Short-Term Synaptic Plasticity in Central Pattern Generators

Synonyms

Augmentation; Depression; Enhancement; Facilitation; Post-tetanic potentiation

Definition

Short-term synaptic plasticity (STP) is a transient (milliseconds to minutes) activity-dependent change in the amplitude of the postsynaptic current in response to presynaptic activity. Central pattern generators (CPGs) are neural networks in the central nervous system capable of producing coordinated rhythmic output without rhythmic input from sensory organs or from higher control centers.

Detailed Description

Short-term synaptic plasticity (STP) is a transient (milliseconds to minutes) activity-dependent change in the amplitude (strength) of the postsynaptic current in response to presynaptic activity. It has clear implications for neural signaling and has been studied for several decades. Much of the modeling work has focused on the events in the presynaptic terminal and primarily on the role of Ca^{2+} in synaptic release of neurotransmitters (Zucker & Regehr 2002; Fioravante and Regehr 2011). However, postsynaptic effects such as saturation of postsynaptic receptors can also contribute to STP (Hennig 2013; Xu-Friedman and Regehr 2004). A complete understanding of short-term synaptic plasticity requires knowing how the pre- and postsynaptic neurons interact to alter synaptic strength.

The contribution of short-term synaptic plasticity to network-level output has probably been best examined in studies of central pattern generator (CPG) networks. CPG networks produce rhythmic patterned outputs without patterned input and are best understood in the analysis of rhythmic motor activities such as locomotion and respiration. For instance, the CPG underlying the inspiratory phase of respiration is located in the pre-Bötzinger complex found within the ventrolateral medulla of the mammalian brain (Grillner 2003). Identified CPG circuits are known to govern locomotion in invertebrates, including leeches, mollusks, and crustaceans (Arshavsky Yu et al. 1993; Ayers 2004; Friesen and Kristan 2007). Additionally, locomotion in mammals is believed to be governed by CPG networks in the spinal cord (MacKay-Lyons 2002). The understanding of CPGs in producing motor behaviors has been greatly advanced through the use of computational models (Butera et al. 1999; Tabak et al. 2000; Oh et al. 2012; Vavoulis et al. 2007; Sherwood et al. 2011).

Almost all synapses are regulated by a variety of short- or long-term activity-dependent processes that alter the strength of the synapse. Depending on the behavioral needs, CPGs alter their rhythmic activity patterns by changing the cycle frequency and the relative activity phases of the participating neurons. Synapses in CPG networks are naturally subject to short-term activity-dependent modifications due to the rhythmic nature of the network output. This review examines the mechanisms and consequences of short-term changes in synaptic strength within CPGs. Although both pre- and postsynaptic mechanisms have been implicated in short-term plasticity, the majority of known STP effects are presynaptic (Wadiche and Jahr 2001).

Neurobiology of Central Pattern Generators

CPG networks often involve neurons that produce bursting oscillations. Bursting refers to an interval of rapid firing of spikes, bookended by intervals of quiescence. Bursting activity in neurons is often the result of a slow-wave oscillation in the membrane potential which, on the depolarized portion, crosses spike threshold. The slow-wave oscillations that underlie bursting activity result from the interaction of low-threshold-activated inward currents and slow voltage- or Ca^{2+} -gated outward currents.

In cases where the mechanisms underlying rhythm generation have been described, CPG oscillations have been shown to arise in one of two ways: either through the activity of endogenously oscillatory (pacemaker) neurons or through the synaptic interactions of neurons within a network (Goldin-Meadow et al. 2001). Pacemaker neurons produce oscillations when they are synaptically isolated from the network. However, these oscillations may be conditional upon the presence of the appropriate neuromodulatory substances. Although pacemaker neurons can be the rhythm-generating kernel of a

CPG network, the proper output of the CPG usually requires the synaptic interaction of the pacemaker neurons with non-oscillatory (follower) neurons whose activity is important in producing the proper output pattern.

In contrast to pacemaker-driven CPGs, network oscillators produce rhythmic output through synaptic interactions of pairs or groups of neurons, which may not be oscillatory when synaptically isolated. The most prominent example of such network oscillations is half-center oscillators that drive the activities of antagonistic muscles. First proposed by T. Graham-Brown in the early 1900s, half-center oscillators are responsible for producing rhythmic behavior in these types of networks (Brostoff et al. 2008). Half-center oscillators are driven by neurons (or neuron groups) that are antagonistic in their activity. The two groups of neurons are rhythmically active but activity in one group inhibits the activity of the other. In the first classification of half-center oscillators by Wang and Rinzel, they demonstrated that the transition between the two halves of the half-center oscillation can occur through one of two distinct mechanisms: escape and release. In escape mode, the inhibited neurons transition to active mode due to their own intrinsic properties. In contrast, in release mode, the active neurons terminated their activity due to their intrinsic properties and thereby release the inhibited neuron which rebounds from inhibition to produce activity (Wang and Rinzel 1992). The frequency and relative phases of the two halves of the half-center are controlled by the intrinsic properties of the neurons as well as the strength and dynamics of the reciprocal synapses. The extent to which intrinsic versus synaptic properties control the half-center oscillations can be used to further divide these networks into intrinsic or synaptic (Skinner et al. 1994). In biological systems, the transitions between the two halves of the half-center oscillator are often through a combination of escape and release mechanisms (Nadim et al. 1995).

Invertebrate CPG studies provided crucial results for the understanding of the mechanisms of neural network connectivity and CPG functions. The ease of accessibility of many of the invertebrate networks has allowed for a mapping of the synaptic connectivity and therefore the identification of the CPG circuits. Additionally, in many invertebrate networks, the voltage-gated ionic currents of the component neurons and the short-term dynamics of the synapses have been characterized. Examples of well-studied invertebrate CPG networks include those underlying tritonia swimming, feeding in crustaceans, and leech heartbeat (Marder and Calabrese 1996).

CPGs have also been the subject of intensive research in vertebrate systems, in particular, lamprey swimming, salamander locomotion, and rodent models of respiration. Lampreys are primitive fish whose spinal cords are easily dissected and are capable of producing fictive locomotion in vitro. As such, this preparation has become the best studied example of rhythmic locomotor activity in vertebrates (Grillner 2003). Salamanders offer an insight into the switching of two different types of locomotor modalities: swimming or stepping. Of particular interest is the stepping gait, in which the body makes an S-shape wave with coordinate movement of the limbs (Ijspeert et al. 2007). This stepping gait can either be fast or slow, but salamanders prefer the faster trotting gait. When trotting, diagonal limbs are in phase while opposite limbs are out of phase. Both the switching between swimming and stepping, as well as the simulation of stepping, have been modeled and studied (Ijspeert et al. 2007) but the full understanding of the behaviors has been elusive.

The medullar pre-Bötzinger complex contains the CPG responsible for the genesis of breathing in mammals (Smith et al. 1991). The pre-Bötzinger complex controls the inspiratory phase of breathing through the activity of a set of pacemaker neurons that are state dependent. In particular, there are two subsets of pacemaker neurons within the system which have been characterized based on their pharmacological properties. During normoxia, respiratory rhythm generation is driven through a heterogeneous population of pacemaker neurons, while during hypoxia the respiratory rhythm is driven by only one type of pacemaker (Pena et al. 2004). The pacemaker groups and the properties of the network have been the subject of many computational models (Butera et al. 1999; Del Negro et al. 2002a, b; Cordovez et al. 2010).

Molecular Mechanisms of Neurotransmitter Release

Presynaptic Machinery Responsible for Neurotransmitter Release

Neurotransmitter release is achieved through the interplay of a variety of proteins associated with the presynaptic terminal. Once transmitter-filled vesicles are transported to the synaptic terminal, they dock and are primed for release. This process involves the attachment of vesicles to the membrane through the SNARE complex, a set of interacting proteins found on the vesicle and cytoplasmic membranes (Jahn and Fasshauer 2012). Only primed vesicles can fuse with the membrane and release neurotransmitter into the presynaptic cleft through the process of exocytosis, triggered by the interaction of Ca^{2+} with the SNARE complex. Depolarization of the presynaptic terminal, usually due to the arrival of an action potential, activates voltage-gated Ca^{2+} channels (VGCCs) and results in a rapid increase of the local

concentration of Ca^{2+}, which then binds to synaptotagmin, causing the vesicle membrane to fuse with the plasma membrane (Mehta et al. 1996). The SNARE complex is a helical protein complex composed of the v-SNARE protein synaptobrevin (also known as vesicle-associated membrane protein [VAMP-2]) and the t-SNARE ("target" SNARE) proteins localized to the presynaptic plasma membrane, SNAP-25 (synaptosome-associated protein of 25 kDa), and syntaxin. Apart from its interaction with v-SNARE, t-SNARE proteins syntaxin also directly interact with the Ca^{2+} channels to promote vesicular fusion (Stanley 1997). Finally, synaptic function also requires the interaction of SNARE proteins with Munc-18, which has been found to allow for syntaxin and SNAP-25 to form a complex that serves as an intermediate in the exocytic pathway (Zilly et al. 2006). The three SNARE proteins, syntaxin, SNAP-25, and synaptobrevin, have been found to be the minimal set of proteins required for fusion (Sudhof 2012).

Pools of Neurotransmitters: Ready or Not

The presynaptic terminal may contain hundreds of neurotransmitter vesicles; however, only a fraction of these, the readily releasable pool (RRP), are docked at the active zones of the membrane awaiting release. The remaining vesicles are divided between the reserve pool, the vesicles that are ready to be moved to the docking position, and the non-recycling pool (Regehr 2012).
Short-term synaptic plasticity is affected by the size of the RRP. The number of vesicles in the RRP varies across species and measuring it could be difficult due to the replenishment from the reserve pool. Earlier studies estimated the range of the RRP to vary from 7 to 130 depending on the type and location of synapse (Rosenmund and Stevens 1996; Xu-Friedman et al. 2001; Zucker & Regehr 2002). However, that number can average as high as 1,700 as measured in the mouse neuromuscular junction (Ruiz et al. 2011) and is also high at special high-throughput synapses such as calyx of Held, which contains hundreds of active zones (Schneggenburger et al. 2002). More recent studies have found those numbers to be much smaller than originally estimated. For instance, at certain GABAergic synapses within the cerebellum, the number of vesicles was found to be maximally 4 (Trigo et al. 2012). The size of the RRP may be regulated by a variety of factors, including the actions of the Na^{+}/K^{+} ATPase pump (Taruno et al. 2012).

Postsynaptic Factors Influence Short-Term Plasticity

While many studies have concentrated on the presynaptic mechanism of short-term plasticity, postsynaptic factors also contribute to changes in the synaptic transmission strength. The postsynaptic response depends on the amount of transmitter release from the presynaptic neuron, kinetics of the receptor, and other factors. Postsynaptic Ca^{2+} contributes significantly to post-tetanic potentiation in sensory-motor neurons of Aplysia, by facilitating the induction of plasticity at neighboring neurons (Schaffhausen et al. 2001). Additionally, when postsynaptic receptors are saturated, this may limit responses by the cell, as shown at the climbing fiber synapse (Wadiche and Jahr 2001). Desensitization of postsynaptic receptors can cause a temporary decrease in synaptic responses (Xu-Friedman and Regehr 2004). Additionally, saturation of the postsynaptic receptors may have a significant impact on recovery from depression (Foster et al. 2002).

The Role of Ca^{2+} in Neurotransmitter Release

Ca^{2+} entry through VGCCs in the presynaptic terminal results in vesicle fusion and the release of neurotransmitters. Synaptic strength is dependent on Ca^{2+} levels in the presynaptic active zone. This is believed to be partially due to Ca^{2+} interaction with multiple low-affinity binding sites on synaptotagmin, several of which have to be bound to trigger vesicle fusion (Felmy et al. 2003). If Ca^{2+} binds one or more sites, it increases the probability of release upon subsequent depolarization of the presynaptic membrane. Elevated amounts of local Ca^{2+}, however, are transient and highly sensitive to the distance from the VGCCs and the site of release. Local Ca^{2+} concentrations are also affected by Ca^{2+}-binding proteins that exist in the presynaptic bouton (Regehr 2012). Not all Ca^{2+} that enters the presynaptic cell, however, binds to the docked vesicles: it diffuses away from the active site, is rapidly buffered (Burrone et al. 2002; Burnashev and Rozov 2005), or is actively pumped out of the presynaptic terminal (Regehr 2012). The residual Ca^{2+} is then gradually removed from the presynaptic bouton (Scott and Rusakov 2006). Ca^{2+} diffusion in the presynaptic terminal has been extensively studied and modeled (Simon and Llinas 1985; Zucker and Fogelson 1986; Bertram et al. 1999; Matveev et al. 2004).

Multiple Forms of Synaptic Plasticity Coexist at a Synapse

The interactions of different types of synaptic plasticity found at most synapses allows for an alteration in synaptic strength. Short-term depression, facilitation, augmentation, and post-tetanic potentiation can coexist at the synapse; however, the dominance of each of the mechanisms at a given time point is controlled by the activity of the presynaptic neuron.

Short-term plasticity is often measured using a paired-pulse protocol. The presynaptic neuron is stimulated with a square pulse two to five times with an appropriately chosen interpulse interval. The postsynaptic response is then measured for each stimulus and the ratio of the postsynaptic response to the presynaptic response becomes the measure of short-term plasticity. If the ratio is greater than 1, the response is deemed facilitatory, and when it is less than 1 then it is deemed depressing. This method has been used in a variety of systems including different CPGs such as the pre-Bötzinger complex, the pyloric network of the stomatogastric system, and leech feeding behavior.

Facilitation

Synaptic facilitation is a type of short-term plasticity where the amount of neurotransmitter released is increased during a sequence of action potentials reaching the synaptic bouton. This increase leads to a prolonged effect of the neurotransmitter on the postsynaptic membrane. This type of short-term plasticity occurs at the fastest time scale and is measured using a paired-pulse protocol. Facilitation is subdivided into two different stages: F1 facilitation which lasts tens of milliseconds and F2 facilitation which lasts hundreds of milliseconds (Zucker and Regehr 2002).

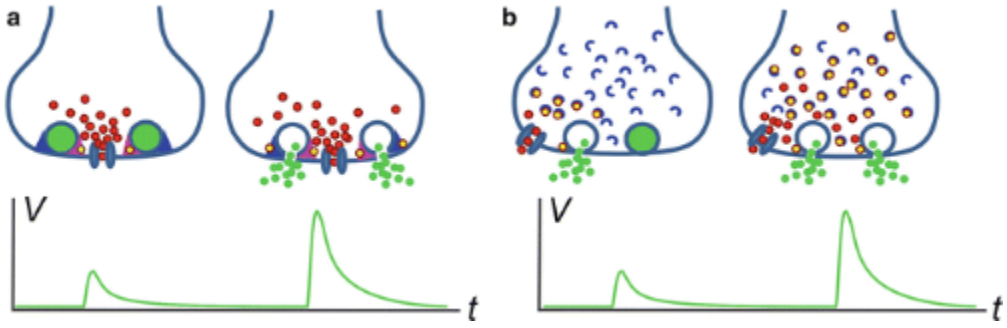

Fig. 1 Models of facilitation

(a) Residual-free Ca $^{2+}$ accumulation: the two-site model of synaptic facilitation. Exocytosis requires simultaneous binding of Ca^{2+} (red circles) to a low-affinity sensor located within the channel nanodomains (magenta at the vesicle base) and more remotely located low-affinity sensors (blue on the far side of the vesicle). The accumulation of free residual Ca^{2+} is small but more significant far from the channel, allowing for a significant increase in the binding of remote Ca^{2+} sensor from the first stimulus to the second and, therefore, more transmitter release and a larger postsynaptic response (bottom traces). (b) Facilitation by saturation of high-affinity buffer. The postsynaptic response (bottom trace) to the first presynaptic stimulus is small, because most of the free Ca^{2+} ions entering the presynaptic site are bound (yellow circles) by the Ca^{2+} buffer molecules (blue crescents) before they reach the vesicles. However, the postsynaptic response to the second presynaptic stimulus will be large because there are fewer free buffer molecules around, thus increasing the probability of Ca^{2+} ions reaching the targets for exocytosis

Many ideas were put forward to explain presynaptic facilitation (Regehr 2012). The simplest hypothesis states that the arrival of the action potential at the presynaptic bouton evokes a rise in local Ca^{2+} which triggers neurotransmitter release and which then persists at a lower concentration in the presynaptic bouton. Since such low residual Ca^{2+} concentration is insufficient by itself to trigger low-affinity vesicle release gates, this hypothesis requires the residual Ca^{2+} to act at a high-affinity presynaptic Ca^{2+} sensor other than synaptotagmin. Further, such a high-affinity second sensor should be located farther from the channel in order to prevent its rapid saturation; for this reason, this model is sometimes referred to as the two-site model of synaptic facilitation (Matveev et al. 2002) (Fig. 1a). A second possibility is that this second, high-affinity Ca^{2+} binding site possesses slower Ca^{2+} kinetics, allowing its Ca^{2+}-bound state to outlive the Ca^{2+} residual signal. This mechanism is often referred to as the bound residual Ca^{2+} mechanism of synaptic facilitation (Matveev et al. 2006) and was historically the first facilitation model proposed in the pioneering studies by Katz and Miledi (1968), who called such bound Ca^{2+} the "active" Ca^{2+} (Bornschein et al. 2013; Isope 2013). Finally, it is also possible that this

additional slower Ca^{2+} binding process may represent Ca^{2+}-dependent vesicle priming or other Ca^{2+}-dependent process upstream of vesicle (Pan and Zucker 2009).

The action of endogenous Ca^{2+} buffers has been proposed as an alternative mechanism of synaptic facilitation. Both fast, high-affinity Ca^{2+} buffers and those that slowly bind Ca^{2+} can influence facilitation. Ca^{2+} binding proteins reduce the concentration of local Ca^{2+} at the release site (Regehr 2012). However, high-affinity Ca^{2+} buffers bind Ca^{2+} at the presynaptic bouton when concentrations are sufficiently high, which leaves them unable to bind additional Ca^{2+}. As a result, the additional Ca^{2+} that enters and is not bound by buffers will reach the release site. In this manner, local buffer saturation can contribute to paired-pulse facilitation (Burnashev and Rozov 2005; Matveev et al. 2006; Neher 1998) (Fig. 1b). Slow Ca^{2+} binding proteins can also influence facilitation. By controlling the concentration of residual Ca^{2+} and accelerating its decay in the presynaptic bouton, slow endogenous buffers act like the slow buffer EGTA (Atluri and Regehr 1996), which then provides a mechanism to control the rate of Ca^{2+} decay, thereby influencing facilitation rates (Regehr 2012). However, the contribution of both fast and slow buffers to facilitation is still a matter of debate (Bornschein et al. 2013).

An important example of a CPG where synaptic facilitation has been observed and studied both experimentally and using computational modeling is the lamprey swim CPG. In control conditions, activity-dependent plasticity does not contribute to the patterning of network activity. However, Kozlov et al. found that substance P can lead to an activity-dependent facilitation during repetitive activation of the inhibitory cross caudal interneurons (CCINs) in the lamprey swim CPG (Parker and Grillner 1999; Kozlov et al. 2001). This is accomplished through control of the release of the neuromodulators from the presynaptic side as well as postsynaptic modulation of different ionic conductances (Kozlov et al. 2001). In order to examine the activity-dependent facilitation in this system, they used a compartmentalized Hodgkin-Huxley model neuron with the synaptic activation modeled as a leaky integrator and synapse activation summing input spike events of constant duration. Their study aimed to elucidate the two alternate modes of activity within the lamprey spinal locomotor network, showing that facilitation has a strong effect on frequency regulation in this CPG (Kozlov et al. 2001).

Facilitation has also been observed in the crustacean stomatogastric nervous system, specifically in the synapses of the pyloric CPG. The synapse from the lateral pyloric (LP) neuron to the pyloric dilator (PD) neurons is the sole chemical feedback to the pacemaker group and exhibits short-term depression. This synapse possesses both a graded and spike-mediated component (Zhao et al. 2011). However, the presence of the endogenously released neuromodulatory peptide proctolin switches the dynamics of this synapse from depression to facilitation. The mechanism of this switch was investigated in the modeling study of Oh et al. (2012), who proposed that the low-voltage-activated Ca^{2+} current possesses both fast and slow kinetic components and that proctolin adjusts the activation rate of the slow component, leading to an accumulation of local Ca^{2+} in response to low-voltage presynaptic stimuli, resulting in synaptic facilitation (Oh et al. 2012).

Depression

At many synapses, elevated activity or repeated stimulation leads to a decrease in synaptic strength. As is the case for facilitation, multiple mechanisms can contribute to synaptic depression (Zucker & Regehr 2002; Regehr 2012). Depression is believed to be caused in large part by the reversible depletion of available synaptic resources, mainly the release-ready pool of vesicles (RRP; Fig. 2a). Such vesicle depletion is an example of use-dependent synaptic depression, with higher levels of use associated with larger degree of synaptic depression (Markram et al. 1998). Reducing the level of synaptic transmission relieves use-dependent synaptic depression, while at high sustained synaptic activity, the replenishment of the RRP from the reserve vesicle pool cannot keep up with the depletion of the RRP (Zucker & Regehr 2002; Regehr 2012). Therefore, the extent to which depletion occurs is dependent on the number of vesicles in the RRP at each active zone and the number of vesicles that are released by an action potential. This depletion model accounts for the properties of the paired-pulse depression that is seen in many different types of synapses. According to the depletion model, the more vesicles released with the initial stimulus, the fewer will be released by the second and subsequent pulses. Depression by vesicle depletion is particularly pronounced following high-frequency tetanic stimulation, which strongly depletes the RRP so that the subsequent recovery may take tens of seconds, rather than seconds.

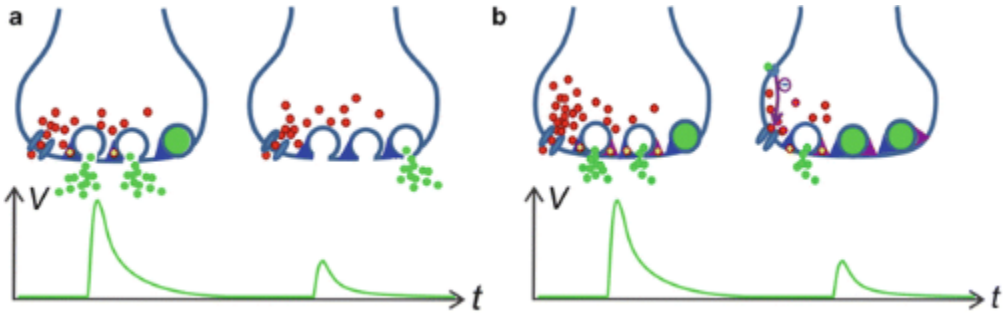

Fig. 2 Models of depression

(a) Synaptic depression by vesicle depletion. The postsynaptic response (bottom panel) to the second presynaptic stimulus is greater compared to the response to the first presynaptic stimulus because of the reduction in the number of available neurotransmitter-filled vesicles (green circles). (b) Ca^{2+} channel inactivation/presynaptic modulation. Presynaptic Ca^{2+} channel opening probability may decrease during the presynaptic stimulus train, due to one of two mechanisms: (i) inactivation of presynaptic voltage-dependent Ca^{2+} channels or (ii) activation of presynaptic metabotropic receptors that modulate the gating of presynaptic Ca^{2+} channels (e.g., through G-protein-regulated pathways). Reduction in the presynaptic Ca^{2+} current leads to a reduction in the vesicle release rate

Another mechanism of activity-dependent depression involves inhibition of the response caused by the vesicle fusion with the active zone. Vesicle fusion may transiently disrupt the morphology of the active zone and may inhibit the time it takes for membrane proteins to clear the active zone. This mechanism is supported by experimental evidence that blocking endocytosis can increase synaptic depression during pulse trains (Regehr 2012).

Other depression mechanisms may depend on the intensity of stimulation rather than amount of neurotransmitter released. This is true, for instance, in the case of inactivation of Ca^{2+} channels that has been found to account for depression at some synapses (Bertram et al. 2003). Presynaptic recordings from the calyx of Held have shown that high-frequency stimulation reduces Ca^{2+}entry. Decreased Ca^{2+}entry was found at frequencies greater than 30 Hz and depletion was found when the stimulus was in excess of 100 Hz (Xu and Wu 2005).

Also on the presynaptic side, depression can arise through the activation of metabotropic presynaptic receptors activated by modulatory substances released from the activated presynaptic terminals, postsynaptic cells, or neighboring cells (Fig. 2b). Metabotropic receptors may be selective either for the neurotransmitter released by the terminal itself (autoreceptor-mediated depression), for retrograde messengers (e.g., endocannabinoid receptors), or for neuromodulatory substances projecting from elsewhere in the nervous system (neuromodulatory receptors). Depression may also arise from postsynaptic mechanisms such as postsynaptic receptor desensitization, which in fact represents another form of use-dependent synaptic depression. Another mechanism of synaptic depression was demonstrated in the developing spinal cord (Tabak et al. 2000, 2001). In this system, GABA is functionally excitatory because intracellular Cl^- is high. During an episode of activity, Cl^- ions leave the neurons so the GABA reversal potential becomes more negative. This mechanism seems quite important for the episodic activity in the developing spinal cord.

Regulation of and recovery from depression are also important factors in short-term synaptic plasticity. Bassoon, a large presynaptic protein present at the active zone, has been found to minimize depression by replenishing vesicles at release sites (Hallermann et al. 2010; Regehr 2012). When Bassoon is experimentally removed, synaptic depression is enhanced. Rab3-interacting molecules (RIM) are vital components of the active zone (Kaeser et al. 2011), serving two critical functions: priming of synaptic vesicles and tethering of Ca^{2+} channels to the active zone (Kaeser 2011; Kaeser et al. 2011). RIM proteins have been implicated in influencing depression: when they are removed, depression is dramatically alleviated (Calakos et al. 2004; Sudhof 2012).

The role of synaptic depression in CPG networks has been studied in great detail. For instance, synaptic depression has been determined to be pivotal in the maintenance of phase relationships within CPGs (Mamiya et al. 2003; Manor et al. 2003). Depression of synapses of the pyloric network leads to synaptic weakening during fast rhythmic behavior while allowing the synapses to remain strong during a slow rhythm (Marder et al. 2005). Manor et al. examined the effect of synaptic depression using a model of an oscillator neuron and a follower neuron coupled with an inhibitory synapse from the oscillator to the follower (Manor et al. 2003). An important result from their study was that depression in inhibitory synapses always promotes a constant relative phase between the pre- and postsynaptic neurons in an oscillatory network. The strength of a depressing synapse in an oscillatory network is dependent on the cycle frequency: the faster

the oscillation, the more depression and therefore the weaker the synapse. This frequency dependence implies that synaptic inhibition gets weaker if the network operates at a faster pace, thus reducing the latency between the pre- and postsynaptic neuron activity. Because relative phase is defined as latency over period, this simple observation implies that a depressing synapse will always promote phase constancy (as opposed to a constant latency) compared to a synapse that is nondepressing.

In order to maintain stability, a network may reconfigure itself to produce different patterning behaviors. Li et al. explored the mechanisms by which sensory activity led to the selection and generation of swimming and struggling in Xenopus tadpoles (Li et al. 2007). In Xenopus tadpoles, two different behaviors can be triggered: struggling, which is elicited if the animal is held or pinned against a silicone-gel-lined Petri dish and involves strong head-to-tail bends, and swimming, which is elicited if the animal is touched lightly and involves low-amplitude bends (Kahn and Roberts 1982; Li et al. 2007). In immobilized tadpoles, stimulation of the skin causes a switch of the struggling CPG by reconfiguration of the locomotor network. This switch is thought to be caused by a context-dependent short-term depression of the reciprocally inhibitory synapses between two CPG neurons, the commissural interneurons (cINs). When synaptic depression was included in these synapses in a model network, activation of the network at higher firing frequencies characteristic of struggling led to robust bursting activity. In contrast, when the network was activated at lower firing rates, depression was not active and the network output resembled more the swimming behavior which involves a single spike per cycle (Li et al. 2007). Thus, as shown in this system, synaptic depression of reciprocal inhibition may play a key role in one behavior (struggling) but be mostly absent in another (swimming).

Synaptic depression was also proposed as the principal mechanism of rhythmogenesis in the developing chick spinal cord (Tabak et al. 2000). These studies proposed that synaptic depression accumulates during the active burst phase of the rhythm, ultimately terminating the active phase, and that the recovery from depression during the inactive state allows the bursting activity to resume in the next cycle of activity. Within certain networks, rhythm generation may depend on specific types of synaptic depression which are more complex than simple vesicle depletion. For example, this is the case in the group pacemaker model of rhythmic activity in the pre-Bötzinger complex developed by Rubin et al. (2009) based on a Hodgkin-Huxley style conductance-based model of spiking activity. In this model, glutamatergic synapses and short-term depression of excitatory transmission have roles in the rhythmogenesis of a particular type of pacemaker group within the pre-Bötzinger complex. A network-wide burst is generated through recurrent synaptic excitation that initiates the postsynaptic Ca^{2+}-activated nonspecific cation current (I_{CAN}). The depolarization due to I_{CAN} causes a voltage-dependent spike inactivation, diminishing recurrent excitation and therefore attenuating the postsynaptic accumulation of Ca^{2+}. The burst is then terminated through activity-dependent outward currents, resulting in a quiescent state in the network. A new cycle is then initiated when sporadic spiking activity rekindles excitatory interactions (Rubin et al. 2009).

Augmentation and Post-tetanic Potentiation

While facilitation has been shown to last no more than hundreds of milliseconds, two other forms of potentiating short-term synaptic plasticity, last tens of seconds to minutes in duration. Augmentation and post-tetanic potentiation (PTP) are related forms of synaptic plasticity that are observed after sustained high-frequency stimulation (Zucker & Regehr 2002; Regehr 2012). Augmentation is an increase in the synaptic potential amplitude that is produced by repetitive stimulation which has been found to act by potentiating vesicle fusion (Zucker & Regehr 2002). Post-tetanic potentiation is a common form of short-term plasticity that leads to an increase in synaptic strength for several minutes after increased stimulation. PTP is closely related to augmentation and lasts tens of seconds to minutes in duration and increases with the presence of additional or sustained stimuli.

Augmentation was originally described in the frog neuromuscular junction and now has been observed in many synapses, including in mammalian cortex (Regehr 2012). Augmentation increases during a stimulus train, but decays slower than facilitation with a time constant of 5-8 s. The decay of augmentation has been shown to be insensitive to stimulation duration and frequency. Additionally, augmentation shares other properties with facilitation. Augmentation is dependent on the buildup of Ca^{2+} in the presynaptic terminals during spike trains, after the development of a significant level of facilitation. Several mechanisms are believed to contribute to augmentation and PTP, including action potential broadening, increase in quantal size, and changes in the RRP (Zucker & Regehr 2002).

Several functional roles of augmentation and PTP in synaptic plasticity have been suggested. Augmentation is believed to be a counteracting mechanism against depression during times of high levels of neural activity (Deng and Klyachko 2011

). Furthermore, it has been shown that transmitter release is sustained during trains of stimuli by increasing the release probability of vesicles within the RRP. In addition to maintaining transmitter release during high-frequency stimulation, augmentation has been found to directly counteract depression in hippocampal excitatory synapses (Deng and Klyachko 2011). The mechanisms for both augmentation and PTP have been studied and debated for many years. Early studies proposed the accumulation of residual Ca^{2+} as a primary mechanism, but more recent results have implicated both PKC activation and CaM kinase II activity (Hennig 2013). However, very few studies have concentrated on these phenomena in CPGs.

In the crustacean STG, the gastric mill network is responsible for movement of muscles that control chewing within the foregut. Stein et al. characterized the temporal dynamics of the gm6 gastric mill muscle and explored the response of this muscle to different patterns of input during the gastric mill CPG activity (Stein et al. 2006). Using train stimulations of various frequencies, they found that augmentation increased the amplitude of the EJPs at certain frequencies while not at others. During the ongoing gastric mill rhythm, augmentation contributed to the response of the muscle as well as muscle force.

Outlook

Theoretical models have contributed greatly to the advancement in understanding of synaptic transmission and short-term plasticity in CPGs. In concert with experimental data, studies of both vertebrates and invertebrate CPGs have provided insight and mechanisms by which neural circuits reconfigure in order to generate different patterns to alter behavior. Many of the models discussed capture the processes involved in short-term synaptic release in a relatively simple way. Additionally, many studies on the effects of short-term synaptic plasticity on CPG activity suggest that neuromodulators play an important role in the network behavior through their effects on synaptic properties. As CPG circuits continue to be mapped, it will be essentially to gain insight about mechanisms which cause switches in behavior, changes in synaptic strength, and remodeling of the circuits in general. The mutual relationship between computational modeling and experimental studies will continue to be important for the understanding of the role of STP in CPG function.

Cross-References

Calcium-Dependent Exocytosis, Biophysical Models of
Rhythm Generation in Embryonic Chick Spinal Cord

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