This Week in The Journal

SK Channels Selectively Attenuate Parallel-Fiber EPSCs

Gen Ohtsuki

(see pages 267–282)

EPSCs spread along neuronal dendrites and combine with other EPSCs before reaching the spike initiating zone. Passive conduction of EPSCs, and thus synaptic integration, are influenced by several factors, including cell morphology and the density, distribution, and properties of ion channels. Opening of potassium channels counters depolarization and limits passive conduction and summation of EPSCs. The expression and function of these channels can be altered by synaptic activity, resulting in long-lasting changes in synaptic integration. For example, bursts of parallel-fiber spikes produce long-lasting increases in synaptic responses in Purkinje cells by reducing the function of small-conductance calcium-activated potassium (SK) channels. This intrinsic plasticity can be restricted to individual dendritic branches, increasing the ability of inputs to those branches to drive spiking.

To elucidate how this form of plasticity works, Ohtsuki recorded from the soma and individual dendrites of Purkinje cells in cerebellar slices and examined instances in which spontaneous EPSCs (sEPSCs) were detected at both sites within a narrow time window. These paired sEPSCs were assumed to arise from the same synaptic event. The amplitude of such sEPSCs differed in the soma and dendrite, and this discordance was greater for distal than for proximal dendrites. Notably, an abrupt μm increase in discordance occurred $\sim 80 \mu\text{m}$ from the soma, a position where the dendrite bifurcates and which demarcates the boundary between climbing-fiber and parallel-fiber input.

After calculating the ratio of dendritic EPSC amplitude to somatic EPSC amplitude for each event, Ohtsuki examined the distribution of ratios for proximal and distal dendrites. Whereas the ratios were distributed uniformly for proximal dendrites, the distribution for distal dendrites had multiple peaks, suggesting distal inputs were functionally clustered. Importantly, inducing intrinsic plasticity or blocking SK channels eliminated the difference in discordance between proximal and distal dendrites and made the distribution of am-

plitude ratios for distal dendrites more uniform.

These data suggest that SK channels suppress the passive conduction of EPSCs evoked by parallel fibers and create functional clusters of parallel-fiber inputs. Activity patterns that downregulate these channels facilitate EPSC conduction, increasing the ability of parallel-fiber inputs to shape neuronal output. This may influence whether long-term potentiation or depression occurs at coactive synapses, and may thus alter motor learning.

Illustrations of recording configurations (left) and physiological recordings of sEPSCs (right) detected in the soma (black) and dendrites (red) of Purkinje cells. The difference in sEPSC amplitude between dendrite and soma is much greater for distal (top) than for proximal (bottom) dendrites. See Ohtsuki for details.

Neuronal ER Stress Shapes Microglial Phenotype

Tanusree Sen, Pampa Saha, Rajaneesh Gupta, Lesley M. Foley, Tong Jiang, et al.

(see pages 424–446)

After traumatic brain injury (TBI), microglia begin to produce proteins that facilitate tissue repair. Some activated microglia assume a proinflammatory M1 phenotype, secreting molecules that attract additional microglia and peripheral immune cells to the injury site. Other microglia assume an M2 phenotype, secreting molecules that suppress inflammation and promote tissue repair. Although both

phenotypes serve important functions, an overabundance of M1 microglia can result in prolonged inflammation. This often occurs after TBI, and the prolonged inflammation is thought to underlie secondary neuronal degeneration and long-lasting functional impairment.

Sen et al. suggest that excessive induction of M1 microglia after TBI stems from endoplasmic reticulum (ER) stress in neurons. A component of the ER stress pathway, protein-kinase-R-like ER kinase (PERK), was activated selectively in neurons in the pericontusional cortex of mice after controlled cortical impact (CCI). Phosphorylation of a stimulator of interferon genes and interferon regulatory factor 3 also increased, resulting in increased production of interferon- β . Previous work has shown that interferon- β drives microglia toward the M1 phenotype by activating microglial STAT1. Consistent with this, STAT1 expression and the density of M1-like microglia increased in the pericontusional cortex after CCI. Consequently, the production of M1-specific chemokines increased, resulting in invasion of the cortex by proinflammatory T cells.

These results suggest that the induction of ER stress in neurons leads to release of interferon- β , which in turn activates microglia and drives them toward an M1 phenotype. This was confirmed by treating cultured microglia with conditioned medium from neurons cultured with an inducer of ER stress: the medium activated microglia and increased expression of M1-type molecules, but this effect was prevented when interferon- β was knocked down in neurons before ER stress was induced. In addition, blocking neuronal ER stress pathways *in vivo*—either by knocking down PERK or by treating mice with a PERK inhibitor—blunted CCI-induced increases in interferon- β , M1 microglia, and proinflammatory T cells. Instead, CCI led to increases in M2 microglia and anti-inflammatory T cells when PERK function was reduced. Importantly, these changes were associated with reduced demyelination and axon loss and more normal behavior in tests of anxiety- and depression-related behaviors. Thus, this work suggests that reducing PERK function may improve functional recovery after TBI.

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