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It Takes T to Tango

Of three recently cloned T-type voltage-gated calcium channels, α_{1g} is most likely responsible for burst firing in thalamic relay cells. These neurons burst during various thalamocortical oscillations including absence seizures. In this issue of *Neuron*, Kim et al. inactivated α_{1g}, and resultant mice were deficient in relay cell bursting and resistant to $GABA_B$ receptor-dependent absence seizures, suggesting roles for α_{1g} and relay cell bursting in absences.

Epilepsy is a common neurological disorder affecting approximately 1% of the population. One form of this disorder, childhood absence epilepsy, is characterized by brief behavioral absences with staring spells and 3 Hz spike and wave electroencephalographic (EEG) activity. It is a nonconvulsive seizure disorder that occurs primarily in children, and it has been extensively studied in various animal models over the last half-century (Huguenard, 1999). This experimental work has demonstrated that both thalamic and cortical circuits participate in spike-wave activity, leading to the hypothesis that the thalamocortical circuit can become synchronized into a widespread 3 Hz oscillation and that disruptions in either thalamic or cortical portions of the circuit can contribute to seizures. Yet there is controversy over which components of the thalamocortical circuit are strictly required for the *generation* of absence seizures. This is a fundamental issue regarding treatment of absences because pharmacotherapies should target the appropriate epileptogenic region. In this issue of *Neuron*, Kim et al. (2001) present findings in mice deficient in the T-type calcium channel gene α_{1g} (Perez-Reyes et al., 1998) that demonstrate that calcium-dependent spike bursts in thalamic relay neurons play a central role in the genesis of absence seizures.

The long-standing controversy regarding thalamic versus cortical roles arises from experimental evidence in various animal absence models. A major cortical role is supported by the feline generalized penicillin model, in which diffuse application of penicillin to cortex can trigger spike-wave activity (Gloor et al., 1990). In addition, electroencephalographic episodes containing spike-wave events can be recorded in isolated cortical circuits (Marcus and Watson, 1966; Steriade and Contreras, 1998). However, the precise relationship between such intracortical spike-wave events and clinical absence seizures remains unclear (Ajmone-Marsan, 1969). Indirect evidence for a strong cortical role derives from the inbred GAERS rat strain, in which recordings from thalamic relay neurons during spike-wave activity have demonstrated less activity than expected if thalamus played a major epileptogenic role (Pinault et al., 1998).

Yet other studies suggest a central role for thalamus in seizure genesis. For example, intrathalamic injection of $GABA_A$ or $GABA_B$ receptor agonists can exacerbate absence-like seizures in GAERS rats, while antagonists have the opposite result (Marescaux et al., 1992). In the feline penicillin model, spike-wave activity requires both cortical and thalamic structures—inactivation or disconnection of thalamus abolished the cortical activity (Gloor et al., 1990). Finally, synchronized epileptiform 3 Hz activity can be obtained in isolated thalamic slices, and this is antagonized by medications used in the treatment of absence epilepsy, such as succinimides (see below; reviewed in Huguenard, 1999).

The T-type calcium channel plays a key role in the phase-locked firing of thalamic neurons during both seizures and spindle oscillations, which occur normally during slow-wave sleep. During both types of oscillations, thalamic relay neurons are hyperpolarized by rhythmic inhibitory postsynaptic potentials, which deinactivate the T current, sometimes resulting in rebound bursts. Thus, phase-locked firing by thalamic relay cells results from the interplay of rhythmic synaptic inhibition and T-type calcium channels.

The study of Kim et al. was designed to test whether thalamic burst firing, mediated by α_{1g}, is necessary for spike-wave activity. These researchers generated a mouse deficient in α_{1g} and demonstrate that T-type calcium currents and Ca^{2+}-dependent spike bursts were abolished in thalamic relay neurons, while tonic firing was unaffected. The authors proceeded to test whether agents that have been shown to produce thalamocortical spike-wave discharges can do so in ${\alpha_{1g}}^{-/-}$ mice. Systemic injection of baclofen or a pro-drug for γ-hydroxybutyrate (both $GABA_B$ receptor agonists) produced prominent spike-wave discharges in wild-type mice but not in ${\alpha_{1g}}^{-/-}$ animals. Interestingly, other types of seizures were much less affected by α_{1g} knockout. For example, α_{1g} and wild-type mice were equally susceptible to seizures induced by systemic injection of $GABA_A$ antagonist bicuculline methbromide. These seizures were associated with brief episodes of spike-wave discharge, but within an overall context of ongoing iterictal and ictal epileptiform discharges with varied motor components. These findings reinforce two ideas: (1) thalamic involvement via α_{1g} is required for spontaneous, isolated spike-wave events superimposed on a normal EEG background, as occurs in typical absence epilepsy, and (2) cortical mechanisms can also produce a spike-wave pattern independent of the thalamus (Marcus and Watson, 1966; Steriade and Contreras, 1998).

This study is important because it strongly suggests that typical absence seizures require T-type calcium channels, specifically those encoded by α_{1g}, confirming that these channels, and the Ca^{2+}-dependent spike bursts they mediate, are appropriate pharmacological targets for the treatment of absence epilepsy. This may explain the antiabsence effects not just of succinimides and related compounds, which may directly block T channels (Coulter et al., 1989; but see Pfrieger et al., 1992), but also of agents like $GABA_B$ antagonists, which functionally antagonize T channels by preventing the hyperpolarization necessary for their deinactivation (Huguenard, 1999). T channels in other neurons may also

play a role in absence seizures. In particular, such channels are also expressed in neurons of the thalamic reticular nucleus, which during seizures and spindles provide the rhythmic IPSPs that drive bursting in thalamic relay neurons. Unlike relay neurons, cells in the reticular nucleus primarily express the α_{1I} and α_{1H} subunits of the T channel family (Talley et al., 1999). Based on this, one would predict that disruption of these subunits in thalamic reticular neurons would produce animals which, like the $\alpha_{1g}^{-/-}$ mice, are resistant to spike-wave seizures.

Two caveats must be raised with this study: (1) the specific abolition of typical absence seizures, as produced by $GABA_B$ receptor activation, should be reproduced in other models of absence such as the low-dose picrotoxin model, and (2) the implication from this study is that T channels in thalamic relay neurons are required for absence seizures. Although α_{1g} is predominately expressed in thalamus, it is also expressed in cortex (Talley et al., 1999), suggesting that the effects of α_{1g} knockout on spike-wave activity cannot yet be totally attributed to a thalamic locus.

The $\alpha_{1g}^{-/-}$ mice were fertile and had apparently normal behavior, suggesting that T channels in thalamic relay neurons are not essential for any obvious function. This contrasts with the fact that T channels are responsible for bursts in relay neurons during sleep spindles. Indeed, Kim et al. found that electrical field activity in the spindle range (10–12 Hz) was weaker in $\alpha_{1g}^{-/-}$ thalami than in that in wild-type animals. Sleep spindles occur in concert with the replay of hippocampal activity patterns that reflect recent experiences, leading to the proposal that they play a role in memory consolidation (Siapas and Wilson, 1998). It will be very interesting to explore whether $\alpha_{1g}^{-/-}$ mice are deficient in sleep, memory consolidation, and/or sensory processing.

Vikaas S. Sohal and John R. Huguenard
Department of Neurology and Neurological Sciences
Stanford University School of Medicine
Stanford, California 94305

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Making the Pain Connection

Dorsal root ganglia (DRG) neurons include multiple types of sensory neurons with well-appreciated anatomical and physiological distinctions. In this issue of *Neuron*, Chen et al. adds to our molecular understanding of these differences by reporting that DRG11, a paired homeodomain transcription factor, is specifically required for the proper development of pain-sensing nociceptive neurons.

Somatic sensory neurons detect various stimuli from peripheral tissues and transmit these signals to their central targets in the spinal cord. The cell bodies of somatic sensory neurons are organized into the DRG, a shared segmented structure lining the torso along the spinal cord (Scott, 1992). Somatic sensory neurons are functionally heterogeneous: distinct classes of these neurons recognize painful stimuli (nociception), innocuous stimuli such as light touch (mechanoreception), and positional information (proprioception). The neurons serving these distinct modalities can also be classified by their unique target innervations, as well as some biochemical and morphological characteristics. For example, proprioceptive neurons are large myelinated neurons that innervate muscle spindles and Golgi tendons peripherally and send central projections to the ventral horn of the spinal cord. Nociceptive and thermoceptive neurons, on the other hand, are small-diameter unmyelinated or lightly myelinated neurons that receive peripheral cutaneous inputs and densely innervate the dorsal horn of the spinal cord.

Interestingly, despite their high degree of functional and anatomical specialization, all somatic sensory neurons originally develop from a single precursor population, the neural crest. We understand remarkably little about the molecular mechanisms that initiate specification of these neurons during development. Nor are the mechanisms that allow for their accurate connectivity well defined. In this issue of *Neuron*, a paper from David Anderson's lab (Chen et al., 2001) examines the phenotype of mice lacking the gene encoding the paired homeodomain transcription factor DRG11 and presents new insight into these processes.

A handful of other transcription factors required for sensory neuron development has been identified. For instance, neurogenin (ngn) 1, ngn2, and Brn3a are known to be required by DRG neurons of more than one subtype at different developmental time points (Huang et al., 1999; Ma et al., 1999). The ETS domain transcription factors ER81 and PEA3 are present in both a subset of proprioceptive neurons and their central targets, the motor neurons, and Er81 is required for the proper es-