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Differential Dendritic Integration of Synaptic Potentials and Calcium in Cerebellar Interneurons

Highlights

- Large, fast dendritic EPSPs favor sublinear integration, but not channel activation
- Supralinear dendritic [Ca^{2+}] integration is concomitant with sublinear integration
- Supralinear [Ca^{2+}] integration drives a transient, local synaptic plasticity

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In Brief

Dendritic integration of synaptic potentials and calcium generally follows similar mathematical operations. Tran-Van-Minh et al. found that, in cerebellar interneuron dendrites, these operations diverge, with supralinear calcium changes driving dynamic regulation of neuronal computations without altering sublinear voltage integration.

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Differential Dendritic Integration of Synaptic Potentials and Calcium in Cerebellar Interneurons

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SUMMARY

Dendritic voltage integration determines the transformation of synaptic inputs into output firing, while synaptic calcium integration drives plasticity mechanisms thought to underlie memory storage. Dendritic calcium integration has been shown to follow the same synaptic input-output relationship as dendritic voltage, but whether similar operations apply to neurons exhibiting sublinear voltage integration is unknown. We examined the properties and cellular mechanisms of these dendritic operations in cerebellar molecular layer interneurons using dendritic voltage and calcium imaging, in combination with synaptic stimulation or glutamate uncaging. We show that, while synaptic potentials summate sublinearly, concomitant dendritic calcium signals summate either linearly or supralinearly depending on the number of synapses activated. The supralinear dendritic calcium triggers a branch-specific, short-term suppression of neurotransmitter release that alters the pattern of synaptic activation. Thus, differential voltage and calcium integration permits dynamic regulation of neuronal input-output transformations without altering intrinsic nonlinear integration mechanisms.

INTRODUCTION

Understanding how a neuron transforms the spatio-temporal pattern of excitatory synaptic inputs into a neuronal output is fundamental to understanding information processing in the brain (Silver, 2010). Non-linear integration of excitatory postsynaptic potentials (EPSPs) within the dendritic tree is thought to increase the computational abilities of single neurons (Cazé et al., 2013; Katz et al., 2009; Poirazi and Mel, 2001) and has been shown to play a fundamental role in neuronal computations, such as tuning the selectivity of pyramidal neuron firing to specific sensory features during behavioral tasks (Lavzin et al., 2012; Smith et al., 2013; Xu et al., 2012). Nonlinear dendritic integration can be described by either sublinear or supralinear functions (dendritic operations) depending on whether the dendritic depolarization, evoked by concomitant activation of multiple synapses, is less or larger, respectively, than the arithmetic sum of individual EPSPs.

Linear voltage integration is often associated with the activation of small numbers of inputs (Losonczy and Magee, 2006), the activation of inputs located onto separate dendritic compartments (Polsky et al., 2004), or when summed nonlinear mechanisms are balanced (Cash and Yuste, 1999; Krueppel et al., 2011; Scott et al., 2010). For a larger number of clustered synaptic inputs, activation of Na^+ channels, voltage-gated Ca^{2+} channels (VGCCs), and/or NMDA receptors (NMDARs) often results in supralinear voltage integration (Branco and Häusser, 2011; Larkum et al., 2009; Losonczy and Magee, 2006; Schiller et al., 2000). Under such conditions, the dendritic intracellular $[Ca^{2+}]$ changes also exhibit supralinear transformations (Harnett et al., 2013; Katona et al., 2011; Losonczy and Magee, 2006; Schiller et al., 2000). These dendritic $[Ca^{2+}]$ signals can in turn activate biochemical pathways that engage synaptic and branch-specific, long-term plasticity, a process that may underlie memory storage of correlated input activity (Cichon and Gan, 2015; Gordon et al., 2006; Losonczy et al., 2008; Makara et al., 2009; Makino and Malinow, 2011; Takahashi et al., 2012). Sublinear dendritic operations, however, result from passive cable properties that cause large dendritic depolarization, resulting in decreased driving force for synaptic current (Abrahamsson et al., 2012; Rall, 1967; Vervaeke et al., 2012; Figure 1A), or in some cases, from the activation of K^+ channels (Hu et al., 2010). Yet, how activity- and Ca^{2+}-dependent synaptic plasticity is triggered when synaptic integration is sublinear is not known.

In cerebellar stellate cells (SCs), a significant fraction of the Ca^{2+} entry is mediated by Ca^{2+}-permeable AMPA receptors (AMPARs) (Soler-Llavina and Sabatini, 2006), as for many other interneurons (Goldberg and Yuste, 2005; Matta et al., 2013). Since synaptic voltage is integrated sublinearly in SCs in response to clustered synaptic activation (Abrahamsson et al.,