

THE BEST MODEL FOR A CAT IS THE SAME CAT...OR IS IT?

Effect of Antiepileptic Drugs on Spontaneous Seizures in Epileptic Rats. Nissinen J, Pitkänen A. *Epilepsy Res* 2007;73: 181–191. The present study investigated whether spontaneously seizing animals are a valid model for evaluating antiepileptic compounds in the treatment of human epilepsy. We examined whether clinically effective antiepileptic drugs (AEDs), including carbamazepine (CBZ), valproic acid (VPA), ethosuximide (ESM), lamotrigine (LTG), or vigabatrin (VGB) suppress spontaneous seizures in a rat model of human temporal lobe epilepsy, in which epilepsy is triggered by status epilepticus induced by electrical stimulation of the amygdala. Eight adult male rats with newly diagnosed epilepsy and focal onset seizures were included in the study. Baseline seizure frequency was determined by continuous video-electroencephalography (EEG) monitoring during a 7 days baseline period. This was followed by a 2–3 days titration period, a 5–7 days treatment period, and a 2–3 days wash-out period. During the 5–7 days treatment period, animals were treated successively with CBZ (120mg/kg/day), VPA (600mg/kg/day), ESM (400mg/kg/day), LTG (20mg/kg/day), and VGB (250mg/kg/day). VPA, LTG, and VGB were the most efficient of the compounds investigated, decreasing the mean seizure frequency by 83, 84, and 60%, respectively. In the VPA group, the percentage of rats with a greater than 50% decrease in seizure frequency was 100%, in the LTG group 88%, in the VGB group 83%, in the CBZ group 29%, and in the ESM group 38%. During the 7 day treatment period, 20% of the VPA-treated animals and 14% of the CBZ-treated animals became seizure-free. These findings indicate that rats with focal onset spontaneous seizures respond to the same AEDs as patients with focal onset seizures. Like in humans, the response to AEDs can vary substantially between animals. These observations support the idea that spontaneously seizing animals are a useful tool for testing novel compounds for the treatment of human epilepsy.

COMMENTARY

In recent years, intense discussion has evolved around the question of which experimental models are better suited for studying human epilepsy. For example, recommendations for the development of epilepsy models have been outlined at two NIH workshops (1,2); analyzed in both opening and closing chapters of the book *Models of Seizures and Epilepsy* (3,4); and most recently, were a subject of heated debate at an Investigator's Workshop session of the 1st North American Regional Epilepsy Congress in San Diego, California (5). The major reason for the debate is to close the gap between bench and bedside through development of standardized test systems for clinically predictable, high-throughput screening of prospective antiepileptic drugs (AEDs). Furthermore, the discussion reflects different and often conflicting viewpoints on "what good are animal models?" (4). These differences generally indicate a preference toward one of two approaches.

One approach is referred to as analogical modeling; it is based on the maxim, "the best material model for a cat is another, or preferably the same cat" (6). This approach contends that the more an animal's condition resembles human epilepsy, the closer the former reflects the latter. From this perspective, models such as pentylenetetrazole seizures, maximal electroshock, and kindling have very limited clinical relevance, as they clearly fail the analogy test. At the same time, models that are characterized by spontaneous seizures, such as post-status epilepticus

or posttraumatic epilepsy in rats, are considered to be more compelling. A second approach, conceptual modeling, is best embodied by a René Magritte's painting "The Treachery of Images," in which a picture of a pipe is accompanied by the subtitle "this is not a pipe" (meaning: this is only an image, not a pipe). Conceptual modeling asserts that a model cannot merely bear a resemblance to a subject but rather has to reproduce sufficiently the subject or the process of interest.

The difference between the two approaches is obvious. While analogical models strive to encompass all factors of the human condition, conceptual models are explicitly incomplete regarding some details (i.e., idealized). A key rationale underlying the conceptual model is to establish logical relationships among variables rather than simply to account for as many variables as possible. Idealization is a key feature of the conceptual model, allowing for simplification of the phenomenon to such an extent that it can be studied effectively. From the practical standpoint, idealization also permits more efficiency, which in the case of AED development translates into high throughput of a large number of prospective AEDs within a reasonable time frame and at an affordable cost. Presently, basic epilepsy research offers a large variety of animal models; consequently, model development has focused on validation of existing models to select which ones are most relevant for either basic (studies of mechanisms) or translational (development of diagnostic and treatment tools) research.

The manuscript by Nissinen and Pitkänen is an example of validation of an animal model for translational research. The authors attempted to answer the question of whether spontaneous, recurrent seizures that develop in rats after status epilepticus may be used as a tool for identifying prospective AEDs.

They tried to combine advantages of analogical and conceptual approaches by adopting a multifaceted phenomenon (i.e., post–status epilepticus chronic epilepsy) and by simplifying this phenomenon through reducing the number of the parameters presumed to be indicative of AED efficacy in humans. The study design was based on the assumption that if the AED profile of the post–status epilepticus model in rats is similar to that in human temporal lobe epilepsy, it might be a good model to screen human AED efficacy. The authors chose five AEDs with known efficiency in human temporal lobe epilepsy and examined how they worked in rat epilepsy.

Post–status epilepticus epilepsy in rats includes a wide assortment of variables. Spontaneous seizures per se vary in terms of frequency, duration, and severity, both among the animals and within the same animal. Interictal changes include spikes, high frequency oscillations, and behavioral deficits, such as cognitive, memory, and mood impairments. Clearly, when assessing the effectiveness of AEDs, all these features are difficult, if not impossible, to take into the account. To simplify the analysis, Nissinen and Pitkänen selected just two symptoms of epilepsy: seizure frequency and seizure duration. They found that by and large the variability of spontaneous seizures as well as their responsiveness to AEDs was similar to human temporal lobe epilepsy. Hence, the investigators assumed that the drugs that perform best in this model also are the best AEDs in human epilepsy. Did the study succeed? Do the results suggest that post–status epilepticus epilepsy in animals indeed represents the best system for AED screening for temporal lobe epilepsy?

The authors state that the variability of analyzed parameters (both baseline and in response to AED treatment) is an advantage, since rat epilepsy can be used “to mimic clinical study designs of preclinical trials.” Thus, from the analogical modeling standpoint, the validation process was a success. However, as discussed, the very same features that are advantageous in analogical modeling represent substantial flaws for conceptual models. The latter would prefer uniformity to variability in both seizure phenotype and AED effects. The authors admitted that additional tuning of the model might be necessary, for example, through selective examination of animals with “severe” versus “mild” epilepsy. Further scrutiny of the model also might be useful, including examination of the effects of prospective of AEDs on seizure prevention versus seizure spread; modification of interictal epileptic phenomena, such as spikes; and improvement in nonconvulsive comorbidities, such as cognition, memory, and mood disorders. Development of alternative treatment protocols and optimization of evaluation criteria also should be explored (7).

Then again, is it worth pursuing other models for the development and validation of AED screening? It has been correctly emphasized that depending on the purpose (e.g., drug discovery versus mechanistic studies), models for the same condition

may and probably should be different (2). Thus, translational epilepsy research does not have to limit itself to models that have similar epidemiological and clinical characteristics to those under conditions of human epilepsy.

An appeal of post–status epilepticus epilepsy is that seizures develop in a seemingly spontaneous and erratic fashion, thus resembling the human condition. The vast majority of other models require seizure induction by certain external stimuli. However, the differences between post–status epilepticus epilepsy and other types of models are not necessarily as significant as they might seem. For example, under the conditions of the kindling model, the ratio of seizure response (overt secondary generalized seizures) to the strength of the applied stimulus (very low current, which is subconvulsant in naïve animals) is very high. At the same time, the assertion that seizures in post–status epilepticus models seizures are spontaneous is not necessarily correct. Indeed, seizures depend on circadian rhythms as well as minute fluctuations of concentrations of K^+ , Ca^{2+} , hormones, and other factors. In effect, they likely are induced by a variety of both accounted and unaccounted for endogenous stimuli. Yet, kindling has an obvious advantage over spontaneous seizure models, as it offers full control over seizure induction—seizures only develop when needed for the given study design. Thus, no long-term monitoring with expensive equipment is required, and both the variable and erratic nature of seizure occurrence is easily avoided. More importantly, AED profiles of kindling and post–status epilepticus epilepsy are strikingly similar (8). Therefore, while kindling might not be a very good model for mechanistic and histopathological studies, it represents a viable alternative to spontaneous seizure epilepsy for the purpose of AED testing.

In summary, the study by Nissinen and Pitkänen emphasizes that choosing and validating an epilepsy model is a not a trivial task. Selection of appropriate parameters for analysis and criteria for the efficacy of AEDs is far from complete. Furthermore, the pursuit of more “user-friendly,” yet clinically relevant, models is not to be forgotten.

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