

THE “REEL” PATHOLOGY OF TEMPORAL LOBE EPILEPSY

Role for Reelin in the Development of Granule Cell Dispersion in Temporal Lobe Epilepsy

Haas C, Dudeck O, Kirsch M, Huszka C, Kann G, Pollak S, Zentner J, Frotscher M

J Neurosci 2002;22:5797–5802

The reelin signaling pathway plays a crucial role during the development of laminated structures in the mammalian brain. Reelin, which is synthesized and secreted by Cajal–Retzius cells in the marginal zone of the neocortex and hippocampus, is proposed to act as a stop signal for migrating neurons. Here we show that a decreased expression of reelin messenger RNA (mRNA) by hippocampal Cajal–Retzius cells correlates with the extent of migration defects in the dentate gyrus of patients with temporal lobe epilepsy. These results suggest that reelin is required for normal neuronal lamination in humans, and that deficient reelin expression may be involved in migration defects associated with temporal lobe epilepsy.

COMMENTARY

The etiology of temporal lobe epilepsy has occupied some of the best minds in epilepsy research for decades, and yet new insights continue to develop. One intriguing new finding has come from examination of tissue from patients that have undergone surgical resection because their seizures were pharmacologically intractable. The results suggest, surprisingly, a new perspective on temporal lobe epilepsy (TLE): that it may be, at least in part, a disorder of neuronal migration. Certainly the evidence that developmental abnormalities can lead to epilepsy is well accepted, but mostly with respect to other types of epilepsy, such as cortical dysplasia. This concept has not dominated mechanistic discussions of TLE in the past.

Haas et al. (1) may change this perspective. They compared surgical tissue from 22 patients with samples from seven individuals whose hippocampi were removed during autopsy. The control and epilepsy samples were similar in age, and

there was no evidence of neurologic abnormality in controls, although the cause of death was not provided. There was variability in some potentially important factors, such as age, frequency of seizures, time between onset of epilepsy and surgery, etc. There also may have been variability in other factors, such as the site of the sample within the hippocampus. These drawbacks are common to studies of human surgical specimens and are often the price paid for a reasonable sample size, problems that are quite difficult to avoid.

Despite the variability, there was a remarkable correlation between the degree of granule cell dispersion in the dentate gyrus and the expression of reelin, a protein important for normal development in hippocampus and neocortex. Reelin is normally expressed in the Cajal–Retzius cells of hippocampus and cortex. Work by these investigators and others showed that, in the dentate gyrus of the rat, Cajal–Retzius cells normally lie at the hippocampal fissure during hippocampal development, potentially guiding the axons and neurons of the dentate gyrus to their appropriate lamina (2). The authors show that reelin deficiency in epileptic tissue was associated with dispersion of granule cells, a hallmark of TLE (3). This is consistent with the hypothesis that reelin is essential for the appropriate lamination and organization of dentate gyrus granule cells.

The authors used stereology to measure the width of the granule cell layer in several sections of each specimen. This was used to define granule cell dispersion. In addition, reverse transcriptase–polymerase chain reaction (RT-PCR) was used to estimate relative mRNA abundance. Use of both approaches together strengthened the study greatly, because each has its weaknesses. For example, how does one objectively define the borders of an extremely dispersed granule cell layer, a critical step in measurements of layer width? How does one account for variation in dispersion within a single patient's dentate gyrus? What is “true” dispersion relative to apparent dispersion that accompanies a tangential section through one of the contortions of the human dentate gyrus? These difficult questions challenge even the most accomplished investigators, and yet it is difficult to be skeptical, because the investigators conducting this study have such extensive anatomic expertise.

A potential complication, pointed out by the authors, is the nature of Cajal–Retzius cells. Those studies in the past that used calretinin as a marker of Cajal–Retzius cells found in-

creased cell numbers in epileptic tissue, not a decrease (4). It is pointed out that the Cajal–Retzius cells are not necessarily a single cell type, and not all express reelin. Thus the current study should be interpreted not necessarily as a study of Cajal–Retzius cells, but as a study of reelin.

The results thus raise the possibility that TLE is a developmental disorder. This is not exactly the perspective that most individuals have of this type of epilepsy. More commonly, TLE is associated with an incident in early life such as encephalopathy, birth injury, or severe febrile seizures, and this leads to changes that in time, perhaps associated with a second insult or injury, lead to epilepsy. Important to bear in mind is that TLE may not be one disorder, but a group of seizure disorders with pathology in the temporal lobe, not always including the same degree of Ammon's horn sclerosis (or granule cell dispersion), and sometimes not even including hippocampal atrophy. The authors add an interesting piece of information in their discussion: Cajal–Retzius cells are vulnerable to excitotoxic insults *in vitro*. This work, also from their own laboratory, suggests that some of the insults or injury that have been associated with TLE in early life could indeed be critical because they lead to the death of the Cajal–Retzius cells.

The results imply that granule cell dispersion may itself contribute to increased seizure susceptibility. Before this study, granule cell dispersion was more likely considered to be a result of seizures, rather than a cause. One reason for this point of view is that granule cell dispersion has not always been observed in TLE, and there is general hesitancy in defining the dentate gyrus as the critical area in TLE. Spontaneous focal discharges do not necessarily come from the dentate gyrus, and even if they did, it has been debated whether a dentate gyrus that is essentially isolated within a sclerotic hippocampus could have a role in seizure generation.

But perhaps deficient reelin leads not only to abnormalities of granule cells, but also to other defects in the normal organization of the dentate gyrus, its nonprincipal cells, and the afferents that normally enter the dentate gyrus. Or perhaps the abnormalities in reelin act not in isolation but in concert with defects in other guidance molecules. Misguidance of neuronal processes could have far-reaching implications, given the

fine control they normally exert on hippocampal pathways. For example, inappropriate guidance cues could conceivably lead to sprouting of mossy fibers to CA1/CA2, a pathway that could support seizure propagation from dentate to cortex. It might be premature to assume that a deficit in reelin leads only to altered somatic locations of granule cells, that reelin is the only abnormal guidance cue in TLE, and that we can make conclusions about function from an abnormality of structure. Further studies of the regulators of dentate gyrus development, abnormalities in the hippocampus that occur in the presence of these abnormalities, and recordings to determine the functional outcome of pathology should provide insight into these questions. However, a question that is perhaps the most critical, and yet unfortunately difficult to answer, is when the defect in reelin occurs relative to granule cell dispersion and spontaneous chronic seizures. At some point, it will be important to prove that the proverbial cart comes before the horse.

Although the usual caveats of a correlative study hold (correlation does not imply causation), this study provides new insight into TLE. This alone is laudatory. Moreover, the study shows that, yet again, some of the most basic studies in the rat not only are applicable to human, but also are potentially helpful in clarifying potential “reel” mechanisms.

by Helen Scharfman, Ph.D.

References

1. Haas CA, Dudeck O, Kirsch M, Huszka C, Kann G, Pollak S, Zentner J, Frotscher M. Role for reelin in the development of granule cell dispersion in temporal lobe epilepsy. *J Neurosci* 2002;22:5797–5802.
2. Del Rio JA, Heimrich B, Borrell V, Forster E, Drakew A, Alcantara S, Nakajima K, Miyata T, Ogawa M, Mikoshiba K, Derer P, Frotscher M, Soriano E. A role for Cajal–Retzius cells and reelin in the development of hippocampal connections. *Nature* 1997;385:70–74.
3. Houser CR. Granule cell dispersion in the dentate gyrus of humans with temporal lobe epilepsy. *Brain Res* 1990;535:195–204.
4. Blumcke I, Beck H, Suter B, Hofmann D, Fodisch JH, Wolf HK, Schramm J, Elger CE, Wiestler OD. An increase of hippocampal calretinin-immunoreactive neurons correlates with early febrile seizures in temporal lobe epilepsy. *Acta Neuropathol* 1999;97:31–39.