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Review

The mystery of sudden death: Mechanisms for risks ☆

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Abstract

This review addresses the possible overlapping mechanisms that may apply to the risk of sudden unexpected death occurring in epilepsy and in cardiac disease. It explores the interaction between the central and peripheral autonomic nervous systems and the cardiopulmonary systems. Included is a discussion of the potential interactive role of genetically determined subtle cardiac risk factors for arrhythmias with a predisposition for seizure-related cardiac arrhythmias. We address the possible mechanisms that are operant in producing both epileptogenic and cardiogenic arrhythmias. Finally, we speculate about potential preventive measures to minimize the risk of both sudden unexpected death in epilepsy and sudden cardiac death.

Keywords: Sudden death; Sudden unexpected death in epilepsy; Epilepsy; Cardiac risk factors for sudden death; Stress; Interventions

1. Preclinical studies related to sudden unexpected death in epilepsy

Although the mechanisms involved in sudden unexpected death in epilepsy (SUDEP) are not known, many published epidemiological studies and review articles have speculated about these mechanisms. Relatively few basic research studies have addressed the question of mechanism. Epilepsy-associated cardiac arrhythmia is speculated to be a factor in the mechanism of SUDEP.

In earlier studies of animal models, cardiac arrhythmias were induced with ouabain, as it is known that high doses of ouabain place a person at risk for toxicity-induced arrhythmias and/or death [1–8]. A nonuniform cardiac postganglionic sympathetic neural discharge, characterized by an increase, decrease, or no change in discharge activity, was associated with the ouabain-induced arrhythmia. It is interesting to note that differences exist in the ability of different glycosides to trigger nonuniform neural discharges, arrhythmia, and death; for example, the polar molecule of ouabain does and the nonpolar digoxin does not [7]. In addition, some pharmacological agents, for example, beta blockers, quinidine, and procainamide, modify the neural nonuniform discharges and arrhythmogenic activity of the heart, whereas others do not exert a proven beneficial effect [6–9]. Lathers et al. [4,8,10] extended the model of nonuniform neural discharges associated with arrhythmias using a nonpharmacological coronary occlusion model of arrhythmia and sudden coronary death. Both the ouabain and the coronary occlusion models resulted in nonuniform autonomic neural discharges, cardiac arrhythmias, and/or sudden death.

One established mechanism of sudden death involves hypoxia leading to ischemia and to myocardial infarction or ventricular fibrillation. Myocardial ischemia is a major mechanism of sudden death in cardiovascular diseases

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and can be provoked both by hypoxia and by adrenergic surges. There are data suggesting that the latter mechanism could contribute to SUDEP. Lathers et al. [4,8,10] demonstrated that nonuniform cardiac sympathetic neural discharges are associated with cardiac arrhythmias and/or death induced by abrupt coronary occlusion of the left anterior descending coronary artery in an animal model used to induce cardiac ischemia and mimic sudden death in patients with myocardial infarction. Evans and Gillis [11] elicited blood pressure increases through stimulation of the hypothalamus and concluded that arrhythmias that occurred after, but not during, such stimulation were the result of a sudden surge in parasympathetic activity reflexly evoked by the rise in blood pressure.

Subsequently, Lathers and Schraeder [12–16] developed a cat model to explore epilepsy/autonomic neural/cardiopulmonary system relationships as an investigative tool to examine possible mechanisms of SUDEP and reported associated cardiac neural autonomic dysfunction and cardiac arrhythmias in an animal model of epilepsy. These studies established that, similar to the ouabain-induced and/or coronary occlusion models of cardiac arrhythmia, neural activity is characterized by an increase, decrease, or no change in simultaneously recorded postganglionic cardiac sympathetic neural discharges in association with cortical seizure discharges. The observation of cardiac sympathetic neural nonuniform discharges in association with seizure discharges was congruent with that of Han and Moe [17], who demonstrated that cardiac sympathetic neural disturbances, whether secondary to direct sympathetic nerve stimulation, ouabain toxicity, or coronary occlusion, increased temporal dispersion of recovery of ventricular excitability and led to an underlying electrical instability that predisposes the ventricular myocardium to arrhythmia.

In addition to the effect of ictal discharges on sympathetic and parasympathetic cardiac neural discharges, subconvulsant interictal cortical discharges induced by pentylenetetrazol (PTZ) were also associated with autonomic cardiac neural nonuniform discharges and cardiac conduction and rhythm changes [12–16]. Subsequent studies examined the relationship of the effect of this interictal activity, arrhythmias, and death to altered autonomic nonuniform postganglionic cardiac and sympathetic and parasympathetic postganglionic cardiac neural discharges. Other experiments examining the effect of pretreatment with phenobarbital reported a delay in the onset time of interictal and ictal activity, but no protective effect on the associated autonomic neural changes once the epileptiform discharges were established [18,19]. The same observations were extant in a model of focal epilepsy in which penicillin was injected into the hippocampus of the cat [20,21]. Another series of experiments [22–24] explored the *lock-step phenomenon*, that is, the synchronization of interictal cortical discharges with postganglionic cardiac sympathetic and parasympathetic neural discharges and changes in blood pressure, cardiac conduction, and rhythm, including the effects of phenobarbital on this phenomenon [23,24]. Timolol (intracerebrovenricular injection) exhibited an anticonvulsant effect [25]. Subsequent experiments by Mameli et al. [26], using hemispherectomized rats, induced epilepsy by applying penicillin to the rat hypothalamus. In this model, both interictal and ictal activity induced cardiac arrhythmias. These data confirmed the data documenting the arrhythmogenic potential of epileptiform discharges obtained in the cat model [12–16].

Other experimental evidence supports the possibility of a role for prostaglandin E_2 and enkephalins in autonomic dysfunction characterized by nonuniform discharge [27–32]. The question of whether the modulation of presynaptic γ-aminobutyric acid (GABA) release by prostaglandin E_2 could provide the explanation for epileptogenic activity and dysfunction in autonomic cardiac neural discharges leading to arrhythmias was raised [27]. Kraras et al. [28], Lathers et al. [29–31], and Schwartz and Lathers [32] inquired into whether enkephalins elicit epileptogenic activity by inhibiting the release of GABA, resulting in associated autonomic dysfunction and cardiac arrhythmias. Prolonged elevation of immunoreactive methionine (Met)-enkephalin content in the septum, hypothalamus, amygdala, and hippocampus of rats occurred after PTZ-induced convulsions [33], with increased concentrations of Met-enkephalins associated with a greater percentage inhibition of potassium-stimulated GABA release [34]. Snead and Bearden [35] found that leucine (Leu)-enkephalin in the central nervous system may induce epileptogenic activity. In addition, [D-alanine2-Met]-enkephalin has been shown to produce a centrally mediated vasopressor response, as well as to attenuate the baroreceptor reflex in conscious cats [36], possibly leading to autonomic imbalance. The latter effect may precipitate arrhythmias. Resolution of the question of whether enkephalins elicit epileptogenic activity and autonomic dysfunction via inhibition of GABA release is important, because an understanding of this mechanism should eventually allow the design of pharmacological agents that prevent epileptogenic activity and autonomic dysfunction and possibly diminish the risk of associated SUDEP. This possibility is emphasized in a work [37] published a number of years after Suter and Lathers [27] and Kraras et al. [28] first raised questions about a possible role for prostaglandin E_2 and enkephalins in autonomic dysfunction characterized by nonuniform discharges associated with seizure activity and cardiac arrhythmias. Dhir and Kulkarni [37] noted that numerous studies have implicated prostaglandins as potential moduators in seizure activity. They reported that rofecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, potentiates the anticonvulsant activity of tiagabine against PTZ-induced convulsions in mice. They proposed that rofecoxib, or similar drugs, may have a place as adjuvant therapy in reducing the risk of adverse cardiac events when used in combination with standard antiepileptic drugs (AEDs) in the treatment of epilepsy.