GLUR5 KAINATE RECEPTORS AND TOPIRAMATE: A NEW SITE OF ACTION FOR ANTIEPILEPTIC DRUGS?

Selective Antagonism of GluR5 Kainate Receptor–Mediated Synaptic Currents by Topiramate in Rat Basolateral Amygdala Neurons

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Topiramate (TPM) is a widely used antiepileptic agent whose mechanism of action is poorly understood. The drug has been reported to interact with various ion channel types, including α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)/kainate receptors. In whole-cell voltage-clamp recordings from principal neurons of the rat basolateral amygdala, TPM at low concentrations [median inhibitory concentration (IC_{50}), $\sim$0.5 μM] selectively inhibited pharmacologically isolated excitatory synaptic currents mediated by kainate receptors containing the GluR5 subunit. TPM also partially depressed predominantly AMPA-receptor–mediated excitatory postsynaptic currents (EPSCs), but with lower efficacy. TPM did not alter the degree of facilitation in paired-pulse experiments, and it reduced the amplitude of miniature EPSCs without affecting their frequency, demonstrating that the block of synaptic responses occurs postsynaptically. Inhibition of GluR5 kainate receptors could represent a key mechanism underlying the anticonvulsant activity of TPM. Moreover, these results support the concept that GluR5 kainate receptors represent a novel target for antiepileptic drug development.

COMMENTARY

Topiramate (TPM) is one of the newer antiepileptic drugs (AEDs) and has been beneficial for the treatment of refractory epilepsy. TPM, possibly more than other AEDs, has led to the hypothetical concept of rational polytherapy because several lines of experimental evidence have suggested that it acts on multiple mechanisms to block a variety of different types of epileptic seizures. By using slices of the basolateral nucleus of the amygdala, the researchers tested the hypothesis that TPM has a selective action on the GluR5 type of kainate receptor. The effects of TPM at 1 μM, for example, were far greater on the GluR5 type of kainate receptor than on α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors. These experiments were performed at a clinically relevant series of concentrations. However, as the authors point out, the possibility that other mechanisms, such as an effect on sodium channels, were involved cannot be ruled out or also could be important at higher TPM concentrations.

The experiments in this study provide evidence that TPM acts over tens of minutes, a time course considerably slower than would be expected if it acted only extracellularly at a kainate-type glutamate receptor. These data suggest that TPM acts at an intracellular site to modify other hypothetical mechanisms of action. An area for future research is to evaluate quantitatively whether other mechanisms [e.g., sodium channel inactivation, augmentation of γ-aminobutyric acid $(GABA)_A$-receptor function] are altered at the same dose and with a similar time course as the GluR5 type of kainate receptor. This approach would potentially indicate whether TPM has a diversity of cellular actions mediated through a common intracellular pathway.

An interesting component of this study is that the hypothetical action on the GluR5-type kainate receptor potentially represents a novel target for the site of action of an AED. The authors point out that no other AED has been shown to act on this type of receptor. An interesting series of questions in neurobiology has centered on the role of kainate receptors in normal brain function, and these data suggest that kainate receptors play an important role in seizure generation. The amygdala, including the basolateral nucleus, is potentially involved in epileptogenesis. An interesting area for future investigation would be to determine whether TPM is more effective in tissue that has undergone epileptogenesis. If GluR5 kainate-receptor expression was enhanced during epileptogenesis and TPM acted on this mechanism preferentially, then the GluR5 type of kainate receptor would potentially be a promising target for future drug-discovery efforts. The issue of selectivity of TPM for the GluR5-type kainate receptor during epileptogenesis also deserves further attention to determine how many cellular mechanisms may be involved in the actions of TPM.

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