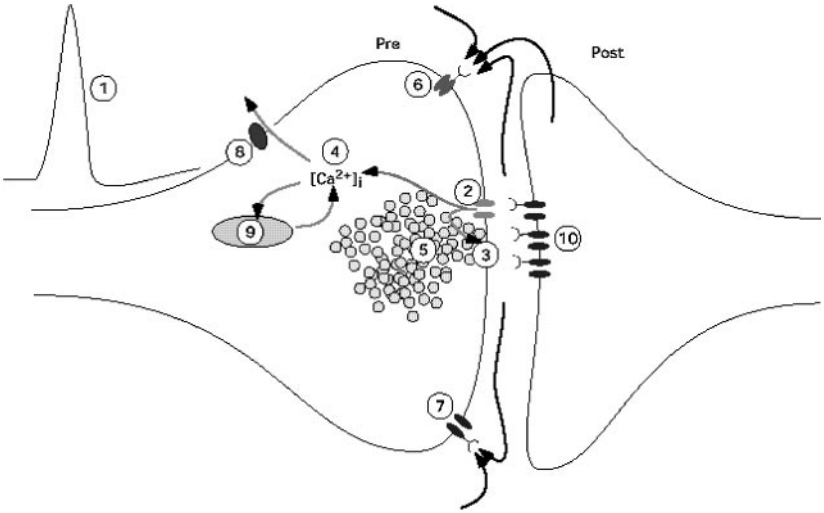

Figure 4 Sites of regulation of short-term synaptic plasticity. (1) AP waveform, (2) Ca^{2+} channel activation, (3) facilitation trigger and the readily releasable pool, (4) residual $[Ca^{2+}]_i$, (5) reserve pool, (6) metabotropic autoreceptors, (7) ionotropic autoreceptors, (8) Ca^{2+}-ATPase, regulating residual $[Ca^{2+}]_i$ in augmentation, (9) mitochondrial regulation of residual $[Ca^{2+}]_i$ in PTP, (10) postsynaptic receptor desensitization.

properly be considered an example of a decremental form of long-term potentiation, sometimes called short-term or slowly-decrementing potentiation, known to depend on postsynaptic Ca^{2+} (358, 359).

At cricket central synapses, a form of short-term synaptic depression appears to be mediated by a rise in postsynaptic $[Ca^{2+}]_i$ (360). The mechanism of this effect remains to be elucidated.

This summary of the search for molecular targets and regulatory influences indicates how important it is to distinguish effects on synaptic plasticity from effects on baseline transmission (Figure 4). If baseline transmission is in fact affected, alterations in external $[Ca^{2+}]_i$ or $[Mg^{2+}]_i$ can be used to restore transmission to comparable levels in experimental and control preparations. Effects on depression can usually be distinguished from short-term enhancement by their kinetic differences and by the relief of depression by reducing external $[Ca^{2+}]$.

Why is reducing external $[Ca^{2+}]_i$ usually so much more effective in relieving depression than in reducing synaptic enhancement? The reason is that baseline transmission normally depends on about the third power of external $[Ca^{2+}]$ near normal $[Ca^{2+}]$ levels. Thus a reduction of $[Ca^{2+}]$ to half will reduce transmission to about one tenth. Because depression by depletion is proportional to transmission strength, depression is also reduced to 10%. However, because synaptic enhancements all seem to be approximately linearly dependent on $[Ca^{2+}]_i$ accumulation,

they should be reduced to only half and can now easily be studied in relative isolation from depression.

CONCLUSIONS, PERSPECTIVES

An impressive array of mechanisms have been identified that contribute to short-term synaptic plasticity (Figure 4). In coming years advances will be made on several fronts. First, it is likely that additional mechanisms of short-term synaptic plasticity will be discovered. The past decade saw a new appreciation of retrograde control of synapses, glial contributions to short-term plasticity, the discovery of Ca^{2+}-dependent recovery from depression, and contributions of presynaptic metabotropic ionotropic receptors. It therefore seems likely that new, perhaps unanticipated, forms of short-term plasticity remain to be discovered. A second area of interest is the clarification of the various mechanisms that give rise to different forms of short-term plasticity. Short-term presynaptic depression is one of the least understood forms of plasticity, despite its prevalence. Although more is known about the mechanisms that give rise to facilitation and posttetanic potentiation, a more detailed understanding awaits the identification of the proteins that give rise to these forms of synaptic enhancement. A third challenging area of investigation is the determination of the physiological roles of these various forms of short-term plasticity.

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