SYMPOSIUM REPORT

Regulation of synaptic signalling by postsynaptic, non-glutamate receptor ion channels

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Activation of glutamatergic synapses onto pyramidal neurons produces a synaptic depolarization as well as a buildup of intracellular calcium (Ca^{2+}). The synaptic depolarization propagates through the dendritic arbor and can be detected at the soma with a recording electrode. Current influx through AMPA-type glutamate receptors (AMPARs) provides the depolarizing drive, and the amplitudes of synaptic potentials are generally thought to reflect the number and properties of these receptors at each synapse. In contrast, synaptically evoked Ca^{2+} transients are limited to the spine containing the active synapse and result primarily from Ca^{2+} influx through NMDA-type glutamate receptors (NMDARs). Here we review recent studies that reveal that both synaptic depolarizations and spine head Ca^{2+} transients are strongly regulated by the activity of postsynaptic, non-glutamate receptor ion channels. In hippocampal pyramidal neurons, voltage- and Ca^{2+}-gated ion channels located in dendritic spines open as downstream consequences of glutamate receptor activation and act within a complex signalling loop that feeds back to regulate synaptic signals. Dynamic regulation of these ion channels offers a powerful mechanism of synaptic plasticity that is independent of direct modulation of glutamate receptors.

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In pyramidal neurons of the hippocampus and cortex, NMDARs are the predominate source of synaptically evoked calcium (Ca^{2+}) signals but contribute little to the synaptic depolarization (Collingridge *et al.* 1983; Koester & Sakmann, 1998; Schiller *et al.* 1998*b*; Yuste *et al.* 1999; Kovalchuk *et al.* 2000; Sabatini *et al.* 2002; Nevian & Sakmann, 2006; Bloodgood & Sabatini, 2007*b*). In contrast, AMPARs in these cells are typically Ca^{2+} impermeable but contribute the majority of the synaptic current that gives rise to the synaptic potential (Blake *et al.* 1988; Ogoshi & Weiss, 2003). Many forms of synaptic plasticity have been revealed in these cells that are mediated by changes in the numbers or properties of AMPARs and NMDARs and that modulate, respectively, the amplitudes of synaptic potentials and Ca^{2+} transients (reviewed in Malenka & Bear, 2004; Bloodgood & Sabatini, 2007*a*).

Non-glutamate receptor classes of ion channels are also found in dendrites and dendritic spines (reviewed in Johnston *et al.* 1996, 2000). Dendritic voltage-gated Ca^{2+}, sodium (Na^+) and potassium (K^+) channels as well as the hyperpolarization-activated cation conductance I_h are known to influence the integrative and propagative properties of the postsynaptic cell (reviewed by Gulledge *et al.* 2005). Furthermore, during strong or repeated synaptic stimulation the activities of voltage-sensitive Ca^{2+} and Na^+ channels influence postsynaptic signalling, and Ca^{2+} influx through the former contributes to dendrite Ca^{2+} accumulation (Miyakawa *et al.* 1992; Magee *et al.* 1995*a*; Losonczy & Magee, 2006; Carter *et al.* 2007). However, although voltage-gated Ca^{2+} and Na^+ channels are also active during subthreshold activity (Magee *et al.* 1995*a*; Magee & Johnston, 1995*b*), their roles in regulating unitary signals that arise from the activation a single synapse were unknown.

Two obstacles have limited studies of the roles of postsynaptic ion channels in regulating synaptic signals. First, many classes of voltage-gated channels in dendrites are also active in presynaptic terminals and are necessary for action potential (AP)-evoked neurotransmitter release. For example, blockade of voltage-gated Na^+ channels prevents AP propagation in the axon whereas blockade of voltage-sensitive Ca^{2+} channels (VSCCs) prevents AP-induced Ca^{2+} influx. Second, the distribution of ion

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Table 1. Major VSCC subclasses discussed

Channel	Gene	Current	Example antagonist
$Ca_v1.2$	α_{1C}	L-type	$< 1\ \mu$M nimodipine
$Ca_v1.3$	α_{1D}	L-type	$\sim 3\ \mu$M nimodipine
$Ca_v2.1$	α_{1A}	P/Q-type	ω-Agatoxin-IVA
$Ca_v2.2$	α_{1B}	N-type	ω-Conotoxin-GVIA
$Ca_v2.3$	α_{1E}	R-type	SNX-482, mibefradil
$Ca_v3.1$–$Ca_v3.3$	α_{1G}–α_{1I}	T-type	Mibefradil

channels throughout the dendrites is not spatially uniform and ion channels that are selectively found in the spine may only locally influence synaptic signals. These effects may not be detectable in the excitatory postsynaptic potentials (EPSPs) and currents (EPSCs) measured by somatic recording electrodes.

In order to overcome these obstacles, we and other labs have used two-photon laser photoactivation (2PLP) of caged glutamate to directly stimulate the postsynaptic terminal located on dendritic spines in brain slices (Matsuzaki *et al.* 2001; Smith *et al.* 2003; Carter & Sabatini, 2004; Sobczyk *et al.* 2005). This approach bypasses the presynaptic terminal and allows the study of postsynaptic signalling in pharmacological conditions that normally prevent the release of neurotransmitter (Losonczy & Magee, 2006; Bloodgood & Sabatini, 2007*b*). By using two-photon instead of one-photon induced photolysis of caged glutamate it is possible to produce light-evoked synaptic currents in brain slices that mimic the time course of endogenous EPSCs. Furthermore, when combined with two-photon laser scanning microscopy (2PLSM), this approach allows the study of synaptic potentials and spine head Ca^{2+} transients resulting from the activation of individual, visualized dendritic spines (Carter & Sabatini, 2004; Ngo-Anh *et al.* 2005; Noguchi *et al.* 2005; Sobczyk *et al.* 2005; Bloodgood & Sabatini, 2007*b*; Carter *et al.* 2007; Sobczyk & Svoboda, 2007).

Inhomogeneous dendritic distribution of voltage-gated ion channels

Electrophysiological studies have revealed that apical dendrites and dendritic spines of pyramidal neurons contain a complex assortment of voltage- and ligand-gated ion channels that may potentially regulate synaptic signals (reviewed in Johnston *et al.* 1996, 2000). For example, direct recordings from the main apical dendrite of CA1 pyramidal neurons revealed voltage-gated Na^+ channels,

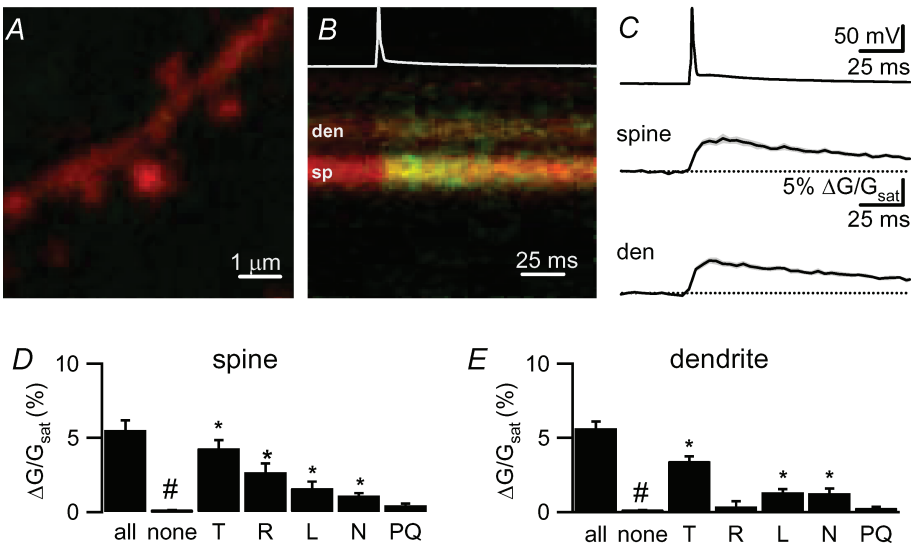

Figure 1. Multiple and distinct sets of VSCC classes contribute to bAP-mediate Ca^{2+} transients in spines and dendrites

A, image of a spiny apical dendrite filled with 5 μM Alexa Fluor-594 (red fluorescence) and the Ca^{2+} indicator 150 μM Fluo-5F (green fluorescence). *B*, fluorescence collected in a line scan across the spine (sp) and dendrite (den) shown in panel *A* during stimulation of a bAP by somatic current injection. A bAP (white trace, top) rapidly increases green fluorescence in the spine and dendrite, indicating increased $[Ca^{2+}]$ in both compartments. *C*, quantification of the fluorescence transients ($\Delta G_{bAP}/G_{sat}$) in the spine head (middle) and neighbouring dendrite (bottom) evoked by a bAP (top). The continuous lines and shaded regions depict the averages $\pm$ the standard errors of the mean (S.E.M.), respectively. *D*, summary of the contribution of each VSCC class to the bAP-evoked Ca^{2+} transients measured in spines in response to a single bAP. The $\Delta G_{bAP}/G_{sat}$ measured in the absence ('none') and in the presence ('all') of all the VSCC antagonists is also plotted. *E*, as in panel *D* for bAP-evoked Ca^{2+} transients measured in the dendrite. # and * indicate statistically significant ($P < 0.05$) differences compared to control conditions ('none') or the condition including all VSCC blockers ('all'), respectively.

voltage-gated K^+ channels, as well as various classes of pharmacologically identified VSCCs (Magee & Johnston, 1995*a*; Hoffman *et al.* 1997). In addition, imaging studies of AP and synaptically evoked Ca^{2+} transients have revealed multiple classes of VSCCs (Table 1) that contribute to dendrite and dendritic spine Ca^{2+} influx (Christie *et al.* 1995; Magee *et al.* 1995*a*; Schiller *et al.* 1998*a*; Sabatini & Svoboda, 2000; Yasuda *et al.* 2003; Carter & Sabatini, 2004; Egger *et al.* 2005; Bloodgood & Sabatini, 2007*b*). Based on these studies and others, it is clear that the classes of VSCCs that are active in dendritic shafts and spines differ between different segments of dendrite as well as across classes of neurons and species.

We performed a systematic pharmacological analysis of VSCCs that contribute to AP-evoked Ca^{2+} transients in dendritic spines and their parent dendrites (Fig. 1) (Bloodgood & Sabatini, 2007*b*). Analysis was limited to spines located within ~150 μm of the soma on secondary and tertiary apical dendrites. In addition, in order to avoid a potential complication of Ca^{2+}-dependent regulation of the AP waveform, SK-type Ca^{2+}-dependent K^+ channels were blocked with the peptide antagonist apamin.

APs were triggered by current injection into the soma of current clamped hippocampal CA1 pyramidal neurons of juvenile mice. In these cells, somatic APs trigger back-propagating APs (bAPs) that invade into the proximal portion of the dendrite (Spruston *et al.* 1995). By filling each cell through the recording electrode with a combination of a green-fluorescing Ca^{2+} indicator (Fluo 5F) and a Ca^{2+}-insensitive, red-fluorescing fluorophore (Alexa 594), the morphology of the dendrite and its intracellular $[Ca^{2+}]$ can be monitored with 2PLSM (Sabatini *et al.* 2002). bAPs trigger increases in green fluorescence in the spine and neighbouring dendrite whose amplitudes ($\Delta G_{AP}/G_{sat}$) are, in these recording conditions, linearly related to the magnitude of bAP-evoked Ca^{2+} increases ($\Delta[Ca^{2+}]_{AP}$) (Bloodgood & Sabatini, 2007*b*). Using specific antagonists of VSCC classes, we found

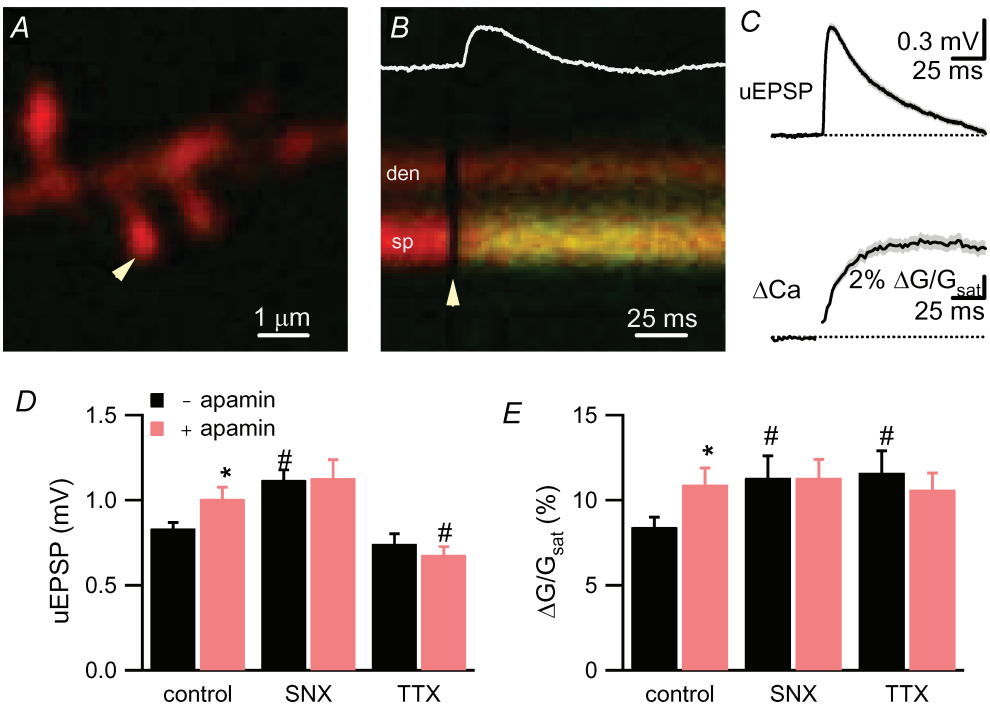

Figure 2. Differential regulation of uEPSP and $\Delta[Ca^{2+}]_{syn}$ by multiple, non-glutamate receptor ion channels

A, 2PLSM image of a spiny region of apical dendrite of a CA1 hippocampal pyramidal neuron filled with 10 μM Alexa Fluor-594 (red fluorescence) and 300 μM of Fluo-5F (green fluorescence). *B*, fluorescence collected in a line that intersects the spine head (sp) and neighbouring dendrite (den) shown in panel *A* during glutamate uncaging onto the spine head. The arrowheads in *A* and *B* indicate the location and timing, respectively, of a 500 μs pulse of 725 nm laser light used to trigger 2-photon mediated photolysis of MNI-glutamate. The increase in green fluorescence indicates increased intracellular $[Ca^{2+}]$. The white trace shows the uEPSP recorded simultaneously at the soma. *C*, uEPSP (top) and $\Delta G_{syn}/G_{sat}$ (bottom) measured in control conditions. The continuous lines and shaded regions depict the averages ± the standard errors of the mean (S.E.M.), respectively. *D* and *E*, summary of the amplitudes of the uEPSP (*D*) and $\Delta G_{syn}/G_{sat}$ (*E*) in a variety of pharmacological conditions. The effect of each antagonist was measured in absence (black bars) or in the presence of the SK antagonist apamin (red bars). $^*P < 0.05$ for each apamin condition compared to the corresponding apamin-free condition. $\#P < 0.05$ compared to control condition – i.e. in the absence of all antagonists.

that mibefradil, nimodipine, and ω-agatoxin-IVA sensitive VSCCs contribute to $\Delta[Ca^{2+}]_{AP}$ in both the dendritic shaft and the spine. By their pharmacological sensitivity these channels correspond, respectively, to Ca_V3 encoded T-type VSCCs; $Ca_V1.2$ or $Ca_V1.3$ encoded L-type VSCCs; and $Ca_V2.2$ encoded N-type VSCCs. In addition, a SNX-482 sensitive component of $\Delta[Ca^{2+}]_{AP}$ was seen in the spine but not in the dendrite, indicating a selective activation or presence of $Ca_V2.3$ encoded R-type VSCCs in the spine. The fractional contribution of each VSCC class to $\Delta[Ca^{2+}]_{AP}$ was similar when either a single or triplet of bAPs was used to trigger Ca^{2+} influx (not shown).

Regulation of synaptic signals by nonglutamate receptor ion channels

Dendrite-attached recordings from CA1 pyramidal neurons revealed that subthreshold stimuli are capable of activating VSCCs and voltage-sensitive Na^+ channels in CA1 dendrites (Magee *et al.* 1995*b*). To examine the possible contribution of VSCCs, voltage-sensitive Na^+ channels, and Ca^{2+}-activated K^+ channels to EPSPs and synaptically evoked Ca^{2+} influx into the spine head ($\Delta[Ca^{2+}]_{syn}$), we measured synaptic potentials and Ca^{2+} transients evoked by glutamate uncaging onto individual dendritic spines in a variety of pharmacological conditions (Fig. 2). Application of the $Ca_V1.2/1.3$ antagonist nimodipine had little effect on either component whereas application of the $Ca_V2.2$ antagonist ω-agatoxin-IVA did not affect $\Delta[Ca^{2+}]_{syn}$ but slightly boosted the uEPSP. This latter effect is likely to be due to increased input resistance of the cell in the presence of the antagonist. Thus, neither of these VSCC subclasses appears to contribute significantly to synaptic signals triggered by the stimulation of a single postsynaptic terminal.

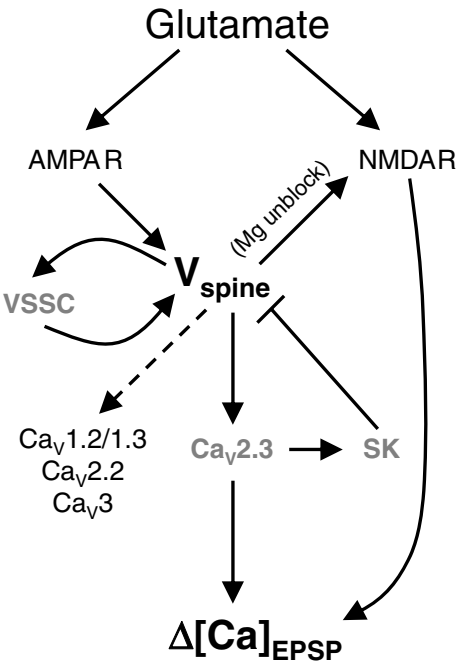

Figure 3. A model of the regulation of spine head Ca^{2+} transients by ionotropic glutamate receptors, voltage-gated Na^+ and Ca^{2+} channels, and SK channels
Glutamate release activates AMPARs and NMDARs in the spine. AMPAR opening increases the potential in the spine (V_{spine}), enhancing current flow through NMDARs by relief of Mg^{2+} block. The local depolarization also activates a variety of VSCCs and voltage-sensitive Na^+ channels (VSSCs) that contribute additional depolarization or Ca^{2+} entry into the spine. Ca^{2+} through $Ca_V2.3$ channels specifically activates SK channels that repolarize the spine and terminate NMDAR signalling. Channels whose modulation could serve as glutamate-receptor independent mechanisms of synaptic plasticity are shown in grey (Bloodgood & Sabatini, 2007*b*).

Counterintuitively, in the presence of the $Ca_V2.3$ antagonist SNX-482, uEPSPs and $\Delta[Ca^{2+}]_{syn}$ were larger than in control conditions. An increase in synaptic Ca^{2+} influx following blockade of a Ca^{2+} source indicates that suppressive, nonlinear interactions occur between Ca^{2+} sources in the spine. Blockade of SK class Ca^{2+}-activated K^+ channels with apamin produced similar increases in uEPSPs and $\Delta[Ca^{2+}]_{syn}$ amplitudes (Ngo-Anh *et al.* 2005). Since synaptically evoked Ca^{2+} transients are limited to the active spine, the Ca^{2+}-activated K^+ channels opened by synaptic stimulation must be found directly on the spine. Lastly, blockade of voltage-sensitive Na^+ channels with tetrodotoxin (TTX) also produced an unexpected boost in $\Delta[Ca^{2+}]_{syn}$ with no effect on uEPSP amplitude (Bloodgood & Sabatini, 2007*b*).

Experiments performed in the presence of multiple pharmacological antagonists indicated that $Ca_V2.3$, voltage-sensitive Na^+, and SK channels act in a common pathway to regulate synaptic potentials and NMDAR-dependent Ca^{2+} influx. Thus, the SK channel antagonist apamin had no effect on synaptic signals if NMDARs were blocked with CPP and MK801, if $Ca_V2.3$ channels were blocked with SNX-482, or if voltage-sensitive Na^+ channels were blocked with TTX (Ngo-Anh *et al.* 2005; Bloodgood & Sabatini, 2007*b*). In contrast, the effects of apamin on synaptic signals are still observed in the presence of $Ca_V1.2/1.3$ and $Ca_V2.2$ antagonists.

Several conclusions can be drawn from these results and incorporated into a model of the regulation of synaptic signalling by ion channels in the spine (Fig. 3). First, the amplitude of synaptic potentials and spine head Ca^{2+} transients are set by a complex, multistep signalling system that involves sequential activation of several ligand- and voltage-gated ion channels. The effects of this loop on synaptic signals are independent of regulation of AMPARs and NMDARs. Second, the spine does not operated as a single Ca^{2+} signalling domain and functional Ca^{2+} microdomains must exist within it. This conclusion has been drawn previously since activation of NMDARs is able to trigger the induction of synaptic plasticity whereas repeated activation of VSCCs by bAPs is not. In our work, the functional subdivision of the spine into multiple Ca^{2+}

signalling domains is made clear by the finding that in the presence of SNX-482, apamin no longer affects synaptic signals. This indicates that SK channels are not activated when $Ca_V2.3$ channels are blocked despite the fact that the average Ca^{2+} levels in the spine are larger than in control conditions. Third, the depolarization reached in the spine during synaptic activation must be sufficient to locally activate VSCCs. This indicates that depolarization of many tens of millivolts from rest is likely to occur in the spine and suggests that electrical resistance to current flow across the spine neck must be large (Segev & Rall, 1988).

Future directions

The spine-based feedback loop described here demonstrates that modulation of synaptic signals can occur via postsynaptic mechanisms that are independent of changes in the properties or numbers of AMPARs and NMDARs. Inhibition of any of at least three classes of ion channels in the spine (SK, $Ca_V2.3$ and voltage-sensitive Na^+ channels) has the capacity to boost synaptic potentials and spine head Ca^{2+} transients. Opening of R-type, presumable $Ca_V2.3$, VSCCs is enhanced by activation of muscarinic acetylcholine receptors (Tai *et al.* 2006) whereas SK channels are found in large protein complexes that include casein kinase 2, a kinase that regulates SK opening (Bildl *et al.* 2004; Allen *et al.* 2007). Thus upstream modulators of essential components of the feedback loop are known and future studies can address if such modulatory systems are active in spines of CA1 pyramidal neurons. Further experiments will also be needed to examine the conditions under which regulation of these channels dynamically sets synaptic strength.

The activation of VSCCs such as $Ca_V2.3$ in the spine head by unitary stimuli that generate a submillivolt EPSP at the soma also indicates that the attenuation of the synaptic potential from the spine to the soma is larger than had previously been thought. VSCCs opening in the spine suggests that either large voltage swings occur in the spine during an EPSP or that the spine resting potential is significantly depolarized compared to the in that soma and main apical dendrite. Either explanation requires that the spine operate as a semiautonomous electrical signalling compartment. This concept and the proposal that regulation of spine to dendrite electrical coupling may regulate synaptic signals are found in classic studies and, due to the work of several laboratories, have recently been reconsidered (Segev & Rall, 1988; Harris & Stevens, 1989; Koch & Zador, 1993; Svoboda *et al.* 1996; Bloodgood & Sabatini, 2005; Araya *et al.* 2006).

Lastly, biochemical and biophysical studies have suggested that Ca^{2+}-activated K^+ channels can be found in close proximity to or physically associated with VSCCs, as would be required for microdomain based activation (Roberts *et al.* 1990; Berkefeld *et al.* 2006; Marrion *et al.* 1998). Although SK channels are found in large polyprotein signalling complexes (Bildl *et al.* 2004), protein–protein interactions that specifically link SK channels with VSCCs have yet to be described biochemically.

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