

ABSTRACT

HETEROGENEOUS THALAMIC RETICULAR NUCLEUS NEURONS AND THEIR FUNCTIONAL ROLE IN THALAMOCORTICAL PROCESSING

By

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The thalamic reticular nucleus (TRN) is an integral regulator of information flow between the thalamus and cortex. The TRN receives synaptic inputs from both cortical and thalamic regions and based upon this information it selectively inhibits thalamic activity. TRN neurons produce action potentials in two distinct modes: a fast, transient burst discharge from a hyperpolarized state, and a prolonged, tonic discharge from a relatively depolarized state. While previous studies have characterized burst discharge as a transient high frequency discharge (> 250 Hz), these electrophysiological studies reveal a highly variable range of burst frequencies (4-342 Hz). In these studies, I aim to discover the mechanisms underlying these highly variable burst frequencies, as well as their functional role in thalamocortical processing.

In Chapter 2, I found that bursts from TRN neurons with relatively higher frequency discharge (> 100 Hz) contain more action potentials per burst. These neurons also have higher input resistances, broader action potentials, higher action potential thresholds, and larger somas. The amplitude of the T-type calcium channel-mediated low-threshold spike, which underlies the burst discharge, is positively correlated with both the burst discharge frequency and the number of action potentials per burst. I next investigated whether small conductance calcium-activated potassium channels (SK channels) could mediate the differences in burst firing rate and action potential number. Blocking SK channels increased the frequency and duration of the burst but did not increase the amplitude of the underlying T-type calcium current.

Prior studies suggest that T-type calcium channels are distributed along the dendrites in TRN neurons with high frequency burst discharge. In Chapter 3, I examine the distribution of dendritic calcium activity within the lower frequency bursting neurons. While the calcium signal was lower in these neurons all along the dendrites, the calcium signal was evenly distributed across proximal, intermediate, and distal dendritic regions. Investigation of SK channel activity revealed significant location-specific effects. In lower frequency bursting neurons, SK channels had the greatest influence at proximal and distal locations. In higher frequency bursting neurons, SK channels had the greatest influence at proximal and intermediate dendritic locations. Heterogeneous TRN burst discharge frequencies may represent a diverse cell population with unique dendritic ion channel composition and distribution. These results may improve our understanding of the mechanisms of TRN neuron afferent synaptic integration as well as modulation of thalamocortical inhibition.

In Chapter 4 I investigate whether intrinsic properties of TRN neurons are altered in the *Fmr1*-KO mouse model of Fragile X Syndrome (FXS). Individuals with FXS experience a variety of comorbidities that could involve TRN function, such as altered sensory perceptions, sleep disorders, and epilepsy. Analysis of intrinsic cellular properties revealed no differences in TRN neuron properties. Further investigation of synaptic plasticity, which is an abnormal finding in several other brain regions in FXS, also revealed no pathology. These findings suggest that TRN dysfunction does not contribute to FXS pathology.