Changes in mIPSCs and sIPSCs after kainate treatment: possible actions mediated by the direct activation of kainate receptors

**To the Editor:** In a very interesting paper, Shao and Dudek (2005) described the changes in miniature inhibitory postsynaptic currents (mIPSCs) and spontaneous inhibitory synaptic currents (sIPSCs) that occur after kainate treatment recorded in hippocampal dentate granule cells. Basically, in acutely and chronically treated rats, the authors observed a 30% decrease in the frequency of mIPSCs that did not recover over a prolonged period of time, whereas the sIPSC frequency of action-potential-dependent events remained unaffected. In contrast to the diminution of mIPSC frequency, which is indicative of a presynaptic events reducing quantal release, if anything, the authors observed an increase in the mIPSC amplitudes reporting changes in postsynaptic parameters. The primary observation of a decrease in the mIPSC frequency was interpreted by the authors as being due to a decrease in the number of presynaptic interneurons, perhaps being compensated for in situ by increased firing of the surviving interneurons. Notwithstanding this conclusion purporting interneuron loss, alternative explanations of the reported effect of kainate are equally tenable.

The notable fact is that there is a 30% decrease of mIPSC frequency after kainate reported by Shao and Dudek (2005) is indeed reminiscent of results obtained previously by direct activation of presynaptic kainate receptors (KARs) in slices from the CA1 region of the rat hippocampus (Cossart et al. 1998; Maingret et al. 2005; Rodriguez-Moreno and Lerma 1998; Rodriguez-Moreno et al. 1997). There the interpretation of the data was that a decrease of mIPSC is effectively mediated by the activation of KARs situated in the inhibitory terminals. Accordingly, as pointed out by Echegoyen and Soltesz (2005), a decrease in the probability of GABA release provides a plausible alternative explanation for the decrease in mIPSC frequency observed by Shao and Dudek (2005). The question is whether it is possible that the activation of KAR receptors, classically considered to be ionotropic, can produce a long-lasting effect on GABA release by changing the probability of release. Arguing against an ionotropic effect of KARs in this context, Rodriguez-Moreno and Lerma (1998) and Rodriguez-Moreno et al. (2000) have found that KARs can act via a novel metabotropic mechanism. In fact, the inhibition of GABA release at hippocampal inhibitory interneurons could be described as overtly metabotropic given that it was supported by the activation of a G_{i/o} protein and a phospholipase C (PLC)/protein kinase C (PKC) pathway. In light of these observations, the possibility exists that the long-lasting decrease of mIPSC seen by Shao and Dudek (2005) in dentate granule cells was mediated by the activation of metabotropic KARs in the terminals of the GABAergic interneurons.

In line with the dual mechanism of action of KARs, in the hippocampal interneurons, the existence of two populations of KARs has been postulated with specific compartmentalization. The first is suggested to be localized at the interneuron nerve terminals where they have a metabotropic action and mediate a decrease in the release probability of GABAergic synaptic vesicles. The second population KARs is thought to be localized in the somatodendritic compartment where an ionotropic action produces a transient increase of the sIPSCs (Rodriguez-Moreno et al. 2000). Although these observations in adult hippocampus have been replicated using neonatal animals (Maingret et al. 2005), surprisingly Shao and Dudek (2005) found little or no significant increase in sIPSCs in dentate granule cells that would attest to the presence and function of somatodendritic ionotropic KARs. This may reflect one of several possibilities. First that the population of interneurons being considered have a low density of ionotropic KARs or indeed lack them entirely. Second, given the observed differential affinity for agonist described for the ionotropic and metabotropic KAR populations (Rodriguez-Moreno et al. 2000), the KA concentration used by Shao and Dudek (2005) may have been insufficient to activate somatodendritic receptors, while being adequate for effecting activation of metabotropic axonal KARs. Finally, the ionotropic actions of ionotropic KAR activation may have been too fast and transient to be observable some days after KA application as would be the case in the experimental paradigm being used.

In conclusion, in our view, the intriguing results of Shao and Dudek (2005) are entirely consistent with KA actions mediated by the direct activation of presynaptic metabotropic KARs without recourse to an interpretation involving interneuron ablation as a result of kainate administration. In future experiments, it would be interesting to see whether a metabotropic mechanism for KAR action persists over an extended time course (months) akin to that implemented in the kainate-lesion experiments conducted by Shao and Dudek (2005).

**REFERENCES**


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