Role of Ca\textsuperscript{2+} channels in short-term synaptic plasticity
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Repetitive nerve activity induces various forms of short-term synaptic plasticity that have important computational roles in neuronal networks. Several forms of short-term plasticity are caused largely by changes in transmitter release, but the mechanisms that underlie these changes in the release process have been difficult to address. Recent studies of a giant synapse — the calyx of Held — have shed new light on this issue. Recordings of Ca\textsuperscript{2+} currents or Ca\textsuperscript{2+} concentrations at nerve terminals reveal that regulation of presynaptic Ca\textsuperscript{2+} channels has a significant role in three important forms of short-term plasticity: short-term depression, facilitation and post-tetanic potentiation.

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Introduction
Neurons fire repetitively at frequencies that range from less than one to hundreds of hertz for various periods of time [1,2]. Repetitive firing can temporarily change synaptic strength, resulting in various forms of short-term plasticity, such as facilitation (which lasts for less than a few seconds), depression (which lasts for a few to tens of seconds) and post-tetanic potentiation (which can last for minutes). These forms of short-term plasticity are crucial for neuronal network computations [3]. Therefore, it is important to understand how short-term plasticity is generated.

Accumulated evidence suggests that the origin of short-term plasticity is largely presynaptic, although postsynaptic mechanisms are involved in certain conditions [4–6]. It remains not well understood how transmitter release is regulated to achieve short-term plasticity. Although transmitter release is triggered by Ca\textsuperscript{2+} influx through voltage-gated Ca\textsuperscript{2+} channels, regulation of Ca\textsuperscript{2+} channels has not generally been considered as a major mechanism in short-term plasticity. Recent studies at a large mammalian central synapse, the calyx of Held in the rat (or mouse) medial nucleus of the trapezoid body, indicate that regulation of voltage-gated Ca\textsuperscript{2+} channels is important in mediating short-term plasticity. This review focuses on these studies of the calyx of Held synapse.

The relationship between transmitter release and the presynaptic Ca\textsuperscript{2+} current
When an action potential arrives at the nerve terminal, voltage-activated Ca\textsuperscript{2+} channels open to allow Ca\textsuperscript{2+} influx that triggers transmitter release. About four decades ago, transmitter release at the neuromuscular junction was found to be proportional to the extracellular Ca\textsuperscript{2+} concentration raised to power of three or four [7,8]. A similar power relationship was subsequently observed between transmitter release and the presynaptic Ca\textsuperscript{2+} current (I\textsubscript{Ca}) or the presynaptic intracellular Ca\textsuperscript{2+} concentration at many synapses, such as the squid giant synapse [9], hippocampal CA3–CA1 synapses [10], the goldfish retinal bipolar synapse [11] and the calyx of Held synapse (Figure 1a) [12–15,16**]. According to this nonlinear (e.g., fourth power) relationship, a small change in the Ca\textsuperscript{2+} influx (e.g., 90% of control) is amplified to a large change in transmitter release (e.g., 66%). Thus, modulation of Ca\textsuperscript{2+} influx or Ca\textsuperscript{2+} channels provides an efficient and economic way to modulate transmitter release. Ca\textsuperscript{2+} channels can be regulated by various factors, such as voltage, Ca\textsuperscript{2+} and various neurotransmitters and neuro-modulators [17–19]. However, regulation of Ca\textsuperscript{2+} channels had not been considered the dominant mechanism mediating short-term plasticity. Ca\textsuperscript{2+} currents are difficult to record at most synapses, where nerve terminals are too small for voltage-clamp recordings. The ability to perform simultaneous presynaptic and postsynaptic voltage-clamp recordings at the calyx of Held synapse [20,21] made it possible to study quantitatively the contribution of Ca\textsuperscript{2+} channels to short-term plasticity at this synapse.

The calyx of Held synapse is a glutamatergic synapse located in the auditory brainstem of the rat or mouse [5]. In rats aged ten days old or younger, the calyx of Held contains three types of voltage-gated Ca\textsuperscript{2+} channel — P/Q-type, N-type and R-type — whereas older calyces contain only P/Q-type channels [13,22–24]. In mouse, P/Q-type and N-type channels are present in immature calyces, but only P/Q-type channels are present in more mature calyces [25,26*]. P/Q-type channels are more efficient than N-type and R-type channels in controlling transmitter release, probably because they are physically located closer to the release site than other types [13]. Similarly, P/Q-type channels are more efficient in controlling release than...
N-type and/or R-type channels at cerebellar synapses [27] and neuromuscular junctions [28,29]. It is suggested that as the calyx matures during development, there is a reduction in the number of Ca$^{2+}$ channels that control transmitter release at single release sites [30]. The physical distance between Ca$^{2+}$ channels and the release site or the endogenous Ca$^{2+}$ buffer capacity also decreases, which increases the efficiency of Ca$^{2+}$ channels in controlling release [30]. Thus, developmental changes and the types of Ca$^{2+}$ channel can affect the efficiency of Ca$^{2+}$ channels in regulating transmitter release.

**Short-term depression**

Repetitive stimulation causes short-term depression (STD) of synaptic transmission at many synapses [1,4,5]. At the calyx of Held synapse, STD is more prominent in immature than in mature animals [31], so the majority of studies have been performed in immature calyces (Figure 1b). STD during repetitive firing at ≤10 Hz is caused by a presynaptic mechanism [32]. As the frequency of firing is increased, postsynaptic AMPA receptor desensitization [33,34] also contributes to STD [35,36]; however, significant depression remains after relieving postsynaptic receptor desensitization, indicating that the presynaptic mechanism is a dominant source of STD [35,36].

What is the presynaptic mechanism that underlies STD? Depletion of a readily releasable pool of vesicles (RRP) is the most popular hypothesis [4], and this hypothesis has been confirmed at the calyx after a 10 ms presynaptic depolarization that depletes the RRP [37–39]. However, depletion of the RRP is not the only mechanism that...
underlies STD after a 10 ms presynaptic depolarization. A decrease in the release probability downstream of the presynaptic \( I_{\text{Ca}} \) and a decrease in presynaptic \( I_{\text{Ca}} \) itself also contribute to STD after a 10 ms depolarization [37]. Which of these presynaptic mechanisms mediate STD induced by action potential trains? Recent studies indicate that although all of these mechanisms can contribute to STD [16**,38,40,41], a decrease in the presynaptic \( I_{\text{Ca}} \) is the dominant mechanism during repetitive action-potential-like stimulation at frequencies ranging from <2 Hz to 30 Hz in 7–10-day-old rats [16**].

Inactivation of the presynaptic \( I_{\text{Ca}} \) was first found after a prolonged (e.g. 10 s) train of action potentials at 100 Hz [40]. The decrease in the \( I_{\text{Ca}} \) largely accounts for STD after the prolonged train of stimulation. However, this mechanism was discounted, because an atypically intense stimulus was used to generate it, and STD during 100 Hz stimulation was not caused by \( I_{\text{Ca}} \) inactivation [40]. A recent study has shown inactivation of \( I_{\text{Ca}} \) for a wide range of stimulation conditions that are typically used to induce STD [16**]. The stimulus includes 2–20 action-potential-equivalent stimuli (AP-e) at 0.2–100 Hz. Except during 100 Hz stimulation, \( I_{\text{Ca}} \) is decreased during and after stimulation. Because release is proportional to \( I_{\text{Ca}} \) raised to a power of 3.6 (Figure 1a), the decreased \( I_{\text{Ca}} \) raised to a power of 3.6 gives an estimate of the contribution of \( I_{\text{Ca}} \) inactivation to STD (Figure 1b). The estimated contribution matches closely to the measured STD during and after trains of AP-e, particularly ≤30 Hz (Figure 1b). Furthermore, STD, including paired-pulse depression, is largely relieved when the \( I_{\text{Ca}} \) decrease is compensated by a change in the voltage command [16**] or when \( I_{\text{Ca}} \) is replaced with photolysis of a caged Ca\(^{2+}\) compound that evokes release without activating Ca\(^{2+}\) channels [42]. These results suggest that \( I_{\text{Ca}} \) decrease, but not depletion of the RRP, is the major cause of STD during 2–20 AP-e at ≤30 Hz and after 2–20 AP-e at frequencies from <2 Hz to 100 Hz.

\( I_{\text{Ca}} \) inactivation is mainly due to inactivation of P/Q-type Ca\(^{2+}\) channels [16**,40]. The decrease of \( I_{\text{Ca}} \) during stimulation is largely relieved by the Ca\(^{2+}\) buffer bis-(o-aminophenoxy)-ethane-N,N,N\(^\prime\),N\(^\prime\)-tetraacetic acid (BAPTA; Figure 1c) or by replacing the extracellular Ca\(^{2+}\) with Ba\(^{2+}\) or Na\(^{+}\), suggesting that Ca\(^{2+}\) induces \( I_{\text{Ca}} \) inactivation [16**,40]. Calmodulin, a Ca\(^{2+}\)-binding protein, might mediate Ca\(^{2+}\)-induced \( I_{\text{Ca}} \) inactivation, because three calmodulin inhibitors — including a 17 amino acid myosin light chain kinase peptide (Figure 1c), a calmodulin-binding domain peptide and an organic calmodulin inhibitor calmidazolium — significantly reduce \( I_{\text{Ca}} \) inactivation [16**].

Why is depletion of the RRP not the major mechanism during 2–20 AP-e at ≤30 Hz? This is because each AP-e depletes only ~5% of the RRP [16**] and, even after a complete depletion, more than half of the RRP is replenished within ~200–300 ms [16**,37,38]. Only during AP-e trains at ≥100 Hz is depletion the dominant mechanism [16**]. In addition, during prolonged high-frequency (≥100 Hz) firing, activation of presynaptic adenosine A1 receptors and group III metabotropic glutamate receptors can contribute to STD [43,44] by inhibition of \( I_{\text{Ca}} \) [22,45].

**Short-term facilitation**

Short-term synaptic facilitation (STF) is generally thought to be caused by an elevated intracellular Ca\(^{2+}\) concentration that remains from the previous stimulus, termed residual Ca\(^{2+}\) [4,46,47]. The main evidence for this is the ability of Ca\(^{2+}\) chelators to attenuate both residual Ca\(^{2+}\) and STF [4]. It is hypothesized that residual Ca\(^{2+}\) enhances the release probability by binding to a Ca\(^{2+}\) sensor different from the one that mediates evoked exocytosis [4].

At the calyx of Held, STF is not observed in normal extracellular solution because STD is overwhelming [5]. However, during repetitive action-potential-like depolarizing pulses at 100–200 Hz, \( I_{\text{Ca}} \) is facilitated by a maximum of 10–20% (Figure 2a), owing to an increased rate of activation [48,49]. In this situation, only P/Q-type Ca\(^{2+}\) channels are facilitated [25,26*]. Facilitation of \( I_{\text{Ca}} \) is attenuated by loading the calyx with Ca\(^{2+}\) chelators or by replacing the extracellular Ca\(^{2+}\) with Ba\(^{2+}\) (Figure 2a), suggesting that residual Ca\(^{2+}\) mediates \( I_{\text{Ca}} \) facilitation [48,49]. Loading the calyx with neuronal Ca\(^{2+}\) sensor 1 (NCS1), a neuron-specific high-affinity Ca\(^{2+}\)-binding protein, increases \( I_{\text{Ca}} \) induced by a brief depolarization by accelerating the activation time of \( I_{\text{Ca}} \) in a Ca\(^{2+}\)-dependent manner, and largely occludes \( I_{\text{Ca}} \) facilitation (Figure 2b) [50]. Furthermore, loading the calyx with a C-terminal peptide of NCS1 greatly reduces \( I_{\text{Ca}} \) facilitation [50]. These results suggest that Ca\(^{2+}\) facilitates \( I_{\text{Ca}} \) by binding to NCS1 [50].

Given that STD overwhelms STF at the calyx-type synapse in normal extracellular solution, the role of \( I_{\text{Ca}} \) facilitation might be to counteract mechanisms that cause STD. When postsynaptic AMPA receptor desensitization is relieved by application of competitive AMPA receptor blockers such as kynurenate acid or γ-D-glutamylglycine (γ-DGG), the excitatory postsynaptic current (EPSC) is initially facilitated during a train of action potentials or action-potential-like depolarizing pulses at 50–100 Hz [16**,35,51]. The facilitated EPSCs during the first four stimuli are of approximately the same size as the EPSC predicted from \( I_{\text{Ca}} \) facilitation (raising the facilitated \( I_{\text{Ca}} \) to a power of 3.6; Figure 2c), suggesting that \( I_{\text{Ca}} \) facilitation contributes significantly to STF [16**]. In mice that have P/Q-type Ca\(^{2+}\) channels knocked out, both \( I_{\text{Ca}} \) facilitation and the EPSC facilitation are absent (Figure 2d) [25,26*]. This correlation provides strong
evidence that $I_{Ca}$ facilitation is a major source of STF [25,26*].

However, not all studies agree quantitatively with this conclusion. In one study [51], the EPSC was facilitated to ~220% of control, whereas $I_{Ca}$ was facilitated to only ~110% of control during paired-pulse stimulation (Figure 2e) [51]. $I_{Ca}$ facilitation could account for only about one-third of paired-pulse facilitation [51]. A supra-linear summation of residual Ca$^{2+}$ with the Ca$^{2+}$ influx, probably caused by saturation of the Ca$^{2+}$ buffer, was considered to be the major mechanism underlying paired-pulse facilitation [51]. This conclusion is consistent with a study of the mossy fiber–CA3 synapse [52], in which saturation of an endogenous Ca$^{2+}$ buffer (calbindin) in the nerve terminal contributed to STF. However, the ~120% increase in paired-pulse facilitation of the EPSC reported in [51] is much larger than the ~0–40% increases reported in other studies (e.g. [16**,35], and a report of no apparent change [36] from the same laboratory as [51]). The reason for this apparent discrepancy is unclear. It seems likely that the contribution of $I_{Ca}$ facilitation to STF varies depending on the degree of STF, and thus the condition of the synapse. Nevertheless, all studies agree that $I_{Ca}$ facilitation contributes to STF.

At other synapses, the block of STF by Ca$^{2+}$ chelators such as glycol-bis(2-aminoethylether)-N,N,N′,N′-tetraacetic

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**Figure 2**

$I_{Ca}$ facilitation induced by Ca$^{2+}$ and neuronal Ca$^{2+}$ sensor 1 (NCS1) significantly contributes to short-term facilitation. (a) The $I_{Ca}$ facilitation (lower) induced by a train of action potential waveforms (upper) at 100 Hz in control conditions (i) was largely abolished when the calyx was loaded with 10 mM BAPTA (ii). Adapted, with permission, from [48]. (b) Superimposed $I_{Ca}$ traces evoked by paired pulses at different intervals from a calyx in control conditions (i) and a calyx loaded with exogenous NCS1 (20 μM; ii). Note that NCS1 largely occludes $I_{Ca}$ facilitation. Adapted, with permission, from [50]. (c) (i) Sampled $I_{Ca}$ and EPSC induced by a train of AP-e at 100 Hz. (ii) $I_{Ca}$ charge (open circles) and EPSC amplitude (black triangles) during a train of AP-e at 100 Hz (n = 13). Only the first eight stimuli are shown. The measured $I_{Ca}$ charge was also raised to a power of 3.6 (red). Kynurenic acid (1 mM) and cyclothiazide (100 μM) were added in the bath solution. The error bars indicate standard error of the mean. Adapted, with permission, from [16**]. (d) (i) Superimposed $I_{Ca}$ traces recorded from mouse calyces by paired 2 ms depolarizing pulses with intervals of 5–45 ms. $I_{Ca}$ facilitation was observed in the wild-type mouse (WT) but not in a P/Q-type channel knockout mouse (KO). (ii) Paired-pulse facilitation of the EPSC was observed in the wild-type but not in the P/Q-type knockout mouse, suggesting that $I_{Ca}$ facilitation causes paired-pulse facilitation. Adapted, with permission, from [25]. (e) Superimposed samples of presynaptic $I_{Ca}$ and EPSC evoked by paired pulses with various intervals (Δt) at a calyx of Held synapse. The bath solution contained cyclothiazide to relieve AMPA receptor desensitization. The results in this study suggest that $I_{Ca}$ facilitation is insufficient to fully account for paired-pulse facilitation. Adapted, with permission, from [51].
acid (EGTA) is often interpreted as activation of a Ca\textsuperscript{2+} sensor that enhances the release probability \cite{4,46}. The findings at the calyx of Held provide an alternative explanation: that Ca\textsuperscript{2+} chelators attenuate STF by diminishing Ca\textsuperscript{2+}-induced \(I_{\text{Ca}}\) inactivation. In addition, Ca\textsuperscript{2+} chelators might block STF by minimizing saturation of Ca\textsuperscript{2+} buffers in the nerve terminal \cite{51,52}.

**Post-tetanic potentiation**

Post-tetanic potentiation (PTP) is also caused by residual Ca\textsuperscript{2+} at the nerve terminal \cite{4,46}. It is hypothesized that residual Ca\textsuperscript{2+} enhances the release probability by acting on a molecular target different from the Ca\textsuperscript{2+} sensor that mediates evoked exocytosis \cite{4}. At the calyx of Held, PTP can be induced by intense afferent fiber stimulation, such as 4 s stimulation at 100 Hz (Figure 3a) \cite{53*} or 5 min stimulation at 20 Hz \cite{54*}. Similar to other synapses \cite{4}, at the calyx of Held the Ca\textsuperscript{2+} chelator EGTA attenuates the increase of residual Ca\textsuperscript{2+} and thus PTP (Figure 3a) \cite{53*,54*}. Knowing that residual Ca\textsuperscript{2+} can facilitate \(I_{\text{Ca}}\) in the calyx (Figure 2), it is natural to ask whether EGTA attenuates PTP by blocking Ca\textsuperscript{2+}-induced \(I_{\text{Ca}}\) facilitation. To address this question, \(I_{\text{Ca}}\) was recorded from the calyx in the whole-cell configuration; however, in this configuration PTP was absent, probably owing to washout of molecules that mediate PTP \cite{53*,54*}. Thus, instead of whole-cell recordings of \(I_{\text{Ca}}\), fluorescent Ca\textsuperscript{2+} indicator dyes were loaded into the calyx via a whole-cell patch pipette for a few minutes, followed by pipette removal to maintain PTP \cite{55**}. The Ca\textsuperscript{2+} influx in the calyx evoked by a single action potential was found to increase by \(\sim 15\%\) at the peak of the PTP (Figure 3b). This increase gradually returned to the baseline with a time course similar to that of PTP. Based on the highly non-linear relationship between the EPSC and the presynaptic Ca\textsuperscript{2+} influx, the increase in the presynaptic Ca\textsuperscript{2+} influx largely accounts for the PTP \cite{55**}. The increased Ca\textsuperscript{2+} influx was probably caused by Ca\textsuperscript{2+}-induced \(I_{\text{Ca}}\) facilitation \cite{55**}; however, action potential broadening could not be ruled out. In addition, an increase in the RRP size might contribute up to 30\% of the PTP induced by 5 min stimulation at 20 Hz \cite{55**}, although this phenomenon is not observed when PTP is induced by 4 s stimulation at 100 Hz \cite{53*}.

**Conclusions and future directions**

Regulation of presynaptic Ca\textsuperscript{2+} channels is traditionally not considered a major mechanism underlying synaptic plasticity. Recent studies at the giant calyx of Held synapse reveal that regulation of Ca\textsuperscript{2+} channels, particularly those of the P/Q-type, in nerve terminals contributes significantly to STD and STF. During STD, \(I_{\text{Ca}}\) is inactivated by a Ca\textsuperscript{2+}-calmodulin-mediated pathway, whereas during STF, \(I_{\text{Ca}}\) is facilitated by Ca\textsuperscript{2+} that binds to NCS1. A Ca\textsuperscript{2+}-induced increase of Ca\textsuperscript{2+} influx, possibly via facilitation of \(I_{\text{Ca}}\), also contributes significantly to the generation of PTP. These findings suggest that Ca\textsuperscript{2+}-induced regulation of presynaptic Ca\textsuperscript{2+} channels is a common mechanism to generate short-term plasticity at the calyx of Held synapse.

It is generally thought that STF and PTP are caused by residual Ca\textsuperscript{2+}, which enhances the release probability by binding to a Ca\textsuperscript{2+} sensor different from the one that mediates evoked release, whereas STD is largely caused by depletion of the RRP. The finding of Ca\textsuperscript{2+}-induced \(I_{\text{Ca}}\) facilitation at the calyx provides an additional mechanism by which residual Ca\textsuperscript{2+} can enhance the release probability during STF. The finding of Ca\textsuperscript{2+}-induced \(I_{\text{Ca}}\) inactivation at the calyx provides another major mechanism by which STD can be achieved. It is therefore important to determine whether the findings at the calyx

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**Figure 3**

A Ca\textsuperscript{2+}-induced increase in presynaptic Ca\textsuperscript{2+} influx contributes significantly to the generation of post-tetanic potentiation (PTP). (a) Afferent fiber stimulation (applied at time 0) at 100 Hz for 1 s (gray) or 4 s (black) induced PTP of the EPSC in control conditions (i) but not after application of the membrane-permeant Ca\textsuperscript{2+} chelator EGTA-AM (ii). Adapted, with permission, from \cite{55*}. (b) The presynaptic Ca\textsuperscript{2+} transients (i) and the EPSCs (ii) evoked by an action potential before PTP (black) and during PTP (gray). PTP was induced by 20 min fiber stimulation at 20 Hz. Each trace is an average of ten individual traces. The calyx was preloaded with 200 \(\mu\text{M Fluo-4, a fluorescent Ca}^{2+}\) indicator. Fluorescence transients [%] are shown as the fluorescence increase (\(\Delta F_{\text{FAP}}\)) divided by the basal fluorescence level (\(F_0\)). Adapted, with permission, from \cite{55**}.
of Held apply to other synapses. In addition, we think it is important to address the following three questions at the calyx of Held in the near future. First, why does Ca2+ induce $I_{\text{Ca}}$ facilitation during STF, but $I_{\text{Ca}}$ inactivation during STD? Is the choice between upregulation or downregulation of $I_{\text{Ca}}$ a balanced output of two separate Ca2+-dependent pathways? Second, given that calmodulin can mediate Ca2+-induced $I_{\text{Ca}}$ facilitation and inactivation [56,57], why is $I_{\text{Ca}}$ inactivation but not facilitation mediated by calmodulin at the calyx of Held? Third, is the increase of the presynaptic $I_{\text{Ca}}$ influx during PTP mediated by Ca2+-induced $I_{\text{Ca}}$ facilitation?

### Update

In addition to $I_{\text{Ca}}$ inactivation and depletion of the RRP, a decrease in the release probability, caused by a mechanism independent of $I_{\text{Ca}}$ inactivation, contributes to STD induced by prolonged depolarization [37], and probably contributes to STD during high-frequency trains of action-potential-like stimulation [16**,41]. Two recent studies shed light on how the decrease in the release probability is achieved at the calyx of Held [58,59]. One suggests that after depletion of the RRP, newly recruited vesicles are likely to be at a site further away from the Ca2+ channel cluster [58]; the other study suggests that the stimulation-induced increase of the intracellular Ca2+ concentration decreases the sensitivity of readily releasable vesicles to Ca2+ [59].

As discussed in the main text, two studies do not agree on whether an increase in the RRP size contributes to PTP at the calyx of Held [53**,55**]. This controversy is resolved by a recent study, which shows a significant increase of the RRP size >60 s, but not 20 s, after a train of action potential stimulation at 100 Hz for 4 s [60]. Thus, the lack of an increase in the RRP size, as previously reported at 20 s after 4 s stimulation at 100 Hz [53*], is due to measurement of the RRP size at an earlier time. Furthermore, the new study suggests that at physiological temperatures, the increase in the RRP size lasts longer than the increase in the release probability (which is caused by an increase of the Ca2+ influx), and is a more significant mechanism underlying PTP [60].

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### References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

the presynaptic Ca\(^{2+}\) currents were absent in P/Q-type knockout mice, the calyx of Held synapse in wild-type mice and in P/Q-type channel


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the EPSC, suggesting that PTP is caused mainly by an increase in presynaptic Ca\(^{2+}\) influx.


