EPILEPSY CURRENTS

Current Literature
In Basic Science

Rapamycin for Treatment of Epilepsy: Antiseizure, Antiepileptogenic, Both, or Neither?

Pharmacological Inhibition of the Mammalian Target of Rapamycin Pathway Suppresses Acquired Epilepsy

Huang X, Zhang H, Yang J, Wu J, McMahon J, Lin Y, Cao Z, Gruenthal M, Huang Y. *Neurobiol Dis* 2010;40:193–199.

Inhibition of mTOR by rapamycin has been shown to suppress seizures in TSC/PTEN genetic models. Rapamycin, when applied immediately before or after a neurological insult, also prevents the development of spontaneous recurrent seizures (epileptogenesis) in an acquired model. In the present study, we examined the mTOR pathway in rats that had already developed chronic spontaneous seizures in a pilocarpine model. We found that mTOR is aberrantly activated in brain tissues from rats with chronic seizures. Furthermore, inhibition of mTOR by rapamycin treatment significantly reduces seizure activity. Finally, mTOR inhibition also significantly suppresses mossy fiber sprouting. Our findings suggest the possibility for a much broader window for intervention for some acquired epilepsies by targeting the mTOR pathway.

Commentary

Current medications for epilepsy are recognized to have a couple of major limitations. First, despite over a dozen existing drugs, one third of epilepsy patients continue to have seizures and can be defined as medically intractable after failure of just two or three drugs. Second, even in patients whose seizures are well-controlled on medication, it is generally accepted that most current drugs simply suppress seizures as symptomatic therapy; they do not prevent the initial development or progression of epilepsy. In other words, these drugs primarily act as *anticonvulsant* or *antiseizure* agents but do not possess actual *antiepileptogenic* or *disease-modifying* properties. To address these limitations, completely different types of drugs with novel mechanisms of action are needed.

Although there are some differences in the molecular targets of available drugs, most antiseizure medications work by similar mechanisms of action: to directly suppress neuronal excitability by reducing excitatory neurophysiological mechanisms (e.g., sodium or calcium channels, glutamate receptors) or enhancing inhibitory mechanisms (e.g., potassium channels, GABA receptors). A novel mechanistic approach to address the issues of medical intractability and disease modification in epilepsy is to modulate primary cell signaling pathways that initially trigger various downstream mechanisms mediating epileptogenesis and increased neuronal excitability. The mammalian target of rapamycin (mTOR) pathway has recently received attention as a candidate signaling pathway that may be central to epileptogenesis and could be targeted therapeutically with mTOR inhibitors, such as rapamycin (1, 2).

mTOR is a ubiquitous protein kinase with multiple physiological functions, including regulation of cell growth, proliferation, and survival (1, 2). In the brain, mTOR is also involved in numerous functions that can affect neuronal signaling and excitability, such as axonal and dendritic morphology, neurotransmitter receptor expression, and synaptic plasticity, under physiological conditions, and could potentially contribute to epileptogenesis under pathological conditions. In the disease, tuberous sclerosis complex (TSC), an important genetic cause of epilepsy, hyperactivation of the mTOR pathway triggered by *TSC* gene mutations has been strongly implicated in promoting tumor growth, as well as contributing to epilepsy and other neurological symptoms in this disease. In mouse models of TSC, early treatment with rapamycin appears to have antiepileptogenic effects in preventing the development of epilepsy and the underlying molecular and histopathological mechanisms of epileptogenesis in presymptomatic mice (3, 4). In addition, later treatment with rapamycin in symptomatic mice can suppress or reverse seizures, as well as learning deficits, in TSC mouse models (4, 5). Furthermore, in related genetic mouse models of PTEN inactivation, rapamycin also decreased seizures, behavioral deficits, and histopathological abnormalities (6, 7). Thus, mTOR inhibitors may have both antiepileptogenic and antiseizure applications in specific types of genetic epilepsy. In fact, initial clinical studies already suggest that mTOR inhibitors decrease seizures in TSC patients with established epilepsy (1, 8), although early antiepileptogenic drug treatment to prevent epilepsy has not been reported.

While genetic epilepsies involving mTOR hyperactivation are relatively rare, the widespread functions of mTOR suggest

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that mTOR pathway dysregulation could also be involved in epileptogenesis in other, more common types of epilepsy, such as acquired epilepsy as a result of brain injury. In the kainate rodent model of epilepsy, kainate administration induces an acute episode of status epilepticus and subsequent neuronal death, mossy fiber sprouting, and other cellular changes in hippocampus that have been implicated in promoting epileptogenesis and acquired epilepsy. Kainate status epilepticus causes abnormal activation of the mTOR pathway, and rapamycin, administered prior to the onset of spontaneous seizures, retards the development of epilepsy, suggesting that rapamycin has antiepileptogenic actions in this model (9).

Although the findings from both the kainate and TSC models highlight the potential utility of mTOR inhibitors as antiepileptogenic agents for multiple types of epilepsy, from a practical standpoint, many people are not eligible for an antiepileptogenic approach. By the time patients present with seizures and are diagnosed with epilepsy, the process of epileptogenesis is likely in its advanced stages, and any window of opportunity for therapeutic intervention to prevent epilepsy may have closed. However, some cases of epilepsy may involve a continued process of progressive epileptogenesis. Furthermore, drugs with novel mechanisms of action, such as inhibition of the mTOR pathway, may still have other beneficial effects that decrease ongoing seizures. Thus, it is worthwhile to explore the efficacy of rapamycin for ongoing acquired epilepsy.

The study by Huang et al. directly addresses the issue of whether mTOR inhibition is an effective treatment for acquired epilepsy that is already established. They used the pilocarpine model in rats, which is closely related to the kainate model; but, in contrast to previous studies of rapamycin in the kainate model (9), rapamycin treatment was not initiated until after the rats were documented to have spontaneous seizures. Despite the relatively late initiation of treatment relative to the process of epileptogenesis, rapamycin still caused a remarkable decrease in seizure frequency. Although a weakness of this study was that only video, not EEG, monitoring was used, the reported effects appeared quite robust and suggest that there is a wide therapeutic window of opportunity for mTOR inhibitors in acquired epilepsy.

Besides the obvious clinical applications of these findings, this study raises some intriguing questions about the overlapping relationship between mechanism of epileptogenesis and seizure generation and the corresponding distinction between antiepileptogenic and antiseizure strategies. The inhibitory effect on seizures in this study reversed upon stopping the rapamycin, suggesting a direct antiseizure action. While the mechanism of this apparent seizure suppression is not known, Huang and colleagues showed that the rapamycin effect on seizures was correlated with a decrease in mossy fiber sprouting. While mossy fiber sprouting is often viewed as an early, permanent epileptogenic process, this finding suggests that mossy fiber sprouting may be a progressive, reversible process that actively stimulates and maintains recurrent seizures. In contrast, a previous study found that early rapamycin treatment inhibited mossy fiber sprouting in the pilocarpine model, but that later treatment did not reverse established sprouting (10), shedding some doubt on the relevance of this mechanism to late antiseizure effects. Alternatively, rapamycin could target other molecular processes, either through mTOR-dependent or mTOR-independent mechanisms, which directly control neuronal excitability, more akin to a traditional anticonvulsant effect. However, rapamycin has been found to have minimal direct effects on neuronal excitability (11, 12). Furthermore, other recent studies have found no effects of rapamycin on seizures in the pilocarpine model (13) and paradoxical effects of rapamycin on mTOR activation and cell death in the kainate model (14), suggesting a complex, potentially dual regulation of epileptogenic mechanisms by mTOR. Thus, further investigations are needed to clarify the mechanisms by which rapamycin may affect both the initial development and the ongoing maintenance of epilepsy and to determine the corresponding timing and clinical applications (presymptomatic/antiepileptogenic vs symptomatic/antiseizure) of rapamycin for epilepsy.

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