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Sprouting in human temporal lobe epilepsy: Excitatory pathways and axons of interneurons

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Summary Changes of hippocampal GABAergic interneuronal circuits are known to play a central role in epileptogenesis. Fate of functionally different hippocampal interneuron types has been investigated in surgically removed hippocampi of therapy resistant human TLE patients.

Perisomatic inhibitory cells containing parvalbumin are responsible for controlling the output of principal cells. Electron microscopic examination revealed that perisomatic innervation of the principal cells was preserved in both sclerotic and non-sclerotic samples, and the ratio of the initial segment synapses increased among the postsynaptic targets, which might give rise to an increased synchrony of granule cell firing.

Calbindin-containing dendritic inhibitory cells are well preserved, and they terminate on other interneurons in larger proportion than in the control both in sclerotic and non-sclerotic cases. Substance P receptor-immunopositive cells possessed significantly larger numbers of dendritic branches in the epileptic CA1 region, and the synaptic input of their dendrites has notably increased, whereas the ratio of inhibitory and excitatory synaptic inputs has not changed.

Our results suggest that an intense synaptic reorganization takes place in the epileptic hippocampus, including axonal sprouting of certain interneuron types, both in sclerotic and non-sclerotic tissue. Thus, axonal sprouting is a more general phenomenon of TLE than cell loss.

Introduction

The vulnerability of principal cells in temporal lobe epilepsy has been studied since the 19th century (Sommer, 1880), and hippocampal sclerosis was defined as the most frequent morphological change in the brain of patients with temporal lobe epilepsy (Corsellis, 1955; Corsellis and Meldrum, 1976; Falconer et al., 1964; Falconer, 1974; Green, 1991).

Hippocampal GABAergic interneuronal circuits are known to play a central role in epileptogenesis (Arellano et al., 2004; Buckmaster and Dudek, 1997; Ferrer et al., 1994; Houser, 1991; Magloczky and Freund, 2005; Marco and DeFelipe, 1997). Interneurons can be classified according to their calcium binding protein and neuropeptide contents, which show a close correlation to input—output relationships (for review see Freund and Buzsaki, 1996). They are known to play crucial roles in the regulation of network activity

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patterns in the hippocampus, and some types were found to be vulnerable in epilepsy. Although preservation of the majority of GAD-positive neurons was found in most of the epileptic human hippocampal samples (Babb et al., 1989), some interneuron types showed selective loss in the surgically removed tissues. The number of somatostatin-positive cells decreased significantly in the epileptic hippocampus (Buckmaster and Dudek, 1997; de Lanerolle et al., 1988; Sundstrom et al., 2001), whereas the calbindin (CB)-positive neurons were found to be mostly spared (Sloviter et al., 1991). The vulnerability of calretinin (CR)-positive neurons has also been demonstrated in the dentate gyrus (Magloczky et al., 2000). Cell loss and sprouting of somatostatin- and NPY-containing cells were shown previously (de Lanerolle et al., 1989).

In the present summary, the number, distribution and connections of parvalbumin-containing (PV) perisomatic inhibitory cells, and calbindin-containing and substance P receptor expressing (SPR) dendritic inhibitory cells of surgically removed hippocampi of 104 therapy resistant temporal lobe epileptic patients were analyzed in order to examine the fate of functionally different hippocampal interneuron types in the different pathological states and hippocampal subfields. Target distribution and output properties of PV- and CB-containing non-principal cells were analyzed to shed light on the axonal reorganization of GABAergic cells. The relationship between the duration of epilepsy and the degree of cell loss was also examined.

The patients had different degrees of hippocampal atrophy and/or sclerosis. Epileptic patients were divided into four groups (Toth et al., 2007; Wittner et al., 2005) based on the principal cell loss and interneuronal changes examined at the light microscopic level as follows (Fig. 1): Epileptic Type 1 (mild): similar to control, no considerable cell loss in the CA1 region, pyramidal cells are present, layers are visible and intact, their borders are clearly identified. There is a slight loss in certain interneuron types, mostly in the hilus and the str. oriens of the CA1 region. Epileptic Type 2 (patchy): Pyramidal cell loss in patches in the CA1 pyramidal cell layer, but these segments of the CA1 region are not atrophic. Interneuron loss is more pronounced. Epileptic Type 3 (sclerotic): the CA1 region is shrunken, atrophic, more than 90% of principal cells is missing, occasionally scattered pyramidal cells remained in the CA1 region. Only the str. lacunosum-moleculare is present in the CA1 region as a distinct layer, the others could not be separated from each other due to the lack of pyramidal cells and their dendrites, as well as the shrinkage of the tissue. Epileptic Type 4 (gliotic): all subfields of the hippocampus are shrunken, atrophic. Beside the vulnerable neurons, resistant cells like granule cells or calbindin-containing interneurons also degenerate.

Type 1 and type 2 are usually referred together as ''non-sclerotic cases'', Type 4 was excluded from the study because of its rare occurrence and unique features.

The number, morphology and distribution of cells were similar in patients that belonged to the same pathological groups, but differed between the groups. The control samples with short (2—4 h) post-mortem delay were similar to each other, and differed from the epileptic groups.

Experimental procedure

Hippocampi of eight control subjects (post-mortem 2—4 h) and 104 temporal lobe epileptic patients were involved in this study.

Hippocampal samples were obtained from patients with therapy resistant temporal lobe epilepsy. Patients with intractable temporal lobe epilepsy underwent surgery within the framework of the Hun-

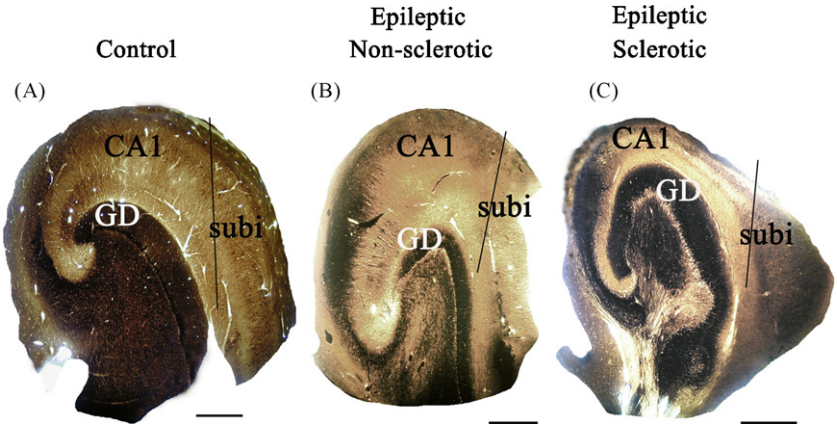

Figure 1 Control (A), non-sclerotic (Type 1) (B) and sclerotic (Type 3) (C) hippocampi are shown at low power light micrographs. The sections are stained for CB. Loss of CB from CA1 pyramidal cells is visible in the non-sclerotic hippocampus (B), hippocampus of a sclerotic patient shows significant shrinkage. Granule cell dispersion is also visible (C). Pathological groups of epileptic patients were based on the principal cell loss and interneuronal changes examined at the light microscopic level as follows: Type 1 (mild, B): similar to control, minimal cell loss in the CA1 region, pyramidal cells are present, layers are visible, their borders are clearly identified. There is a slight loss in certain interneuron types, mostly in the hilus and the str. oriens of the CA1 region. Type 2 (patchy): Pyramidal cell loss in patches in the CA1 pyramidal cell layer, but these segments of the CA1 region are not atrophic. Interneuron loss is more pronounced (not shown). Type 3 (sclerotic, C): the CA1 region is shrunken, atrophic, more than 90% cell loss, occasionally scattered pyramidal cells remained in the CA1 region, separation of the layers is impossible. Mossy fiber sprouting and considerable changes in the distribution and morphology of interneurons can be observed in the samples of this group. Scale: 1.2 mm. *Abbreviations*: CA1: subfield of the cornu Ammonis according to Lorente de no; GD: gyrus dentatus; Subi: subiculum