KAINATE RECEPTORS "SPROUT" ON EPILEPTIC GRANULE CELLS

Recurrent Mossy Fibers Establish Aberrant Kainate Receptor-Operated Synapses on Granule Cells from Epileptic Rats

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Glutamatergic mossy fibers of the hippocampus sprout in temporal lobe epilepsy and establish aberrant synapses on granule cells from which they originate. There is currently no evidence for the activation of kainate receptors (KARs) at recurrent mossy fiber synapses in epileptic animals, despite their important role at control mossy fiber synapses. We report that KARs are involved in ongoing glutamatergic transmission in granule cells from chronic epileptic but not control animals. KARs provide a substantial component of glutamatergic activity, because they support half of the non–NMDA receptor mediated excitatory drive in these cells. KAR-mediated $EPSC_{KA}$s are selectively generated by recurrent mossy fiber inputs and have a slower kinetics than $EPSC_{AMPA}$. Therefore, in addition to axonal rewiring, sprouting of mossy fibers induces a shift in the nature of glutamatergic transmission in granule cells that may contribute to the physiopathology of the dentate gyrus in epileptic animals.

COMMENTARY

Mossy fiber sprouting is considered one of the pathological hallmarks of temporal lobe epilepsy in humans and animal models (1,2). With the seizure-induced death of hilar mossy cells, mossy fiber axons reroute to the inner molecular layer of the dentate gyrus and innervate granule cell dendrites. The reactive synaptic reorganization that takes places with mossy fiber sprouting creates a hyperexcitable circuit in the hippocampus, particularly in the dentate gyrus, that predisposes the circuit to paroxysmal firing, especially under conditions in which inhibition is simultaneously depressed or excitation is concomitantly enhanced (unmasking the hyperexcitability of the circuit). While it is known that the newly created mossy fibers that synapse onto dentate granule cells are excitatory (3–5), these synapses have not been well characterized in terms of receptor type and details of synaptic physiology. For example, whether the newly formed synapses mediate α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid (AMPA), *N*-methyl-D-aspartate (NMDA), and/or kainate receptors has not been established.

In the normal dentate gyrus, granule cells have no kainate receptors, whereas kainate receptors do play a role in normal mossy fiber transmission onto CA3 neurons (6). Epsztein and colleagues examined the hypothesis that newly formed mossy fiber to dentate granule cell synapses operate via kainate receptors, and examined the relative contributions of AMPA and kainate-mediated transmission involved in these synapses. This issue is important because the pattern, duration, and effectiveness of transmission at this crucial synapse could play an important role in the modulation of epileptic firing in this novel circuit.

Epsztein et al. studied hippocampal slices from control (i.e., nonepileptic) rats and rats that were rendered epileptic by administration of pilocarpine 2–8 months earlier. All of the pilocarpine-treated rats were epileptic in the sense that they were experiencing spontaneous seizures. By recording from dentate granule cells in the presence of NMDA-receptor and GABA-receptor blockers, the investigators could isolate non–NMDA–mediated excitatory postsynaptic currents (EPSCs). EPSCs in dentate granule cells in hippocampal slices from epileptic rats featured a prominent kainate-mediated component that remained after blockade of AMPA receptors. The kainate-mediated component of the excitatory current was longer in duration and had slower kinetics than that mediated by AMPA receptors in control slices. The kainate-receptor–mediated EPSCs were not present 5 days after pilocarpine-induced status epilepticus, suggesting that the plasticity of neurotransmission takes longer than 5 days to develop. The kainate-receptor–mediated component of the EPSCs could be isolated in several conditions, including spontaneously, in response to weak electrical stimulation in the inner molecular layer, and with miniature EPSCs in the presence of tetrodotoxin. In all situations, EPSCs mediated by kainate receptors and AMPA receptors could be differentiated. Overall, kainate receptors were responsible for half of the spontaneous and miniature glutamatergic currents in granule cells from epileptic rats.

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Kainate-receptor–mediated EPSCs were never seen in control, nonepileptic slices. Furthermore, application of SYM 2081, an agent that selectively desensitizes kainate receptors, suppressed kainate-receptor–mediated EPSCs; and, in the condition of high potassium applied to enhance synchronized network firing, SYM 2081 coapplication reduced epileptiform activity. These results provide convincing evidence that new sprouted mossy fiber synapses onto dentate granule cells in epileptic rats possess a prominent kainate-receptor–mediated component that could well serve as a basis for enhanced network excitability.

The main implication of these results for temporal lobe epilepsy is that the epileptic state is characterized not only by structural synaptic reorganization (i.e., mossy fiber sprouting) but also by plasticity of the receptor type mediating neurotransmission in the reorganized hippocampus. While the findings do not address how or why postsynaptic glutamatergic receptors change to create this new palette of receptor types, they do suggest a possible therapeutic strategy for future research. If kainate receptors can be targeted specifically, it is possible that the excess excitatory current can be curtailed without losing the critical AMPA component.

by Carl E. Stafstrom, MD, PhD

References

1. Sutula T, Cascino G, Cavazos J, Parada I, Ramirez L. Mossy fiber synaptic reorganization in the epileptic human temporal lobe. *Ann Neurol* 1989;26:321–330.
2. Nadler JV. The recurrent mossy fiber pathway of the epileptic brain. *Neurochem Res* 2003;28:1649–1658.
3. Waurin JP, Dudek FE. Excitatory synaptic input to granule cells increases with time after kainate treatment. *J Neurophysiol* 2001;85:1067–1077.
4. Buckmaster PS, Zhang GF, Yamawaki R. Axon sprouting in a model of temporal lobe epilepsy creates a predominantly excitatory feedback circuit. *J Neurosci* 2002;22:6650–6658.
5. Scharfman HE, Sollas AL, Berger RE, Goodman JH. Electrophysiological evidence of monosynaptic excitatory transmission between granule cells after seizure-induced mossy fiber sprouting. *J Neurophysiol* 2003;90:2536–2547.
6. Lerma J. Roles and rules of kainate receptors in synaptic transmission. *Nat Rev Neurosci* 2003;4:481–495.