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Non-linear calcium signalling and synaptic plasticity in interneurons

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Understanding of how intracellular calcium (Ca^{2+}) signals regulate the efficacy of transmission at excitatory and inhibitory synapses in the central nervous system (CNS) has been a focus of intense investigation. This review discusses recent findings on how Ca^{2+} signals are integrated in dendrites of inhibitory interneurons to regulate their synapses. In particular, Ca^{2+} signaling through intracellular Ca^{2+} release plays an essential role in synaptic signal transduction and experience-dependent plasticity in dendrites of interneurons. Understanding the alternative pathways of Ca^{2+} signaling in the absence of canonical voltage-gated Ca^{2+} mechanisms is beginning to shed light on how their regulation can contribute to interneuron function and dysfunction in disease.

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Introduction

Dendrites, the receiving apparatus of the neuron, evolved to sample ongoing brain activity and to adjust the neuron's operation according to immediate network needs. Calcium (Ca^{2+}) signaling in neuronal dendrites plays a pivotal role in neuronal development and functioning [1–5,6••], but may also underlie dendritic signal miscoding and structural abnormalities observed in multiple disorders, including autism, epilepsy and Alzheimer's disease [7–10]. Activity-dependent fluctuations in dendritic Ca^{2+} ion concentration are shaped via dynamic interaction between the Ca^{2+} influx and extrusion mechanisms, comprising different voltage-gated and ligand-gated channels, intracellular stores and carrier proteins/transporters. These Ca^{2+} mechanisms form a complex signal transduction system capable of regulating the efficacy of transmission at excitatory synapses throughout the CNS. In most central neurons, activation of excitatory synapses is associated with generation of local Ca^{2+} events, which are commonly triggered by Ca^{2+} ion influx via postsynaptic glutamate Ca^{2+} permeable receptors and voltage-gated Ca^{2+} channels (VGCCs). Furthermore, near-synchronous activation of several excitatory inputs has been associated with supralinear summation of both Ca^{2+} events and membrane voltage signals, leading to generation of the so-called Ca^{2+} spikes, which shape the neuron's output and regulate synaptic strength [1,11,12]. Supralinear input integration relies on the presence of voltage-dependent postsynaptic mechanisms, such as NMDA receptors, Na^{+} channels and different types of VGCCs expressed in neuronal dendrites. While voltage and Ca^{2+} nonlinearities may be critical in predicting the direction of synaptic plasticity, recent research indicates that canonical voltage-dependent mechanisms amplifying excitatory input integration in principal neurons may not operate in inhibitory interneurons due to specific biophysical properties of interneurons' dendrites, as well as distinct postsynaptic Ca^{2+} signaling pathways [13,14,15••]. Here, we emphasize recent experimental advances examining dendritic signal integration in interneurons by focusing on local Ca^{2+} signaling and its role in synaptic plasticity. In particular, we highlight the important role of intracellular Ca^{2+} release in dendritic Ca^{2+} nonlinearities (CaNLs) and plasticity induction at interneuron excitatory synapses.

Ca^{2+} signaling in dendrites of interneurons

Local circuit GABAergic inhibitory interneurons control the integration and transfer of information in many brain regions. As a rule, these cells are aspiny and receive glutamatergic inputs directly onto dendritic shafts via synapses that can experience several distinct forms of Ca^{2+}-dependent plasticity. Dendritic integration studies in interneurons have been traditionally hampered by the aspiny nature of their dendrites, which precludes high-resolution activation and imaging of Ca^{2+} signals at visually identified postsynaptic structures like dendritic spines. However despite this limitation, the detailed organization of dendritic Ca^{2+} signaling and its functional significance in interneurons has been recently advanced [16–19].

Current evidence indicates that, similarly to pyramidal cells, dendrites of interneurons exhibit a large repertoire of Ca^{2+} sources, including ionotropic and metabotropic glutamate receptors and Ca^{2+}-permeable ion channels.

These Ca^{2+} sources show a cell- and input-specific distribution and respond differentially to changes in presynaptic and postsynaptic activity, providing a means for a highly versatile regulation of synaptic plasticity [14,16,19,20,24]. The activity-dependent properties of dendritic Ca^{2+} transients have been characterized in several types of anatomically identified interneurons in hippocampal, neocortical and cerebellar slices *in vitro* [14,15••,16–25]. It was found that postsynaptic NMDA and Ca^{2+}-permeable AMPA (CP-AMPA) receptors mediate Ca^{2+} influx at interneuron excitatory synapses but that the distribution of different receptor subtypes may vary between different regions and cell types [14,16,17,22]. For example, in cortical circuits, including the hippocampus, the expression of NMDARs in interneurons is highly variable and is particularly low in dendrites of parvalbumin-expressing (PV+) cells [22,26]. Accordingly, in these cells, CP-AMPARs play a major role in postsynaptic Ca^{2+} influx and, together with Na^+/Ca^{2+} exchangers, are responsible for spatial compartmentalization of Ca^{2+} transients (CaTs) within postsynaptic microdomains in the absence of dendritic spines. In particular, the fast activation/deactivation kinetics of CP-AMPARs limits the spread of the associated Ca^{2+} signal [23]. The CP-AMPAR- and a7 nicotinic receptor-mediated Ca^{2+} elevations are sufficient for induction of anti-Hebbian long-term-potentiation (LTP), which is triggered by conjoint synaptic stimulation and membrane hyperpolarization [27–30]. In addition, repetitive activity in some interneuron types can initiate Ca^{2+} influx via activation of the transient receptor potential (TRP) channels coupled to group I metabotropic glutamate receptors (mGluR1/5) [16,18,19]. TRP-mediated CaTs are potentiated by membrane depolarization and can be involved in Hebbian forms of LTP at interneuron excitatory synapses [16,19]. In fact, this voltage-gated Ca^{2+} mechanism may compensate for the lack of the action potential back-propagation (bAP) in interneuron dendrites resulting from the distance-dependent decline in Na^+ channels and high K^+ channel density [21,31]. While the distance-dependent decrease in bAP-CaT amplitude is observed in most interneuron types [20,21,24,31,32], bAP-CaTs can still be potentiated by changes in network activity. For example, a long-lasting potentiation of the L-type VGCCs via activation of mGluR5 following high-frequency stimulation has been reported in hippocampal CA1 oriens/alveus (O/A) interneurons [25]. The potentiation of L-type VGCCs resulted in the enhancement of CaTs evoked by pairing the theta-burst synaptic stimulation with membrane depolarization, which induces Hebbian LTP at excitatory synapses of O/A interneurons. Thus, potentiation of bAP-CaTs may decrease the Ca^{2+} threshold for Hebbian LTP under limited AP back-propagation. As most of the plasticity mechanisms presented here have been studied in different cell types, it is still unclear which ones may be common and which are the cell type-specific or input-specific. Recent evidence suggests that, at least, the CP-AMPAR-dependent Ca^{2+} mechanisms may be shared by different interneuron types (e.g. fast-spiking basket and bistratified cells [14]), and that Hebbian and anti-Hebbian plasticity mechanisms may coexist in the same cell type [33]. It is to be noted that no experiments were performed with simultaneous Ca^{2+} imaging and plasticity induction due to technical limitations (such as extensive cell wash-out and changes in intracellular Ca^{2+} buffering following Ca^{2+} indicator loading), calling for a note of caution when concluding on the Ca^{2+} mechanisms of plasticity.

Summation of Ca^{2+} signals in interneuron dendrites

The summation of Ca^{2+} signals has been examined in dendrites of hippocampal CA1 and cerebellar interneurons [14,15••]. When several inputs were activated synchronously in CA1 fast-spiking (FS) cells, Ca^{2+} influx via CP-AMPARs triggered the generation of local dendritic CaNLs, which occurred independently of NMDARs but required the activation of CP-AMPARs and Ca^{2+}-induced Ca^{2+} release (CICR) (Figure 1). Moreover, once generated, CaNLs were able to change the direction of plasticity at excitatory synapses from LTP to short-term or long-term depression (STD or LTD) [14]. The duration of depression was determined in this case by the additional recruitment of group I mGluRs, which could significantly slow down the CaNL decay. Furthermore, supralinear Ca^{2+} signal generation has also been reported in thin dendrites of cerebellar stellate cells [15••]. In this case, CaNLs resulted from the activation of NMDARs and VGCCs, which, due to a low Ca^{2+} current density, were unable to contribute efficiently to dendritic depolarization. These Ca^{2+} signals could induce both homo- and heterosynaptic STD at parallel fiber to stellate cell synapses [15••]. Together, these data point to supralinear Ca^{2+} signal integration in interneuron dendrites affecting locally the direction of synaptic plasticity.

Interestingly, in both CA1 FS cells and cerebellar stellate cells, supralinear summation of Ca^{2+} signals was associated with linear voltage integration at the soma. In particular, in stellate cells, supralinear Ca^{2+} generation occurred in parallel with a sublinear subthreshold input/output relationship due to the passive cable properties of dendrites [13,15••]. By contrast, a recent computational study on biologically constrained biophysical models of FS basket cells predicted a heterogeneity in the input/output relationship of FS dendrites, with some undergoing supralinear and some — sublinear synaptic integration. In this case, interneuron morphological properties, such as dendritic volume, appeared to have the most influence on the dendrite's integration mode. These observations indicate that interneurons, and FS cells in particular, have different integrative capacity for Ca^{2+} and voltage signals, and that, in addition to canonical forms of