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Calcium Channels, Synaptic Plasticity, and Neuropsychiatric Disease

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Voltage-gated calcium channels couple depolarization of the cell-surface membrane to entry of calcium, which triggers secretion, contraction, neurotransmission, gene expression, and other physiological responses. They are encoded by ten genes, which generate three voltage-gated calcium channel subfamilies: Ca_V1; Ca_V2; and Ca_V3. At synapses, Ca_V2 channels form large signaling complexes in the presynaptic nerve terminal, which are responsible for the calcium entry that triggers neurotransmitter release and short-term presynaptic plasticity. Ca_V1 channels form signaling complexes in postsynaptic dendrites and dendritic spines, where their calcium entry induces long-term potentiation. These calcium channels are the targets of mutations and polymorphisms that alter their function and/or regulation and cause neuropsychiatric diseases, including migraine headache, cerebellar ataxia, autism, schizophrenia, bipolar disorder, and depression. This article reviews the molecular properties of calcium channels, considers their multiple roles in synaptic plasticity, and discusses their potential involvement in this wide range of neuropsychiatric diseases.

Voltage-gated calcium channels activate in response to membrane depolarization and conduct calcium into the cell, where it initiates many physiological responses, including secretion, contraction, and gene transcription (Catterall, 2011; Zamponi et al., 2015). Calcium often binds to target proteins rapidly and locally, creating a microdomain or nanodomain of calcium signaling (Llinás et al., 1992; Stanley, 1997; Wang and Augustine, 2015), and calcium channel function is regulated by binding calcium itself, by binding other ligands, and by protein phosphorylation in this local domain of calcium signaling (Catterall, 2011; Zamponi et al., 2015). Mutations of calcium channels and dysregulation of their function is implicated in a wide range of diseases, including hypertension, arrhythmia, and heart failure in the cardiovascular system (Liao and Soong, 2010; Venetucci et al., 2012); periodic paralysis of skeletal muscle (Jurkat-Rott and Lehmann-Horn, 2006; Venance et al., 2006); failure of insulin release and apoptosis of pancreatic beta cells in diabetes (Yang et al., 2014); migraine and chronic pain (Bourinet et al., 2014; Pietrobon, 2013); and numerous brain disorders (Heyes et al., 2015; Liao and Soong, 2010; Ortner and Striessnig, 2016). Voltage-gated calcium channels in sensory neurons are also implicated in chronic pain syndromes, as reviewed recently elsewhere (Patel et al., 2017; Snutch and Zamponi, 2017). This review focuses on recent research that elucidates molecular mechanisms for local calcium channel regulation and suggests new implications for calcium channel mutation and dysfunction in neuropsychiatric diseases, such as migraine, cerebellar ataxia, Parkinson's disease, autism, schizophrenia, bipolar disorder, and depression.

Voltage-Gated Calcium Channels

Voltage-gated calcium channels are multi-subunit complexes of a central pore-forming α_1 subunit with multiple auxiliary subunits (Catterall, 2011). The overall structure of the skeletal muscle calcium channel is illustrated in cartoon form from early biochemical studies (Takahashi et al., 1987) and in three-dimensional form from recent cryoelectron microscopic studies (Wu et al., 2015, 2016) in Figure 1. The α_1 subunit forms the pore in the center of four homologous domains composed of six transmembrane segments each. The S1–S4 segments form the four voltage sensors located on the periphery of the pore, whereas the S5 and S6 segments and the P loop form the central pore itself. The long C terminus of the α_1 subunit is a major target for regulation by intracellular signaling processes.

Skeletal muscle calcium channels have four auxiliary subunits (Figure 1; Catterall, 2011; Takahashi et al., 1987; Zamponi et al., 2015). The disulfide-linked α_2 and δ subunits are encoded by a single gene and produced by posttranslational proteolytic cleavage, disulfide linkage, and addition of a glycophosphatidylinositol lipid anchor (Davies et al., 2010; De Jongh et al., 1990; Jay et al., 1991). The β subunit is bound on the intracellular surface of the channel (Pragnell et al., 1994). The γ subunit has four transmembrane segments that interact with the voltage sensor in domain IV of the α_1 subunit (Jay et al., 1990; Wu et al., 2016).

Calcium Channel Diversity

Early electrophysiological studies detected distinct types of calcium currents. L-type calcium currents were first recorded in cardiac myocytes (Reuter, 1983). They are distinguished by slow voltage-dependent inactivation and block by calcium antagonist drugs, such as dihydropyridines and phenylalkylamines. N-, P/Q-, and R-type calcium currents have faster voltage-dependent inactivation, are found primarily in neurons, and are blocked by peptide toxins from spiders and snails (Llinás et al., 1989; Nowycky et al., 1985; Olivera et al., 1994). T-type calcium currents are activated at negative membrane potentials, and they

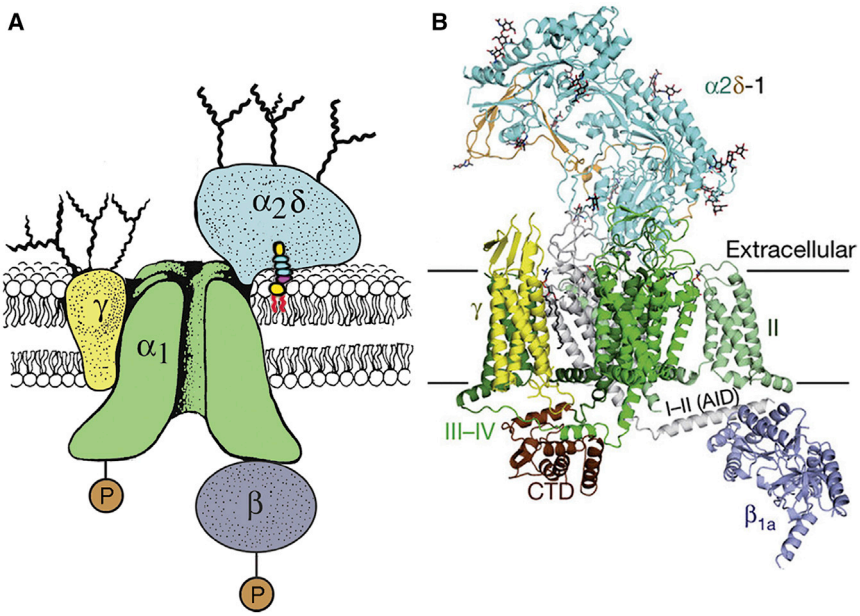

Figure 1. Subunit Architecture of Calcium Channels

(A) Model of the skeletal muscle calcium channel from biochemical studies (Takahashi et al., 1987) showing the central pore-forming α1 subunit with associated intracellular β subunit, a transmembrane complex of α2 and δ subunits, and a transmembrane γ subunit. Black curved lines represent carbohydrate chains. P in a circle represent sites of protein phosphorylation. This model has been updated to show the αδ2 subunit with a glycophosphatidylinositol anchor as discovered by A. Dolphin and colleagues (Davies et al., 2010).

(B) The structure of the skeletal muscle calcium channel from cryoelectron microscopy (Wu et al., 2016). Colors match those of (A), except that the large C-terminal domain of the α1 subunit is seen separately in reddish gray. Note that the lipid anchor of the δ subunit (brown) is displaced upward away from the apparent position of the cell membrane in this cryoelectron microscopy (cryo-EM) structure, probably because it is interacting with detergent rather than the cell membrane, which is not present in the cryo-EM preparation.

This figure was adapted with permission from Wu et al., 2016.

have fast deactivation upon repolarization and fast voltage-dependent inactivation during sustained depolarizations (Carbone and Lux, 1984; Nowycky et al., 1985). They are prominent in cardiac myocytes in the sinoatrial node and in neurons in the thalamus (Deleuze et al., 2012; Mesirca et al., 2015).

Three calcium channel families with ten distinct α_1 subunits are primarily responsible for the diversity of calcium current types observed physiologically (Catterall, 2011; Zamponi et al., 2015). $Ca_V1.1$, $Ca_V1.2$, $Ca_V1.3$, and $Ca_V1.4$ channels conduct L-type calcium currents. These channels have diverse functions, including initiation of contraction, hormone secretion, and local calcium signaling to gene transcription. $Ca_V2.1$, $Ca_V2.2$, and $Ca_V2.3$ channels conduct P/Q-, N-, and R-type calcium currents, respectively (Olivera et al., 1994). These channels initiate synaptic transmission in neurons and also serve important functions in calcium signaling in neuronal cell bodies and dendrites. $Ca_V3.1$, $Ca_V3.2$, and $Ca_V3.3$ channels conduct T-type calcium currents, which drive rhythmic generation of action potentials in the sinoatrial node of the heart, thalamic neurons important in sustaining sleep rhythms, and other types of neurons and endocrine cells (Zamponi et al., 2015). Many of these calcium channel subunits are extensively modified by alternative splicing of their mRNAs, which leads to further significant functional differences (Liao et al., 2009; Lipscombe et al., 2013).

The auxiliary subunits also contribute to calcium channel diversity, as they are encoded by four α2δ genes, four β subunit genes, and nine γ subunit genes (Arikkath and Campbell, 2003). Ca_V1 and Ca_V2 families of calcium channels have α2δ and β subunits, which are broadly distributed across the different channel subtypes. Surprisingly, only the γ_1 subunit is associated with calcium channels. The other eight γ subunit genes encode transmembrane regulators of glutamate receptors that initiate excitatory neurotransmission in the brain (Nicoll et al., 2006).

Calcium Channel Signaling Complexes in the Synapse

Presynaptic Calcium Channel Signaling Complexes

At synapses in the CNS and peripheral nervous system, P/Q-type calcium currents conducted by $Ca_V2.1$ channels and N-type calcium currents conducted by $Ca_V2.2$ channels serve as the primary sources of calcium entry that trigger fast neurotransmission (Dunlap et al., 1995; Olivera et al., 1994; Wheeler et al., 1994). Calcium entry through them generates a local microdomain of high calcium concentration that has molecular dimensions, on the order of 10-fold the diameter of the calcium channel itself (Llinás et al., 1992; Stanley, 1997; Wang and Augustine, 2015).

Presynaptic calcium channel proteins form large signaling complexes at active zones, which serve to bring many proteins into the microdomain of high calcium surrounding the intracellular mouth of the presynaptic calcium channels (Catterall and Few, 2008). Interactions of $Ca_V2.1$ and $Ca_V2.2$ proteins with the SNARE proteins that mediate exocytosis at the synaptic protein interaction ("synprint") site gave the initial evidence for presynaptic calcium channel signaling complexes (Lévêque et al., 1994; Sheng et al., 1994). This protein interaction increases the efficiency of neurotransmission (Mochida et al., 2008; Rettig et al., 1997) and also regulates calcium channel function (Bezprozvanny et al., 1995; Zhong et al., 1999). Presynaptic calcium channels are regulated by G protein βγ subunits released by activation of G-protein-coupled autoreceptors for many different neurotransmitters, which provide feedback inhibition of calcium channels during periods of high synaptic activity (Herlitze et al., 1996; Ikeda, 1996). These channels are also regulated by protein phosphorylation by multiple protein kinases. In two well-studied examples, phosphorylation of calcium channel proteins was found to modulate G protein regulation, providing crosstalk between these two major intracellular cell-signaling pathways (Raingo et al., 2007; Zamponi et al., 1997).

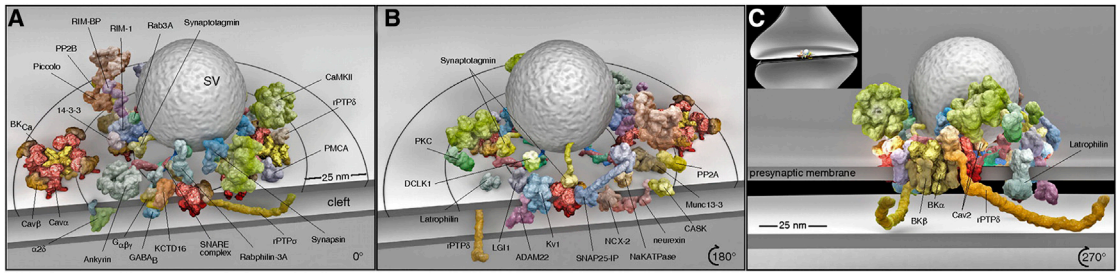

Figure 2. Model of the Protein Complex Surrounding a Presynaptic Calcium Channel

$Ca_V2.1$ channels were isolated by immunoaffinity chromatography from mouse brain, and the interacting proteins were identified by mass spectrometry (Müller et al., 2010). Mice with deletion of $Ca_V2.1$ were used as a negative control. Interacting proteins are shown to scale from structural biology studies. Selected proteins of the Ca_V2 channel proteome with documented localization to the presynaptic compartment are arranged to reflect their function, molecular structure (based on the pdb), abundance, and clustering. All proteins are represented as space-filling models, and the BK_{Ca}-Cav2 complex (*A*, left side; ~1.6 MDa) may serve as a size reference. SV, releasable synaptic vesicle.

(A–C) Views are related to each other by the indicated rotations around an axis perpendicular to the membrane.

(A) Rotation of 0°.

(B) Rotation of 180°.

(C) Rotation of 270° plus additional rotation by ~60° around a horizontal axis to reveal proteins underneath the SV. (Inset) Projection of the nano-environment into a small synapse is shown (diameter = 1 μm). This figure was adapted from (Müller et al., 2010) with permission.

The voltage-dependent conformational change that activates presynaptic calcium channels may also serve as a signal for neurotransmitter release itself, through protein interactions with the synprint site of $Ca_V2.2$ channels (Mochida et al., 1998). Recent studies provide strong support for this mechanism of voltage-dependent but calcium-independent exocytosis of ATP from dorsal root ganglion neurons at low frequency of stimulation (Chai et al., 2017). This unconventional mechanism of secretion may complement the more conventional calcium-dependent exocytosis of neurotransmitters triggered at high stimulus rates in these sensory neurons.

Protein interactions are also required for regulating cell surface expression of calcium channels and docking them at active zones. RIM and RIM-binding proteins bind to C-terminal sites on Ca_V2 channels and mediate localization and docking at active zones (Acuna et al., 2015; Han et al., 2011; Kaeser et al., 2011; Kiyonaka et al., 2007). Activity-dependent changes in calcium channel density at active zones are mediated by interactions with RIM proteins on the intracellular side (Han et al., 2011) as well as interactions of $\alpha_2\delta$ subunits on the extracellular side (Hoppa et al., 2012).

In addition to these one-on-one regulatory interactions, proteomic studies have revealed up to 100 proteins interacting with $Ca_V2.1$ and $Ca_V2.2$ channels in presynaptic terminals (Figure 2; Khanna et al., 2007; Müller et al., 2010). It is likely that many of these proteins bind to calcium channels indirectly through interactions with scaffolding proteins. However, all of the members of this large protein complex are close enough to the presynaptic calcium channels to sense and respond to changes in calcium concentration in the calcium channel microdomain. Evidently, it requires a densely packed ensemble of proteins to trigger, mediate, and regulate neurotransmitter release.

Calcium Channel Signaling Complexes in the Postsynaptic Compartment

Calcium channels in the Ca_V1 family form signaling complexes on the postsynaptic side of the membrane. $Ca_V1.2$ and $Ca_V1.3$ channels are localized in synaptic spines, dendritic shafts, and neuronal cell bodies (Hell et al., 1993, 1996). Interaction of β2 adrenergic receptors with a site in the C-terminal domain of $Ca_V1.2$ channels is important for β2-adrenergic regulation of calcium channel activity and long-term postsynaptic plasticity (Davare et al., 2001; Patriarchi et al., 2016). Protein kinases and phosphoprotein phosphatases also bind to $Ca_V1.2$ channels and are important in regulating their function (Davare et al., 2000; Dittmer et al., 2014; Fuller et al., 2010; Gray et al., 1998; Murphy et al., 2014; Oliveria et al., 2007). Thus, whereas the postsynaptic signaling complex associated with Ca_V1 channels is less extensive than the presynaptic complexes formed by Ca_V2 channels, this form of local regulation of channel function is also important for synaptic plasticity.

Calcium Channels and Short-Term Presynaptic Plasticity

In the nervous system, information is encoded in bursts and trains of action potentials rather than in single spikes. Classical studies of the neuromuscular junction first revealed short-term facilitation and rapid depression of synaptic transmission and showed that facilitation is dependent upon residual calcium that builds up in the nerve terminal during rapid trains of action potentials (Katz and Miledi, 1968; Mallart and Martin, 1967, 1968). This activity-dependent increase and decrease in synaptic strength has important implications for transmitting information encoded in the frequency and pattern of action potential generation to the postsynaptic cell in the form of changes in synaptic strength (Zucker and Regehr, 2002), and this form of synaptic plasticity is important in neural computations (Abbott and Regehr, 2004). However, in spite of their importance, the mechanisms responsible for synaptic facilitation and the rapid phase of synaptic depression have remained uncertain.

Calcium-Dependent Facilitation and Inactivation of Presynaptic Calcium Channels

$Ca_V2.1$ channels that conduct P/Q-type calcium currents in nerve terminals or transfected cells exhibit paired-pulse facilitation and facilitation during trains of depolarizing stimuli (Borst and Sakmann, 1998; Cuttle et al., 1998; Lee et al., 1999,

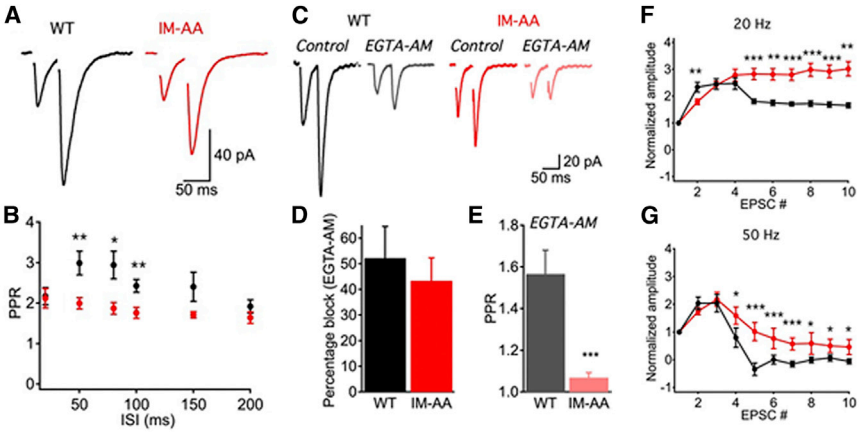

Figure 3. Altered Synaptic Plasticity in Hippocampal Neurons from IM-AA Mice
Hippocampal slices were prepared from wild-type (WT) (black) and IM-AA mutant (red) mice. Synaptic transmission from CA3 pyramidal cells to CA1 pyramidal cells was measured by whole-cell voltage clamp of the postsynaptic cell (Nanou et al., 2016b).
(A) Paired pulse facilitation.
(B) Paired-pulse ratio (PPR) as a function of inter-stimulus interval (ISI) from 20 to 200 ms.
(C) Paired-pulse facilitation in control and in the presence of intracellular EGTA.
(D) Percentage block of EPSC by treatment with 100 μM EGTA-AM.
(E) PPR in the presence of 100 μM EGTA-AM.
(F) Normalized EPSC amplitude during a train of stimuli at 20 Hz.
(G) Normalized EPSC amplitude during a train of stimuli at 50 Hz.

2000a). This upregulation of channel activity results from calcium interaction with the high-affinity C-terminal EF hands 3 and 4 of calmodulin bound to a calcium sensor (CaS) protein regulatory site in the C-terminal domain of $Ca_V2.1$ channels (DeMaria et al., 2001; Lee et al., 1999, 2000a, 2003). Local increases in intracellular calcium are sufficient to cause facilitation of channel activity, because facilitation is not prevented by intracellular EGTA, which prevents global increases in intracellular calcium concentration (DeMaria et al., 2001; Lee et al., 2000a). Prolonged or repetitive activation of $Ca_V2.1$ channels causes progressive inactivation of the calcium current on the 100 ms to 1 s timescale as calcium binds to the lower affinity N-terminal EF hands 1 and 2 of calmodulin in the CaS protein regulatory site (DeMaria et al., 2001; Lee et al., 2000a, 2003). Prevention of calmodulin regulation by introducing the IM-AA mutation in the calmodulin regulatory site (Zühlke et al., 2000) blocks facilitation of the $Ca_V2.1$ channel (DeMaria et al., 2001; Lee et al., 2003). These forms of regulation of calcium channels in presynaptic nerve terminals could be major contributors to local generation of synaptic facilitation and rapid depression in response to incoming calcium (Catterall et al., 2013). Although $Ca_V2.2$ channels and $Ca_V2.3$ channels also undergo calcium-dependent regulation, they do not have a comparable high-affinity phase of calcium-induced facilitation of their N-type and R-type calcium currents (Liang et al., 2003), suggesting that $Ca_V2.1$ channels may confer unique facilitating properties on synaptic function.

Calcium Sensor Proteins Modulate Facilitation and Inactivation of $Ca_V2.1$ Channels

There is a large family of CaS proteins related to calmodulin in structure and function that are differentially expressed in the CNS, including neural calcium sensor-1 (NCS-1), calcium binding protein-1 (CaBP-1), and visinin-like protein 2 (VILIP-2) (Girard et al., 2015; Haeseleer and Palczewski, 2002). These calmodulin-related CaS proteins displace calmodulin from their common regulatory site in the C-terminal domain of $Ca_V2.1$ channels and alter the ratio of facilitation to inactivation (Lautermilch et al., 2005; Lee et al., 2002; Yan et al., 2014). VILIP-2 and NCS-1 increase facilitation and oppose inactivation (Lautermilch et al., 2005; Tsujimoto et al., 2002; Yan et al., 2014). CaBP-1 opposes facilitation and increases rapid inactivation (Lee et al., 2002). Thus, these CaS proteins can serve as a biphasic switch, converting $Ca_V2.1$ channels from facilitation to inactivation and vice versa.

Calcium Channel Regulation and Synaptic Facilitation

In the large Calyx of Held synapse, where presynaptic calcium currents can be measured by voltage clamp recording, $Ca_V2.1$ channels are required for synaptic facilitation (Inchauspe et al., 2004). Calcium-dependent facilitation and inactivation of $Ca_V2.1$ channel currents correlates in voltage and time with calcium-dependent facilitation and the rapid phase of depression of synaptic transmission (Borst and Sakmann, 1998; Cuttle et al., 1998; Forsythe et al., 1998; Xu and Wu, 2005). Exogenous expression of $Ca_V2.1$ channels in superior cervical ganglion (SCG) neurons in cell culture, with endogenous Ca^{2+} currents specifically blocked by a toxin, induces synaptic facilitation that requires binding of calmodulin to the CaS protein regulatory site and is prevented by the IM-AA mutation (Mochida et al., 2008). Regulation of these transfected $Ca_V2.1$ channels by co-expressed CaS proteins induced bidirectional changes in synaptic strength: NCS-1 and VILIP-2 enhanced facilitation and blocked rapid depression whereas CaBP1 blocked facilitation and enhanced depression (Leal et al., 2012; Yan et al., 2014). Thus, the results from both the Calyx of Held and transfected SCG neurons support an important role for regulation of $Ca_V2.1$ channels by CaS proteins in generation and regulation of short-term facilitation and rapid depression of synaptic transmission (Catterall et al., 2013).

Important information on the function of CaS protein regulation of $Ca_V2.1$ channels *in vivo* has come from studies of a mouse line in which the IM-AA mutation was inserted in the gene encoding $Ca_V2.1$ (Nanou et al., 2016b). The IM-AA mutation reduced synaptic facilitation at the neuromuscular junction (Nanou et al., 2016c) and at the synapses made by Schaffer collaterals from CA3 neurons onto CA1 neurons in the hippocampus by ~50% (Figures 3A and 3B; Nanou et al., 2016b). Moreover, the IM-AA mutation completely prevented synaptic facilitation at the hippocampal synapses when intracellular EGTA was present to prevent global increases in calcium concentration (Figures 3C–3E; Nanou et al., 2016a, 2016b). Thus, at these important synapses, regulation of $Ca_V2.1$ channels by calcium and CaS proteins is required for essentially all synaptic facilitation that is mediated by local calcium signaling.

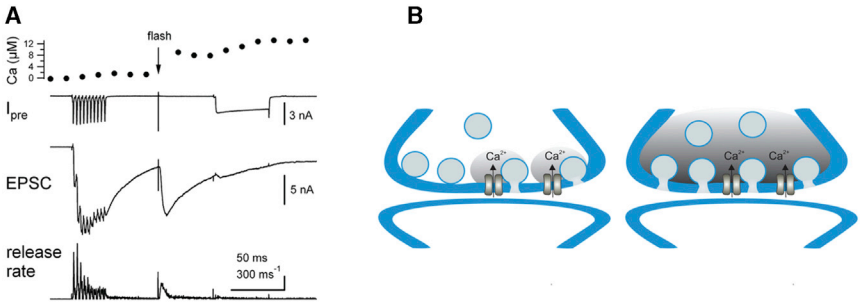

Figure 4. Calcium Dependence of the Readily Releasable Pool at the Calyx of Held

(A) Local calcium entry defines the readily releasable pool. In the first phase of the experiment on the Calyx of Held, the presynaptic terminal was stimulated to generate a series of presynaptic Ca^{2+} currents (I_{pre}; upper trace), which elicited a series of excitatory postsynaptic currents (EPSCs) (middle trace). Calculation of the total neurotransmitter release showed a rise and fall in the release rate during the train (lower trace). Following the train, a single light flash was given (arrow), and the resulting EPSC and neurotransmitter release were recorded. Integration of the EPSCs showed that 66% of the total pool of synaptic vesicles was released during the train of action potentials, and 34% was released by uncaging of Ca^{2+}. The rate and Ca^{2+} sensitivity of the synaptic vesicles released by the light flash were the same as those released by action potentials. These results show that proximity to a source of cytosolic calcium limits the size of the readily releasable pool. This figure was reproduced with permission (Wadel et al., 2007).

(B) A model illustrating four docked synaptic vesicles, two tethered near $Ca_V2.1$ channels and two docked farther away. (Left) Ca^{2+} entry through $Ca_V2.1$ channels induces exocytosis from the two synaptic vesicles docked near the channels, but not from the two docked farther away. (Right) A general increase in Ca^{2+} from photo-uncaging causes neurotransmitter release from all four docked synaptic vesicles.

This figure was adapted with permission from Catterall et al., 2013.

Calcium Channel Inactivation and Rapid Synaptic Depression

Classical studies showed that repeated stimulation of the neuromuscular junction and SCG synapses for several minutes caused physical depletion of synaptic vesicles as assessed by electron microscopy (Dickinson-Nelson and Reese, 1983; Heuser and Reese, 1973). These studies led to the assumption that synaptic depression is caused by physical depletion of synaptic vesicles. At most synapses, rapid depression in paired pulses or brief trains of stimuli occurs on the ms timescale (Zucker and Regehr, 2002). Measurement of the number of physically docked synaptic vesicles on this timescale in general is impractical (but see Watanabe et al., 2013); therefore, measurement of the readily releasable pool of vesicles that can be mobilized by a train of stimuli of 1 s duration has been widely used as a functional surrogate for the physically docked pool of synaptic vesicles. This approach shows that the readily releasable pool of synaptic vesicles is indeed reduced during rapid depression (Schneggenburger et al., 2002). However, is it correct that rapid reduction of the readily releasable pool of synaptic vesicles can be equated with loss of physically docked synaptic vesicles or are other functional mechanisms involved?

In addition to docking at the plasma membrane, it seems evident that docked synaptic vesicles must be located near active calcium channels to provide calcium influx to trigger their release in order to be included in the functionally defined readily releasable pool. In a provocative study, Wadel et al. (2007) used uncaging of calcium within the presynaptic terminal of the Calyx of Held to test the idea that proximity to active calcium channels is required for synaptic vesicles to be in the readily releasable pool (Figure 4). They found that, even after complete exhaustion of the readily releasable pool of vesicles by repetitive stimulation, a large pool of remaining synaptic vesicles could also be released with similar kinetics and calcium sensitivity if intracellular calcium was increased rapidly and globally by photoactivated uncaging (Figure 4A; Wadel et al., 2007). Their results suggest that inactivation of presynaptic calcium channels would cause nearby synaptic vesicles to leave the functional readily releasable pool, even though such docked vesicles would not have moved physically (Figure 4B).

In fact, strong evidence has accumulated that the rapid phase of synaptic depression is indeed caused by calcium channel inactivation. At the Calyx of Held, the rapid phase of synaptic depression is temporally correlated with calcium-dependent inactivation of the P/Q-type calcium current conducted by $Ca_V2.1$ channels (Forsythe et al., 1998; Xu and Wu, 2005). In SCG neurons in cell culture, synaptic transmission driven by exogenously expressed $Ca_V2.1$ channels shows rapid depression during paired pulses or rapid trains of stimuli, and this synaptic depression is prevented by a mutation that blocks CaS protein regulation of the inactivation of $Ca_V2.1$ channels (Mochida et al., 2008). Similarly, in mice harboring the IM-AA mutation in their CaS protein regulatory site, rapid synaptic depression is delayed at neuromuscular and hippocampal Schaffer collateral-to-CA1 synapses (Nanou et al., 2016b, 2016c). Moreover, in the inhibitory synapse of parvalbumin-expressing, fast-spiking interneurons onto CA1 pyramidal neurons in the hippocampus, rapid depression is observed without prior facilitation, and even this form of rapid synaptic depression was prevented by the IM-AA mutation (Nanou et al., 2018). Therefore, quite unexpectedly, inactivation of presynaptic calcium channels is the major determinant of rapid synaptic depression in this wide range of excitatory and inhibitory synapses.

Expression of Calcium Sensor Proteins Controls the Pattern of Synaptic Facilitation and Rapid Depression

The patterns of synaptic facilitation and rapid depression are diverse in different types of synapses (Abbott and Regehr, 2004). If regulation of $Ca_V2.1$ channels by calmodulin were primarily responsible for facilitation and rapid depression at all synapses, these key functional characteristics would be invariant at synapses where neurotransmission is driven by P/Q-type calcium currents because calmodulin is ubiquitously expressed. How can calcium channel regulation contribute to the diversity of synaptic function? Perfusion of NCS-1 into the presynaptic nerve terminal at the Calyx of Held increases P/Q-type calcium currents and synaptic facilitation (Tsujimoto et al., 2002). NCS-1 and VILIP-2 increase facilitation and oppose inactivation

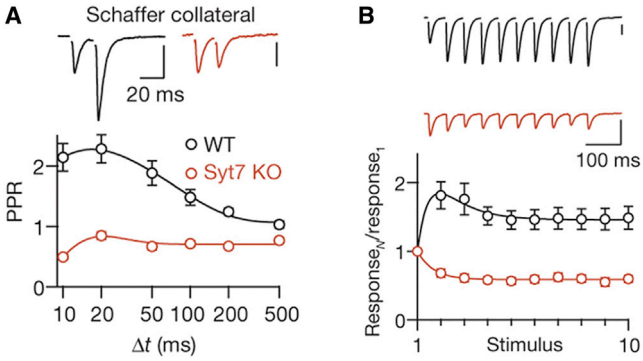

Figure 5. Synaptotagmin-7 and Short-Term Synaptic Facilitation
Hippocampal slices were prepared, and synaptic transmission was measured from CA3 pyramidal cells to CA1 pyramidal cells by whole-cell voltage clamp of the postsynaptic cell (Jackman et al., 2016).
(A) PPR.
(B) Normalized EPSCs recorded in response to a train of stimuli at 20 Hz.
This figure was adapted with permission from Jackman et al., 2016.

of the $Ca_V2.1$ calcium current (Lautermilch et al., 2005; Yan et al., 2014), whereas CaBP-1 blocks facilitation and enhances rapid inactivation (Lee et al., 2002). Remarkably, expression of these CaS proteins in SCG synapses in cell culture whose neurotransmission is driven by exogenously expressed $Ca_V2.1$ channels causes increased facilitation in the case of VILIP-2 and NCS-1 but enhanced depression in the case of CaBP-1 (Leal et al., 2012; Yan et al., 2014). Moreover, in mice bearing the IM-AA mutation, the rapid depression of the inhibitory synapse of parvalbumin-expressing, fast-spiking basket cells onto CA1 neurons is prevented by gene deletion of CaBP-1/caldendrin, indicating that short-term synaptic plasticity is governed by regulation of $Ca_V2.1$ channels by CaBP-1 at this important synapse *in vivo* (Nanou et al., 2018).

Physiological Roles of Calcium-Channel-Dependent Synaptic Facilitation and Rapid Depression In Vivo

The IM-AA mouse line bearing a mutation in the CaS protein regulatory site on $Ca_V2.1$ channels has allowed the first tests of the significance of calcium-channel-dependent synaptic plasticity for neural circuit function and for physiological processes *in vivo*. Surprisingly strong physiological effects were observed. At the neuromuscular junction, block of synaptic plasticity by the IM-AA mutation reduced muscle strength in the critical range of stimulation frequency from 50 to 100 Hz, which impaired motor coordination and decreased total exercise capacity (Nanou et al., 2016c). In the hippocampus, input to CA1 pyramidal neurons via the disynaptic circuit from CA3 neurons through inhibitory parvalbumin-expressing basket cells was reduced in IM-AA mice compared to the direct connection from CA3 Schaffer collaterals to CA1 neurons, which increased the excitation-to-inhibition ratio for input to CA1 cells by up to 10-fold (Nanou et al., 2018). This dramatic effect on local neural circuit function was accompanied by weakened long-term potentiation (LTP) at the synapse of Schaffer collaterals onto CA1 neurons and by major losses of spatial learning and memory in the context-dependent fear conditioning and Barnes maze tests (Nanou et al., 2016a). Although the detailed mechanisms remain under investigation, the alterations in synaptic plasticity caused by the IM-AA mutation may contribute directly to impairment of spatial learning by altering generation of sharp-wave ripples, which occur on the same ms timescale, and the changes in excitation/inhibition ratio and LTP may indirectly alter the formation and extinction of place cells on the longer timescales relevant for memory formation and retention. These results illuminate the long-expected (Zucker and Regehr, 2002) large physiological effects of seemingly small disruptions of calcium channel regulation and short-term synaptic plasticity.

SNARE Protein Regulation and Short-Term Synaptic Plasticity

As originally defined (Katz and Miledi, 1968), short-term synaptic facilitation results from residual calcium that remains in the nerve terminal from one action potential and adds to the effects of calcium entering in the subsequent closely spaced action potential on the ms timescale. The second excitatory or inhibitory postsynaptic response has similar kinetics as the first one, rising and decaying in a few milliseconds. As discussed above, the presynaptic calcium channel itself can serve as a calcium sensor for this residual calcium through calcium-dependent facilitation or inactivation of the second calcium current itself. What other mechanisms might also contribute to short-term synaptic plasticity within the nerve terminal? It has often been hypothesized that the SNARE protein complex that serves as the effector of synaptic vesicle exocytosis might be the target of calcium-dependent regulation that supports short-term synaptic plasticity (e.g., Rettig and Neher, 2002). However, no results have emerged to date that provide support for this mechanism on the timescale necessary to contribute to physiological short-term plasticity. In contrast, recent results clearly implicate synaptotagmin, the key calcium-dependent regulator of SNARE protein function, in short-term synaptic plasticity (Jackman et al., 2016).

A family of 13 synaptotagmin isoforms regulates calcium-dependent membrane fusion in all cellular compartments and in all cell types. At the synapse, synaptotagmin-1, -2, and -9 have been shown to support rapid release of neurotransmitters in synaptic transmission (Südhof, 2012). No regulatory mechanisms have been reported that control the function of these synaptotagmins on the ms timescale necessary for short-term synaptic plasticity. However, a recent study shows that synaptotagmin-7 is required for short-term facilitation at several synapses, including the widely studied synapse of the Schaffer collaterals of CA3 neurons onto CA1 neurons (Jackman et al., 2016). Complete ablation of this synaptotagmin isoform by gene deletion has no effect on basal synaptic transmission but blocks paired-pulse facilitation (Figure 5A) and facilitation in trains of stimuli (Figure 5B) essentially completely with no observable change in global calcium accumulation. These results provide the first clear evidence for upregulation of SNARE protein function in short-term synaptic plasticity.

How does synaptotagmin-7 generate short-term synaptic facilitation? One straightforward idea is that calcium binding to synaptotagmin-7 directly induces an increase in SNARE protein function and thereby increases neurotransmitter release during the postsynaptic response. However, synaptotagmin-7 binds calcium to its C2A domain slowly in biochemical experiments

and does not participate in fast synaptic transmission (Maximov et al., 2008; Voleti et al., 2017). It is possible that synaptotagmin-7 binds residual calcium and interacts with the SNARE complex in a way that enhances the function of a fast synaptotagmin (synaptotagmin-1, -2, or -9) in triggering exocytosis of synaptic vesicles. In any case, these recent studies of calcium channels and synaptotagmin-7 indicate that facilitation of $Ca_V2.1$ channels is required for synaptic facilitation that is dependent on local calcium transients, whereas synaptotagmin-7 is required for all phases of synaptic facilitation.

Calcium Buffering in Short-Term Synaptic Plasticity

Calcium that accumulates in nerve terminals during trains of action potentials is controlled by the balance of calcium entry versus calcium buffering through binding to calcium-binding proteins and uptake into intracellular organelles. Parvalbumin, calbindin, and related calcium-binding proteins are expressed at high levels in many cell types, where they control calcium transients, participate in calcium signaling pathways, and are protective against calcium overload (Schwaller, 2010). Experiments at several types of synapses indicate that loss of these calcium-binding proteins modulates synaptic plasticity and homeostatic regulation of synaptic strength (Cheron et al., 2008; Chevaleyre and Piskorowski, 2014; Gainey and Feldman, 2017). If calcium entry in response to the first action potential in a pair saturates local calcium buffers, calcium entry during a second action potential may elicit a larger intracellular calcium transient because entering calcium is less effectively buffered and thereby could induce rapid short-term facilitation as well as slower forms of synaptic plasticity.

The slow calcium buffer parvalbumin (Lee et al., 2000b) is expressed at the Calyx of Held. Loss of parvalbumin in knockout mice did not affect the peak of short-term facilitation, but it slowed both the rate of decay of the global calcium transient in the nerve terminal and the rate of decay of short-term facilitation (Müller et al., 2007). These parameters were returned to normal by perfusion of parvalbumin into the nerve terminal from the recording pipette. These results indicate that parvalbumin is not directly involved in causing short-term facilitation. However, as calcium buffering by parvalbumin slows the rate of decay of the global calcium transient, it could increase calcium-dependent inactivation of $Ca_V2.1$ channels and thereby accelerate the onset of rapid synaptic depression.

In synapses of cerebellar fast-spiking interneurons onto cerebellar Purkinje neurons, deletion of parvalbumin changed the paired-pulse depression observed in wild-type synapses into paired-pulse facilitation, a striking change of sign of short-term plasticity (Caillard et al., 2000). The effect of deletion of parvalbumin on calcium transients in these small synapses was not measured; however, it would seem necessary for parvalbumin to reduce the peak calcium transient as well as increase its rate of decay in order for it to prevent short-term facilitation in wild-type synapses. Alternatively, deletion of parvalbumin may induce compensatory changes in calcium signaling that indirectly prevent facilitation.

Calbindin D_{28K} is a rapid calcium buffer (Nägerl et al., 2000) that is expressed in many types of neurons. At inhibitory synapses of multipolar bursting interneurons onto layer II/III cortical pyramidal cells, washout of intracellular buffers during prolonged whole-cell voltage clamp caused loss of paired-pulse facilitation, as did targeted deletion of calbindin (Blatow et al., 2003). Perfusing calbindin D_{28K} protein into the presynaptic cell through the whole-cell voltage clamp pipette greatly reduced the strength of the first excitatory postsynaptic current (EPSC) and restored paired-pulse facilitation (Blatow et al., 2003). At the glutamatergic synapse of Schaffer collaterals onto CA1 pyramidal cells, depletion of calbindin D_{28K} with anti-sense RNA did not affect presynaptic short-term facilitation, although it did alter postsynaptic LTP (Jouvenceau et al., 1999). However, complete loss of calbindin D_{28K} in knockout mice increased short-term synaptic facilitation at excitatory synapses on CA1 pyramidal neurons, even though it impaired the maintenance of LTP (Westerink et al., 2012). Overexpression of calbindin D_{28K} in the synapses of dentate granule cell mossy fibers onto CA3 pyramidal neurons increased excitatory postsynaptic potentials, decreased paired-pulse facilitation, and impaired LTP (Dumas et al., 2004). These experiments show that calcium buffering by calbindin D28K does alter short-term synaptic facilitation in multiple ways at different synapses, but they do not reveal how these functional effects are mediated.

Working Together in Short-Term Synaptic Plasticity

The three molecular mechanisms described above—calcium channel regulation, synaptotagmin-7, and intracellular calcium buffering—may combine and complement each other to generate short-term synaptic plasticity in different synapses. Experimental evidence on this point is still lacking, but studies that probe the intersections among local calcium entry, synaptotagmin-7 function, and calcium buffering now have a high priority. A reasonable working hypothesis based on current results is illustrated in Figure 6. $Ca_V2.1$ channels respond to the most rapid and local calcium transients (green arrows) through CaS protein regulation and increase calcium entry in response to the next action potential. Slower binding of calcium to synaptotagmin-7 (blue arrow) integrates local and global calcium entry and thereby enhances exocytosis by a mechanism yet to be determined. Finally, calcium buffering controls the most widespread calcium accumulations (red arrows) and responds most slowly in its contributions to short-term synaptic facilitation and rapid depression. Variations on this theme may be present in different classes of synapses.

Long-Term Potentiation of the Postsynaptic Response

Synaptic strength is tightly controlled on the postsynaptic side of the synapse by LTP and long-term depression (LTD) of synapse function (Herring and Nicoll, 2016b; Malenka and Bear, 2004). In the extensively studied synapse of Schaffer collaterals of CA3 pyramidal neurons onto CA1 pyramidal neurons in the hippocampus, LTP is generated by high-frequency stimulation on the s timescale, most often 100 Hz stimulation for 1 s in typical experimental protocols (Herring and Nicoll, 2016b). It can also be generated by shorter bursts of stimuli delivered in theta rhythm and by pairing of stimuli impinging on the CA1 cells from different inputs (Herring and Nicoll, 2016b). Repetitive activation of the postsynaptic glutamate receptors by synaptically released glutamate initiates LTP via a cascade of

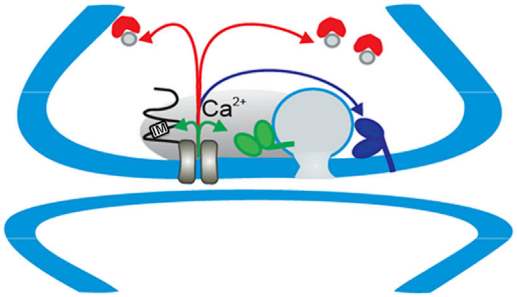

Figure 6. Multiple Phases of Short-Term Synaptic Plasticity
Model for multi-phase short-term synaptic plasticity driven by calcium entry through $Ca_V2.1$ channels. Calcium entering through a presynaptic $Ca_V2.1$ channels forms a domain of high concentration in the range of 100 μM around the intracellular mouth of the pore (gray). This high concentration of calcium first reaches the CaS proteins bound to the C-terminal domain (green arrow, IM) and a nearby fast synaptotagmin (Syt-1, -2, or -9, green), which triggers exocytosis, induces facilitation of the calcium current in response to local increases in calcium, and increases calcium entry during the subsequent action potential. After a longer diffusion path (blue arrow), calcium reaches synaptotagmin-7, which further enhances the efficiency of neurotransmitter release in response to incoming calcium during subsequent action potentials via an unknown mechanism. Finally, calcium diffuses to more distant fixed calcium buffers (red arrows) and is bound there to terminate calcium-dependent responses. When these buffers are saturated, calcium entering during subsequent action potentials increases to higher levels and enhances neurotransmitter release.

postsynaptic signaling events, including activation of the NMDA subtype of glutamate receptors, calcium entry, and activation of calcium/calmodulin-dependent protein kinase II (CaMKII; Herring and Nicoll, 2016b). Phosphorylation of AMPA receptors by CaMKII increases their activation by glutamate (Huganir and Nicoll, 2013), and phosphorylation of membrane targeting proteins increases their insertion into the postsynaptic membrane (Herring and Nicoll, 2016a). Together, these effects result in long-lasting increases in synaptic strength. Continued synaptic stimulation consolidates and stabilizes increased synaptic strength through activation of gene expression and protein biosynthesis, which increase the size of postsynaptic spines and induce additional changes in size and protein composition of the postsynaptic compartment (Mayford et al., 2012).

Calcium Channels and LTP

Although classical induction of LTP by high-frequency stimulation requires NMDA receptors to supply incoming calcium to activate the downstream cascade, L-type calcium currents conducted by $Ca_V1.2$ channels (and possibly by $Ca_V1.3$ channels) contribute to induction of LTP under other experimental conditions. LTP induced chemically by inhibition of K_V channels with tetraethylammonium ion has a substantial component that is blocked by inhibition of L-type calcium currents (Huber et al., 1995). LTP induced *in vivo* is partially blocked by inhibitors of L-type calcium currents (Freir and Herron, 2003). Long-lasting LTP induced in the presence of inhibitors of NMDA-type glutamate receptors is also blocked by inhibitors of L-calcium currents and is prevented by deletion of the gene encoding $Ca_V1.2$ channels (Moosmang et al., 2005). LTP can be efficiently induced by long-term, low-level theta stimulation, which mimics electrical activity in the hippocampus during spatial learning and memory (Staubli and Lynch, 1987). Dihydropyridine $Ca_V1.2$ channel antagonists reduce or block this form of LTP (Figures 7A and 7B; Qian et al., 2017). In young-adult hippocampus, activation of β2-adrenergic receptors to increase cyclic AMP (cAMP) and activate cyclic-AMP-dependent protein kinase (PKA) enhances induction of LTP (Figure 7C; Qian et al., 2017). β2-adrenergic receptors form a complex with $Ca_V2.1$ channels by interaction with their C-terminal domain (Davare et al., 2001), and activation of these receptors can support generation of LTP in response to theta stimulation (Qian et al., 2012). PKA phosphorylation of Ser1928 in the C-terminal domain of $Ca_V1.2$ is required for the effect of β-adrenergic activation on L-type calcium currents and on LTP, and prolonged phosphorylation of this site causes dissociation of the β2-adrenergic receptor/$Ca_V1.2$ channel complex and loss of responsiveness for 3–5 min (Patriarchi et al., 2016; Qian et al., 2017). These studies map out a pathway for β2-adrenergic regulation of synaptic strength by phosphorylation of $Ca_V2.1$ channels in response to stress and fear stimuli, which sharpen learning and memory through these changes in $Ca_V1.2$ channel regulation and synapse function.

Calcium Channels and Signaling from Synapses to the Nucleus

Long-lasting LTP requires activation of gene expression and protein synthesis, and these processes are thought to lead to stabilization of memory (Mayford et al., 2012). Strong evidence indicates that calcium entry via $Ca_V1.2$ channels has a privileged role in activation of gene transcription in response to electrical or synaptic activity (Flavell and Greenberg, 2008). Calcium entry engages CaMKII bound to the C-terminal domain of $Ca_V1.2$ and activates a downstream cascade of calcium-regulated protein kinases, including CaMKIV, which in turn activate the transcription factor CREB among others (Cohen et al., 2015). In parallel, the calcium-regulated phosphoprotein phosphatase calcineurin, which is also bound to the C-terminal domain of $Ca_V1.2$, is activated and dephosphorylates the transcription factor NFAT, allowing it to diffuse into the nucleus and activate gene transcription (Dittmer et al., 2014; Murphy et al., 2014; Oliveria et al., 2007). These activity-dependent changes in gene transcription increase synthesis of mRNA encoding synaptic proteins, which lead to permanent changes in synaptic function (Mayford et al., 2012).

Although calcium entry is the primary signal generated by activation of $Ca_V1.2$ channels, recent studies indicate that the voltage-dependent conformational change in the $Ca_V1.2$ channel itself is effective in triggering signaling to the nucleus (Li et al., 2016). These clever experiments used a chimeric $Ca_V1.2$ channel with drug bound to inhibit its calcium conductance, covalently tethered to a purinergic receptor allowing calcium entry in response to extracellular ATP. Stimulation by ATP (Figure 8, gray bar) triggers a rapid calcium transient (Figure 8, blue) and slower activation and translocation of CaMKII (Figure 8, green). Delayed depolarization acts synergistically to activate phosphorylation of the transcription factor CREB (Figure 8, black bars), which in turn regulates gene transcription. Evidently, voltage-dependent conformational changes in $Ca_V1.2$ plus calcium entry via the purinergic receptor create a synergistic bifurcated pathway leading to gene expression in the nucleus. The downstream signaling pathway engaged by conformational changes in $Ca_V1.2$ remains uncertain, but these novel studies

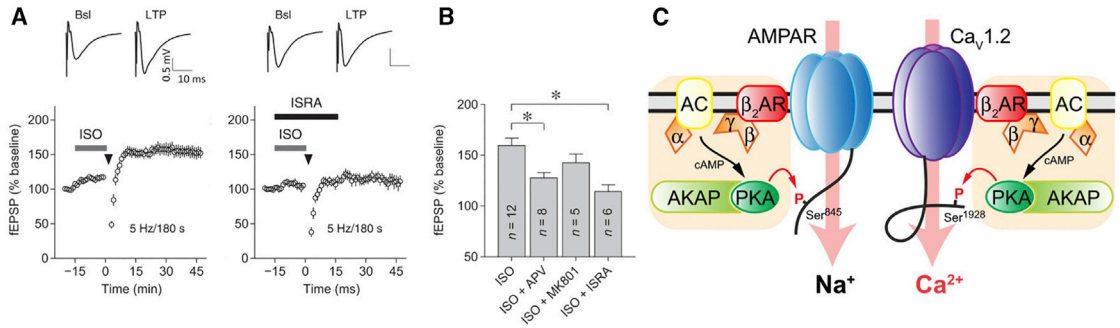

Figure 7. Calcium Channel Function in Postsynaptic Long-Term Potentiation

(A) (Left) β2-adrenergic-dependent long-term potentiation. Hippocampal slices were isolated, and synaptic transmission was measured by recording field potentials from postsynaptic CA1 neurons. After addition of isoproterenol (ISO), theta stimulation at 5 Hz for 180 s causes an increase in postsynaptic EPSP to 150%–160% of baseline control. (Right) In a similar experiment as in the left panel, the dihydropyridine calcium channel antagonist isradipine (ISRA) blocks β2-adrenergic-dependent long-term potentiation (Qian et al., 2017).

(B) Mean results from experiments illustrated in (A) (Qian et al., 2017).

(C) Model for postsynaptic calcium channel signaling in LTP (Qian et al., 2017). Under basal conditions, glutamate released from presynaptic terminals activates AMPA-type glutamate receptors to yield the depolarizing EPSC based on sodium entry. Stimulation of β2-adrenergic receptors that are specifically bound to both AMPA receptors and Ca$_V$1.2 channels in the postsynaptic compartment increases the size of the EPSC directly by stimulating PKA phosphorylation of the AMPA receptor and increases calcium entry by phosphorylation of Ser1928 on Ca$_V$1.2 channels, which induces LTP indirectly via CaMKII phosphorylation and downstream signaling events.

This figure was adapted with permission from Qian et al., 2017.

indicate that both voltage and calcium have key roles in triggering gene expression in response to neuronal activity via Ca$_V$1.2 channels.

Neuropsychiatric Diseases with Mutations and Polymorphisms in Ca$_V$2.1 Channels

Familial Hemiplegic Migraine

Mutations in the presynaptic Ca$_V$2.1 channel cause familial hemiplegic migraine, a severe inherited form of migraine headache with aura (Pietrobon, 2013). These mutations cause a gain of function (Tottene et al., 2002). In single-channel studies, Ca$_V$2.1 channels with familial hemiplegic migraine (FHM) mutations activate at more negative membrane potentials, which would increase calcium entry in response to action potentials in active zones of nerve terminals (Tottene et al., 2002). They behave as though their activity is permanently facilitated, and no further facilitation is observed in response to pairs or trains of stimuli (Adams et al., 2010). These effects cause a greater enhancement of synaptic transmission at excitatory synapses than at inhibitory synapses (Tottene et al., 2009; Vecchia et al., 2015). This increase in excitatory synaptic activity leads to cortical spreading depression, a wave of synchronized depolarization that causes the aura associated with FHM migraine attacks (Tottene et al., 2009; van den Maagdenberg et al., 2010; Vecchia et al., 2015). The mechanism underlying migraine pain remains uncertain, but pathologically increased synaptic activity at synapses that control blood vessel function in the meninges surrounding the brain is likely to contribute. Even though the ultimate pathophysiological events in FHM remain incompletely understood, it seems clear that increased synaptic activity caused by presynaptic Ca$_V$2.1 channels that are facilitated in their basal state is the molecular mechanism that drives this disease of hyperexcitability. It seems likely that these mutations "hijack" the natural facilitation process of Ca$_V$2.1 channels and cause them to be persistently facilitated. Evidently, FHM is a disease of permanent short-term synaptic facilitation.

Episodic Ataxia

Autosomal dominant cerebellar ataxia includes episodic forms (episodic ataxias EA1–EA7) and progressive forms (spinocerebellar ataxias SCA1–SCA29). In EA2, mutations in the Ca$_V$2.1 channel cause reduced channel function by multiple mechanisms, including gene deletions, positive shifts in the voltage dependence of activation, increased inactivation, and slowed recovery from inactivation (Graves et al., 2014; Guida et al., 2001; Jen and Baloh, 2002; Rajakulendran et al., 2010). In addition, some EA2 mutations have dominant negative effects that further impair Ca$_V$2.1 channel expression and function (Dorgans et al., 2017; Jeng et al., 2006, 2008; Mezghrani et al., 2008). Loss of Ca$_V$2.1 channel function leads to impaired electrical signaling and eventually death of cerebellar Purkinje cells, the output neurons of the cerebellar cortex, which coordinate and transmit information on locomotion and navigation to the deep cerebellar nuclei.

Spinocerebellar Ataxia

Mutations in many different target proteins cause spinocerebellar ataxias (SCA1–SCA29). In SCA6, repeated CAG codons in the C-terminal of Ca$_V$2.1 channels encode a long glutamine repeat sequence (Kordasiewicz et al., 2006; Rajakulendran et al., 2010; Solodkin and Gomez, 2012; Zhuchenko et al., 1997). Alternative splicing and posttranslational processing of Ca$_V$2.1 leads to cleavage of the C-terminal tail and release of the polyglutamine repeat segments, which accumulate in the cytosol and are also transported to the cell nucleus, where they may disrupt gene expression (Aikawa et al., 2017; Kordasiewicz et al., 2006; Watase et al., 2008). Alternative splicing of mRNA and proteolytic processing of Ca$_V$2.1 channels containing polyglutamine repeats may also produce an inactive form of a transcription factor translated from an internal ribosome entry site that induces degeneration of Purkinje neurons (Du et al., 2013), but this pathogenic

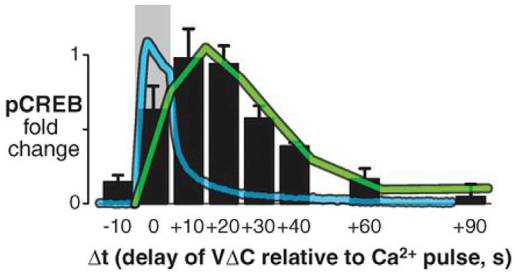

Figure 8. Dual Regulation of Transcription by Voltage-Dependent Conformational Change and Calcium Entry through $Ca_V1.2$ Channels
Hippocampal neurons expressing a P2X2 channel linked to $Ca_V1.2$ in the presence of the inhibitor nimodipine and stimulated by depolarization with 40 mM K^+ and by ATP to activate calcium entry via purinergic P2X2 receptors (gray). Calcium entry was followed by depolarization by the time intervals indicated on the x axis. The results show the delayed action of depolarization, which peaks at 10–20 ms after calcium entry. Calcium entry (blue), translocation of CaMKII (green), and normalized phosphorylation of the transcription factor CREB (pCREB) were measured (Li et al., 2016).
This figure was adapted with permission from Li et al., 2016.

effect was not observed in a study of different mouse models (Aikawa et al., 2017). Polyglutamine tracts longer than ~20 residues are pathogenic in human Purkinje neurons, but even longer polyglutamine tracts are necessary for pathogenesis in mouse models (Watase et al., 2008), perhaps because the mouse lifetime is so much shorter than humans, allowing less time for neuronal damage to accumulate. Expression of long C-terminal fragments of $Ca_V2.1$ with 27 glutamine residues in the Purkinje neurons of mice revealed localization in both cytosol and nucleus, age-related degeneration of Purkinje neurons, failure of action potential generation and repetitive firing, impaired motor coordination, and loss of motor learning and memory in the conditioned eye-blink test (Mark et al., 2015). These results provide a clear connection between expression of the $Ca_V2.1$ C-terminal with a polyglutamate expansion and manifestation of the disease phenotypes *in vivo* in mice.

Nonprogressive Congenital Ataxia

Recent genetic studies show that mutations in $Ca_V2.1$ channels can also cause nonprogressive congenital ataxia (Travaglini et al., 2017). The pathophysiological mechanisms that cause this disease are not yet known.

Neuropsychiatric Diseases with Mutations and Polymorphisms in Ca_V1 Channels

Timothy Syndrome and Autism

Timothy syndrome is caused by two specific missense mutations at the intracellular end of the S6 segment in domain I of the $Ca_V1.2$ channel, which is expressed broadly in the brain, heart, and other tissues (Splawski et al., 2004, 2005). These mutations preferentially block the voltage-dependent inactivation process of these channels (Figures 9A–9C; Splawski et al., 2004). These gain-of-function effects have dire consequences in multiple tissues. In the heart, the prolonged calcium current increases the duration of the ventricular action potential, leading to long QT syndrome and severe cardiac arrhythmias (Splawski et al., 2004). Limb and facial development are adversely affected, and fingers and toes often exhibit syndactyly, in which a web of tissue connects the digits (Splawski et al., 2004). In the brain, Timothy syndrome causes autistic-like behaviors with high penetrance in humans and mice (Bader et al., 2011; Splawski et al., 2004). Altered signaling from $Ca_V1.2$ channels to gene regulation in the nucleus is suspected as the cause of these autistic-like behaviors (Paşca et al., 2011). Neurons induced from pluripotent stem cells from individuals with Timothy syndrome have major alterations in regulation of gene transcription downstream of activity-dependent calcium entry via $Ca_V1.2$ channels (Paşca et al., 2011).

Extensive genome mapping studies aimed at identifying polymorphisms, *de novo* mutations, and copy number variations of genes have revealed numerous genes associated with autism. $Ca_V1.2$ is ranked high among those associated genes (Lee et al., 2013; Kabir et al., 2016, 2017; Li et al., 2015; Lotan et al., 2014; Schaaf et al., 2011). Moreover, the complete set of genes implicated in autism is heavily weighted toward synaptic function and plasticity in general (Pinto et al., 2014). Thus, in addition to the inherited mutations in $Ca_V1.2$ that cause autistic-like behaviors in Timothy syndrome, these channels may be involved more broadly in idiopathic, polygenic autism that arises from synaptic dysfunction.

$Ca_V1.3$ channels also are molecular targets for mutations that cause autistic-like behaviors, together with primary aldosteronism, epilepsy, and intellectual disability (Kabir et al., 2017; Pinggera and Striessnig, 2016). Remarkably, some of these mutations are located in the same position as Timothy syndrome mutations, at the intracellular ends of the S6 segments in domains I and II of $Ca_V1.3$ (Pinggera et al., 2015, 2017). These mutations confer gain of function on $Ca_V1.3$ channels, including increased level of calcium current (not shown) and impaired voltage-dependent inactivation (Figures 9D and 9E; Pinggera et al., 2015). The effects on voltage-dependent inactivation are remarkably similar to those of Timothy syndrome mutations in $Ca_V1.2$ (Figure 9). Because the intracellular ends of the four S6 segments form the activation gate in voltage-gated Ca_V channels (Catterall, 2011; Wu et al., 2016), it is likely that these mutations destabilize the closed conformation of the activation gate and thereby enhance voltage-dependent channel activation. These activating effects may cause an imbalance of excitatory over inhibitory neurotransmission in brain circuits, leading to epilepsy, intellectual disability, and autistic-like behaviors.

Schizophrenia, Bipolar Disorder, and Depression

Genome-wide association studies have found strong associations between the frequency of SNPs in the gene encoding $Ca_V1.2$ channels and schizophrenia (Hamshere et al., 2013; Moskvina et al., 2009; Nyegaard et al., 2012; Ripke et al., 2013; Schizophrenia Psychiatric Genome-Wide Association Study Consortium, 2011). Association of schizophrenia with rare disruptive mutations in CACNA1C suggests that the disease phenotype is caused by loss-of-function mutations and polymorphisms (Purcell et al., 2014). Remarkably, both genome-wide association studies and analysis of *de novo* mutations in $Ca_V1.2$ channels show significant overlap for schizophrenia, bipolar disorder, and major depression (Curtis et al., 2011; Green et al., 2010; He et al., 2014; Kabir et al., 2016, 2017; Moskvina et al., 2009). These genetic associations implicate alterations in expression and/or function of $Ca_V1.2$ channels in a wide range

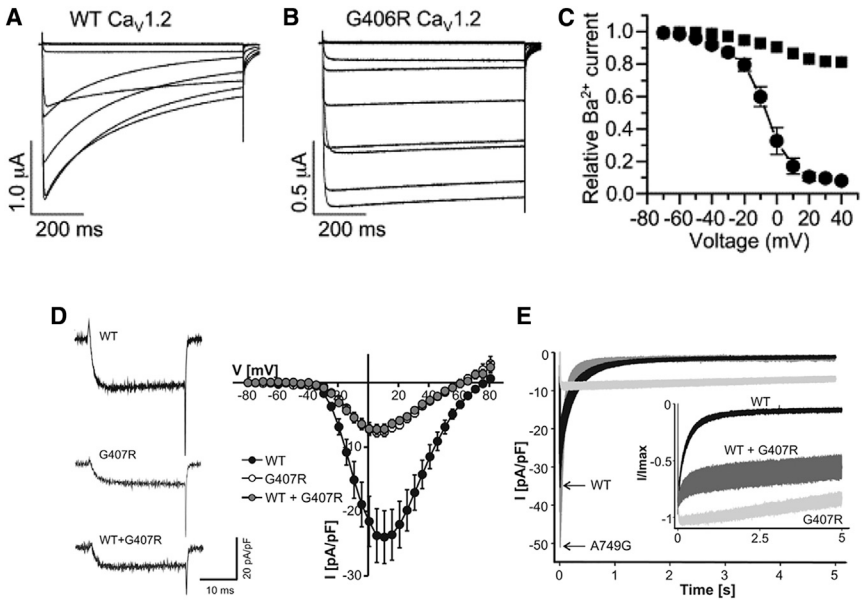

Figure 9. Functional Effects of Calcium Channel Mutations in $Ca_V1.2$ and $Ca_V1.3$ Channels that Induce Autistic-like Behaviors

(A–C) $Ca_V1.2$ channels were expressed in *Xenopus* oocytes, and barium currents conducted by the expressed channels were recorded by two-microelectrode voltage clamp (Splawski et al., 2004).

(A) A family of inward barium currents conducted by WT $Ca_V1.2$ channels evoked by depolarization from a holding potential of −70 mV to test potentials from −70 mV to 40 mV.

(B) A similar experiment as in (A) with $Ca_V1.2$/G406R.

(C) Normalized peak barium currents were recorded at a test potential of −70 mV after depolarization to the indicated potentials for 800 ms. G406R, squares; WT, circles.

(D and E) $Ca_V1.3$ channels were expressed in tsA-201 cells, and calcium currents were measured in whole-cell voltage clamp from a holding potential of −80 mV to the indicated potentials. .

(D) Sample current records in 20-ms test pulses to 10 mV and current-voltage relationships for WT, G407R, and the combination.

(E) Kinetics of activation and inactivation in 5-s test pulses for WT, G407R, and the combination.

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of related psychiatric diseases. This convergence of multiple psychiatric diagnoses on a common set of underlying genetic associations may require revision of the current diagnostic approach in psychiatry toward a more biologically relevant nosology (Kim and State, 2014).

Analysis of pathway ontologies of the wide range of genes that have been implicated in these psychiatric diseases leads to the suggestion that calcium signaling, postsynaptic function, and synaptic plasticity may be the common target of these mutations and polymorphisms (Hall et al., 2015; Hertzberg et al., 2015). In addition to $Ca_V1.2$ channels, which are located in dendritic spines, dendrites, and cell bodies of postsynaptic neurons, mutations in neurotransmitter receptors (e.g., NMDA-type glutamate receptors) and postsynaptic scaffolding proteins (e.g., Shank, PSD-95, Neuroligins, and Ankyin 3) are implicated in psychiatric diseases by these genetic studies. These genetic findings and pathway ontology analyses lead to the general conclusion that postsynaptic calcium signaling processes that control synaptic plasticity and gene expression are likely to be disrupted in this broad range of psychiatric diseases. Alterations in $Ca_V1.2$ channels differentially modulate disease-related phenotypes depending upon when in neurodevelopment they are expressed (Dedic et al., 2018), and specific polymorphisms in $Ca_V1.2$ can alter gene expression and protein interactions (Eckart et al., 2016). Altogether, these studies open an exciting new field of molecular psychiatry in which the functional impacts of genetic polymorphisms and *de novo* mutations on calcium signaling, synaptic function and plasticity, and neurodevelopment can be assessed, and disease-related phenotypes can be connected with specific molecular deficits. We speculate that graded changes in $Ca_V1.2$ channel function, regulation, and downstream signaling caused by polymorphisms and *de novo* mutations may contribute to the graded behavioral deficits of schizophrenia, bipolar (manic-depressive) disorder, and depression through the effects we have reviewed here on postsynaptic plasticity and gene expression.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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