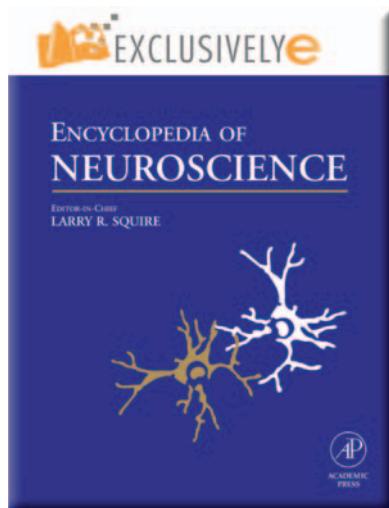


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Post-Tetanic Potentiation (PTP)

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The strength of synaptic transmission can increase or decrease during repetitive presynaptic activity. These changes, usually due to variations in amount of transmitter released by each action potential, dynamically shape the information transfer characteristics of synapses.

Components of Activity-Dependent Synaptic Plasticity

Phases of Enhanced Synaptic Transmission

Chemical synapses are rarely static transmitters of information between neurons. Their effectiveness waxes and wanes, depending upon frequency of stimulation and history of prior activity. At most synapses, repetitive high-frequency action potentials (often called a tetanus) result initially in a rapid growth of successive postsynaptic potential (PSP) amplitudes, called synaptic facilitation (or sometimes frequency facilitation). This process builds to a steady-state within about 1 s and decays equally rapidly when stimulation stops. Decay is measured by single test stimuli given at various intervals after a conditioning train. Facilitation can often be divided into two exponential phases, lasting tens and hundreds of milliseconds, respectively, and called the first and second components of facilitation. It may reach appreciable levels, as high as a doubling or more of the PSP amplitude in the second of two responses at short intervals, and as much as nearly 100-fold increase in PSP amplitude in a high-frequency train in some synapses. If presynaptic activity is sustained, facilitation is followed at most synapses by a slower phase of increased efficacy called augmentation, with a characteristic time constant of several seconds. Finally, prolonged activity results in a final phase of PSP growth, called potentiation and lasting several minutes. These processes can each increase transmission a further several-fold over initial baseline levels. The combination of all three processes, at least some of which (facilitation and potentiation in particular) appear to interact multiplicatively, could in principle elevate synaptic transmission several 100-fold, but in practice saturation of the release mechanisms usually limits the overall enhancement to less than 100-fold.

Synaptic Depression

Often superimposed on these phases of enhanced synaptic strength is a phase of diminishing transmission

called synaptic depression. This process is characterized by a drop in PSP amplitude during repetitive presynaptic action potentials. Depression can be absent or undetectable, quite modest, or so severe that transmission drops to zero. Depression often tends to overlap and obscure the augmentation and potentiation phases. When repetitive activity ceases, recovery from the various components of short-term synaptic plasticity occurs in the same order in which they developed during the previous activity, with facilitation decaying first, then depression and augmentation, and finally potentiation ([Figure 1](#)). Thus, potentiation is often visible as a distinct phase only long after repetitive activity or a tetanus, and so is usually called posttetanic potentiation (PTP).

Short-Term Plasticity due to Changes in Transmitter Release

Presynaptic Locus Implicated by Quantal Analysis

There are many points at which synapses can be modulated to alter the strength of synaptic transmission. The possibilities may initially be divided into presynaptic and postsynaptic processes. A good way to distinguish these two classes is to make use of the fact that synaptic transmission is ‘quantized,’ in the sense that each PSP represents the summed effect of the fusion of a certain number of presynaptic vesicles, each of which causes a reasonably fixed ‘unitary’ postsynaptic response. The number of vesicles that contribute to synaptic transmission is not fixed, even in the complete absence of synaptic plasticity, but rather is a random variable that fluctuates about some average number or mean. By statistical analysis of these fluctuations, it is possible to determine the number of unitary components in a PSP. Furthermore, even in the absence of presynaptic action potentials, vesicles occasionally fuse spontaneously with the plasma membrane, and the secretion of the contents of a single vesicle can be observed as a spontaneously occurring unitary or miniature PSP (MPSP). Comparison of the size of MPSPs to full PSPs evoked by action potentials also allows estimation of the number of vesicles contributing to a synaptic response.

This kind of analysis, called quantal analysis, has been applied to a large number of instances of short-term synaptic plasticity, including facilitation, augmentation, potentiation, and depression in humans, lower mammals, birds, amphibians, crustaceans, mollusks, insects and annelids. In practically all cases, every kind of short-term plasticity is accompanied by changes in the number of quanta released, often called quantal

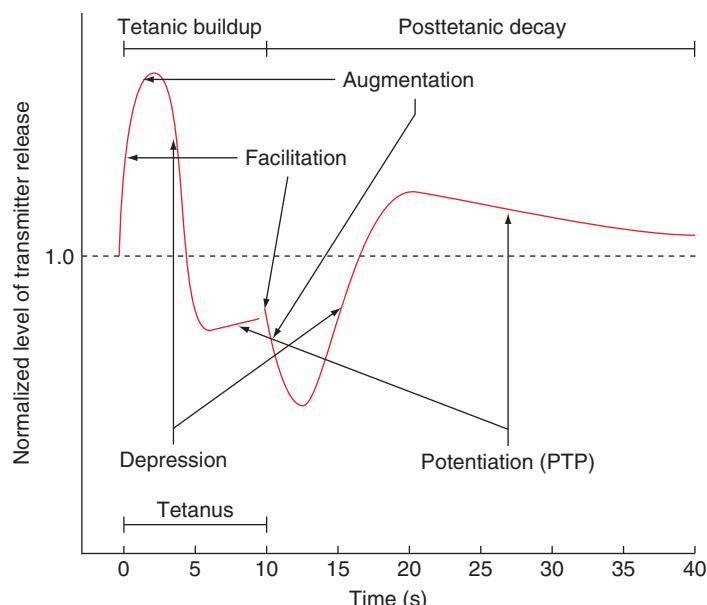


Figure 1 The red traces show the different kinetic components of short-term synaptic plasticity. On the left, transmission is shown as increasing early in a tetanus due to facilitation and then augmentation, and then as decreasing due to depression, and finally increasing again as potentiation is expressed after depression has reached a steady state. This curve represents the successive responses to action potentials during continuous stimulation. After the tetanus is stopped, recovery is measured by single action potentials at various times after the end of the tetanus, shown on the right. At very short intervals, facilitation is slightly higher than the last tetanic stimulus (because the inter-pulse interval is reduced from that during the tetanus), but facilitation decays rapidly, and augmentation more slowly. This is followed by recovery from depression, leaving only PTP. Different synapses have different mixes of facilitation, augmentation, depression, and PTP, and depression may develop and recover more or less rapidly than in this example.

content, with little or no change in the size or postsynaptic effectiveness of the unitary response to a quantum of transmitter. Thus, short-term synaptic plasticity is almost always a consequence of changes in one or more presynaptic process involved in determining the number of vesicles that action potentials cause to be secreted during neurotransmission.

Changes in Statistics of Transmitter Release

The statistics of transmitter release closely resemble those of a binomial process, in which an average of m quanta is released from a pool of n available quanta, each with a probability p of release by an action potential. The values of n obtained in such analyses are usually similar to or somewhat less than the number of anatomical synapses observed ultrastructurally. Each such synaptic contact, or active zone as it is sometimes called, consists of a cluster of presynaptic vesicles, some docked at the plasma membrane, opposed to a cluster of postsynaptic receptors across the synaptic cleft. The approximate correspondence between n and number of active zones suggests that each active zone can only release one docked vesicle in response to an action potential. If all the apparently docked vesicles could be released independently and simultaneously, n would greatly exceed the number of

active zones, since it is usually clear that postsynaptic receptors are not saturated by a quantum, so that multiple quanta released at one site would summate in their effects and be readily detected. Studies of synapses consisting of a single active zone confirm that they are normally capable of releasing only a single vesicle.

Short-term synaptic plasticity is usually accompanied by parallel changes in both n and p . The likely explanation for this is that p is not uniform across all active zones (as assumed in the simple binomial model), and may be near zero for some sites that rarely release a vesicle. Synaptic enhancement increases the probability of release from active zones, and raises previously silent active zones to a level of activity in which they begin to participate in transmission. Depression has the opposite effect – fewer active zones participate effectively in the release process, and those still active have a reduced probability of releasing a vesicle.

Possible Presynaptic Mechanisms

Much experimental effort has gone into exploring presynaptic mechanisms that could underlie facilitation, augmentation, and potentiation. The first step in

synaptic transmission is the invasion of the action potential into presynaptic terminals. In a few preparations, facilitation has been found to be caused by action potential broadening, arising mainly from accumulating inactivation of K^+ channels involved in terminating action potentials. In these synapses, increases in Ca^{2+} influx in prolonged action potentials underlie facilitation of transmitter release.

At most synapses that have been studied, short-term synaptic plasticities occur in the absence of any changes in presynaptic action potential propagation or waveform in presynaptic terminals and can be elicited by trains of constant presynaptic depolarizing pulses. A second possible locus of modulation is the presynaptic Ca^{2+} channel. In a few instances, presynaptic Ca^{2+} channels have been found to show a form of facilitation, with increased duration or probability of opening to repeated depolarizations, but this process contributes little to enhanced synaptic transmission at neurons, although it appears to be involved in facilitation of hormonal secretion from adrenal chromaffin cells.

The Role of Ca^{2+} in Short-Term Synaptic Enhancement

That facilitation, augmentation, and potentiation depend upon presynaptic Ca^{2+} entry is now well established from experiments on several different preparations. The pioneering experiments of Bernard Katz and Ricardo Miledi demonstrated that an action potential that invades a nerve terminal in a Ca^{2+} -free medium not only evokes no transmitter release but also fails to facilitate release to closely following action potentials stimulated after the rapid reintroduction of Ca^{2+} to nerve terminals by local iontophoresis. Facilitation does not require that the first action potential trigger secretion, however, since action potentials that happen to cause no release (at low external $[Ca^{2+}]$ levels) are still effective in inducing facilitation. Experiments on augmentation and PTP also show that these longer-lasting forms of enhanced synaptic transmission depend on Ca^{2+} influx into nerve terminals during conditioning stimulation. Experimental elevation of presynaptic $[Ca^{2+}]_i$ levels has also been shown to substantially increase the number of quanta released by an action potential.

Much attention has focused on how Ca^{2+} ions induce these forms of plasticity. A number of possibilities exist.

The Single Site Summating Residual Ca^{2+} Hypothesis

The simplest possibility is that all forms of synaptic enhancement arise from the cooperative action of

four or more Ca^{2+} ions in triggering secretion. This cooperativity is inferred from the finding that the magnitude of the phasic release of transmitter (i.e., the number of vesicles or quanta released) by an action potential depends on approximately the fourth power of external $[Ca^{2+}]$. Secretion can also be evoked by the rapid elevation of $[Ca^{2+}]_i$ liberated by intense flash irradiation of presynaptically injected photosensitive Ca^{2+} chelators; again, the maximal rate of secretion is related to the fourth power of the peak level of $[Ca^{2+}]_i$. This highly nonlinear dependence of secretory rate on $[Ca^{2+}]_i$ could naturally lead to increased transmitter release in the presence of a residual increase in $[Ca^{2+}]_i$ after action potentials. This is best seen by using a simple hypothetical calculation: suppose an increase of $[Ca^{2+}]_i$ by $1 \mu\text{mol l}^{-1}$ normally underlies an unfacilitated PSP consisting of 10 quanta, or the vesicle fusions occurring in 1 ms, and 20 ms later $[Ca^{2+}]_i$ is still elevated by $0.1 \mu\text{mol l}^{-1}$ above resting level (about 50 nmol l^{-1}). Then another action potential following the first by 20 ms might increase $[Ca^{2+}]_i$ to a peak level of $1.1 \mu\text{mol l}^{-1}$ above the resting level, which owing to the fourth-power dependence of secretion on $[Ca^{2+}]_i$ would facilitate release so that the second PSP is 46% larger (in quantal number) than the first ($1.1^4 - 1$). But the residual $[Ca^{2+}]_i$ itself would only cause secretion to occur at a rate of 1 quantum s^{-1} ($10 \times 0.1^4 \text{ ms}^{-1}$). Such modest increases in MPSP frequency are actually observed during facilitation, augmentation, and potentiation, and have been regarded as evidence for this hypothesis. The different phases of enhanced transmission could arise from different phases of calcium accumulation during nerve activity and its subsequent decay, with rapid phases limited by calcium diffusion away from docked vesicles near Ca^{2+} channels and slow phases representing effects of Ca^{2+} binding to intracellular buffers, Ca^{2+} being sequestered into Ca^{2+} -storing organelles such as endoplasmic reticulum and mitochondria, and Ca^{2+} extrusion from nerve terminals by pumps such as the Ca^{2+} -dependent ATPase and Na^+/Ca^{2+} exchanger at the plasma membrane.

The trouble with this simple and elegant hypothesis is that it should not be possible to obtain the very high levels of posttetanic facilitation/augmentation/potentiation sometimes observed (up to 100-fold increase) without a massive increase in MPSP frequency to levels substantially higher than the maximum rate of release to a single action potential (two times higher for an enhancement of 100: $100^{1/4} - 1$). Such predicted large increases in MPSP frequency are not observed.

The situation is even worse now that it is possible to estimate the peak $[Ca^{2+}]_i$ level needed to trigger phasic

secretion and the residual $[Ca^{2+}]_i$ present during periods of facilitation, augmentation, or potentiation. The former can be obtained from measurements of local $[Ca^{2+}]_i$ elevations using low-affinity indicators, calculations of the effects of presynaptically injected Ca^{2+} buffers on secretion, and the elevations of $[Ca^{2+}]_i$ released by photolysis of photosensitive chelators needed to mimic secretory rates triggered by action potentials. From all these methods, about $20 \mu\text{mol l}^{-1}$ $[Ca^{2+}]_i$ appears to be required to trigger a typical PSP. On the other hand, measurements of residual $[Ca^{2+}]_i$ during facilitation, augmentation, and PTP reveal levels of about $1 \mu\text{mol l}^{-1}$, which would enhance release by only 22% maximally ($1.05^4 - 1$) – far less enhancement than any of these processes is capable of displaying at many synapses. However, at some synapses displaying only very modest facilitation, this nonlinear effect of residual $[Ca^{2+}]_i$ with the $[Ca^{2+}]_i$ transient during an action potential does appear to be responsible for the plasticity observed.

Independent Site Hypotheses

These considerations led to proposals that presynaptic Ca^{2+} acts in eliciting short-term synaptic enhancement at molecular targets different from the target involved in phasically triggering exocytosis. Two versions of this hypothesis may be distinguished. The first proposes that Ca^{2+} entering during action potentials binds to sites that enhance transmitter release to subsequent action potentials, and that the duration of each phase of enhancement reflects the binding time (dissociation rate) of Ca^{2+} from a different site. The second version proposes that synaptic enhancement is due to the continuing action of residual Ca^{2+} ions acting in equilibrium at one or more sites that enhance transmitter release to subsequent action potentials. The different phases of enhancement could reflect the kinetics of different processes removing residual Ca^{2+} . In support of the latter proposal is the finding in a number of synapses that facilitation, augmentation, and potentiation decay in parallel with phases of decay of residual Ca^{2+} in active zones.

The Residual Bound Ca^{2+} Hypothesis

One way to distinguish these possibilities is by use of exogenous Ca^{2+} buffers. Slowly binding buffers (e.g., ethylene glycol bis(β -aminoethyl ether)- N,N -tetraacetic acid (EGTA)), or modest concentrations of fast-acting buffers (e.g., 1,2-bis(*o*-aminophenoxy)ethane- N,N,N',N' -tetraacetic acid (BAPTA)) ought to be able to hold residual rises in $[Ca^{2+}]_i$ to a minimum, while having little effect on the peak $[Ca^{2+}]_i$ concentrations at docked vesicles near Ca^{2+} channels that trigger exocytosis. Synaptic enhancement due

to residual bound Ca^{2+} would be unaffected, while effects due to the continuing action of residual free Ca^{2+} would be blocked. However, experiments with these buffers loaded into presynaptic terminals have yielded variable results. Augmentation and PTP are usually (but not absolutely always) blocked, while facilitation is sometimes blocked and sometimes not. Such variable results may reflect different degrees of success in blocking residual $[Ca^{2+}]_i$ elevations, which have rarely been monitored in these experiments, and different degrees of saturation of the exogenous buffers by the $[Ca^{2+}]_i$ levels reached during action potentials in active zones in different preparations.

The Residual Free Ca^{2+} Hypothesis

In one study, the effect of exogenous BAPTA was monitored, and shown to eliminate the accumulation of residual Ca^{2+} in short trains causing facilitation. Facilitation was greatly reduced, and what was left had a much shorter time constant (40 ms). This was probably due to the effect of Ca^{2+} entering during the action potential on the facilitation site, suggesting that facilitation is a process which itself lasts less than 100 ms and is normally rate-limited by the decay of $[Ca^{2+}]_i$ within active zones, from which Ca^{2+} will diffuse with apparent time constants of tens and hundreds of milliseconds. It is still unclear whether the two components of facilitation are due to the multi-exponential time course of Ca^{2+} removal, or to actions on different molecular targets.

In another study, residual Ca^{2+} was rapidly reduced following conditioning stimulation by brief illumination of a photosensitive buffer that takes up Ca^{2+} on photolysis. Facilitation then disappeared within 10 ms after an action potential, while augmentation and PTP were both truncated to a process lasting less than a second. Since augmentation and PTP also show a similar dependence of magnitude of enhancement of transmitter release on submicromolar levels of residual $[Ca^{2+}]_i$, augmentation and potentiation appear to be due to residual Ca^{2+} acting at a high-affinity site distinct from the sites involved in either facilitation (intrinsically decaying more rapidly) or exocytosis (having a much lower Ca^{2+} affinity than either facilitation or augmentation/PTP).

Saturation of Endogenous Ca^{2+} Buffers – A Special Form of the Second Site Hypothesis

Calcium is buffered in cytoplasm by a variety of proteins with different capacities and affinities for Ca^{2+} ions. At some synapses, an important part of the buffering is accomplished by high-affinity buffers such as calbindin-D28k that are easily saturated by

low levels of residual $[Ca^{2+}]_i$. Following one or more action potentials, less of this buffer is available to capture Ca^{2+} ions entering through Ca^{2+} channels, so that a higher local $[Ca^{2+}]_i$ triggers a facilitated release of vesicles docked near those channels. This process seems to occur at inhibitory synapses from mouse multipolar interneurons onto cortical pyramidal cells and at excitatory mossy fiber synapses onto CA3 hippocampal pyramidal cells. However, such a mechanism failed to account for facilitation at rat somatosensory cortical pyramidal synapses onto bitufted interneurons, or at Schaffer collateral afferents onto CA1 pyramidal neurons, where a different molecular Ca^{2+} target modulating transmitter release appears to be implicated.

Molecular Targets in Short-Term Synaptic Enhancement

The sites of Ca^{2+} action in facilitation, and in augmentation/PTP, have generally not been identified. The rapid rise of facilitation after each action potential and the similarity of its kinetics to the expected diffusion of Ca^{2+} from active zones suggest that it is activated by Ca^{2+} acting at the level of one to a few micromolar on targets on or near docked vesicles. Neuronal Calcium Sensor-1 has been identified as a strong candidate for such a target at excitatory synapses between dissociated hippocampal neurons in culture, but it is not certain whether NCS-1 acts as a Ca^{2+} buffer or a regulator of synaptic transmission. Augmentation/PTP may result from Ca^{2+} acting at more distant sites, for example, on processes that mobilize vesicles to docking sites and ready them for release. Synapses formed between cultured hippocampal neurons seem to rely on Ca^{2+} binding to calmodulin and munc-13 to produce augmentation, which is therefore a strong candidate molecular target for generating augmentation at these synapses.

The Persistence of PTP

If augmentation and potentiation are due to Ca^{2+} acting at the same site with subsecond kinetics and high affinity, why does PTP last so much longer than augmentation? The answer is that both rise with the accumulation of Ca^{2+} in nerve terminals and last until residual Ca^{2+} is removed. Two processes slow down the removal of Ca^{2+} after prolonged activity. (1) Ca^{2+} gradually accumulates in mitochondria during sustained activity, and slowly leaks out afterwards into the cytoplasm. The gradual loading of mitochondria leads to a slow rise in cytosolic Ca^{2+} during activity, and the long time it takes to fully unload mitochondria results in the prolonged small posttetanic residual

Ca^{2+} responsible for PTP. Blocking mitochondrial uptake of Ca^{2+} eliminates PTP. (2) Presynaptic $[Na^+]_i$ rises and reduces the rate of Ca^{2+} extrusion by Na^+/Ca^{2+} exchange. This exchanger uses the normally high external-to-internal sodium gradient as the energy source for removing Ca^{2+} , and reducing this gradient retards the pump. This is why procedures that increase the loading of presynaptic terminals with Na^+ ions magnify and prolong PTP.

Modulation of Short-Term Synaptic Enhancement

Facilitation, augmentation, and potentiation can be differently affected by divalent ion substitutions for Ca^{2+} , hormone treatments, neurotrophic factors, and mutations in genes for Ca^{2+} /calmodulin-dependent protein kinase, synapsins I and II, cyclic AMP phosphodiesterase, Ca^{2+} /calmodulin-dependent adenylyl cyclase, and the type 4 metabotropic glutamate receptor. In one case, postsynaptic hyperpolarization and $[Ca^{2+}]_i$ chelation are also reported to affect PTP, perhaps owing to some sort of retrograde messenger. These manipulations may differentially affect the Ca^{2+} targets in activating short-term synaptic plasticity, or processes involved in the clearance of residual Ca^{2+} ions. Either way, they indicate a modifiability of synaptic plasticity that could have important effects on neural circuitry with plastic synapses (see below).

The Consequences of Short-Term Synaptic Plasticity

The dynamic reshaping of synaptic strength is an essential property of synapses, and is fundamental to the way they respond to inputs, selectively transmit signals, and shape the responses of nerve circuits and the activity of neural networks. Depression makes synapses respond adaptively, reporting mainly changes in signal strength, while facilitation and augmentation allow synapses to distinguish significant signals from noise when the former are represented as sustained or high-frequency activity. These properties can be used by neural circuits to distinguish different patterns of input. The shorter forms of synaptic enhancement, as well as PTP, can also effectively adjust the gain or sensitivity of neuronal circuits following prior activity and lead to alterations in neural circuit responsiveness that last for seconds or minutes. Neuroscientists trying to understand how neural circuits analyze sensory information or produce motor patterns are now paying a good deal of attention to the important consequences of short-term synaptic plasticity for the integrative functions of the nervous system.

See also: Calcium Channels; Neuromuscular Junction (NMJ); Presynaptic Short-Term Plasticity of Neuromuscular Transmission; Plasticity and Activity-Dependent Regulation of Gene Expression; Presynaptic Facilitation; Presynaptic Inhibition; Schwann Cells and Plasticity of the Neuromuscular Junction; Synaptic Plasticity: Neurogenesis and Stem Cells in Normal Brain Aging; Synaptic Depression; Synaptic Plasticity: Short-Term Mechanisms; Voltage-Gated Calcium Channels.

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