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Review article

The pathophysiology of cardiac dysfunction in epilepsy

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ABSTRACT

Alterations in cardiac electrophysiology are an established consequence of long-standing drug resistant epilepsy. Patients with chronic epilepsy display abnormalities in both sinoatrial node pacemaker current as well as ventricular repolarizing current that places them at a greater risk of developing life-threatening cardiac arrhythmias. The development of cardiac arrhythmias secondary to drug resistant epilepsy is believed to be a key mechanism underlying the phenomenon of Sudden Unexpected Death in EPilepsy (SUDEP). Though an increasing amount of studies examining both animal models and human patients have provided evidence that chronic epilepsy can detrimentally affect cardiac function, the underlying pathophysiology remains unclear. Recent work has shown the expression of several key cardiac ion channels to be altered in animal models of genetic and acquired epilepsies. This has led to the currently held paradigm that cardiac ion channel expression may be secondarily altered as a consequence of seizure activity-resulting in electrophysiological cardiac dysfunction. Furthermore, cortical autonomic dysfunction – resulting from seizure activity-has also been suggested to play a role, whereby seizure activity may indirectly influence cardiac function via altering centrally-mediated autonomic output to the heart. In this review, we discuss various cardiac dysrhythmias associated with seizure events-including tachycardia, bradycardia and QT prolongation, both ictally and inter-ictally, as well as the role of the autonomic nervous system. We further discuss key ion channels expressed in both the heart and the brain that have been shown to be altered in epilepsy and may be responsible for the development of cardiac dysrhythmias secondary to chronic epilepsy.

Contents

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1. Introduction

The association between long-standing uncontrolled epilepsy and cardiac dysregulation has gained prominence in recent years, largely due to greater awareness of Sudden Unexpected Death in EPilepsy (SUDEP). Disruptions of normal cardiac and respiratory physiology, as well as dysfunction of the autonomic nervous system, are all well-documented prominent sequelae of chronic epilepsy (Devinsky, 2004; Surges et al., 2009; Devinsky, 2011). Respiratory depression is known to occur both during and between seizures, and can result in oxygen desaturation while heart rate variability, a biomarker for assessing autonomic function, is diminished in patients with chronic epilepsy as compared to the general population (Tomson et al., 1998; Sevcencu and Struijk, 2010; Massey et al., 2014).

Importantly, chronic epilepsy is associated with permanent alterations in cardiac electrophysiology that can lead to the development of arrhythmias, bradycardia and asystole. In patients with temporal lobe epilepsy (TLE), concurrent electroencephalogram (EEG)-electrocardiogram (ECG) monitoring has shown that 90–100% of seizures were accompanied by marked increase in heart rate (Blumhardt et al., 1986; Keilson et al., 1989; Opherk et al., 2002; Zijlmans et al., 2002; Surges et al., 2009) Prolongation of the QT segment on ECG, indicative of abnormal cardiac repolarization, has been reported in 4–10% of seizures (Surges et al., 2009; Moseley et al., 2011). Notably, epilepsy is itself a known risk factor for sudden cardiac arrest (either ventricular tachycardia or fibrillation) in the general population, independent of other cardiac risk factors (Bardai et al., 2012).

Abnormalities of heart rate and conduction are the primary ictal cardiac disorders; the latter may play a role in SUDEP. SUDEP is defined as the unexpected death of an apparently otherwise healthy epileptic individual, usually occurring during or immediately after a seizure, for whom no identifiable cause of death is found (Nashef, 1997). Accounting for 17–38% of all deaths in epilepsy patients, SUDEP provides the greatest single contribution to epilepsy-related mortality, with the risk of sudden unexpected death being more than 20–40 times higher in patients with chronic epilepsy as compared to the general population (Ficker et al., 1998; Ficker, 2000; Mohanraj et al., 2006). Yet, a lack of appreciation of the importance and understanding of SUDEP still prevails amongst clinicians caring for patients with epilepsy; a 2006 survey of UK neurologists showed that only 5% discussed SUDEP with all their patients, with the most common reason for SUDEP discussion being inquiry by the patient (Morton et al., 2006). Epidemiological data on the incidence of SUDEP varies greatly depending on the nature of epilepsy population, ranging from 1.1 to 5.9 per 1000 patient years in those with chronic refractory epilepsy and 6.3 to 9.3 per 1000 patient years in patients with ongoing seizures following epilepsy surgery (Walczak et al., 2001; Téllez-Zenteno et al., 2005; Shorvon and Tomson, 2011). Taken together, these incidence data suggest that while SUDEP remains a relatively uncommon event, by occurring at a young age in many patients it accounts for a disproportionate loss of potential years of life, and is therefore of major importance (Thurman, 2013).

Despite reports of sudden unexplained death in patients with epilepsy dating back over 200 years, insight into the pathophysiologic mechanisms underlying SUDEP have remained elusive, with much debate currently existing as to the causal pathways responsible. It is currently believed that dysregulation of cardiorespiratory and cerebral function, as a direct consequence of recurrent seizures, are responsible for triggering SUDEP.

Moreover, cardiac dysfunction observed in patients with epilepsy partly overlaps with cardiac dysfunction seen in patients at risk of sudden cardiac death in the general population, suggesting that epilepsy-induced derangements in cardiac electrophysiology may, in part, be responsible for SUDEP. Recent work from our group, using both genetic and acquired animal models of epilepsy, has shown that chronic epilepsy results in the development of a secondary cardiac channelopathy, with associated electrophysiological changes, thereby providing a potential explanation for the underlying mechanisms behind cardiac dysfunction in patients with chronic epilepsy (Powell et al., 2014).

2. Autonomic dysfunction in epilepsy

Partial and generalized epileptic seizures have been shown to result in alterations in the activity of the autonomic nervous system (ANS), during ictal, postictal and interictal states (Wannamaker, 1985; Schraeder and Lathers, 1989; Lee and Devinsky, 2005). Structures in the central autonomic network- particularly the insular cortex, periaqueductal gray and central nucleus of the amygdala- as well as various brainstem nuclei, have been implicated as underpinning the autonomic dysfunction stemming from seizure activity (Benarroch, 1993; Baumgartner et al., 2001; Devinsky, 2004). Medullary autonomic nuclei, notably the nucleus of the solitary tract and nucleus ambiguus, can be stimulated by the propagation of hypersynchronous neural activity from epileptic foci, with direct stimulation of these ANS nuclei occurring via the insular cortex, and indirect stimulation spreading via the limbic system (Wannamaker, 1985). Moreover, the central autonomic network can itself be epileptogenic (Benarroch, 1993; Devinsky, 2004; Leung et al., 2006; Specchio et al., 2010). In both cases, the end result is a global modulation of autonomic activity that results in stimulation of autonomic afferents, by proxy (Fig. 1).

The ANS modulates the rate of phase 4 depolarization in diastole, and in this manner controls the firing rate of both the sinoatrial (SA) node and secondary pacemakers (Levy, 1971; Keating and Sanguinetti, 2001). During seizures, sympathetic output to the heart dominates, as evidenced by tachycardia being observed during almost all epileptic seizures (Leutmezer et al., 2003; Rugg-Gunn and Holdright, 2010; Sevcencu and Struijk, 2010). Interictally, heart rate variability (HRV) – determined largely by cyclical variations in sympathetic and parasympathetic inputs to the SA node- is significantly decreased in patients with chronic TLE (Tomson et al., 1998). Moreover, it has been postulated that the activation of the central autonomic network maybe responsible for pre-ictal cardiac changes (Jansen and Lagae, 2010).

The idea that abnormal ANS activity may be responsible for the changes in cardiac electrophysiology observed in epileptic patients, as a result of seizure activity, first arose from