Kainate receptors: knocking out plasticity

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There is increasing evidence that kainate receptors contribute to both postsynaptic and presynaptic signaling. Studies of knockout mice have played a pivotal role in defining the functions of kainate receptors, including a recent study that implicates kainate receptors in frequency-dependent facilitation and long-term potentiation of hippocampal mossy fiber synapses.

Current progress in kainate receptor research has built upon the discovery of selective pharmacological tools, the molecular analysis of recombinant receptors, and the study of knockout mouse lines. Five different protein subunits can contribute to kainate receptor complexes including GluR5, 6, 7, KA1 and KA2 (Ref. 1). Whole-cell currents mediated by recombinant kainate receptors exhibit diverse physiological and pharmacological properties that depend upon the subunit combination[1]. The precise composition of most native kainate receptors is not known with certainty; however, expression patterns for the different subunits show distinct, but overlapping, distributions[2], providing one explanation for the variation in kainate receptor properties observed in different neuronal cell types[3].

Lack of selective antagonists hampered research on kainate receptors for many years, but, with the discovery in 1995 of selective AMPA receptor blockers, a steady stream of work began to reveal the synaptic functions of kainate receptors[1,4]. First, evidence emerged that presynaptic kainate receptors might regulate transmitter release[5–7]. Next, kainate receptors in the postsynaptic membrane were shown to contribute to excitatory synaptic currents[8,9]. Much of this work focused on the hippocampus, however, kainate receptors also participate in synaptic transmission in spinal cord, cortex, retina, amygdala, and striatum (reviewed in Ref. 4). Generation of mice lacking specific kainate receptor subunits has added greatly to this work by providing the most direct evidence concerning the subunit composition of kainate receptors in specific cell populations[10,11].

Collectively, these studies documented the presence of kainate receptors at synapses, but left open many questions about how they participate during ongoing transmission in physiological conditions. Now, two recent papers[12,13] have demonstrated an important role for kainate receptors at mossy fiber-CA3 synapses in frequency-dependent synaptic facilitation, a form of short-term plasticity in which the strength of transmission increases with repetitive stimulation. The paper by Contractor *et al.*[12] also supports earlier evidence that kainate receptors are required for long-term potentiation (LTP) between mossy fibers and CA3 pyramidal cells[14].

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Contractor *et al.*[12] recorded mossy fiber transmission in acutely-isolated hippocampal slices from knockout mice lacking either the GluR5 or GluR6 kainate receptor subunit. Surprisingly, slices from GluR5$^{-/-}$ animals exhibited no abnormalities in synaptic physiology, whereas slices from GluR6$^{-/-}$ mice displayed specific deficits in some, but not all, forms of plasticity. Facilitation during 5 Hz stimulation, and paired-pulse facilitation (PPF) for inter-pulse intervals less than 40 msec, were partially reduced in GluR6$^{-/-}$ slices, whereas PPF for longer intervals was not altered[10]. In addition, LTP at mossy fiber synapses was strongly attenuated in slices from GluR6$^{-/-}$ animals, although there was little apparent change in post-tetanic potentiation.

Both facilitation and LTP at mossy fiber synapses are thought to involve presynaptic changes in transmitter release[15], suggesting that the effects of GluR6 knockout might involve deletion of kainate receptors on presynaptic mossy fiber terminals. However, because the knockout animals have lost GluR6 from all of their cells it is difficult to rule out the possibility that at least some of the deficits observed in the GluR6$^{-/-}$ mice might reflect loss of postsynaptic kainate receptors, which are known to reside on CA3 neurons[10] and GABAergic interneurons[16–18].

Previous work by Contractor and colleagues[11] provided evidence for the existence of kainate receptors on mossy fiber terminals that include the GluR6 subunit, but do not require GluR5. Prolonged activation of these receptors by exposure to exogenous agonists caused a significant reduction in transmission[18,19], possibly by depolarization-induced inactivation of axonal Na^+ and/or Ca^{2+} channels. Schmitz *et al.*[18] demonstrated inhibition of mossy fiber transmission not only by exogenous agonists, but also by endogenous glutamate released during tetanic stimulation of neighboring fibers, suggesting that presynaptic kainate receptors underlie a form of heterosynaptic inhibition. More recently, however, they found that very low doses of kainate (20–50 nM), or weaker stimulation of neighboring fibers, caused potentiation of mossy fiber transmission[13]. In addition, kainate receptor blockade reduced the frequency-dependent facilitation of NMDA receptor-mediated mossy fiber EPSCs (Ref. 13). Collectively, these results suggest that presynaptic kainate receptors suppress excitatory transmission during periods of prolonged or high frequency stimulation, but with more mild levels of activation they might be facilitatory.

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These papers[12,13] clearly demonstrate a role for kainate receptors in short-term plasticity; however, comparison with earlier studies raises several important questions about long-term changes in mossy fiber transmission. First, Bortolotto *et al.*[14] showed that superfusion of slices with the GluR5-selective antagonist LY382884 prevented LTP induction at mossy fiber synapses. Why is this antagonist effective if the GluR5 subunit is not required for LTP, for facilitation, or for modulation of mossy

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fiber transmission by exogenous agonists? One possibility is that dentate granule neurons express heteromeric receptors that include both GluR5 and GluR6 (Ref. 17). The presence of GluR5 in wild-type cells would render their receptors sensitive to LY382884. Mice lacking GluR5 might still produce functional receptors, whereas deletion of GluR6 might prevent either the production of receptors or their delivery to the presynaptic membrane. One argument against this proposal is that granule cells, in addition to CA3 pyramidal neurons, express little if any *GluR5* mRNA, as assessed by *in situ* hybridization[2,16,17]. Alternatively, LY382884 might act on heteromeric kainate receptors that do not include a GluR5 subunit, in analogy with the agonist ATPA, which preferentially activates GluR5-containing receptors[6], but can also activate receptors formed by the heteromeric co-assembly of GluR6 and KA2 (Ref. 17). A third possible scenario is that LY382884 affects mossy fiber transmission indirectly[20], for example, by blocking kainate receptors on GABAergic interneurons, which are known to express the GluR5 subunit[16–18,21]. Indeed, Schmitz *et al.*[18] have shown that inhibition of mossy fiber transmission by ATPA involves the indirect activation of receptors on interneurons, whereas kainate and glutamate affect mossy fibers directly. Although it is difficult to envision how blockade of interneuronal receptors by LY382884 would reduce mossy fiber LTP, this possibility still needs to be examined. A more fundamental question is whether kainate receptors are required for mossy fiber LTP at all. Nicoll and colleagues have argued that they are not[20,22], whereas several groups have produced evidence that mossy fiber LTP can be blocked or reduced under conditions that suppress kainate receptor signaling[12,14,23].

Although further work is needed to resolve these issues, kainate receptors are now clearly established as major players in excitatory transmission. Knockout mice will continue to be an important resource for sorting out the many remaining questions about kainate receptors and their functional roles throughout the nervous system.

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