Dr. Bakay and his colleagues1 have made a substantial contribution to our knowledge of the anatomy and pathophysiology of epilepsy caused by mesial temporal sclerosis. They have demonstrated that large numbers of mossy cells are still present in the hilus of the dentate gyrus when most pyramidal neurons of the CA1 and CA3 areas of the Ammon’s horn are lost. This finding suggests that mossy cells may not be more sensitive to epileptic seizures than the hippocampal pyramidal neurons.

While this result may strike most neurosurgeons as somewhat less than earth shattering, it is emblematic of the importance of neurosurgeons pursuing, in this case doggedly, areas of basic science and clinical research that are uniquely within our purview.

For almost 30 years, the mossy cells in the dentate gyrus were considered the most vulnerable cells in the mammalian hippocampus. Unfortunately, the most common models of epilepsy have been undertaken in rodents, and there has been no specific marker for mossy cells in these animals. It turns out that, without such a marker, mossy cells are difficult to count with any accuracy. Now to the scene comes a newly discovered peptide, the cocaine- and amphetamine-regulated transcript (CART) peptide, which specifically stains human mossy cells. Thus, for the first time, an accurate inventory of these cells can be made in patients with mesial temporal sclerosis. The CART peptide does not stain mossy cells in rodents. Bakay and colleagues’ findings are disruptive to the existing models of epileptogenesis in the hippocampus and may well cause significant dyspepsia in the epilepsy basic science community.

Their paper exemplifies why neurosurgeons must continue to conduct basic research, whether in the laboratory or of the translational variety. There are myriad reasons why we should continue to be fundamentally involved in research, not the least of which are the vigor and vitality such research brings to our field. I specifically mention 3 other rationales here.

As neurosurgeons, we often focus on disorders that would be of relatively little interest to the nonneuroscientific community, for example, glioblastoma multiforme, Chiari malformation, or, as discussed in the following article, medically intractable epilepsy. Although the public health consequences of these disorders are not front-page headlines, as clinicians we are well aware of the human suffering at the individual patient level. We are motivated to study these disorders, to add new knowledge, and to advance the therapy—medical or surgical. We bring attention to these diseases.

Furthermore, neurosurgeons are positioned to do the type of work that Bakay and colleagues have conducted in this instance. Only a neurosurgeon can provide the right tissue at the right time to the right collaborators to answer a question such as that addressed in their work. Frankly, the logistics are too complicated for anyone else.

Lastly, Dr. Bakay and I share at least one common research mentor, Dr. Arthur A. Ward Jr. One of Dr. Ward’s steadfast beliefs is that neurosurgeons have insights from their clinical experiences that allow them to direct their research efforts with greater acuity and efficiency. I still hold this tenet to be true, and I believe this focus, unlike many things in life, improves with time, experience, and age.

I congratulate Dr. Bakay and colleagues on their discovery. I am confident that this disruptive observation has already improved our understanding of mesial temporal sclerosis and hippocampal epileptogenesis.

Reference


Response

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We thank Dr. Burchiel for his kind editorial comments and are happy that he concurs with the seminal points of our paper. In addition, we note that, although the past 30 years of epilepsy research have been focused...
on interneurons, the future emphasis will turn toward the principal cells. The principal neurons of the cortex and hippocampus are frequently considered a homogeneous mass of uniform neurons. The reality is far more nuanced. With regard to mossy cells, authors of a recent publication have shown that these modified pyramidal type principal cells of the hippocampal formation are not uniform. In monkeys, a subpopulation of mossy cells contains the calcium binding protein calretinin, which was previously considered a specific marker for interneurons. In humans, it has not yet been possible to morphologically or neurochemically identify different groups of mossy cells, but with renewed effort such subgroups may be found to exist.

Therefore, it is possible that, as was proposed for rodents, primate hippocampus may contain 2 or more subgroups of mossy cells that have different morphological and physiological characteristics and may behave differently in epilepsy. Some mossy cells may be very sensitive to stress and therefore among the first neurons that disappear after epileptic seizures, whereas others are resistant and persist even after decades of epileptic seizures. Furthermore, recent data have shown that pyramidal cells of the Ammon’s horn are also different, at least functionally, because in behavioral tests CA3 pyramidal cells have a different functional role than the CA3 a,b cells. Morphological differences for CA3 pyramidal cells already have been proposed, but such assertions remained without consequential data support. With the development of research methods we may reach the point when individual pyramidal cells can be differentiated and classified into functionally meaningful subpopulations similar to the way in which interneurons are classified. The general image of the functional circuitry of the cortex will change as soon as the subgroups of principal cells are distinguished.

We wish to call attention to the fact that the team at Rush and the Hungarian group of researchers shared equally in this study and that the senior authors have collaborated for over 2 decades, with the first common publication appearing a decade ago.

References


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