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Animal models of epilepsy for the development of antiepileptogenic and disease-modifying drugs. A comparison of the pharmacology of kindling and post-status epilepticus models of temporal lobe epilepsy

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Abstract

Control of epilepsy has primarily focused on suppressing seizure activity by antiepileptic drugs (AEDs) after epilepsy has developed. AEDs have greatly improved the lives of people with epilepsy. However, the belief that AEDs, in addition to suppressing seizures, alter the underlying epileptogenic process and, in doing so, the course of the disease and its prognosis, is not supported by the current clinical and experimental data. An intriguing possibility is to control acquired epilepsy by preventing epileptogenesis, the process by which the brain becomes epileptic. A number of AEDs have been evaluated in clinical trials

to test whether they prevent epileptogenesis in humans, but to date no drug has been shown to be effective in such trials. Thus, there is a pressing need for drugs that are truly antiepileptogenic to either prevent epilepsy or alter its natural course. For this purpose, animal models of epilepsy are an important prerequisite. There are various animal models with chronic brain dysfunctions thought to reflect the processes underlying human epilepsy. Such chronic models of epilepsy include the kindling model of temporal lobe epilepsy (TLE), post-status models of TLE in which epilepsy develops after a sustained status epilepticus, and genetic models of different types of epilepsy. Currently, the kindling model and post-status models, such as the pilocarpine or kainate models, are the most widely used models for studies on epileptogenic processes and on drug targets by which epilepsy can be prevented or modified. Furthermore, the seizures in these models can be used for testing of antiepileptic drug effects. A comparison of the pharmacology of chronic models with models of acute (reactive or provoked) seizures in previously healthy (non-epileptic) animals, such as the maximal electroshock seizure test, demonstrates that drug testing in chronic models of epilepsy yields data which are more predictive of clinical efficacy and adverse effects, so that chronic models should be used relatively early in drug development to minimize false positives. Interestingly, the pharmacology of elicited kindled seizures in fully kindled rats and spontaneous recurrent seizures in post-status models is remarkably similar. However, when these models are used for studying the antiepileptogenic effects of drugs, marked differences between models exist, indicating that the processes underlying epileptogenesis differ among models, even among different post-status models of TLE. A problem for clinical validation of TLE models is the lack of an AED, which effectively prevents epilepsy in humans. Thus, at present, it is not possible to judge which chronic model is best suited for developing new strategies in the search for antiepileptogenic and disease-modifying drugs, but rather a battery of models should be used to avoid false negative or positive predictions.

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Keywords

Epilepsy; Epileptogenesis; Status epilepticus; Antiepileptic drugs; Progression

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