This Week in The Journal

CaMKIV Regulates Excitability and Excitatory Synaptic Scaling

Annelise Joseph and Gina G. Turrigiano

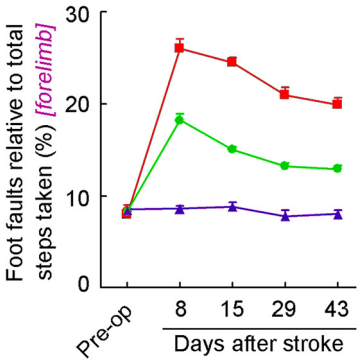
(see pages 6778 – 6785)

Information is transmitted through neural circuits primarily by changes in spike rate. The ability to encode such information is maximal when neurons' mean spike rates are in the middle of their dynamic range, allowing both increases and decreases in firing. In fact, many neurons appear to have a preferred spike rate, and they engage homeostatic mechanisms to increase or decrease spike probability after prolonged periods of silence or elevated spiking. Those homeostatic mechanisms include changes in excitatory and inhibitory synaptic strength and changes in intrinsic excitability.

Efforts to understand the molecular mechanisms underlying homeostatic plasticity have focused primarily on changes in excitatory synaptic strength. Decreased spiking is thought to reduce somatic calcium levels, which decreases activation of calcium/calmodulin-dependent protein kinase IV (CaMKIV) and downstream activation of cAMP responsive element binding protein (CREB). This ultimately leads to increased synaptic expression of AMPA receptors, and thus increased synaptic strength.

Much less is known about the homeostatic regulation of intrinsic excitability and inhibitory synaptic strength. To determine whether these homeostatic processes are also regulated by CaMKIV, Joseph and Turrigiano expressed dominant-negative or constitutively active forms of CaMKIV in individual neocortical pyramidal neurons in culture. Consistent with previous work, expression of dominant-negative CaMKIV decreased phosphorylation of CREB and increased miniature EPSC (mEPSC) amplitudes, whereas expression of constitutively active CaMKIV increased CREB phosphorylation and reduced mEPSC amplitude. Besides increasing excitatory synaptic strength, expression of dominant-negative CaMKIV increased the intrinsic excitability of neurons, as measured by the number of spikes elicited by a given current step. Conversely, constitutively active CaMKIV decreased intrinsic excitability. Finally, dominant-negative CaMKIV increased, whereas constitutively active CaMKIV decreased, spontaneous spike rate. Despite these effects, neither dominant-negative nor constitutively active CaMKIV affected miniature IPSC amplitude.

These results suggest that homeostatic changes in excitatory synaptic strength and intrinsic excitability are both regulated by CaMKIV. The fact that these changes were accompanied by changes in spike rate, but not by changes in inhibitory synaptic strength, suggests that the latter is regulated by other measures of network activity. Future work should confirm this, as well as identifying the downstream effectors that enable CaMKIV to modulate intrinsic excitability.



Phototthrombotic stroke causes motor impairment (red) in mice. Infusing HDAC2 inhibitors into the peri-infarct region reduced motor impairment (green). Blue shows motor function in controls. See Lin et al. for details.

Inhibiting HDAC2 Improves Stroke Outcome

Yu-Hui Lin, Jian Dong, Ying Tang, Huan-Yu Ni, Yu Zhang, et al.

(see pages 6712– 6728)

Stroke is a leading cause of death, and survivors often suffer from major functional impairment. Impairment results not only from death of neurons downstream of the blocked vessel, but also from damage to surrounding (peri-infarct) tissue, which receives inadequate perfusion and is exposed to excitotoxic molecules, reactive oxygen species, and inflammatory mediators that continue to exert damage for several days. Limiting peri-infarct damage should improve stroke outcomes, but despite the development of many promising therapeutics, the only treatment proven effective is thrombolysis, which must be administered soon after stroke onset and cannot be used in most patients.

One reason other stroke treatments have failed clinical trials may be that they were too narrowly focused—exclusively targeting excitotoxic or oxidative damage, for example. Targeting multiple damaging agents while promoting neuronal survival and plasticity might be more effective. This might be accomplished by inhibiting histone deacetylases (HDACs), which regulate transcription of numerous genes. Indeed, HDAC inhibitors reduce infarct size when administered before or shortly after experimental stroke in rodents.

Lin et al. now show that infusing HDAC inhibitors into the peri-infarct region several days after photothrombotic stroke reduced motor impairment in mice. In untreated mice, motor function improved during the first few days after stroke, but declined again on days 5–7. Notably, HDAC2 expression and activity were elevated during this period. Infusion of HDAC inhibitors in this window—but not earlier or later—reduced motor impairment, and the effect was sustained for at least 43 days. Although HDAC inhibitors did not reduce infarct size, they increased neuronal survival and reduced signs of inflammation. The inhibitors also reversed stroke-associated increases in tonic GABA currents. Finally, gene expression analyses indicated that HDAC inhibitors altered the expression of 1000 genes in the peri-infarct region, including genes involved in inflammation, superoxide generation, plasticity, and GABAergic signaling.

These and other results indicate that HDAC2 might be an effective target for improving stroke outcomes. They also emphasize the importance of identifying the correct treatment period for stroke therapies. Examining the time course of molecular changes after stroke in rodent models might reveal other targets for limiting damage and improving functional recovery in the hours to days following stroke.

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