This Week in The Journal

Spontaneous Ca^{2+} Transients in Migrating Neurons

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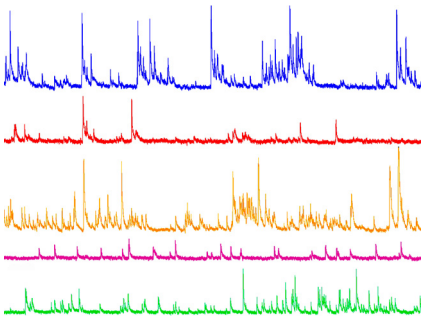
(see pages 5551–5566)

Calcium regulates numerous neuronal functions, including migration, axon guidance, dendritic arborization, and synaptic plasticity. Calcium transients occur in migrating cortical principal neurons, and their frequency increases as the neurons cease migration and elaborate dendrites. Genetic manipulations that depolarize neurons increase the number of calcium transients and cause premature termination of migration and initiation of dendritic branching, suggesting calcium regulates these processes (Bando et al., 2015 Cereb Cortex 26:106).

To identify the source of calcium transients in migrating cortical neurons, Kamijo et al. delivered a membrane-tethered calcium indicator, Lck-G-CaMP7, to newborn neurons destined for cortical layer 2/3 in mouse embryos. Three days later, neurons were dissociated and transferred to culture. Within a few hours, before axons or dendrites had been established, the neurons began exhibiting spontaneous regenerative calcium transients (SRCaTs) unlike transients produced by action potentials or synaptic activity. Some SRCaTs were repetitive and some propagated within neurites, but others remained localized and stationary. Extracellular calcium was required for SRCaT generation, but release from internal stores was not. Overexpression of a potassium channel that caused neuronal hyperpolarization reduced SRCaT frequency, suggesting the transients were mediated by voltage-sensitive calcium channels. Indeed, blocking L-type channels reduced SRCaT generation, whereas pharmacologically activating the channels increased SRCaT production. Notably, SRCaT amplitude was increased by expression of a $Ca_V1.2$ mutant (G406R) that has enhanced permeability and causes Timothy syndrome, a neurodevelopmental disorder. In contrast, blocking N- and P/Q-type channels, action potentials, AMPA receptors, or NMDA receptors had no effect on SRCaTs.

Both $Ca_V1.2$ and $Ca_V1.3$ contributed to SRCaT generation in embryonic cortical neurons. Knocking out $Ca_V1.2$ reduced neurite elongation in cultured neurons, and overexpressing $Ca_V1.2$ modestly impaired cortical neuron migration *in vivo*. Migration was profoundly disrupted by overexpression of the Timothy-syndrome-linked $Ca_V1.2$-G406R, however. Importantly, shutting off production of $Ca_V1.2$-G406R after birth rescued migration defects.

These results support the hypothesis that calcium transients are present in migrating neurons, but increasing their number inhibits migration and promotes dendritic growth. The study extends previous work by suggesting that the transients are mediated by spontaneous opening of L-type calcium channels in the absence of neuronal spiking. Finally, the work provides evidence that migration defects can sometimes be reversed by postnatal treatment.



The frequency and amplitude of IPSCs in BNST SOM^+ neurons is lower in *Erbb4*-deficient mice (red) than in wild-type (blue). This phenotype is rescued by reducing excitation of CeL SOM^+ neurons (yellow), and is replicated by exposing wild-type mice to stress (pink). The phenotype in stressed mice is rescued by inhibiting BNST KORs (green). See Ahrens et al. for details.

An Amygdala – BNST Pathway Underlying Anxiety

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(see pages 5567–5583)

The amygdala and bed nucleus of the stria terminalis (BNST) have essential roles in detecting threats and generating appropriate responses. Much work has detailed amygdala circuits involved in recognizing and responding to signs of imminent danger, such as tones that predict shock. Comparatively little is known about the circuitry underlying anxiety-like responses to less certain, more diffuse threats, such as open spaces. Nevertheless, projections from the centrolateral amygdala (CeL) to the BNST contribute to these responses. Ahrens et al. further elaborate this pathway, showing that somatostatin-expressing (SOM^+) neurons in these areas regulate anxiety-like behaviors.

Mice lacking the receptor tyrosine kinase Erbb4 in SOM^+ neurons spend less time than wild-type mice in the center of arenas and the open arms of elevated plus mazes. This anxiety-like phenotype was rescued by reintroducing Erbb4 selectively to CeL SOM^+ neurons. Furthermore, deleting *Erbb4* selectively in CeL SOM^+ neurons replicated the anxiety-like phenotype and increased excitatory input to these neurons.

Although CeL SOM^+ neurons form inhibitory synapses on BNST SOM^+ neurons, basal activity in both populations was increased in *Erbb4*-deficient mice, and genetically reducing excitation of CeL SOM^+ neurons increased, rather than decreased, inhibitory input to BNST SOM^+ neurons. This paradoxical effect was attributable to elevated release of dynorphin by CeL SOM^+ neurons in mutant mice: dynorphin suppresses inhibitory input from CeL to BNST, and inhibiting dynorphin-activated kappa opioid receptors (KORs) in BNST increased inhibition of BNST SOM^+ neurons in *ErbB4*-deficient mice. Notably, reducing inhibition of BNST SOM^+ neurons by knocking out a GABA receptor subunit produced anxiety-like behaviors, whereas blocking transmitter release from these neurons rescued this phenotype in *ErbB4* mutants. Moreover, infusing KOR antagonists into BNST fully rescued anxiety-like phenotypes in mutant mice. Most importantly, subjecting wild-type mice to repeated foot-shock stress increased anxiety-like behaviors, increased excitatory input onto CeL SOM^+ neurons, and reduced inhibitory input to BNST SOM^+ neurons. KOR antagonists blocked the last effect.

This work suggests that stress promotes anxiety partly by increasing excitatory input to CeL SOM^+ neurons. This increases dynorphin release, and thus blunts inhibition of BNST SOM^+ neurons, which in turn promote production of anxiety-like behaviors. Enhancing inhibition of BNST SOM^+ neurons, for example by blocking KORs, might therefore reduce stress-related anxiety.

This Week in The Journal was written by Teresa Esch, Ph.D.