Voltage-gated Ca\(^{2+}\) channels in presynaptic nerve terminals initiate neurotransmitter release in response to depolarization by action potentials from the nerve axon. The strength of synaptic transmission is dependent on the third to fourth power of Ca\(^{2+}\) entry, placing the Ca\(^{2+}\) channels in a unique position for regulation of synaptic strength. Short-term synaptic plasticity regulates the strength of neurotransmission through facilitation and depression on the millisecond time scale and plays a key role in encoding information in the nervous system. Ca\(^{2+}\) channels are the major source of Ca\(^{2+}\) entry for neurotransmission in the central nervous system. They are tightly regulated by Ca\(^{2+}\)-calmodulin, and related Ca\(^{2+}\) sensor proteins, which cause facilitation and inactivation of channel activity. Emerging evidence reviewed here points to this mode of regulation of Ca\(^{2+}\) channels as a major contributor to short-term synaptic plasticity of neurotransmission and its diversity among synapses.

Ca\(^{2+}\) influx through voltage-gated Ca\(^{2+}\) (term Ca\(_v\)) channels at presynaptic nerve terminals is an essential step in neurotransmission and plays a crucial role in short-term synaptic plasticity. The Ca\(_v\)2 subfamily is predominant in initiating synaptic transmission at fast conventional synapses (1–3). Multiple mechanisms modulate the function of presynaptic Ca\(_v\)2 channels and thereby regulate synaptic transmission (2, 4–6). Ca\(_v\)2 channels bind the ubiquitous Ca\(^{2+}\) sensor protein calmodulin (CaM)\(^2\) to a site in their C-terminal domain, which induces Ca\(^{2+}\)-dependent facilitation and inactivation of Ca\(_v\)2.1 channel activity in response to repetitive stimuli (7–10). Facilitation and inactivation of Ca\(_v\)2 channel activity can cause facilitation and depression of synaptic transmission (11, 12). In this mini-review, we focus on the regulation of the presynaptic Ca\(_v\)2 channels by different calcium sensor proteins and the role of this mechanism in short-term synaptic plasticity. Presynaptic Calcium Channel

The Ca\(^{2+}\) channels in the Ca\(_v\)1 and Ca\(_v\)2 subfamilies are composed of an \(\alpha_{1}\) subunit and auxiliary subunits \(\beta\), \(\alpha_{2}\delta\), and sometimes \(\gamma\) (Fig. 1) (4, 13). The \(\alpha_{1}\) subunit of 190–250 kDa includes the pore, voltage sensors, gating apparatus, and most sites of channel regulation. The auxiliary subunits have an important influence on Ca\(^{2+}\) channel function (4, 13). The intracellular \(\beta\) subunit is a hydrophilic protein of 50–65 kDa (4, 13). Its structure is composed of an SH3 (Src homology-3) domain and a guanylate kinase domain, both well known protein interaction motifs (14, 15). The guanylate kinase domain binds to an \(\alpha\)-helical segment in the intracellular loop connecting domains I and II (Fig. 1), leaving the SH3 domain available for interaction with other binding partners. The transmembrane disulfide-linked \(\alpha_{2}\delta\) subunit complex is encoded by a single gene, but the resulting prepolypeptide is post-translationally cleaved, disulfide-bonded, and lipid-anchored to yield the mature \(\alpha_{2}\) and \(\delta\) subunits (4, 13, 16, 17). A \(\gamma\) subunit having four transmembrane segments is a component of skeletal muscle Ca\(^{2+}\) channels (4, 13) but may not be a component of Ca\(^{2+}\) channels in brain, where related \(\gamma\)-like proteins serve as transmembrane AMPA receptor modulators (18). Ca\(_v\)\(\beta\) subunits greatly enhance cell-surface expression of \(\alpha_{1}\) subunits and shift their kinetics and voltage dependence (4, 13). The \(\alpha_{2}\delta\) subunits enhance cell-surface expression of \(\alpha_{1}\) subunits (16) and are important for efficiently coupling entry of Ca\(^{2+}\) to exocytosis at active zones in nerve terminals (19).

Presynaptic Ca\(^{2+}\) Current and Neurotransmission

Ca\(^{2+}\) influx through Ca\(_v\)2 channels is the predominant source of Ca\(^{2+}\) for initiation of exocytosis of neurotransmitters (2, 3). Ca\(_v\)2.1 channels play a major role in neurotransmission at the neuromuscular junction and most synapses in the central nervous system (2). In contrast, Ca\(_v\)2.2 channels are predominant at synapses in the autonomic nervous system (3) and some synapses in the central nervous system (20, 21). Ca\(_v\)2.3 channels also contribute to neurotransmitter release at central nervous system synapses (22).

Ca\(^{2+}\) entry through a single Ca\(^{2+}\) channel can trigger neurotransmitter release with low efficiency (23), but presynaptic active zones are thought to contain several Ca\(^{2+}\) channels that cooperate in triggering exocytosis (24, 25). The release probability of a single synaptic vesicle increases with the number of Ca\(^{2+}\) channels at the active zone (24–26). Vesicle fusion and exocytosis depend on the SNARE proteins synaptobrevin, syntaxin, and SNAP-25 and on Munc18 (27–29). A primed SNARE complex requires the Ca\(^{2+}\)-binding protein synaptotagmin, which provides rapid Ca\(^{2+}\)-dependent regulation of exocytosis. Five presynaptic proteins (RIM, Munc13, RIM-binding protein, liprin-\(\alpha\), and ELKS) interact with the SNARE complex, dock and prime synaptic vesicles, and recruit docked and primed vesicles to Ca\(^{2+}\) channels (26). Binding of SNARE proteins to the synaptic protein interaction (termed synprint) site (Fig. 2A) regulates expression, localization, and function of Ca\(_v\)2 channels (12, 30–34). The SNARE-interacting protein RIM interacts with the distal C terminus of Ca\(_v\)2.1 channels and with their \(\beta\) subunits, and these interactions are required for recruiting Ca\(_v\)2 channels to active zones (35–37).

Neurotransmitter release is proportional to the third or fourth power of Ca\(^{2+}\) entry (38, 39) and occurs in three modes: synchronous (phasic), asynchronous (tonic), and low-probability spontaneous (miniature) release (40–44). Synchronous...
release driven by precisely timed presynaptic Ca$^{2+}$ current results in fast postsynaptic responses (45, 46). Slower asynchronous release results from residual Ca$^{2+}$ remaining in the terminal after an action potential (44, 47, 48). Spontaneous release results from fluctuations in resting Ca$^{2+}$ concentrations or from Ca$^{2+}$ release from internal stores (49). Synchronous
release is triggered by the Ca$^{2+}$ sensor synaptotagmin (29, 50–52), whereas the Ca$^{2+}$ sensor Doc2 plays an important role in asynchronous release (53). Ca$_V$2 channels may serve as a Ca$^{2+}$ source for asynchronous release by conducting an asynchronously activated Ca$^{2+}$ current that contributes to residual Ca$^{2+}$ (54).

Short-term Synaptic Plasticity

Neurons fire at frequencies of <1 Hz to several hundred Hz. Changes in firing rate induce different forms of synaptic plasticity. Short-term synaptic plasticity represents an increase (facilitation) or decrease (depression) in synaptic strength, which lasts from hundreds of milliseconds to seconds and is crucial for information processing (55–57). Short-term synaptic plasticity is Ca$^{2+}$-dependent and predominantly presynaptic, although postsynaptic mechanisms may also contribute (55, 56, 58, 59).

Regulation of Presynaptic Ca$^{2+}$ Channels by Ca$^{2+}$ and CaM

P/Q-type Ca$^{2+}$ currents recorded in the large calyx of Held synapse in the brain stem or in transfected non-neuronal cells expressing Ca$_V$2.1 channels facilitate in response to pairs or short trains of depolarizations (7, 8, 60, 61) and inactivate in response to prolonged trains (8, 62, 63). Both facilitation and inactivation are Ca$^{2+}$-dependent, and the facilitation process has higher affinity and/or more rapid binding of Ca$^{2+}$ than the inactivation process, as judged by sensitivity to intracellular chelators (8).

Both Ca$^{2+}$-dependent facilitation and inactivation of Ca$_V$2.1 channels are dependent on interaction with CaM (8), which binds to a modified IQ-like domain (IM motif) and a downstream CaM-binding domain (CBD) (Fig. 2A) (7, 9, 10). Ca$^{2+}$-dependent facilitation is reduced by mutations in C-terminal EF-hands of CaM and by complementary mutations in the IM motif of Ca$_V$2.1 channels (7, 9, 10). In contrast, Ca$^{2+}$-dependent inactivation is inhibited by mutations in the N-terminal lobe of CaM and by deletion of the CBD of Ca$_V$2.1 channels (7, 9, 10). Based on these results, a model has been proposed in which local Ca$^{2+}$ causes facilitation through interaction of the C-terminal lobe of CaM with the IM motif, whereas global Ca$^{2+}$ causes inactivation of Ca$_V$2.1 channels by binding of the N-terminal lobe of CaM to the CBD (Fig. 2B).

CaM can bind to Ca$_V$2 channels without or with Ca$^{2+}$ bound (64). Multiphoton microscopy and rapid microfluidic mixing revealed conformational changes in the CaM C-terminal lobe with a time constant of ~0.5 ms and in the CaM N-terminal lobe with a time constant of ~20 ms (65). These rate constants are faster than facilitation and inactivation of Ca$_V$2.1 channels, but lobe-specific conformational transitions in CaM would be slowed by binding to a regulatory target that requires additional conformational changes as part of its regulatory mechanism. Thus, Ca$^{2+}$ binding to CaM prebound to Ca$_V$2.1 channels may induce two sequential conformational changes, which in turn induce facilitation and inactivation (Fig. 2B).

Crystal structures of CaM bound to short peptides containing the IQ motif show that both lobes of Ca$^{2+}$/CaM bind this sequence (66, 67). Complexes of CaM with IQ motif-containing peptides from Ca$_V$2.1, Ca$_V$2.2, and Ca$_V$2.3 channels all have similar structures, even though Ca$_V$2.1 channels show much stronger facilitation (68). Available crystal structures of CaM with the IQ motif bound contain only short peptides from Ca$_V$2.1 (66–68), which may not retain their native structures. Crystal structures of the C-terminal domain of Ca$_V$2 channels containing the IM motif and CBD binding sites in their native structural context with bound CaM would be very informative in determining the structural basis for Ca$_V$2 facilitation and inactivation.

Ca$^{2+}$ Channel Regulation and Short-term Facilitation

Much evidence indicates that short-term facilitation is caused by residual Ca$^{2+}$ that builds up from action potentials (55, 56). However, the molecular mechanism by which residual Ca$^{2+}$ induces synaptic plasticity remains unknown. Two major effector mechanisms have been proposed for facilitation. In one, facilitation is proposed to result from saturation of local Ca$^{2+}$ buffers, such as calbindin-D28k and parvalbumin (69–71). These Ca$^{2+}$ buffers are partially saturated by residual Ca$^{2+}$, resulting in an additional Ca$^{2+}$ increase during subsequent action potentials (69–71). The second mechanism suggests residual Ca$^{2+}$ binds to a Ca$^{2+}$ sensor other than that for exocytosis and activates it to increase the probability of release. Unlike Ca$^{2+}$ buffers, Ca$^{2+}$ sensor proteins bind Ca$^{2+}$ and undergo a conformational change to regulate targets (72). Activation of a Ca$^{2+}$ sensor protein could increase Ca$^{2+}$ entry and thereby enhance neurotransmitter release according to the power law (12) or could directly modulate exocytosis (73, 74). Increased Ca$^{2+}$ entry could result from Ca$^{2+}$-dependent increase in Ca$^{2+}$ channel activity by facilitation, which occurs on the millisecond time scale. Alternatively, Ca$^{2+}$ channel density at the active zone could be increased, which increases synaptic strength (19, 24, 25), but there is no evidence to date that Ca$^{2+}$ channels can be inserted into active zones on the millisecond time scale.

At the calyx of Held, activity-dependent increase in P/Q-type Ca$^{2+}$ current correlates with synaptic facilitation according to the power law (75, 76). In Ca$_V$2.1 ch$_{14}$ subunit-deficient knock-out mice, activity-dependent facilitation of presynaptic Ca$^{2+}$ current and synaptic facilitation are lost (75–77), and the remaining synaptic transmission driven by presynaptic N-type Ca$^{2+}$ currents does not cause facilitation of Ca$^{2+}$ current or synaptic strength (77). These data suggest that Ca$^{2+}$ entry through Ca$_V$2.1 channels is necessary for synaptic facilitation at the calyx of Held; however, quantitative comparisons indicate that facilitation via Ca$^{2+}$ channels accounts for no more than half of the synaptic facilitation at the mature synapse (78).

Analysis of presynaptic Ca$^{2+}$ channel regulation in synaptic transmission using molecular methods is challenging because of the need to alter regulation only in the presynaptic cell. Superior cervical ganglion (SCG) neurons provide a unique expression system. They lack Ca$_V$2.1 channels, which are expressed primarily in central neurons, and their large cell bodies allow microinjection of cDNA encoding Ca$_V$2.1 channels, which triggers synaptic transmission at 30–40% of the level of endogenous Ca$_V$2.2 channels (79). The contribution of Ca$_V$2.1 channels to synaptic transmission can be isolated by blocking...
endogenous Ca\textsubscript{\textalpha}2.2 channels with \omega-conotoxin GVIA. As in the calyx of Held, synaptic transmission mediated by P/Q-type Ca\textsuperscript{2+} currents through transfected Ca\textsubscript{\textalpha}2.1 channels in SCG neurons undergoes short-term facilitation and depression (11). Mutation of the IM motif prevents synaptic facilitation by paired pulses or trains (11). These results show that facilitation of the activity of Ca\textsubscript{\textalpha}2.1 channels by binding of CaM to these motifs is the primary mechanism of synaptic facilitation in transfected SCG neurons expressing Ca\textsubscript{\textalpha}2.1 channels.

**Ca\textsuperscript{2+} Channel Regulation and Short-term Depression**

Synaptic depression reduces the strength of synaptic transmission during paired pulses (paired-pulse depression) or longer trains of stimuli. Depression results primarily from depletion of the readily releasable pool of synaptic vesicles that can be released with high probability in response to Ca\textsuperscript{2+} signals (56, 80). After prolonged stimulation, depletion of the readily releasable pool can result from physical depletion of the total pool of synaptic vesicles observed in electron microscopy at neuromuscular and ganglionic synapses (81, 82). However, studies using short trains of stimuli suggest that short-term synaptic depression is independent of vesicle depletion (63, 83). At the calyx of Held, even after complete depletion of the readily releasable pool of vesicles by repetitive stimulation, substantial neurotransmitter release can be elicited by light-induced uncaging of Ca\textsuperscript{2+} simultaneously throughout the nerve terminal (Fig. 3A) (84). Remarkably, the remaining synaptic vesicles respond as rapidly as those recruited by action potentials and have similar sensitivity to Ca\textsuperscript{2+} (Fig. 3B) (84). Thus, depletion of the readily releasable pool by repeated action potentials reflects selective depletion of docked vesicles near functionally active Ca\textsuperscript{2+} channels, leaving other distant docked vesicles ready to be released with normal sensitivity by the uncaging of Ca\textsuperscript{2+} near them. These results indicate that the pool of vesicles released in response to action potentials is docked near active Ca\textsuperscript{2+} channels. Vesicles docked far from Ca\textsuperscript{2+} channels or near inactivated Ca\textsuperscript{2+} channels cannot participate in the readily releasable pool accessed by action potential-triggered neurotransmission.

Decreased release probability caused by decreased Ca\textsuperscript{2+} entry due to changes in action potential waveform (85) or feed-back inhibition by metabotropic autoreceptors (86, 87) has been proposed to contribute to short-term synaptic depression. Moreover, physiological studies of the calyx of Held showed that Ca\textsuperscript{2+}-dependent inactivation of the presynaptic P/Q-type current correlates with the rapid phase of synaptic depression (62, 63, 88). Because inactivation of Ca\textsuperscript{2+} channels would transiently remove synaptic vesicles docked nearby from the functional readily releasable pool, inactivation of Ca\textsuperscript{2+} channels would contribute to synaptic depression that is measured as a reduction in the readily releasable pool of vesicles in response to action potentials. CaM inhibitors partially relieve inactivation of the presynaptic Ca\textsuperscript{2+} current and reduce synaptic depression (63), suggesting that synaptic depression is Ca\textsuperscript{2+}/CaM-dependent.

An essential role for regulation of Ca\textsuperscript{2+}/CaM-dependent inactivation of Ca\textsubscript{\textalpha}2.1 channels in short-term synaptic depression was demonstrated in transfected SCG neuron synapses (11). Deletion of the CBD in the C terminus of transfected Ca\textsubscript{\textalpha}2.1 channels, which blocks inactivation of P/Q-type Ca\textsuperscript{2+} currents (7, 10), reduced paired-pulse depression and rapid synaptic depression during trains (11). These data show directly that CaM binding to the CBD induces inactivation of presynaptic Ca\textsubscript{\textalpha}2.1 channels, which in turn causes rapid synaptic depression evoked by physiological activity patterns. A slower phase of synaptic depression in SCG synapses expressing mutant Ca\textsubscript{\textalpha}2.1 channels may be caused by physical depletion of the synaptic vesicle pool.
CaV2 channel function is greatly influenced by auxiliary CaVβ subunits, and CaVβ4a and CaVβ2a have marked effects on synaptic plasticity (89). Expression of CaVβ2a in cultured neurons favors synaptic depression, whereas expression of CaVβ4a favors facilitation (89). Expression of the 14-3-3 protein also modulates the rate of synaptic depression in cultured neurons by changing the rate of inactivation of CaV2.2 channels, further supporting a role of inactivation of presynaptic Ca2+ channels in rapid synaptic depression (90). Thus, Ca2+-dependent inactivation of CaV2.2 channels is a negative feedback process that prevents excessive Ca2+ entry and also mediates a rapid phase of depression of synaptic transmission.

**Regulation of CaV2 Channels by Neuronal Ca2+ Sensor Proteins**

CaM belongs to a superfamily of CaS (Ca2+ sensor) proteins, and some CaS proteins are highly expressed in neurons (72, 91). Like CaM, CaS proteins have four EF-hand Ca2+-binding motifs organized in two lobes connected by a central α-helix. However, in contrast to CaM, at least one of the two N-terminal EF-hands of CaS proteins does not bind Ca2+ due to changes in amino acid sequence, and CaS proteins share a consensus sequence for N-terminal myristoylation (72).

CaBP1 (Ca2+-binding protein-1) is similar to CaM in amino acid sequence but is differentially expressed in neurons (92). It is co-localized with presynaptic CaV2.1 channels and binds to the CBD of the CaV2.1 α1 subunit (93). However, binding of CaBP1 causes rapid CaV2.1 inactivation in a Ca2+-independent manner, and it does not support CaV2.1 facilitation (Fig. 4A) (93). Thus, the changes in amino acid sequence of CaBP1 have profound effects on its regulatory properties. VILIP-2 (visinin-like protein-2), which is highly expressed in the neocortex and hippocampus (72), has complementary regulatory effects to CaBP1: it increases CaV2.1 facilitation but inhibits CaV2.1 inactivation (Fig. 4A) (94). Thus, CaBP1 and VILIP-2 bind to the same site as CaM but have opposite effects on CaV2.1 channel activity.

Analysis of chimeras in which intact domains from neuronal CaS proteins were transferred to CaM has begun to unravel the molecular code used by CaS proteins to induce their different effects on CaV2.1 channels. Myristoylation of the N termini of CaBP1 and VILIP-2 is required for their distinctive regulatory effects (95), implicating the unique N-terminal domains of CaS proteins in differential modulation. However, transfer of the N-terminal domains of CaBP1 and VILIP-2 to CaM is necessary, but not sufficient, to induce their distinct regulatory properties (95, 96). The second EF-hand motif of CaBP1, which is inactive in Ca2+ binding, is also required to enhance inactivation of CaV2.1 channels (96). These results imply that EF-hand 2 is in an active conformation with respect to channel regulation, even though it does not bind Ca2+. Unlike CaBP1, transfer of the central α-helix, EF-hands 3 and 4, and the N-terminal domain of VILIP-2 is required for its regulation of CaV2.1 channels (97). Thus, VILIP-2 uses a complex set of interactions of three of its domains with the IM and CBD motifs in regulation of CaV2.1 channels. These results point to the importance of conformationally intact domains of CaS proteins and their target sites on CaV2.1 channels in mediating channel regulation. Defining the structural domains of CaV2.1 channels that interact with these crucial domains of CaS proteins will give much needed insight into the structural basis for their selective modulation of CaV2.1 channels.

**Regulation of Synaptic Plasticity by Ca2+ Sensor Proteins Acting on Ca2+ Channels**

Different synapses show diverse patterns of facilitation and depression, and the underlying mechanism for this diversity is unknown (56, 57). The differential regulatory effects of CaM, CaBP1, and VILIP-2 on CaV2.1 channel activity are potentially important determinants of this diversity of short-term synaptic plasticity, which would substantially change the encoding properties of the synapse in response to trains of action potentials (57). Residual Ca2+ in active zones can act on CaS proteins to enhance synaptic facilitation. For example, NCS-1 (neuronal Ca2+ sensor-1) increases presynaptic facilitation at the calyx of Held by accelerating activation of P/Q-type Ca2+ currents (98). Similarly, in cultured hippocampal neurons, expression of NCS-1 enhances synaptic transmission (74). These results sug-
uggest that residual Ca$^{2+}$ facilitates the activity of Ca$_{v}$2.1 channels via NCS-1. However, no evidence has emerged indicating that NCS-1 acts directly by binding to Ca$_{v}$2.1 channels.

The ability of CaBP1 and VILIP-2 to fine-tune short-term synaptic plasticity by regulation of Ca$_{v}$2.1 channels has been shown directly by expression of wild-type and mutant Ca$_{v}$2.1 channels with CaS proteins in SCG neurons (99). Expression of Ca$_{v}$2.1 channels with CaBP1, which enhances inactivation of Ca$_{v}$2.1 currents, causes loss of synaptic facilitation and enhanced synaptic depression in SCG neurons (93, 99). Expression of Ca$_{v}$2.1 with VILIP-2, which enhances facilitation of Ca$_{v}$2.1 currents (94), causes reduced synaptic depression and enhanced synaptic facilitation (Fig. 4C) (99). These functional effects are lost when the IM motif and CBD are mutated (Fig. 4, B and C) (99). These results show that CaBP1 and VILIP-2 act directly on Ca$_{v}$2.1 channels by binding to their C-terminal regulatory site and cause push-pull regulation of the form of short-term synaptic plasticity, with CaBP1 favoring depression and VILIP-2 favoring facilitation. It is likely that fine-tuning of synaptic facilitation and depression by CaS proteins plays an important role in determining the diversity of short-term synaptic plasticity at CNS synapses.

Conclusion

Classical physiological studies of neuromuscular transmission revealed short-term synaptic facilitation and depression and demonstrated that residual Ca$^{2+}$ resulting from action potentials was involved in synaptic facilitation. However, the molecular mechanisms that underlie short-term synaptic facilitation and depression have remained uncertain until recently. As reviewed here, increasing evidence now supports regulation of presynaptic Ca$_{v}$2.1 channels by direct binding of CaM and CaS proteins as a major contributor to short-term synaptic plasticity in two different experimental preparations: the calyx of Held and the transfected SCG neuron. No doubt, other molecular mechanisms also contribute to this important Ca$^{2+}$ signaling process. However, at this stage, regulation of presynaptic Ca$^{2+}$ channels by binding of CaM and CaS proteins is the only molecular mechanism that has been demonstrated to be capable of generating and regulating short-term synaptic plasticity in situ in synapses. Further analysis of this crucial regulatory mechanism should reveal its molecular and structural basis and its role in neuronal circuits important for learning, memory, and behavior.

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