Antiepileptogenesis Therapy with Levetiracetam: Data from Kindling versus Status Epilepticus Models

Prophylactic Treatment with Levetiracetam after Status Epilepticus: Lack of Effect on Epileptogenesis, Neuronal Damage, and Behavioral Alterations in Rats. Brandt C, Glien M, Gastens AM, Fedrowitz M, Bethmann K, Volk HA, Potschka H, Löscher W. *Neuropharmacology* 2007;53(2):207–221. Levetiracetam (LEV) is a structurally novel antiepileptic drug (AED) which has demonstrated a broad spectrum of anticonvulsant activities both in experimental and clinical studies. Previous experiments in the kindling model suggested that LEV, in addition to its seizure-suppressing activity, may possess antiepileptogenic or disease-modifying activity. In the present study, we evaluated this possibility by using a rat model in which epilepsy with spontaneous recurrent seizures (SRS), behavioral alterations, and hippocampal damages develop after a status epilepticus (SE) induced by sustained electrical stimulation of the basal amygdala. Two experimental protocols were used. In the first protocol, LEV treatment was started 24h after onset of electrical amygdala stimulation without prior termination of the SE. In the second protocol, the SE was interrupted after 4h by diazepam, immediately followed by onset of treatment with LEV. Treatment with LEV was continued for 8weeks (experiment #1) or 5weeks (experiment #2) after SE, using continuous drug administration via osmotic minipumps. The occurrence of SRS was recorded during and after treatment. In addition, the rats were tested in a battery of behavioral tests, including the elevated-plus maze and the Morris water maze. Finally, the brains of the animals were analyzed for histological lesions in the hippocampal formation. With the experimental protocols chosen for these experiments, LEV did not exert antiepileptogenic or neuroprotective activity. Furthermore, the behavioral alterations, e.g., behavioral hyperexcitability and learning deficits, in epileptic rats were not affected by treatment with LEV after SE. These data do not support the idea that administration of LEV after SE prevents or reduces the long-term alterations developing after such brain insult in rats.

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COMMENTARY

The mechanisms responsible for the development of spontaneous recurrent seizures after brain injury remain unknown, but considerable research has been directed at attempts to identify antiepileptogenic drugs. Clinical studies have found that treatment with traditional antiepileptic drugs (AEDs) after brain injury does not affect the development of epilepsy, leading to the conclusion that these AEDs do not alter the course of epileptogenesis (1). In animals, levetiracetam reduces the duration of kindled seizures and the rate of kindling, suggesting that levetiracetam is not only an AED but also might be antiepileptogenic (2). It is not known if these animal studies are predictive of human antiepileptogenic activity, although a clinical trial currently in progress is attempting to find out if levetiracetam can prevent post-traumatic epilepsy. This study by Brandt and colleagues sought to determine whether chronic administration of levetiracetam, after status epilepticus induced by sustained electrical stimulation of the basolateral amygdala, would block or reduce the subsequent epilepsy, mitigate behavioral deficits, and be neuroprotective in the hippocampus. The key result was that chronic treatment with levetiracetam did not reduce the subsequent epilepsy, as measured by the occurrence of spontaneous seizures. In two separate experiments, which used slightly different protocols, seizures were still observed several weeks after status epilepticus. Also, neither the behavior nor neuronal damage was altered with levetiracetam. These results are at odds, as the authors note, with earlier work by Löscher et al. using the kindling model (2).

An important issue in this study is that levetiracetam, an effective AED, did not appear to reduce the frequency of spontaneous recurrent seizures during the treatment protocol, which could explain the failure to observe an antiepileptogenic effect. In this study, levetiracetam was first administered after the stimulation-induced status epilepticus. This protocol is in contrast to the experiments with the kindling model in which the drug was administered during the kindling stimulation. Therefore, it is conceivable that an effect of the drug on the seizures during treatment is necessary for an antiepileptogenic effect. A second important issue is how the drug was administered. Both experiments had an initial brief treatment period with intraperitoneal injections, followed by chronic treatment via osmotic minipumps. Thus, the initial treatment with intraperitoneal injections of levetiracetam was given immediately after the status epilepticus (i.e., a single injection in the first experiment, and three-times-daily injections for 5 days in the second experiment); however, animals that have experienced status epilepticus and then receive repeated drug injections over prolonged periods are difficult to handle and often develop peritonitis (3), which is presumably one reason why Brandt and colleagues shifted from injections to osmotic minipumps in both experiments (4). Because the frequency of spontaneous seizures was not reduced, it is possible that the dose of levetiracetam was too low, even though the authors measured the level of levetiracetam in the blood. Furthermore, the minipumps had to be replaced three times, which involved additional surgeries and death of some animals; thus, the approach of using osmotic minipumps for long-term chronic treatment is not without problems. The study essentially tested a single chronic dose of levetiracetam during either the 5- or 8-week infusion of levetiracetam (first and second experiments, respectively), which is indicative of the significant difficulty in designing animal model studies that guarantee that the required drug levels are maintained during the chronic drug treatment protocol. This unresolved problem might be better addressed with a dose-response protocol that maintains higher dose levels capable of blocking or at least suppressing the spontaneous seizures during treatment.

This study raises the question of which animal model is better for antiepileptogenesis studies: the electrically evoked seizures of kindling or the spontaneous seizures that occur after status epilepticus? Although several studies have suggested that kindling might be a useful model for testing antiepileptogenic and neuroprotective agents, the model has not been validated. Furthermore, this study raises the question of whether results from kindling can be generalized to other models. As discussed above, because the drug under investigation is present during the electrically stimulated seizures associated with the kindling process, it is possible that the drug blunts the electrically stimulated seizures. Thus, a mild anticonvulsant effect in the kindling model could lead to an *apparent* antiepileptogenic effect.

A problem with animal models of chronic epilepsy that depend on status epilepticus is that the experimental design must include enough monitoring of spontaneous seizures to have sufficient statistical power to demonstrate that the intervention has no effect (i.e., avoiding a false negative). In this, seizure monitoring entailed: (i) "recording of all observed seizures," (ii) regular but intermittent video monitoring, and (iii) continuous video-EEG for 1 week, which occurred 10 weeks after status epilepticus (the latter, performed only in the second study). The "recording of all observed seizures" represented only the detection of seizures during handling and animal care procedures; therefore, this monitoring protocol and the video monitoring (i.e., without EEG) would have missed many seizures. Thus, the 1 week of video-EEG was the strongest seizure-monitoring data in the study; the limited amount of seizure monitoring raises the question of how much monitoring is enough, which ultimately is a statistical problem that depends on the actual magnitude of the drug effect to be detected and on the mean and variance of the baseline interseizure intervals. Unfortunately, long interseizure intervals and large interval variances are the rule for animal models of chronic epilepsy, and both of these features substantially increase the time intervals over which ani-

mals must be monitored in order to avoid false-negative conclusions. A possible false-negative conclusion, in this circumstance, is the finding that there was no effect from the intervention, when in fact the intervention may have had an effect but was not detected with the monitoring protocol. Therefore, the answer to the question of how much monitoring is enough is probably that a great deal more would have been much better. Thus, techniques and protocols are needed that allow extensive, if not continuous, monitoring, because it cannot be determined with certainty that an antiepileptogenic therapy is effective or ineffective unless the monitoring has been long enough to reliably show an effect or no effect of the intervention on epileptogenesis.

The Brandt et al. study raises yet another question: why would AED treatment alter epileptogenesis? Most proposed mechanisms (e.g., neuronal death, axon sprouting) for epileptogenesis do not involve mechanisms believed to be involved in protection against seizures. The hypotheses that invoke an important role for ion channels in epileptogenesis (including ion channels that the AEDs may target) do not necessarily predict that a transient period of AED treatment will have a subsequent effect on spontaneous seizures. Furthermore, part of the rationale for studying levetiracetam is that it may block seizures via a new and different mechanism (i.e., neurotransmitter release), but it is unclear why this potential mechanism for levetiracetam might also be considered antiepileptogenic. One possible antiepileptogenesis hypothesis based on an antiseizure mechanism of an AED is that reducing spontaneous seizures with an AED early in the process of epileptogenesis alters the subsequent progressive evolution of the epilepsy. That is, do early seizures beget later seizures, and does blocking the early seizures reduce the occurrence of later seizures? Because levetiracetam was not shown to depress seizures during treatment, this study does not address this hypothesis.

The study by Brandt et al. does not provide a definitive answer as to whether levetiracetam has an antiepileptogenic effect. The issues of appropriate dose, timing of dose, and outcome measures are sufficiently complex that it would take years to work out the answer with any true certainty. This initial study (as substantive as the efforts by Brandt and colleagues were) suggests, within its important limitations, that it does not have an antiepileptogenic effect. Although by no means a final word on the matter, the article does raise the question of whether classes of compounds, other than AEDs, should be considered in the search for epilepsy prophylaxis, as AEDs to date have shown no real promise in this area.

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