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Cardiac phenomena during kainic-acid induced epilepsy and lamotrigine antiepileptic therapy

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Summary
Rationale: Pathologic ECG events are known to accompany seizures and to persist in several chronic epilepsy syndromes. The contribution of antiepileptic drugs (AEDs) to these events and the implications in the etiology of sudden-unexpected death in epilepsy (SUDEP) continue to be a matter of debate. We therefore investigated cardiac parameters during kainic-acid (KA) induced experimental epilepsy and antiepileptic treatment with lamotrigine (LTG).
Methods: Epilepsy was induced in seven C57Bl/6 mice by injections of KA (20 mg/kg) on days 1 and 5, which produced severe acute seizures and spontaneous seizures 10 days later. Treatment with LTG (30 mg/kg) was initiated on day 11 and repeated on day 12. Continuous ECGs and ECoGs were collected telemetrically from freely moving mice.
Results: Mice displayed pre-ictal but not ictal tachycardia. The squared coefficient of variation (SCV) of R—R intervals was significantly elevated 30 s before and during seizures compared to control conditions. LTG produced a significant reversible increase in SCV and LF/HF ratio during slow-wave sleep (SWS), potentially indicative of sympatho-vagal imbalance during this state of vigilance, in which epileptic patients are known to be particularly vulnerable to SUDEP.

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Significance: The KA model used in this study permits the investigation of cardiac phenomena during epilepsy, as it features many effects found in human epileptic patients. Increased LF/HF, a known risk factor for cardiac disease, which is often found in epileptic patients, was observed as a side-effect of LTG treatment during SWS, suggesting that LTG may promote imbalance of the autonomous nervous system in epileptic mice.

Introduction

Kainic-acid (KA) is a non-degradable analog of glutamate, which causes excitotoxicity by agonism of kainate-class ionotropic glutamate receptors (Wang et al., 2005). Animal models involving systemic or local injection of KA are among the most popular models of epilepsy and neurodegeneration, with over 1500 articles published on the subject in the last 10 years[1]. Systemic injection of KA is commonly used to model mesial temporal lobe epilepsy (MTLE), as it produces generalized seizures and progressive sclerosis of the hippocampus, which in turn -like in MTLE patients- leads to recurrent spontaneous seizures (Sharma et al., 2007). Mouse models of human pathology offer several advantages, most notably genetic homogeneity and availability of transgenic animals, but they can be technically challenging due to the small size of mice.

In epileptic patients, seizures have been shown to be preceded and accompanied by ECG changes, fueling the discussion of brain to heart interactions, which may be of great relevance in the context of sudden-unexpected death in epilepsy (SUDEP). Ictal tachycardia is detectable in almost all patients of different age groups (Jansen et al., 2013). Several studies of different epilepsy syndromes have described the occurrence of sympathovagal imbalance (increase of sympathetic and decrease of parasympathetic control of heart rhythm) (Brotherstone and McLellan, 2012; Lotufo et al., 2012; Meghana et al., 2012; Ponnusamy et al., 2012), which is known to contribute to mortality and morbidity in cardiovascular disease (Mortara et al., 1997; Schwartz et al., 1988). Furthermore, pre-ictal tachycardia has been observed in children and adults with generalized seizures (Jansen et al., 2013; Schernthaner et al., 1999), in adults with refractory epilepsy (Zijlmans et al., 2002) and in children with refractory TLE (Mayer et al., 2004). How and whether antiepileptic drugs (AEDs) affect cardiac function of epileptic patients is a matter of debate, as data is conflicting and non-conclusive. One study found AEDs to ameliorate sympathovagal imbalance (Hallioglu et al., 2008), whereas another found AEDs to reduce ECG power and heart rate variability (HRV) (Lossius et al., 2007), possibly predisposing patients to cardiac arrhythmia which may be an important contributor to SUDEP. A recent meta-analysis of 39 studies found a trend of increased low frequency power (LF) in patients taking AEDs, presumably reflecting increased sympathetic tone (Lotufo et al., 2012), possibly posing a cardiac risk. Of AEDs potentially affecting cardiac function, the modern broad spectrum AED lamotrigine (LTG) is of special interest. LTG, FDA approved for treatment of partial seizures in 1994, and later for maintenance treatment of bipolar I disorder, enjoys great popularity and is employed in treatment of several epilepsy syndromes and [also as an off-label drug] of several neuropsychiatric diseases. LTG's wide therapeutic applicability reflects the multi-target nature of the drug which has been shown to modulate several different sodium, calcium and potassium currents (Beck and Yaari, 2012). In particular, LTG has been demonstrated to inhibit the delayed rectifier potassium current, which is crucial for cardiac repolarization and therefore plays a critical role in maintenance of cardiac rhythm (Danielsson et al., 2005). $Ca_v2.3$ (R-type) voltage-gated calcium channels, which contribute to cardiac autonomous control and to intrinsic rhythm propagation (Galetin et al., 2012) are also inhibited by LTG (Hainsworth et al., 2003), representing another potential arrhythmogenic mechanism. Prolongation of the QT-interval, a risk factor of arrhythmia and sudden cardiac death, was an initial concern in regard to LTG treatment, however, some studies could dismiss this concern (Saetre et al., 2009) and a study by GlaxoSmithKline, manufacturer of the initial lamotrigine product Lamictal® found no QT prolongation or related safety concerns (Dixon et al., 2008). Interestingly however, prolonged PR interval due to LTG treatment has been reported (Dixon et al., 2011; Matsuo et al., 1993). Clarification whether LTG has potentially arrhythmogenic effects on the epileptic heart is of great importance, also because it has been reported that LTG increases the risk of SUDEP (Aurlien et al., 2012; Hesdorffer et al., 2011), although findings are controversial. Therefore exact characterization of cardiac phenomena in the murine KA model of epilepsy and investigation of cardiac effects of LTG in this model are of great importance.

Materials and methods

Animals

Seven male C57Bl/6 mice between 18 and 22 weeks of age were used in this study. Mice were kept at 20—22 °C in makrolon type II cages under a 12 h light—dark cycle (7:00 a.m./p.m.) with food and water ad libitum. All animal experiments were in line with the European Communities Council Directive for the care and use of laboratory animals

[1] PubMed search of the words ''kainic'' and ''acid'' occurring in combination with the words ''eplilepsy'', ''seizure'', ''excitotoxicity'', ''neurodegeneration'', ''hyperexcitation'' in the title or abstract of articles published between October 2003 and October 2013.