Genetically Epilepsy-Prone Rats (GEPRs) in Drug Research

Phillip C. Jobe and John W. Dailey

Department of Biomedical and Therapeutic Sciences, University of Illinois College of Medicine, Peoria, IL, USA

Key Words: Affective disorders—Biological basis—Epilepsy—Genetically epilepsy-prone rat—Norepinephrine—Predisposition—Serotonin.

ABSTRACT

Two independently derived, inbred strains of genetically epilepsy-prone rats (GEPRs) have been developed, the moderately epileptic GEPR-3 and the more severely epileptic GEPR-9. Seizures expressed by GEPRs model human generalized tonic/clonic seizures (GTCSs) and partial seizures secondarily generalized to tonic/clonic seizures. Several types of existing antiepileptic drugs have been tested in the GEPR model. Without exception, the seizure suppressing properties of these drugs occur both in GEPR-3s and GEPR-9s. The differential responses of the two GEPR strains separate the antiepileptic drugs into three categories: (1) those effective in GTCSs and partial seizures; (2) those that are additionally effective in absence seizures; and (3) those effective in absence seizures but not in convulsive seizures. No known false positives have yet been detected in GEPR tests. In addition to the utility of the seizures expressed by GEPRs in drug development paradigms, these animals also have potential in the search for drugs that are specifically “antineizure predisposition” rather than merely anticonvulsant. Heretofore, worldwide drug development efforts have emphasized the discovery of drugs that are anticonvulsant in nonepileptic animals. As might have been anticipated, these same drugs have proven to be anticonvulsant in epileptic subjects. Paradigms that would detect drugs with the capacity to correct the biological determinants of predisposition are in early stages of application. Kindling seizures provide a means to identify drugs that might be useful in correcting stimulus-induced seizure predisposition. The GEPR and other genetic models of the epilepsies provide models for developing treatments to correct genetically determined seizure predisposition. Emerging evidence supports the hypothesis that GEPRs model comorbidity between the epilepsies and affective disorders. Understanding the basis of this comorbidity has the potential to enable the development of treatments that reverse the underlying abnormalities of the coexisting disorders. Because human epilepsies and affective disorders are environmentally and genetically complex, the abnormalities of the GEPR probably will not account for all predispositions leading to this comorbidity.