This Week in The Journal

Early Inflammation Changes Cl^- Balance in Adult Male Neurons

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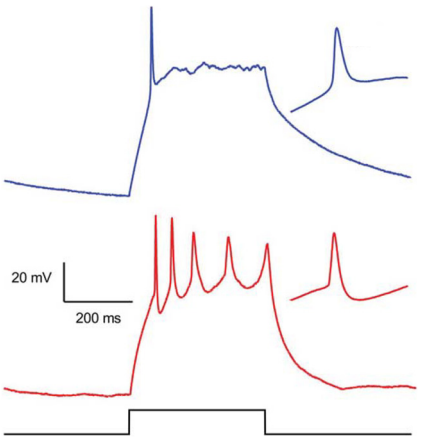
(see pages 7244–7259)

Injuries and infections induce immune cells to release cytokines that promote further immune responses, including inflammation and macrophage activation. In the brain, cytokines also act on neurons to generate sickness behaviors such as lethargy, loss of appetite, and social withdrawal, which motivate animals to rest, thus facilitating recovery. Because the same cytokines are produced by CNS cells to regulate neuronal development and synaptic plasticity, peripheral infections can alter these processes. In fact, infections occurring prenatally or during childhood can lead to persistent alterations in the CNS that increase the risk of a variety of neurological and psychiatric conditions (Bilbo and Schwarz, 2012, Front Neuroendocrinol 33:267).

To elucidate the mechanisms through which neonatal infection causes permanent changes in brain function, Gomez et al. induced inflammation by injecting a bacterial endotoxin, lipopolysaccharide (LPS), peripherally into 2-week-old mice and examined the effects on hippocampal neurons when mice reached adolescence or adulthood. No effects of early-life inflammation were found in adolescent mice or in adult female mice. But the firing rate of CA1 pyramidal neurons was higher in adult males exposed to early-life inflammation than in controls. This increase in firing rate likely resulted partly from an increase in input resistance and from a hyperpolarizing shift in the spike threshold, which occurred only in adult male mice that had been exposed to LPS. These changes in membrane properties did not stem from changes in sodium or potassium currents or from changes in sodium channel expression. Instead, they were attributable to increased expression of the Na+-K+-2Cl− cotransporter 1 (NKCC1), which caused a depolarizing shift in the chloride reversal potential. An NKCC1 blocker reversed the changes in chloride reversal potential, input resistance, action potential threshold, and spike rate in adult mice previously treated with LPS.

These results demonstrate how inflammation early in life can set the stage for changes in neuron function that do not appear until adulthood. Because the effects were seen only in males, the authors hypothesize that differences in sex hormones trigger the changes. Future work will be required to test this hypothesis, determine how changes in NKCC1 expression lead to changes in input resistance and spike threshold, and examine how these changes affect behavior.



A current step (black) evokes more action potentials in KCNT1-mutant neurons (red) than in controls (blue). Action potentials are narrower and have deeper afterhyperpolarizations in mutants (insets). See Quraishi, Stern, Mangan, et al. for details.

How Larger Potassium Currents Might Increase Seizure Risk

Imran H. Quraishi, Shani Stern, Kile P. Mangan, Yalan Zhang, Syed R. Ali, et al.

(see pages 7438–7449)

Seizures are brief periods of excessive and/or hypersynchronous neuronal activity thought to result from an overabundance of excitation or insufficient inhibition. Mutations in multiple genes predispose people to seizures. Many such mutations affect ionic conductance and thus alter the intrinsic excitability of neurons. For example, mutations in KCNT1, which encodes a sodium-activated potassium channel ($K_{Na}1.1$), cause a severe form of childhood epilepsy. Because potassium channels typically limit neuronal depolarization, one might predict that epilepsy-causing mutations in KCNT1 impair channel function. But when mutant channels are expressed in heterologous cell lines, their activity is greater than that of wild-type channels. Whether a similar gain-of-function phenotype occurs in neurons, and if so, how it promotes seizure generation, has been unknown.

To answer these questions, Quraishi, Stern, Mangan, et al. generated forebrain-like neurons from human induced pluripotent stem cells (hiPSCs) harboring an epilepsy-linked KCNT1 mutation, and they compared these with isogenic control neurons. Expression levels of $K_{Na}1.1$ channels were similar in the two populations, but depolarization resulted in much larger sodium-activated potassium currents in mutant neurons than in controls. In addition, action potentials were narrower, the spike afterhyperpolarization was deeper, and the number of spikes generated during 400-ms current steps was greater in mutant neurons than in controls. These differences persisted when other potassium channels were blocked, suggesting that they did not stem from compensatory changes in those channels. Furthermore, numerical simulations with simplified model neurons demonstrated that increases in K_{Na} current were sufficient to produce deeper afterhyperpolarization and elevated spiking in response to depolarizing current steps. Finally, in high-density cultures, mutant neurons exhibited more bursting and more synchronous activity than controls.

These results indicate that epilepsy-causing mutations in KCNT1 potentiate K_{Na} currents in hiPSC-derived neurons, as they do in heterologous cells. The increase in this current, which is activated when sodium enters the cell during depolarization, leads to a deeper spike afterhyperpolarization, which may shorten the refractory period and thus enable faster spiking. Although simulations indicated that increasing the K_{Na} current is sufficient to increase the spike rate, it remains possible that compensatory changes in other channels or interactions of mutant K_{Na} channels with other proteins contribute to the promotion of seizures in people harboring these mutations.

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