Short-Term Plasticity Turns Plastic. Focus on “Synaptic Transmission at the Calyx of Held Under In Vivo-Like Activity Levels”

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Short-term plasticity (STP) is a use-dependent change in synaptic strength on the time scale of millisecond to seconds and is observed in almost every synapse of the CNS. Each type of synapse has its own “personality” with respect to this property. When stimulated a few times within a second, some synapses show facilitation, others depression or else complex sequences of facilitatory and depressing changes (Dittman et al. 2000). It has been shown that terminals at two axonal branches of the same neuron can express very different forms of STP (Reyes et al. 1998; Rozov et al. 2001) and that STP serves important aspects of signal processing in the nervous system. In this issue of the Journal of Neurophysiology (p. 807–820), Hermann et al. (2007) ask the question whether the way we usually characterize STP of a given synapse actually reports that personality, which is relevant for its physiological function. The answer, not surprisingly, is no!

The object of their study is the Calyx of Held, a glutamatergic presynaptic terminal in the auditory pathway. It came to fame by the fact that it is large enough so that it can be voltage clamped (Borst et al. 1995; Forsythe 1994). Furthermore, the terminal contacts the soma of a large, compact postsynaptic neuron, so that voltage clamp can be applied simultaneously to both the pre- and the postsynapse (Borst et al. 1995; Takahashi et al. 1996). This offers unique possibilities for a detailed biophysical analysis of synaptic transmission. The synapse, when studied the usual way, displays pronounced short-term depression, very similar to other glutamatergic synapses (Dittman et al. 2000). The “usual way” means that a short burst of stimuli is applied after a long period of rest. However, unlike many central synapses, for which coding is relatively sparse, the task of the Calyx of Held—as a synapse in the afferent sensory information flow—is to fire on average 10–100 times per second, even in complete silence (Kopp-Scheinpflug et al. 2003). Tone bursts cause short episodes of firing in the auditory nerve of 100–500 action potentials per second. The basic question of the Hermann et al. paper is exactly what type of STP is observed, when firing rate changes from an average of ~40 to a high frequency of several hundred Hertz. They find, first of all, that the synapse is partially depressed after conditioning by a 40-Hz Poisson train. This is expected from previous work on calyces of other species, which had shown that the steady-state excitatory postsynaptic current (EPSC) size only by ~20%. Furthermore, they find that recovery from such depression occurs very rapidly, on the 50- to 100-ms time scale, quite unlike recovery to resting levels, which takes seconds.

Two important questions emerge from this study: what is the mechanism of this activity-dependent alteration of STP, and what is it good for in the context of auditory signal processing?

Hermann et al. discuss the latter question but only give a few clues regarding the mechanisms. This is why I will speculate about the latter issue in the following text.

**PHYSIOLOGICAL SIGNIFICANCE**

Hermann et al. point out that synaptic failures are observed during deep depression at several hundred Hertz. Thus it is quite clear that the Calyx of Held is not the fail-safe relay, which it had been assumed to be in many previous studies. On the other hand, they do point out that first responses to a burst stimulus are transmitted quite safely, even after 60-Hz long-term conditioning. Thus the information, which is most important for sound localization (about the wave-front of sound events) is preserved. Given that there are failures, the synapse contributes to the overall short-term depression (STD) of the auditory pathway and given the importance of STD for information processing [see for example the influence of STD in another type of auditory system; (Cook et al. 2003)] any realistic model of sound processing should consider the STD data after appropriate conditioning and not those of a rested synapse. In that sense, the plasticity of STD needs detailed attention.

**MECHANISMS**

Why does a synapse depress only little during a transition from a 40-Hz Poisson train to a 100-Hz tetanus, while it depresses by ~2/3, when the same tetanus is applied to a rested synapse? Given that the tetanus starts from a state of partial depression, we may ask whether this is a sufficient explanation in the light of past work on STD.

The major mechanism of STD at this synapse is the depletion of release-ready vesicles (Schneggenburger et al. 2002). Any simple model of depletion and recruitment of vesicles predicts that transmission at steady-state should decline with the inverse of frequency beyond a certain characteristic frequency. The transition from conditioning to burst stimulation is a 2.5-fold increase in average frequency, and we would expect to observe additional depression by about that factor, but we observe only a 20% change!

Part of the answer to this discrepancy is that the Calyx of Held, like many other types of synapses, does not conform to the “simple” model of depression. When one uses rested synapses and plots the level of steady-state depression during
high-frequency trains against stimulation frequency, invariably a two-component curve is obtained: depression develops already at very low stimulation frequencies and EPSCs reach a level of ~40–50% of the initial value at frequencies as low as 5–10 Hz (Taschenberger et al. 2005; Weis et al. 1999). Beyond that point the curve becomes shallower with a further half-decline only at 200 Hz and beyond. Therefore actually only very little additional depression is expected when switching from 40 to 100 Hz—as observed by Herman et al. Several studies have been performed to explain the deviation of the depression-versus-frequency curve from a 1/f relationship (Dittman and Regehr 1998; Kusano and Landau 1975). Promising, from the current point of view, are mechanisms that assume an acceleration of vesicle recruitment beyond the “breakpoint” of the relationship at ~10–20 Hz (Taschenberger et al. 2005; Weis et al. 1999). Alternatively, presynaptic Ca\(^{2+}\)-current inactivation may explain part of the decline at low frequencies (Takahashi et al. 2000). The first explanation goes along nicely with the finding of Hermann et al. that vesicle recruitment is fast after “conditioning” of the synapse. The question remains: why is recruitment accelerated by conditioning? A likely explanation is the finding at many synapses (Dittman and Regehr 1998; Stevens and Wesseling 1998) including the Calyx of Held (Sakaba and Neher 2001; Wang and Kaczmarek 1998) that elevated [Ca\(^{2+}\)] speeds up vesicle recruitment.

In conclusion, we are left with the message that STD is plastic, which means that its properties are influenced by “physiological” levels of background activity. The work of Hermann et al. shows that this has functional significance. On the basis of this work, it may well be worthwhile to study the mechanistic basis of vesicle recruitment (Wadel et al. 2007), its modulation by activity and by second messengers, and its precise influence on STD.

REFERENCES


