Targets of Research into Preventing Epileptogenesis

Daniel L. Jones, James O. McNamara

Mesial temporal lobe epilepsy (MTLE) is the most common form of partial epilepsy. Interestingly, up to two-thirds of MTLE patients exhibit a history of complicated febrile seizures, preceding the emergence of MTLE. The clinical study of these febrile seizures has revealed that these seizures are associated with MRI (magnetic resonance imaging) evidence of acute swelling of the hippocampus, which subsequently becomes sclerotic. This hippocampal sclerosis, referred to as Ammon's horn sclerosis, is frequently associated with MTLE. It is therefore thought that this period of intense febrile seizures leads, in the short term, to Ammon's horn sclerosis and, in the long term, to MTLE.

The hypothesis that early complicated febrile seizures cause epilepsy has led to intense research into the mechanisms by which "seizures beget seizures." With a greater understanding of the cellular and molecular mechanisms that underlie this process, it may be possible to identify therapeutic targets that can prevent the progression to epilepsy after febrile seizures have occurred.

Epileptogenesis research, utilizing a number of animal models, seeks to understand these mechanisms and to identify such targets. For example, there are multiple animal models in which chemically induced status epilepticus in mice or rats leads to the emergence of spontaneous recurrent seizures, which mirrors the development of MTLE following complicated febrile seizures in humans (Williams et al., 2009).

Using a number of cellular and molecular approaches to study these animal models, researchers have identified molecules that play important roles in this process and that may therefore be attractive therapeutic targets for preventing epileptogenesis following seizures.

The mammalian target of rapamycin (mTOR) is one such target that has been identified in recent years in research using animal models of epileptogenesis. The mTOR signaling pathway has been found to be upregulated after the chemical induction of status epilepticus in mice and rats. In addition, increased activation of the mTOR pathway is observed in patients with Tuberous Sclerosis Complex (TSC), a genetically caused epilepsy syndrome (see also Box 28). Treatment of mice or rats with the mTOR inhibitor rapamycin following status epilepticus has been found to significantly attenuate the appearance of hallmarks of TLE, including mossy fiber sprouting (Buckmaster & Lew, 2011). Rapamycin-induced reductions in the subsequent emergence of spontaneous recurrent seizures have been observed in some but not all of these studies (Buckmaster & Lew, 2011; Zeng et al., 2009).

In addition, the brain-derived neurotrophic factor (BDNF)-TrkB (see in Ch. 29) signaling pathway has been implicated in epileptogenesis in numerous animal studies. Levels of BDNF, which activates its receptor TrkB, have been found to increase following seizures. Indeed, seizure-induced TrkB activation has been observed in the mossy fiber pathway (Danzer et al., 2004). It is thought that TrkB activation is pro-epileptogenic, because mice lacking TrkB in forebrain neurons are unable to undergo epileptogenesis in the kindling model of epileptogenesis (He et al., 2004). Consequently, selective inhibitors of TrkB may be effective anti-epileptogenic agents.

This research will be greatly assisted by the availability of small molecule libraries that can be screened for favorable interactions with targets identified in animal studies of epileptogenesis. It is hoped that these lines of research will lead to clinical trials for methods of therapeutic intervention after status epilepticus, but before the development of spontaneous recurrent seizures.

References

Buckmaster and Lew, 2011 P.S. Buckmaster, F.H. Lew, Rapamycin suppresses mossy fiber sprouting but not seizure frequency in a mouse model of temporal lobe epilepsy. Journal of Neuroscience. 31 (2011) 2337–2347.

Danzer et al., 2004 S.C. Danzer, X.P. He, J.O. McNamara, Ontogeny of seizure-induced increases in BDNF immunoreactivity and TrkB receptor activation in rat hippocampus. Hippocampus. 14 (2004) 345–355.

He et al., 2004 X.P. He, R. Kotloski, S. Nef, B.W. Luikart, L.F. Parada, J.O. McNamara, Conditional deletion of TrkB but not BDNF prevents epileptogenesis in the kindling model. Neuron. 43 (2004) 31–42.

Williams et al., 2009 P.A. Williams, A.M. White, S. Clark, D.J. Ferraro, W. Swiercz, K.J. Staley, F.E. Dudek, Development of spontaneous recurrent seizures after kainate-induced status epilepticus. Journal of Neuroscience. 29 (2009) 2103–2112.

Zeng et al., 2009 L.H. Zeng, N.R. Rensing, M. Wong, The mammalian target of rapamycin signaling pathway mediates epileptogenesis in a model of temporal lobe epilepsy. Journal of Neuroscience. 29 (2009) 6964–6972.