

NEUROPEPTIDE Y MAY BE AN ENDOGENOUS ANTICONVULSANT IN HIPPOCAMPUS

Plasticity of Y1 and Y2 Receptors and Neuropeptide Y Fibers in Patients with Temporal Lobe Epilepsy

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Marked expression of neuropeptide Y (NPY) and its Y2 receptors in hippocampal mossy fibers has been reported in animal models of epilepsy. Because NPY can suppress glutamate release by activating presynaptic Y2 receptors, these changes have been proposed as an endogenous protective mechanism. Therefore, we investigated whether similar changes in the NPY system may also take place in human epilepsy. We investigated Y1 and Y2 receptor binding and NPY immunoreactivity in hippocampal specimens that were obtained at surgery from patients with temporal lobe epilepsy and in autopsy controls. Significant increases in Y2 receptor binding (by 43–48%) were observed in the dentate hilus, sectors CA1 to CA3, and subiculum of specimens with, but not in those without, hippocampal sclerosis. On the other hand, Y1 receptor binding was significantly reduced (by 62%) in the dentate molecular layer of sclerotic specimens. In the same patients, the total lengths of NPY immunoreactive (NPY-IR) fibers were markedly increased (by 115–958%) in the dentate molecular layer and hilus, in the stratum lucidum of CA3, and throughout sectors CA1 to CA3 and the subiculum, as compared with autopsies. In nonsclerotic specimens, increases in lengths of NPY-IR fibers were more moderate and statistically not significant. NPY mRNA was increased threefold in hilar interneurons of sclerotic and nonsclerotic specimens. It is suggested that abundant sprouting of NPY fibers, concomitant upregulation of Y2 receptors,

and downregulation of Y1 receptors in the hippocampus of patients with Ammon's horn sclerosis may be endogenous anticonvulsant mechanisms.

COMMENTARY

Alterations in epilepsy-associated expression of neuropeptide Y (NPY) and its receptors have received an increasing level of attention during the last decade. NPY and its receptors (Y1 and Y2) are known to be present in the human hippocampus. Based on research in an animal model of temporal lobe epilepsy (TLE), Sperk et al. have postulated that alterations in the NPY system may be part of an endogenous anticonvulsant mechanism. This article uses immunohistochemistry and receptor binding to assess the expression of the peptide and its receptors in hippocampal tissue from patients undergoing surgical treatment for TLE.

One of the key findings of this research is an upregulation of NPY-Y2 receptors in the hippocampus of TLE patients. The observation of marked increases in the number and length of NPY fibers corroborated earlier work. These observations on NPY fibers were specific to sclerotic tissue. Previous electrophysiological data suggest that NPY inhibits glutamate release and depresses seizure activity. The data in this article support the hypothesis that increased expression of NPY in interneurons leads to secretion from sprouted axons near glutamatergic synapses, where the released NPY blocks release of glutamate, potentially at sprouted excitatory fibers. Thus, these changes would hypothetically tend to counteract seizures. The actions of NPY on Y1 receptors have been previously proposed to be proconvulsant; the data in this article suggest downregulation of Y1 receptors, which would reduce the possible proconvulsant effect of NPY. Therefore, the article provides data on a hypothesis that essentially proposes that reorganization of the NPY system in TLE leads to suppression of seizures.

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