Synaptic Plasticity: Short Term

Robert S Zucker, *University of California, Berkeley, California, USA*

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

Advanced article

Article Contents

doi: 10.1038/npg.els.0004054

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 on the frequency of stimulation and the history of prior activity. At most synapses, repetitive high-frequency action potentials (often called a tetanus) initially result 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 are 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 a 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, which lasts several minutes. Each of these processes can further increase transmission 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. **See also**: Chemical synapses; Synapses

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 cumulative 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 is rather a random variable that fluctuates statistically 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

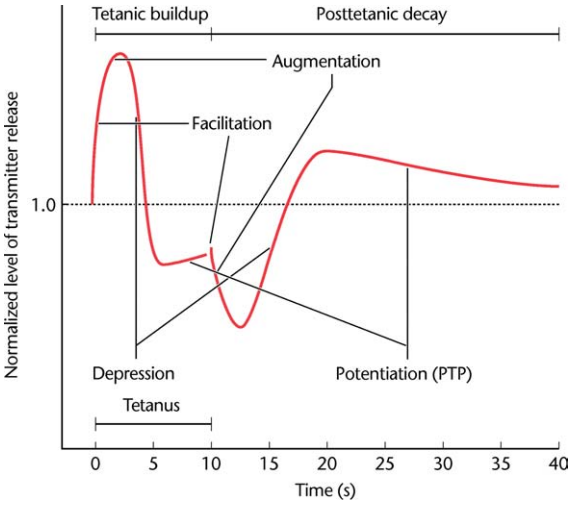

Figure 1 The different kinetic components of short-term synaptic plasticity.

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). A comparison of the size of MPSPs to that of full PSPs evoked by action potentials also allows an 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, molluscs, insects and annelids. In almost all cases, every kind of short-term plasticity is accompanied by changes in the number of quanta released, often called quantal content, with little change in the size or postsynaptic effectiveness of the unitary response to a quantum of transmitter. Thus, short-term synaptic plasticity is usually a consequence of changes in one or more presynaptic processes involved in determining the number of vesicles that action potentials cause to be secreted during neurotransmission. **See also**: Calcium and neurotransmitter release

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 are 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 the 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 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 (Schikorski and Stevens, 1997).

Short-term synaptic plasticity is usually accompanied by parallel changes in both n and p. The probable 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, potentiation and depression. In a few preparations, an increasingly imperfect propagation of action potentials into nerve terminals has been found to be partly responsible for synaptic depression. This can arise from changes in the electrical properties of nerve terminals that may result from changes in the intra- or extracellular concentrations of important ions, such as K^+, Na^+ or Ca^{2+}, that affect action potential propagation. There are also exceptional instances where facilitation is caused by action potential broadening, arising mainly from accumulating inactivation of K^+ channels involved in terminating action potentials. In these cases, decreases or increases in Ca^{2+} influx in reduced or prolonged action potentials cause depression or facilitation, respectively.

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, synaptic depression has been found to be due to accumulating inactivation of Ca^{2+} channels and subsequent reduction in Ca^{2+} influx at nerve terminals. Some Ca^{2+} channels also show a form of facilitation, with

increased duration or probability of opening to repeated depolarizations; however, this process has only rarely been found to be involved in enhanced synaptic transmission at neurons, although it appears to be involved in facilitation of hormonal secretion from adrenal chromaffin cells. **See also**: Calcium channels; Calcium channel diversity

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

It is now well established from experiments on several different preparations that facilitation, augmentation and potentiation depend upon presynaptic Ca^{2+} entry. The pioneering experiments of Katz and Miledi (1968) 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 that were 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, 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 been 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 approximately depends on 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 illustrated by a simple hypothetical calculation. Suppose an increase of $[Ca^{2+}]_i$ by $1\,\mu mol\,L^{-1}$ normally underlies an unfacilitated PSP consisting of 10 quanta or vesicle fusions occurring in 1 ms, and 20 ms later $[Ca^{2+}]_i$ is still elevated by $0.1\,\mu mol\,L^{-1}$ 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 $1.1\,\mu mol\,L^{-1}$ above rest, 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 $1\,quantum\,s^{-1}$ ($10 \times 0.1^4\,ms^{-1}$). Such modest increases in MPSP frequency are actually observed during facilitation, augmentation and potentiation, and have been regarded as strong 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 like endoplasmic reticulum (ER) and mitochondria, and Ca^{2+} extrusion from nerve terminals by pumps such as the Ca^{2+}-dependent adenosine triphosphatase (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 or 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). However, these large increases predicted 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 $50\,\mu mol\,L^{-1}$ $[Ca^{2+}]_i$ 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 $1\,\mu mol\,L^{-1}$, which would enhance release by only 8% maximally (1.02^4–1) – far less enhancement than any of these processes is capable of displaying.

Independent site hypotheses

These considerations led to the 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 the use of exogenous Ca^{2+} buffers. Slowly binding buffers such as ethylene glycol bis(β-aminoethyl ether)-*N*,*N*-tetraacetic acid (EGTA), or modest concentrations of fast-acting buffers such as 1,2-bis(2-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 high $[Ca^{2+}]_i$ levels occurring in active zones.

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 (Atluri and Regehr, 1996). Facilitation was greatly reduced, and what was left had a much reduced 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 that itself lasts less than 100 ms and is normally rate-limited by the decay of $[Ca^{2+}]_i$ at sites near Ca^{2+} channels, from which Ca^{2+} will diffuse with apparent time constants of tens and hundreds of milliseconds.

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 (Kamiya and Zucker, 1994). 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).

One way in which residual Ca^{2+} could cause facilitation is by partly saturating an endogenous Ca^{2+} buffer. If one of these buffers has high mobility and affinity, it can shuttle Ca^{2+} rapidly away from active zones in single action potentials, reducing the Ca^{2+} available to trigger release. Progressive saturation of this buffer by the residual Ca^{2+} accumulating during activity causes the buffer to lose its effectiveness, and the quantity of local $[Ca^{2+}]_i$ transients to successive action potentials increases, facilitating release. A hallmark of this process is that reducing Ca^{2+} influx reduces residual Ca^{2+} accumulation and relieves this saturation, eliminating facilitation. Facilitation seems to work this way at some synapses (Blatow *et al*., 2003), where the saturable Ca^{2+} buffer has been identified as calbindin.

Molecular targets in short-term synaptic enhancement

The sites of Ca^{2+} action in facilitation and in augmentation/PTP remain to be identified, except in one instance where the protein neuronal calcium sensor-1 has been implicated (Sippy *et al*., 2003). 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 micromolars on a target fairly near docked vesicles, although this target is apparently shielded from the very high $[Ca^{2+}]_i$ elevations occurring right at Ca^{2+} channel mouths. Augmentation/PTP may result from Ca^{2+} acting at more distant sites, perhaps mobilizing vesicles to docking sites and priming them for release. But no direct evidence exists to support these ideas.

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 cytoplasmic 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 (Tang and Zucker, 1997). (2) Presynaptic $[Na^+]$ 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. **See also**: Mitochondria: structure and role in respiration

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, mutations in genes for Ca^{2+}/calmodulin-dependent protein kinase, synapsins I and II, cyclic adenine monophosphate (AMP) phosphodiesterase, Ca^{2+}/calmodulin-dependent adenylyl cyclase and the type 4 metabotrophic 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 (refer the associated paper on long-term synaptic plasticity). 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). **See also**: Long-term potentiation; Synaptic vesicle proteins; Metabotropic glutamate receptors; Protein kinases

Depression and Depletion of Transmitter Stores

When synaptic depression is present, it usually develops with a simple exponential time course during repetitive activity. In most cases of depression, its rate increases with action potential frequency, while the rate of recovery is independent of prior frequency. When transmission is enhanced, for example, by increasing $[Ca^{2+}]$ in the medium, depression develops more quickly and is more profound, but recovery is unaffected. A simple mathematical model of depletion of vesicles from an immediately releasable pool, where each action potential releases a constant fraction of that pool and the pool is replenished from a depot, precursor, storage pool or from recovery of vesicles by endocytosis and refilling and redocking, accounts quantitatively very well for these characteristics of depression (Liley and North, 1953).

Synapses with high probabilities of releasing vesicles (determined by the binomial release parameter p) are usually more susceptible to depression and less to facilitation, augmentation and potentiation. This is probably due to the fact that there is little room for enhancing the probability of release at such synapses, and high levels of release more readily deplete vesicle pools.

Depletable vesicle pools

At many synapses, the characteristics of depression deviate somewhat from the simple model. Sometimes the rate of depression slows down gradually during repetitive activity. This may be because some vesicles are more readily released than others, so that as depletion proceeds, the vesicles that remain are released more gradually. At some synapses, an early fast phase of depression is followed by a much slower phase, as if first an immediately releasable pool of vesicles is depleted, and then gradually another antecedent pool of supply vesicles is also depleted. In such cases, there are two phases of recovery, probably reflecting the rapid replenishment of the releasable pool by what is left of the supply pool, followed by the gradual recovery of the larger supply pool. At other synapses, depression to a long tetanus is less severe than would be predicted from the fractional reduction in PSP amplitude during the first few action potentials, because replenishment of the store is accelerated, owing to an accumulation of residual $[Ca^{2+}]_i$. Sometimes recovery from severe depression shows an early rapid phase, perhaps owing to the same mobilization process.

Attempts at anatomically identifying the vesicles corresponding to the immediately releasable pool have not been very successful. This pool seems to correspond to far fewer than the total number of vesicles in nerve terminals, and fewer even than the number of vesicles that appear to be docked at the plasma membrane, and it is usually not possible to observe a reduction in vesicle number corresponding to the fast early phase of depression. The later phase, when it is evident, is usually accompanied by a reduction in total presynaptic vesicle number; the rate of recovery in the late phase of depression corresponds to the rate at which fluorescent membrane-bound dyes can be observed to reenter nerve terminals by the endocytosis of previously released vesicle membrane, and then be filled with transmitter and redocked at active zones.

Other Forms of Synaptic Depression

At some synapses, other processes have been found to underlie synaptic depression. At a few synapses in mammals

and in molluscs, depression is caused at least in part by the inactivation of presynaptic calcium channels, so that action potentials admit less Ca^{2+} and hence trigger less transmitter release. At other synapses there is a reduction in quantal amplitude. This can be either due to incomplete filling of vesicles released after the most releasable vesicles are secreted, or due to reductions in postsynaptic sensitivity due to changes in the state of postsynaptic receptors. Examples of both processes have been found. Reduction in receptor sensitivity, called desensitization, plays a major role in synaptic depression in some molluscan cholinergic synapses, and also contributes to depression in some mammalian and insect glutamatergic synapses with the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) subtype of receptor. Finally, at other synapses, particularly some mammalian central GABA (γ-aminobutyric acid) inhibitory synapses, and at certain frequencies at amphibian neuromuscular junctions, depression is caused by the feedback inhibition of GABA or the enzymatic products of released ATP on presynaptic autoreceptors located on the nerve terminals, where a substance released by the nerve acts to inhibit its own terminals and reduce the effects of later action potentials. **See also**: AMPA receptors; $GABA_B$ receptors

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. Synaptic depression can also have behavioural manifestations, such as sensory adaptation and habituation to repeated or persistent stimuli. 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 analyse 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.

References

Atluri PP and Regehr WG (1996) Determinants of the time course of facilitation at the granule cell to Purkinje cell synapse. *Journal of Neuroscience* **16**: 5661–5671.

Blatow M, Caputi A, Burnashev N, Monyer H and Rozov A (2003) Ca^{2+} buffer saturation underlies paired pulse facilitation in calbindin-D28k-containing terminals. *Neuron* **10**: 79–88.

Katz B and Miledi R (1968) The role of calcium in neuromuscular facilitation. *Journal of Physiology* **195**: 481–492.

Kamiya H and Zucker RS (1994) Residual Ca^{2+} and short-term synaptic plasticity. *Nature* **371**: 603–606.

Liley AW and North KAK (1953) An electrical investigation of effects of repetitive stimulation on mammalian neuromuscular junctions. *Journal of Neurophysiology* **16**: 509–527.

Schikorski R and Stevens CF (1997) Quantitative ultrastructural analysis of hippocampal excitatory synapses. *Journal of Neuroscience* **17**: 5858–5867.

Sippy T, Cruz-Martin A, Jeromin A and Schweizer FE (2003) Acute changes in short-term plasticity at synapses with elevated levels of neuronal calcium sensor-1. *Nature Neuroscience* **6**: 1031–1038.

Tang Y-G and Zucker RS (1997) Mitochondrial involvement in post-tetanic potentiation of synaptic transmission. *Neuron* **18**: 483–491.

Further Reading

Fisher SA, Fischer TM and Carew TJ (1997) Multiple overlapping processes underlying short-term synaptic enhancement. *Trends in Neurosciences* **20**: 170–177.

Zador AM and Dobrunz LE (1997) Dynamic synapses in the cortex. *Neuron* **19**: 1–4.

Zucker RS (1989) Short-term synaptic plasticity. *Annual Review of Neuroscience* **12**: 13–31.

Zucker RS (1994) Calcium and short-term synaptic plasticity. *Netherlands Journal of Zoology* **44**: 495–512.

Zucker RS (1996) Exocytosis: a molecular and physiological perspective. *Neuron* **17**: 1049–1055.

Zucker RS, Kullmann DM and Schwarz TL (2003) Release of Neurotransmitters. In: Byrne JH and Roberts J (eds) *Fundamental from Molecules to Networks. An Introduction to Cellular and Molecular Neuroscience*, pp. 197–244. San Diego: Academic Press.

Zucker RS and Regehr WG (2002) Short-term synaptic plasticity. *Annual Review of Physiology* **64**: 355–406.