Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Dendritic T-type Ca^{2+} Channels: Giving a Boost to Thalamic Reticular Neurons

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Review of Crandall et al.

Most neurons have complex distinctive dendritic trees that receive the majority of synaptic contacts made onto each cell. Rather than acting as simple conduits conveying synaptic information to the soma, dendrites are actively involved in synaptic integration. This can be achieved by the expression of active dendritic conductances (allowing, for example, active action-potential backpropagation), as well as by nonlinear local interactions between synaptic events. Therefore, determining the expression patterns of various ion channels within dendrites is essential for understanding cellular integration. Although significant advances have been made in this regard for many neuron types (e.g., CA1 hippocampal pyramidal cells and neocortical neurons) (Spruston, 2008), little information has been obtained for thalamic neurons.

GABAergic neurons of the thalamic reticular nucleus (TRN) have a pivotal role in corticothalamic circuits: they provide both corticothalamic feedforward and thalamothalamic feedback inhibition to the primary thalamic nuclei and thus modulate sensory information flow between thalamus and neocortex. The TRN is also involved in generating and modulating oscillatory activities associated with sleep, including spindles and slow (<1 Hz) oscillations, and it is crucial in the propagation of pathological spike and wave activity characteristic of absence epilepsy (Crunelli and Leresche, 2002; Crunelli and Hughes, 2010). Therefore, knowledge of the active integrative properties of TRN dendrites is essential for understanding sensory information processing in corticothalamic networks.

In a recent article in the *The Journal of Neuroscience*, Crandall et al. (2010) studied the active properties of dendrites from neurons of the TRN using whole-cell recording and simultaneous two-photon Ca^{2+} imaging. These neurons, like many thalamic neurons, undergo a behavioral-state-dependent switch between burst and tonic firing patterns that depends on T-type ($Ca_V3.1$–3.3) Ca^{2+} channels. Although it has previously been hypothesized that T-type channels are widely expressed in TRN dendrites (Destexhe et al., 1996), Crandall et al. (2010) provide direct evidence for this. The authors demonstrate that somatically evoked T-type Ca^{2+} channel-dependent low-threshold spikes (LTS) produced significant transient increases in Ca^{2+} concentration ($\Delta[Ca^{2+}]$) throughout the entire dendritic arbor of TRN neurons. But unlike thalamocortical neurons of the dorsal lateral geniculate nucleus and ventrobasal nuclei, which showed more uniform spatial distribution of LTS-evoked $\Delta[Ca^{2+}]$ (Errington at al., 2010), neurons of the TRN had significantly larger $\Delta[Ca^{2+}]$ in distal dendritic regions than in proximal locations. In addition, Crandall et al. (2010) showed that LTS-evoked dendritic Ca^{2+} signals in TRN do not rely on back-propagating action potentials (because they demonstrate little sensitivity to TTX), but instead are largely dependent on T-type Ca^{2+} channels (they were blocked by mibefradil). In fact, dendritic Ca^{2+} signals evoked by a burst of action potentials in a depolarized TRN neuron (held at −60 mV), in which T-type channels were mostly inactivated, were significantly smaller than those observed with LTS-associated burst firing. Neither single nor trains of backpropagating action potentials resulted in significant dendritic $\Delta[Ca^{2+}]$ in intermediate or distal dendrites of TRN neurons. Therefore, as a result of dendritic T-type channel expression, TRN neurons might display very different state-dependent intrinsic Ca^{2+} signaling profiles in their dendrites during sleep-associated burst firing and wakefulness-associated tonic firing.

Although these results demonstrate a clear distinction between dendritic LTS-dependent Ca^{2+} signaling in TRN and thalamocortical neurons, an important caveat should be considered. Calcium indicators act as buffers and can alter the

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dynamics of Ca^{2+} signaling, resulting in a reduction of $\Delta[Ca^{2+}]$ amplitudes and slowing of decay time constants (τ) (Helmchen et al., 1996) that is proportional to the amount of added buffer. Thus, differential distribution of Ca^{2+} indicator within dendrites can result in varying degrees of signal distortion, giving the appearance of larger signals in more distal locations. In Crandall et al. (2010), distal $\Delta[Ca^{2+}]$, in addition to being consistently larger than proximal $\Delta[Ca^{2+}]$, appeared to decay more rapidly (their Figs. 3–5). Although these transients may not be representative of the entire population of dendrites tested (a quantitative assessment of this is not presented), these data suggest that the observed increase in distal Ca^{2+} may have been partially the result of incomplete dye loading of the very long (measurements were made up to ~200 μm from the soma) and fine (~1 μm) TRN distal dendrites during the course of the experiment. Because the inverse of the $\Delta[Ca^{2+}]$ amplitude (A^{-1}) and τ show linear dependence on the amount of exogenous Ca^{2+} buffer (K_B), the integral ($A\tau$) of the $\Delta[Ca^{2+}]$ gives a measure of dendritic Ca^{2+} influx that is independent of added buffer concentration. Although not shown in the article, these data would be useful to determine whether the reported spatial gradient is truly a physiological characteristic of these neurons. It is difficult to extrapolate T-type Ca^{2+} channel density from intradendritic $\Delta[Ca^{2+}]$; however, these findings are supported by a recent anatomical study that also described higher channel density in thin TRN dendrites (Kovács et al., 2010). Furthermore, although performed at nonphysiological temperatures (~23°C), the experiments by Crandall et al. (2010) demonstrate relatively rapid decay of $\Delta[Ca^{2+}]$ throughout the entire TRN neuron dendritic tree. Thus, in the presence of completely functional extrusion mechanisms and the absence of exogenous Ca^{2+} buffers, TRN dendrites may have robust mechanisms for Ca^{2+} clearance and/or intracellular Ca^{2+} uptake, a property that may be critical in sustaining T-type Ca^{2+} channel-driven intrinsic oscillations.

These new findings by Crandall et al. (2010) add further weight to the idea that dendritic T-type channel expression may contribute to Ca^{2+} influx during bursting and thus help to regulate oscillatory activity through Ca^{2+}-dependent processes. For example, it has previously been shown that a signaling triad of T-type Ca^{2+} channels, SK2 potassium channels, and sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPases in proximal TRN dendrites plays a crucial role in modulating oscillatory activity characteristic of sleep (Cueni et al., 2008). The widespread dendritic expression of T-type Ca^{2+} channels, as demonstrated by Crandall et al. (2010), suggests that this mechanism may not be restricted to proximal locations. Another recent study reported that LTSs in TRN neurons result in activation of ryanodine receptors (RyR 2/3) and Ca^{2+}-induced Ca^{2+} release that can regulate oscillatory burst discharges (Coulon et al., 2009), but the data presented by Crandall et al. (2010) cast some doubt upon the physiological relevance of this mechanism, given the dendritic dominance of T-type Ca^{2+} channel-mediated influx and the apparent somatic expression of the predominant RyR 3 subtype in TRN (Coulon et al., 2009).

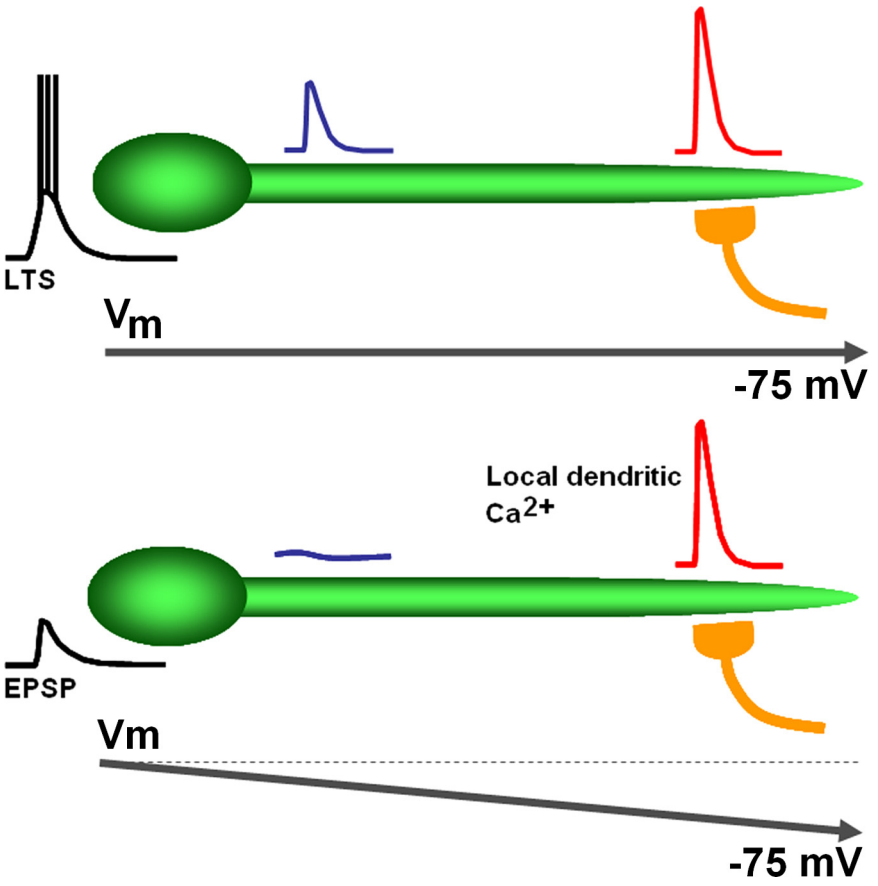

Figure 1. Both global and local dendritic Ca^{2+} signaling could occur in TRN neurons in response to distal synaptic inputs, depending on membrane potential along the somatodendritic axis and local availability of T-type channels. Amplified distal synaptic inputs could thus have markedly different effects upon cellular output, depending on the spatial and temporal distribution of neuromodulatory inputs.

It has been previously proposed that the functional significance of dendritic T-type channel expression may be the amplification of relatively small distal synaptic inputs. In TRN neurons, Crandall et al. (2010) demonstrated not only that focal glutamate application to distal dendrites was able to evoke LTS and distal $\Delta[Ca^{2+}]$, but that local $\Delta[Ca^{2+}]$ can be initiated independently of the soma/proximal dendrites. In fact, little difference was observed in glutamate-evoked $\Delta[Ca^{2+}]$ in distal dendrites when the membrane potential was held at −60 mV and when it was held at −80 mV, despite the absence of a somatic LTS at the more depolarized potential. It appears therefore, that dendritic T-type Ca^{2+} channels are able to boost small distal synaptic inputs, allowing them to contribute more readily to somatic output and perhaps produce both local and global dendritic Ca^{2+} signals, depending on the degree of membrane polarization along the somatodendritic axis (Fig. 1). Indeed, because almost 70% of synaptic inputs into TRN neurons are from corticothalamic afferents that are evenly distributed throughout the dendritic tree, this amplification mechanism could provide more consistent weighting to each synaptic input, regardless of its location within the dendritic arbor, by

compensating for the effects of passive dendritic attenuation. As suggested by Crandall et al. (2010), this could give the neocortex a strong top-down modulatory influence that would shape dendritic integration in TRN by altering the cellular resting membrane potential either locally or globally.

In conclusion, the article by Crandall et al. (2010) has brought a new insight into the function of dendrites in the TRN and will undoubtedly contribute to our further understanding of how this important inhibitory nucleus modulates sensory information flow within corticothalamic circuits.

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