



Reactive Plasticity With a Kainate Receptor Twist: Rhythmic Firing in Granule Cells Breaks Down the Gate?

Synaptic Kainate Receptors in Interplay With I_{NaP} Shift the Sparse Firing of Dentate Granule Cells to a Sustained Rhythmic Mode in Temporal Lobe Epilepsy.

Artinian J, Peret A, Marti G, Epsztein J, Crépel V. *J Neurosci* 2011;31:10811–10818.

Dentate granule cells, at the gate of the hippocampus, use coincidence detection of synaptic inputs to code afferent information under a sparse firing regime. In both human patients and animal models of temporal lobe epilepsy, mossy fibers sprout to form an aberrant glutamatergic network between dentate granule cells. These new synapses operate via long-lasting kainate receptor-mediated events, which are not present in the naive condition. Here, we report that in chronic epileptic rat, aberrant kainate receptors in interplay with the persistent sodium current dramatically expand the temporal window for synaptic integration. This introduces a multiplicative gain change in the input-output operation of dentate granule cells. As a result, their sparse firing is switched to an abnormal sustained and rhythmic mode. We conclude that synaptic kainate receptors dramatically alter the fundamental coding properties of dentate granule cells in temporal lobe epilepsy.

Commentary

Animal models of acquired temporal lobe epilepsy (TLE) have informed hypothesis-driven research on the cellular correlates—and possible mechanisms—of epileptogenesis for decades. In particular, electrically- or chemically-induced status epilepticus (SE) in naive animals results in modification of brain circuits critically involved in seizure generation and propagation. The article by Artinian et al. builds upon what is known about well-established changes in synaptic connectivity in the dentate gyrus that correlate to epileptogenesis in a rodent model of TLE—the pilocarpine-treated rat (1). They analyzed functional increases in both neuronal synchrony and action potential activity arising from a combination of synaptic reorganization, intrinsic ion currents, and glutamate receptor subtype expression changes as components of the reactive plasticity that occurs in the dentate gyrus subsequent to SE induction and development of TLE.

An important feature of the TLE model used in this paper is the stereotyped nature of synaptic reorganization occurring after pilocarpine-induced SE. After a latent period of relative inactivity following SE induction, reactive cellular and synaptic plasticity leads to the eventual remodeling of neural circuitry that acts as a substrate upon which seizures appear more likely to be generated. After SE, regulation and expression of numerous genes are altered, select neurons are typically killed, and axons of principal neurons in key areas sprout to form

new synaptic connections—often with cells to which they had sparse or no connection before. These events have been especially well-documented in the rodent dentate gyrus, where myriad studies have shown that, coincident with development of spontaneous seizures, new glutamatergic synapses form between granule cells, increasing their overall excitability. The hypothesis that synaptic reorganization among granule cells contributes to hippocampal excitability in the epileptic state has become a staple of many discussions regarding causes and correlates of TLE development in adults.

Glutamate released from sprouted mossy fiber terminals results in enhanced excitatory neurotransmission in the dentate gyrus after synaptic reorganization (2), a result consistent with increased activity of NMDA and non-NMDA receptors, and a phenomenon that has been extensively studied for more than two decades. Thus, synaptic reorganization in the dentate gyrus in this and other TLE models, as well as in TLE patients, has been hypothesized to underlie at least some components of the increased seizure susceptibility associated with development of TLE. Recently, a breakthrough finding was added to the reactive plasticity mix. Whereas descriptions of non-NMDA receptor-mediated synaptic responses have typically lumped AMPA and kainate (KA) receptors together, the relatively recent development of selective pharmacological tools allowed Epsztein et al. (3) to unveil distinct KA and AMPA responses in granule cells from epileptic rats. In naive animals, glutamate-mediated EPSCs in granule cells are mediated by AMPA receptors, whereas after mossy fiber sprouting and synaptic reorganization in the dentate gyrus has occurred, additional KA receptor-mediated responses are expressed. Differentiated



receptor responses have similarly been identified at mossy fiber synapses on CA3 pyramids (4), and it is reasonable to hypothesize that new granule cell-to-granule cell connections might utilize the same postsynaptic mechanisms. Although typically smaller in amplitude than their AMPA receptor-mediated cousins, KA receptor-mediated excitatory postsynaptic events tend to have slower kinetics, a characteristic that allows for their summation, increased current density, and the development of a depolarizing “envelope” under conditions of increased synaptic activation. In other words, not only are there excessive synaptic connections between otherwise sparsely interconnected granule cells in epileptic rats, but the connections themselves are more effective when activated because of the novel utilization of KA receptors at the new synapses (3, 5). Moreover, the synaptic currents recruit the persistent sodium current (I_{NaP}), an intrinsic inward current active near resting membrane potential, to augment the synaptic currents and allow them to contribute even more to granule cell excitability.

In the study by Artinian et al., this concept is advanced to the next level. After previously showing that activation of recurrent mossy fiber synaptic connections evoked short KA receptor-mediated bursts of action potentials in other granule cells recorded in slices from epileptic rats, the authors now use low-amplitude bursts of evoked synaptic activity at relevant frequencies (i.e., 10 Hz theta and 30 Hz gamma) to activate the new circuit. The slower kinetics of KA receptor-mediated EPSPs allow for enhanced temporal summation, effectively increasing the input–output gain of the system. The depolarizing synaptic envelope caused by summed EPSPs is additionally augmented by recruitment of the I_{NaP} to support a type of bursting behavior that is exceedingly unlikely to evolve in tissue from normal animals.

Granule cells are thought to tune afferent signals in a precise temporal manner. Insertion of the KA receptor into the recurrent circuit diminishes this precision, effectively changing the circuit from one that “gates” information to one that amplifies signals that might otherwise be filtered. Another significant finding was that KA, but not AMPA receptor-mediated synaptic activity drives rhythmic firing in granule cells from epileptic rats. Activation of NMDA receptors exacerbates the KA receptor-mediated excitability, but AMPA receptors contributed little to the new firing pattern. One hypothetical outcome of increased cellular and network excitability is an increased propensity for seizure initiation downstream in the hippocampus. The reduced synaptic precision conferred by additional synapses, synaptic summation, and conversion to rhythmic bursting might also adversely affect the ability of the dentate gyrus to correctly process temporally relevant afferent information relevant to cognitive function in epileptic animals.

Importantly, this study builds on previous findings to provide context to the rather novel view that synaptic reorganization can combine with altered receptor expression and intrinsic currents to alter cellular and circuit function in a multiplicative fashion. The increase in excitability this combination causes in the dentate gyrus is profound. The reduction in synaptic precision conferred by this arrangement offers an intriguing mechanistic basis for development of new medications based on KA receptor pharmacology to reduce seizures and/or their cognitive comorbidities. The ultimate consequence of increased excitability in dentate gyrus granule cells remains unclear because increased action potentials might be expected to drive inhibitory interneuron activity in addition to that of principal neurons (6, 7), a mechanism that may also involve KA receptors opposite mossy fiber terminals (8). How and whether synapses between granule cells contribute directly to seizures or epileptogenesis remains uncertain, but the work of Artinian et al. sets the stage for new and integrative hypotheses to examine complex neural and synaptic plasticity events associated with chronic seizure disorders.

by Bret N. Smith, PhD

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