Reviews in the Neurosciences, 14, 285-301 (2003)

On the Role of Somatostatin in Seizure Control: Clues from the Hippocampus

Anna Binaschi, Gianni Bregola and Michele Simonato

Department of Clinical and Experimental Medicine, Section of Pharmacology, and Neuroscience Center, University of Ferrara, Ferrara, Italy

SYNOPSIS

The role of the hippocampal somatostatin (somatotropin release-inhibiting factor, SRIF) system in the control of partial complex seizures is discussed in this review. The SRIF system plays a role in the inhibitory modulation of hippocampal circuitries under normal conditions: 1) SRIF neurons in the dentate gyrus are part of a negative feedback circuit modulating the firing rate of granule cells; 2) SRIF released in CA3 interacts both with presynaptic receptors located on associational/commissural terminals and with postsynaptic receptors located on pyramidal cell dendrites, reducing excitability of pyramidal neurons; 3) in CA1, SRIF exerts a feedback inhibition and reduces the excitatory drive on pyramidal neurons. Significant changes in the hippocampal SRIF system have been documented in experimental models of temporal lobe epilepsy (TLE), in particular in the kindling and in the kainate models. SRIF biosynthesis and release are increased in the kindled hippocampus, especially in the dentate gyrus. This hyper-function may be instrumental to control the latent hyperexcitability of the kindled brain, preventing excessive discharge of the principal neurons and the occurrence of spontaneous seizures. In contrast, the hippocampal SRIF system undergoes damage in the dentate gyrus following kainate-induced status epilepticus. Although surviving SRIF neurons appear to hyperfunction, the loss of hilar SRIF interneurons may compromise inhibitory mechanisms in the dentate gyrus, facilitating the occurrence of spontaneous seizures. In keeping with these data, pharmacological activation of SRIF1 (sst_2) receptors, i.e. of the prominent receptor subtype on granule cells, exerts antiseizure effects. Taken together, the data presented suggest that the hippocampal SRIF system plays a role in the control of partial complex seizures and, therefore, that it may be proposed as a therapeutic target for TLE.

KEY WORDS

neuropeptides, hippocampus, temporal lobe epilepsy, kindling, kainate

I. INTRODUCTION

The epilepsies comprise a number of neurological disorders characterized by the unpredictable occurrence of seizures. Altogether, these disorders affect an estimated 1% of the population. Although many antiseizure drugs are available for therapy, more than a quarter of epileptic patients do not respond to pharmacological treatment /76/. Therefore, a great effort is devoted to identifying new antiepileptic drugs, with action mechanisms different from those currently in use.

In the search for new therapeutic targets, much investigation has focused on seizure-induced gene expression, and it is now clear that seizures cause dramatic changes in the expression of gene products related to neuropeptide systems /24,48/. Although the role played by neuropeptides in

Accepted: 19 February, 2003

Reprint address:
Michele Simonato, M.D.
Department of Experimental and Clinical Medicine
Section of Pharmacology
University of Ferrara
via Fossato di Mortara, 17-19
44100 Ferrara, Italy
e-mail: m.simonato@unife.it