Symposium

How Do Short-Term Changes at Synapses Fine-Tune Information Processing?

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Synaptic transmission is highly dependent on recent activity and can lead to depression or facilitation of synaptic strength. This phenomenon is called "short-term synaptic plasticity" and is shown at all synapses. While much work has been done to understand the mechanisms of short-term changes in the state of synapses, short-term plasticity is often thought of as a mechanistic consequence of the design of a synapse. This review will attempt to go beyond this view and discuss how, on one hand, complex neuronal activity affects the short-term state of synapses, but also how these dynamic changes in synaptic strength affect information processing in return.

Introduction

Chemical synaptic transmission involves the physical movement of ions, molecules, and membranes as part of the signaling event, as well as during recovery from a signaling event. These mechanistic constraints limit the time scale at which synaptic transmission can function and dynamically alter the amplitudes of synaptic responses in ways that depend on recent history. Such dynamic changes, generally termed "short-term synaptic plasticity" (STP), can last from milliseconds to tens of seconds. While the mechanisms of STP are relatively well understood (Zucker and Regehr, 2002), this type of plasticity is often thought of as simply a mechanistic consequence of the design of a synapse. The functional significance of STP for information processing is much less well understood and remains controversial. On one hand, STP may serve critical roles in the processing of complex and natural streams of activity (Klyachko and Stevens, 2006; Kandaswamy et al., 2010). On the other hand, several recent studies have directly challenged the importance of STP in information processing, for example, by showing that synaptic information transmission is stochastic (Lorteije et al., 2009), or broad-band and frequency independent (Lindner et al., 2009; Yang et al., 2009). Furthermore, some synapses have been described in which EPSC amplitude is frequency independent (vestibular afferents: Bagnall et al., 2008; Purkinje cell synapses: Telgkamp et al., 2004), which raises questions about whether STP plays much of a role in

information processing at these synapses. In this review, we discuss recent findings that address the functional role of STP in a number of neural systems. The described work examines both how complex neuronal activity affects the short-term state of synapses, as well as how this changed state affects information processing in return.

Hippocampus: the role of STP in regulating synaptic information transfer

Synapses that fire continuously at high frequencies eventually reach a steady-state condition (Lindner et al., 2009, Hermann et al., 2009, Yang et al., 2009). However, many types of synapses, such as excitatory hippocampal synapses, are not likely to experience such extensive periods of high-frequency activity under natural conditions (Fenton and Muller, 1998), and therefore do not reach a steady state (Kandaswamy et al., 2010). Klyachko and Stevens (2006) have examined the information transfer across hippocampal synapses under realistic conditions and evaluated the role of STP in synaptic information transmission during natural activity (Rotman et al., 2011). They used a realistic model of STP in excitatory hippocampal synapses (Kandaswamy et al., 2010), and found that to correctly determine the influence of STP on information transfer a temporal analysis was needed in addition to rate calculations. Their results demonstrate that under more realistic conditions, STP contributes significantly to increasing information transfer in a frequency- and time-dependent manner. Specifically, STP in excitatory hippocampal synapses increases information transfer in a wide range of input rates of ~2–40 Hz, which corresponds well to the naturally occurring spike frequencies in these neurons. Interestingly, time-dependent information analysis predicted that in low-release probability synapses, STP acts to maximize information transfer specifically for short high-frequency bursts, which are a common firing pattern of excitatory hippocampal neurons. This prediction was confirmed by analyzing synaptic information transfer

during natural spike trains recorded in hippocampal place cells in behaving rodents. Time-dependent information analysis further predicted that this optimization of information transfer for spike bursts depends on the presence of facilitation/augmentation and is not present in high-release probability, depressing synapses. Instead, depressing synapses are predicted to optimally transmit information for single spikes rather than bursts. Klyachko and Stevens (2006) confirmed this prediction using analysis of recordings in inhibitory hippocampal synapses that predominantly exhibit short-term depression. This result fits well with the observations that inhibitory interneurons do not commonly fire spike bursts. This study thus directly established the importance of STP in synaptic information transmission within an information-theoretic framework, and demonstrated that STP serves to maximize information transfer for specific patterns of neural activity in both excitatory and inhibitory synapses.

Hippocampus: abnormal STP in a mouse model of fragile X syndrome

Klyachko and Stevens (2006) then extended the analysis of STP functions to neurodevelopmental disorders, specifically fragile X syndrome (FXS). FXS is the most common inherited form of intellectual disability and the leading genetic cause of autism. Despite the importance of STP in synaptic information processing, very little is known about STP dysfunctions in FXS. The limited number of studies that considered some of the STP components in *Fmr1* KO mice, a widely used mouse model of FXS, came to contradictory conclusions (Centonze et al., 2008; Gibson et al., 2008; Zhang et al., 2009; Olmos-Serrano et al., 2010), and no coherent picture of STP dysfunction in FXS has emerged so far. Klyachko and Stevens (2006) revealed marked STP defects in hippocampal synapses of *Fmr1* KO mice (Deng et al., 2011). This altered STP resulted in abnormal synaptic computations, specifically excessive synaptic enhancement during high-frequency spike discharges associated with hippocampal place fields. Detailed analysis of individual forms of STP has shown that augmentation is strongly potentiated in *Fmr1* KO mice, and activity-evoked calcium influx in presynaptic neurons is also increased. Moreover, short-tem depression is decreased in *Fmr1* KO mice, paralleled by increased size of synaptic vesicle pools and faster vesicle recycling kinetics in these animals. These results suggest that FXS is associated with abnormal STP and information processing in excitatory hippocampal synapses.

Auditory nerve: converging synapses develop matched release probabilities

A major issue concerning short-term plasticity is how it is determined at different synapses. Some synapses depress with activity, while others facilitate, depending on the probability of neurotransmitter release (P_r) (Zucker and Regehr, 2002). When P_r is high, activity causes depletion of releasable vesicles from the presynaptic terminal, as well as accumulation of neurotransmitter in the synaptic cleft, which can lead to postsynaptic receptor desensitization. Both of these mechanisms cause depression of EPSC amplitudes. When P_r is low, activity does not cause significant depletion or desensitization. Rather, calcium has an opportunity to accumulate in the presynaptic terminal, and this residual calcium can cause an increase in P_r, and facilitation of EPSC amplitude. Furthermore, recovery mechanisms influence the time course of plasticity, through calcium sequestration and vesicle mobilization (Renden and von Gersdorff, 2007; Neher, 2010). Typically, a given synapse type demonstrates a consistent form and kinetics of plasticity. For example, parallel fiber synapses onto Purkinje neurons always facilitate in normal physiological saline, while climbing fiber synapses onto Purkinje neurons always depress (Perkel et al., 1990).

Remarkably, the synapses formed by a single cell onto different target neurons can show different plasticity. This phenomenon was discovered in cerebral cortex (Reyes et al., 1998) and is called "target cell-specific synaptic plasticity." This phenomenon indicates that P_r is regulated by communication from the postsynaptic to the presynaptic neuron, although the molecular basis for this is not known.

It is also clear that there is still considerable variability in plasticity even within a uniform population of synapses made by one cell type onto another. Xu-Friedman and colleagues have investigated this issue in depth at synapses made by auditory nerve fibers onto bushy cells in the anteroventral cochlear nucleus of the mouse. These synapses, called "endbulbs of Held," consistently show depression, while auditory nerve synapses onto neighboring T-stellate cells show less depression, or even facilitation (Isaacson and Walmsley, 1996; Cao and Oertel, 2010; Chanda and Xu-Friedman, 2010). Endbulbs vary in the amount of depression they show, and dynamic-clamp experiments indicate that this has consequences for bushy cell spiking (Yang and Xu-Friedman, 2009). Increased depression reduces the likelihood that bushy cells will spike during bouts of high activity. However, it is not clear how the specific P_r at a given endbulb is regulated, or indeed if it is precisely regulated at all. To test this, Xu-Friedman and colleagues analyzed the plasticity of distinct endbulbs converging on the same bushy cell. They found that, strikingly, these had similar plasticity (Yang and Xu-Friedman, 2009, 2012), suggesting that plasticity is closely regulated. Further experiments with the use-dependent blocker MK-801 suggest that P_r is similar for converging endbulbs, indicating that P_r is somehow coordinated between them. This is a qualitatively finer scale of regulation than that accounted for by target cell-specific synaptic plasticity. Rather P_r is regulated on a cell-by-cell basis.

The mechanisms underlying this regulation are not yet clear, but may involve activity: the similarity between converging endbulbs becomes evident shortly after the onset of hearing (Yang and Xu-Friedman, 2012). It will be interesting to establish whether activity in the auditory nerve contributes to regulating P_r, such as through processes akin to homeostatic synaptic scaling (Turrigiano, 2008).

Calyx of Held and auditory brainstem: the role of STP decreases with age

The calyx of Held synapse is a fast, glutamatergic, axosomatic relay synapse in the auditory brainstem, which is formed by fibers from globular bushy cells of the cochlear nucleus with principal neurons of the medial nucleus of the trapezoid body (MNTB) (Borst and Soria van Hoeve, 2012). Thus, in the ascending auditory system, the calyx of Held is located only one synaptic station downstream of the endbulb of Held discussed above. Each MNTB principal neuron is innervated by a single calyx. The principal neurons provide well timed inhibition to many areas in the auditory brainstem, including the sound localization nuclei. Because of the accessibility of the calyx for patch-clamp recordings in slice studies, STP has been relatively well studied in this system. These studies have provided mechanistic insights into different forms of STP, including short-term facilitation, short-term depression, and post-tetanic potentiation. More recently, the importance of STP for auditory processing was studied. An advantage of the calyx of Held synapse for *in vivo* recordings is that

both presynaptic and postsynaptic signals can be recorded with a single, extracellular pipette (Guinan and Li, 1990), and that juxtacellular (loose-patch) recordings can be used to quantify both the strength of synaptic transmission and postsynaptic excitability (Lorteije et al., 2009).

Borst and colleagues have studied STP in the calyx of Held both *in vitro* and *in vivo*. Somewhat unexpectedly, they found little evidence for a dependence of the size of EPSPs on recent activity in the adult rodent calyx of Held synapse, indicating that the impact of STP is much smaller *in vivo* than in slice studies (Lorteije et al., 2009; Sonntag et al., 2011). Several factors are responsible for this discrepancy. One important factor is that slice studies commonly use a much higher extracellular calcium concentration than is present *in vivo* (Borst, 2010). As a result, the release probability will be higher in slices than in the intact brain, resulting in more synaptic depression. A second important difference is that most slice studies on STP at the calyx of Held synapse have been performed in immature animals. However, the adult synapse is much more resistant to synaptic depression, due to a lower release probability and an increase in the size of the readily releasable pool (RRP) (Taschenberger and von Gersdorff, 2000; Iwasaki and Takahashi, 2001; Taschenberger et al., 2002). Moreover, synaptic facilitation also becomes smaller after hearing onset, since both the amount of facilitation triggered per action potential becomes smaller, and its decay becomes faster (Crins et al., 2011). As a result, the impact of STP on the variability in the size of synaptic potentials is much larger before hearing onset than after (Crins et al., 2011; Sonntag et al., 2011).

Model fits of the relation between the size of synaptic potentials and recent history for *in vivo* recordings indicated that throughout development, synapses generally recover from synaptic depression quite slowly, with a time constant on the order of seconds (Crins et al., 2011). This is in agreement with slice studies in which recovery from modest synaptic depression was studied (von Gersdorff et al., 1997), but contrasts with the biphasic recovery observed following strong depression (Wang and Kaczmarek, 1998). An inevitable consequence of the slow recovery time constant is that the adult synapse will be to some extent tonically depressed (Hermann et al., 2007, 2009), because the spontaneous firing rates are on average ~30 Hz *in vivo* (Kopp-Scheinpflug et al., 2008a), whereas the calyx of Held synapse is not spontaneously active during slice recordings.

In conclusion, three factors largely explain the apparent discrepancy in release probability between *in vivo* and slice recordings in the adult calyx of Held synapse, as well as the strongly reduced impact of short-term depression on the fluctuations in synaptic potentials observed in the adult calyx synapse: (1) calcium concentration and possible other differences in the extracellular solution; (2) developmental changes in release probability and RRP size; and (3) spontaneous activity *in vivo*. Developmental changes in the amount and decay time course of short-term synaptic facilitation are an important factor in explaining why the decrease in release probability in the adult synapse is not accompanied by a strong increase in the amount of synaptic facilitation (Crins et al., 2011). Together, these mechanisms contribute greatly to the ability of the calyx of Held synapse to deliver precise and reliable inhibition to many nuclei in the central auditory pathway at rates exceeding 300 Hz.

Calyx of Held: excitation dynamically integrates with fast inhibition

The excitatory inputs to MNTB neurons mediated by the calyx of Held have been studied in detail and are fairly well understood (Schneggenburger and Forsythe, 2006; Kochubey et al., 2011). Much less well understood is the role of additional glycinergic inhibitory inputs to MNTB neurons. *In vivo*, the glycinergic inputs selectively suppress MNTB firing in response to certain sound stimuli (Kopp-Scheinpflug et al., 2008b), suggesting specific computational roles in auditory information processing. When tested in brain slices under experimental conditions lacking the chronic spontaneous background activity that is typical for auditory brainstem neurons, the inhibitory events have conductances that are approximately as large as those of the calyceal excitatory inputs and can reliably suppress MNTB firing when activated (Awatramani et al., 2004). However, auditory brainstem neurons are chronically active even in the absence of any sound due to ongoing spontaneous activity (Smith et al., 1998; Kadner et al., 2006; Hermann et al., 2007, 2009). This background activity results from auditory nerve spontaneous activity (Kiang, 1965; Liberman, 1978; Geisler et al., 1985; Hudspeth, 1997) and is one of the hallmarks of most auditory brainstem neurons. As a result, in the intact brain various mechanisms of STP are chronically active in auditory brainstem synapses, even in the absence of any sound. During the preparation of brain slices, the auditory nerves are severed and, as a result, the ongoing background activity ceases. In this unphysiologically silent environment, synapses recover from the chronic steady-state levels of STP, and exhibit different properties from the intact brain. For example, the number of releasable vesicles is reduced in active synapses or the elevated calcium levels favor faster recovery time constants from synaptic depression (Hermann et al., 2007).

Inhibitory inputs to MNTB neurons operate under levels of background activity that are similar to those of the corresponding excitatory inputs, and thus are also in a state of chronic depression and facilitation. Since the specific properties of STP in inhibitory synapses are different from those in excitatory synapses, the relative strength of excitatory inputs versus inhibitory inputs dynamically changes from moment to moment, depending on recent activity patterns. Although both excitation and inhibition have similar conductances in brain slices lacking chronic background activity (Awatramani et al., 2004), the steady-state conductances of active excitatory synapses are overall larger than the steady state of active inhibitory synapses, suggesting that the relative impact of neural inhibition during ongoing activity may be smaller than that measured in rested slices (F. M. Mayer and A. Klug, unpublished observations). However, inhibitory synapses facilitate much more prominently during stimulation with high-frequency trains than the corresponding excitatory synapses do, causing brief periods during which the computational impact of inhibition is especially high (Mayer et al., unpublished observations). Additionally, glycinergic inputs exhibit a slightly longer latency than their corresponding excitatory inputs, causing the inhibitory activity stream to lag just a moment behind the excitatory activity stream (F. M. Mayer and A. Klug, unpublished). Thus, the specific properties of excitatory and inhibitory synapses and the differential properties of STP are the basis for very complex interactions during responses to natural and ongoing neural activity patterns.

Mormyrid midbrain: synaptic filters for the processing of communication signals

Although the mechanisms of STP influence synaptic strength *in vitro*, it remains a challenge to relate these processes to the processing of behaviorally relevant sensory information (Abbott and Regehr, 2004). A group of African weakly electric fishes called the *Mormyridae*, or elephant fishes, provides a unique opportunity for linking *in vivo* studies of sensory coding with *in vitro* studies of synaptic, cellular, and network physiology. These fishes generate all-or-none pulses of electricity, and they communicate with each other by actively varying the intervals between pulses on a time scale of tens to hundreds of milliseconds (Hopkins, 1986; Carlson, 2002; Carlson and Hopkins, 2004a,b; Arnegard and Carlson, 2005; Wong and Hopkins, 2007).

Mormyrids have an electrosensory pathway that is exclusively devoted to processing electric communication signals (Xu-Friedman and Hopkins, 1999). Peripheral electroreceptors respond to each stimulus pulse with a fixed latency spike, thereby directly coding the sequence of interpulse intervals into the sequence of interspike intervals (Hopkins and Bass, 1981). After filtering out responses to self-generated signals in the hindbrain (Bell and Grant, 1989), these precisely timed spikes are relayed to the midbrain, where a diverse population of neurons acts as temporal filters of interspike interval sequences, some responding selectively to short intervals, others to long intervals, and still others to intermediate intervals (Carlson, 2009). These neurons are the first ones in the sensory pathway that are tuned to interpulse intervals. Furthermore, they exhibit the same tuning to temporal patterns of sensory stimulation as they do to temporal patterns of electrical stimulation of incoming afferent fibers. Thus, the temporal filtering of spike trains arises locally within this population of neurons (Carlson, 2009). These various features of the circuit make it relatively straightforward to directly manipulate presynaptic spike timing *in vivo* and *in vitro*, and to relate temporal filtering of these inputs at synapses to the coding of behaviorally relevant sensory stimuli.

Carlson and colleagues studied the role that local inhibitory interneurons play in establishing the diversity of interval tuning observed across this population of neurons (George et al., 2011). They performed paired whole-cell recordings *in vitro* and revealed extensive local excitatory interactions. Differences in the relative strength and duration of excitatory and inhibitory synaptic inputs act to shape interval tuning through temporal summation, with temporally summating excitation enhancing responses to short intervals and temporally summating inhibition suppressing responses to short intervals (George et al., 2011). This basic "push–pull" mechanism can create many different types of interval tuning. In addition, paired whole-cell recordings from synaptically connected neurons *in vitro* as well as synaptic conductances estimated from whole-cell recordings *in vivo* reveal that short-term depression is ubiquitous in this circuit. Further, the relative extent of depression in excitatory and inhibitory pathways varies with respect to the interval tuning of postsynaptic neurons. Together, these findings suggest that the interplay between temporal summation and depression in excitatory and inhibitory pathways shapes the synaptic filtering of presynaptic inputs to mediate the detection of communication signals. Short-term depression has also been implicated in frequency tuning in South American electric fish (Fortune and Rose, 2000), tuning to sound pulse rate and pulse number in frogs (Edwards et al., 2007), and motion detection in visual and electrosensory systems (Chance et al., 1998; Chacron et al., 2009), suggesting that it represents a general strategy for the temporal processing of behaviorally relevant stimuli (Fortune and Rose, 2001).

Auditory brainstem: activity-dependent tuning of chloride driving force for inhibitory signaling

The traditional mechanisms of STP described above are all geared toward regulating and dynamically altering the conductance of synapses through changes in P_r, pool size, or postsynaptic receptor open probabilities. Alternatively, synaptic current amplitudes and thereby synaptic strength can be regulated by altering the ion flow through open synaptic receptors through an alteration of the ion's driving force. There is increasing evidence for modulation of target neuron excitability (Steinert et al., 2008, 2011) or of inhibitory circuits (Chen et al., 2011) contributing to experience-dependent plasticity. Recently, Kopp-Scheinpflug et al. (2011) described a novel inhibitory mechanism underlying offset-responses in the superior paraolivary nucleus (SPN) (Felix et al., 2011).

A powerful IPSP input from the MNTB can trigger an offset burst of action potentials through a highly negative chloride driving force combined with a fast HCN1-mediated I_h current (hyperpolarization-activated cation current). Increased synaptic activity in the MNTB releases nitric oxide (NO), a gaseous messenger molecule that is involved in the regulation of synaptic transmission and neuronal function (Garthwaite, 2008; Steinert et al., 2008, 2011). New results revealed that NO also modulates inhibitory transmission via the potassium-chloride cotransporter (KCC2) responsible for the negative chloride reversal potential E_{Cl} (Löhrke et al., 2005) in the SPN. Blockade of KCC2 by furosemide allows passive equilibration of chloride and shifts E_{Cl} toward the Nernst prediction (Kopp-Scheinpflug et al., 2011). Mimicking MNTB activity by perfusion of NO donors also causes E_{Cl} to shift toward more positive values, suggesting a suppression of KCC2 by NO. Despite the depolarizing shift in the IPSC reversal potential, there was no direct effect of NO signaling on IPSC conductance, neither by reducing transmitter release nor by modulation of the postsynaptic glycine receptors.

NO suppression of KCC2 is a novel finding and has broad relevance for control of inhibitory synaptic transmission in the CNS. Raising KCC2 activity shifts E_{Cl} to more negative voltages and thereby increases IPSP driving force, while lowering KCC2 activity had the opposite effect. Nitrergic modulation of other KCC genes by NO, such as KCC3a/b spliced genes has been described in non-nervous tissue (Di Fulvio et al., 2003). In the brain, GABA/glycinergic signaling without moderate KCC2 activity is limited to shunting the membrane conductance. The absence of KCC2 in immature states results in depolarizing synaptic responses (Rivera et al., 2005), while a reduction of KCC2 and altered Cl^- homeostasis also occurs in adult models of neuropathic pain (Lu et al., 2008), ischemic brain injury (Papp et al., 2008), or after spinal cord injury (Boulenguez et al., 2010). Activity-dependent regulation of nitrergic signaling therefore provides a powerful means of regulating the strength of synaptic inhibition. For example, NO selectively tunes inhibitory synapses to modulate vertebrate locomotion by an as yet unknown mechanism (McLean and Sillar 2002). One mechanism of regulating KKC2 activity is via PP1-mediated dephosphorylation of KCC2 triggered by NMDA receptor activation (Lee et al., 2011). Our previous work has shown that in the MNTB, NMDA receptor activation leads to intracellular NO signaling, subsequently altering the balance of phosphorylation and dephosphorylation (Steinert et al., 2008). Nitrergic downregulation of KCC2 will suppress all IPSPs and will have profound effects on regulating rhythm generation throughout the CNS.

Summary

Short-term plasticity generally refers to a number of mechanisms that dynamically alter the strength of synaptic events in response to periods of repeated activity. From a mechanistic point of view, these mechanisms are relatively well understood, but their functional roles are still unclear. In this review, we discussed recent work from several neural systems in which this plasticity has been shown to play an active role in dynamically shaping the neurons' responses to ongoing trains of activity. In the systems described, STP participates in ensuring normal functioning of its neurons, and in the enhancement, depression or filtering of certain aspects of the ascending information train. Synapse-, cell-, and activity-specific regulation of synaptic strength suggests that, at least in some of the systems described above, STP is not simply an inherent byproduct of chemical synaptic transmission, but is actively used in information processing.

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