SYNAPTIC REORGANIZATION OF PERISOMATIC AND DENDRITIC INHIBITION IN HUMAN TEMPORAL LOBE EPILEPSY REVEALED BY ELECTRON MICROSCOPY

Lucia Wittner¹ (wittner@koki.hu), Zsolt Borhegyi¹, Lóránd Erőss², Sándor Czirják³, Péter Halász⁴, Tamás F. Freund¹, Zsófia Maglóczky¹

¹ Institute of Experimental Medicine, Hungarian Academy of Sciences, ² Neurosurgical Department, MÁV Hospital Budapest, ³ National Institute of Neurosurgery and ⁴ National Institute of Psychiatry and Neurology, Epilepsy Center, Budapest, Hungary

Abstract

Epilepsy is thought to be related to a changed balance between excitation and inhibition. The sprouting of mossy fibers and the supramammillary afferent pathway provide an excess excitation to the dentate gyrus, whereas the CA1 region receives an enhanced excitatory input from the CA3 region and from the sprouting of CA1 pyramidal cell axons. However, it is still not clear whether inhibition is decreased or preserved in the human epileptic hippocampus. There is evidence for interneuronal cell death, as well as for the preservation of GAD-positive cells. To examine the fate of perisomatic and dendritic inhibitory cells in human epilepsy, two functionally different interneuron types were studied in human control and epileptic hippocampi. Calbindin (CB)-immunopositive interneurons are dendritic inhibitory cells, thought to control the input of principal cells, whereas parvalbumin (PV) is present in perisomatic inhibitory neurons which control the output of principal cells. In these studies the number, distribution, morphology and input-output connections of CB- and PV-immunopositive interneurons were examined in the dentate gyrus and CA1 region of human control subjects and epileptic patients.

Immunohistochemistry, light and electron microscopy were used to reveal fine morphological changes, as well as input-output connections of neurochemically identified interneurons of control and epileptic human hippocampus. Autopsy tissue and surgically removed human hippocampi were immunostained against calbindin and parvalbumin. After the light microscopic examination, areas of interest were re-embedded and processed for electron microscopy, then qualitative and quantitative analyses of synaptic inputs and outputs were performed.

In non-sclerotic epileptic samples, the morphology and distribution of CB-positive cells was only slightly changed. In the sclerotic hippocampus the morphology of CB-stained interneurons was distinctly different, they displayed a large number of short, distorted dendrites, which were usually spiny. Large cell bodies were more frequently present, and they were also often decorated with spines. Their input and output connections were considerably different: in the dentate gyrus CB-positive interneurons received more synapses from mossy fibers, whereas in the CA1 region the ratio of their inhibitory input increased significantly. In the sclerotic CA1 region CB-immunoreactive interneurons changed their postsynaptic targets. Instead of their usual pyramidal cell targets, they terminated on the surviving interneurons, including themselves. The number of PV-positive interneurons was moderately reduced in non-sclerotic epileptic hippocampus, but in the strongly sclerotic tissue was dramatically decreased with a preserved axonal staining. Quantitative electron microscopy showed that synaptic coverage of granule cell axon initial segments (AISs) considerably increased in the epileptic tissue, but remained unchanged for CA1 pyramidal cell AISs. The synaptic input of both principal cell somata remained unchanged in the epileptic tissue.
Quantitative electron microscopy gives us the possibility to examine fine morphological features, as well as their changes in pathological conditions. Epileptic synaptic reorganisations, some of them not visible at the light microscopic level, can be also revealed. Our results point to a profound synaptic reorganisation in the epileptic dentate gyrus and CA1 region, even in the non-sclerotic tissue, before the death of considerable numbers of pyramidal cells. Interneurons, beside the surviving principal cells, are also able to sprout in the epileptic hippocampus. Dendritic inhibitory CB-positive interneurons participate in this reorganisation, they show plastic changes in response to epilepsy. In the epileptic dentate gyrus, perisomatic inhibitory interneurons hyperinnervate granule cells, and may participate in the induction or maintenance of hypersynchronous population events. The lack of profound changes in perisomatic inhibitory input in the CA1 region suggests that other factors are likely to account for the selective vulnerability of pyramidal cells to epileptic injury.
PV-positive interneurons in the human epileptic dentate gyrus