Epilepsy & Behavior 26 (2013) 410–414

Contents lists available at SciVerse ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Potential mechanisms of sudden unexpected death in epilepsy

Gleb P. Tolstykh [a,b,c,d], José E. Cavazos [a,b,c,d,e,*]

[a] Research Division — ALM VAMC, South Texas Veterans Health Care System, San Antonio, TX, USA
[b] Department of Neurology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA
[c] Department of Pharmacology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA
[d] Department of Physiology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA
[e] San Antonio VA Epilepsy Center of Excellence and Research Division, South Texas Veterans Health Care System, San Antonio, TX, USA

ARTICLE INFO

Article history:
Accepted 6 September 2012
Available online 8 January 2013

Keywords:
SUDEP
Neuron loss
NTS
Nucleus of the solitary tract
KCNK channels

ABSTRACT

Sudden unexpected death in epilepsy (SUDEP) accounts for 15% of all deaths in people with epilepsy and 50% in refractory epilepsy. The underlying mechanisms are not well understood, but seizure-induced cardiac and respiratory arrests are involved. The cardiovascular and respiratory systems are subject to precise reflex regulation to ensure appropriate oxygen supply under a wide range of circumstances. Barosensory and chemosensory afferents project into the nucleus tractus solitarius (NTS), which relays systemic data to higher brain centers for integration of homeostatic responses in heart rate, peripheral resistance, respiration, and other autonomic reactions. Being the afferent autonomic gatekeeper, NTS plays a critical role in cardiovascular and respiratory regulation. In the course of studying the kainic acid model, we became aware of progressive neuronal loss in the NTS and noted SUDEP-like deaths in rats with frequent convulsions. Increased autonomic susceptibility with inhalation anesthetics was also observed, often seen after impairment of baroreceptor and chemoreceptor reflex loops. Seizure-induced neuron loss in NTS may play a role impairing the integrative functions of NTS resulting in poor homeostatic responses during seizures and leading to SUDEP.

This article is part of a Special Issue entitled "The Future of Translational Epilepsy Research".
Published by Elsevier Inc.

1. Introduction

Epilepsy affects approximately 1% of the US population. Sudden unexpected death in epilepsy accounts for up to 17% of all cases of death in people with epilepsy, which increases the rate of sudden death by 24-fold as compared to the general population [1–4]. Sudden unexpected death in epilepsy is defined as an unexpected death in a person who has epilepsy with no other obvious cause of death. Usually, the victim was in relatively good state of health, and the death may or may not be caused by seizure. If postmortem examination is obtained and no evidence for other causes of death is found, the case is considered as definite SUDEP. If the occurrence meets all the above criteria, but autopsy was not performed, then it will be considered as probable SUDEP [3,5,6]. Over the last two decades, there has been an increased interest in SUDEP, but the literature primarily consists of epidemiological studies and case reports [7]. Only recently, experimental models have revealed exciting details on potential mechanisms of SUDEP, beginning to broaden our limited understanding about the pathogenesis and mechanisms of SUDEP.

The most consistent risk factors for SUDEP are the following: poor compliance with antiepileptic medication, young age, early age of onset of seizures, increased refractoriness of epilepsy, presence of generalized tonic-clonic seizures, male gender, and being in bed at the time of death [4,7,8]. There are several proposed pathophysiological mechanisms of SUDEP including ictal arrhythmias, ictal or postictal central apnea, acute neurogenic pulmonary edema, and autonomic "dysregulation." Case reports for each potential mechanism have been described, but there is lack of a unifying mechanism for SUDEP.

Central apnea and acute neurogenic pulmonary edema have been documented by clinical and postmortem observations [9–11]. Recently, Bateman et al. demonstrated ictal oxygen desaturation in about a third of patients with intractable epilepsy and hypoventilation in two case reports of SUDEP [12,13]. In a primary generalized baboon model with spontaneous epilepsy, signs of neurogenic pulmonary edema were found in cases of sudden death, suggestive of SUDEP [14]. In our experimental model of Kainic Acid-induced Status Epilepticus (KA-SE), we have personally observed agonal apnea-like events immediately before death after a spontaneous convulsion many months after KA-SE. In addition, KA-SE rats with frequent seizures that have been found dead in the morning often have bubbled fluid out of the nostrils and signs of pulmonary edema [2].

* Corresponding author at: Neurology Section — Mail Code 111D, Audie L. Murphy VA Hospital, 7400 Merton Minter Blvd., San Antonio, TX 78229, USA. Fax: +1 210 567 4659.
E-mail address: cavazosj@uthscsa.edu (J.E. Cavazos).

1525-5050/$ – see front matter. Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.yebeh.2012.09.017

Primary or secondary cardiac mechanisms might be also very important through a number of possible scenarios. The most significant and widely discussed cardiac mechanism of SUDEP is ictal cardiac arrhythmias and associated heart rate variability. In the amygdala kindling model, evoked generalized tonic-clonic seizures induce a 50% increase in mean arterial pressure (MAP) that lasts for 20–30 s after initiation of the seizure as well as cardiac arrhythmias [15]. Ictal tachycardia or bradycardia during epilepsy is also frequently associated with changes in the Q–T interval, which sometimes precedes the onset of seizures [16–21]. Epilepsy itself is a risk factor for acute myocardial infarction [22]. Another recent exciting development is the demonstration by Goldman et al. [23] of the expression of cardiac LQT genes with dual phenotype of epilepsy and cardiac arrhythmias. This genetic model has a phenotype of generalized seizures, autonomic dysregulation in the heart in correlation to the hypersynchronous brain activity, and SUDEP [23]. It also provided the first evidence of KCNQ1 gene expression in the brain and brainstem suggesting a novel molecular mechanism for SUDEP. Coincidently, we were looking into the expression of KCNQ 2, 3, and 5 potassium channels in the brainstem area since 2007 and have demonstrated electrophysiological and immunocytochemical evidence of the presence of at least KCNQ 2 and 3 channels in the nucleus of the solitary tract (NTS) [24–26].

The cardiorespiratory system is regulated tightly by the autonomic nervous system (ANS). There is a balance between the parasympathetic and sympathetic drive to maintain normal homeostasis. Experimental evidence of dysregulation or overactivity of the ANS has been found during sudden death in SUDEP cases [4,27,28]. Sakamoto et al. [29] demonstrated autonomic overactivity during non-convulsive status epilepticus in an acute anesthetized preparation given kainic acid. They reported up to 10-fold increase in parasympathetic activity during acute KA-SE, leading to reductions of cardiac output and systemic blood pressure [29]. Elevated parasympathetic activity is also responsible for airway secretions that can cause obstructive apneic episodes [30,31]. The laboratory of Dr. Stewart has demonstrated that an acute evoked seizure results in considerable sympathetic and parasympathetic outflow activity aimed to homeostatically compensate and partially contribute to large variations in blood pressure, heart rate, and other systemic variables. One limitation of this acute approach is that these animals do not have epilepsy yet as they have not developed the neurobiological alterations associated with recurrent spontaneous seizures. The process of epileptogenesis requires several weeks after the initial insult for plasticity and other phenomena to ensue, and the risk of SUDEP dramatically increases with emergence of recurrent convulsions. Furthermore, Stewart's laboratory has carefully examined the efferent pathways (i.e., the sympathetic and parasympathetic branches) of the ANS, but the afferent pathways have not been investigated in chronic epilepsy or acute convulsive models. There is considerable evidence that the spread of epileptic activity to brainstem centers is involved in events that trigger SUDEP. Convulsive seizures up-regulate c-fos activity in a few brainstem nuclei including, prominently, the principal neurons of the NTS [32–34]. It is very important to examine the properties of primary neurons responsible for barosensation and chemosensation in the brain stem (the afferent ANS pathway) during the development of chronic epilepsy, as recurrent and frequent convulsions increase the risk for SUDEP. If the integrative properties of these neurons progressively become impaired, their homeostatic regulation might eventually fail, perhaps, explaining the increased susceptibility to SUDEP in patients with frequent convulsions. Low baroreceptor sensitivity is a risk factor for sudden cardiac death and predisposition to heart rate variability [35–37]. Heart rate variability is a substantial risk factor for SUDEP and is a sign of autonomic disturbance in epilepsy [38,39]. It is beyond the scope of the current review to describe all ANS neuronal networks, but we will elaborate further on the ANS afferent pathways.

2. Nucleus of the tractus solitaries (NTS)

The NTS plays a critical integrative role in cardiovascular and respiratory regulation since it is the initial step in barosensory and chemosensory information processing that culminates in homeostatic reflex responses (see Fig. 1; [40–44]). However, little is known about NTS physiology in models of chronic epilepsy. Most of the studies of this brainstem area have focused upon their role in pathophysiological conditions such as hypertension hypoxia, and adaptation by homeostatic reflexes. For example, electrical stimulation of the NTS in cats interferes with the development of convulsive evolution and secondary generalization [45]. The mechanism is not well understood. Interruption of the baroreceptor reflex, by either sinoaortic denervation or NTS lesions, elevates sympathetic nerve activity and arterial pressure [46]. This indicates the key role of the NTS in the regulation of the blood pressure. Mean arterial pressure variability has been associated with increased risk for stroke and end-organ (heart, kidney, etc.) damage [47–53] and could be related to SUDEP. Housley and Sinclair made experimental lesions of the neurons transmitting the carotid chemoreceptor stimulus determining the principal site of carotid chemoreceptor synapses in the NTS caudal to the obex [54]. Another brainstem region that might be important to the autonomic homeostatic reflexes is the retrotrapezoid nucleus (RTN), which contains pH-sensitive neurons that are putative central chemoreceptors and express KCNQ potassium channels. It is important to remember that RTN neurons respond to brain pCO_2 changes, in part, via a direct glutamatergic pathway from commissural NTS that bypasses the respiratory network [55]. Unfortunately, the properties and function of NTS neurons in epilepsy have received little attention despite their critical role in cardiorespiratory regulation. Preliminary data examining neuronal densities in brainstem nuclei showed that the KA-SE model of epilepsy is associated with selective decrease of neuronal populations in the NTS [1]. We hypothesize that recurrent convulsions induce progressive neuronal loss in the NTS, leading to alterations of the physiological properties of the NTS circuitry that predisposes KA rats to SUDEP due to impaired integrative function. Further characterization of the neural circuitry of the NTS in epilepsy is needed.

3. M-current/KCNQ channels

Fast synapses of the nervous system make possible the rapid coordinated actions of the body and control the responses to the

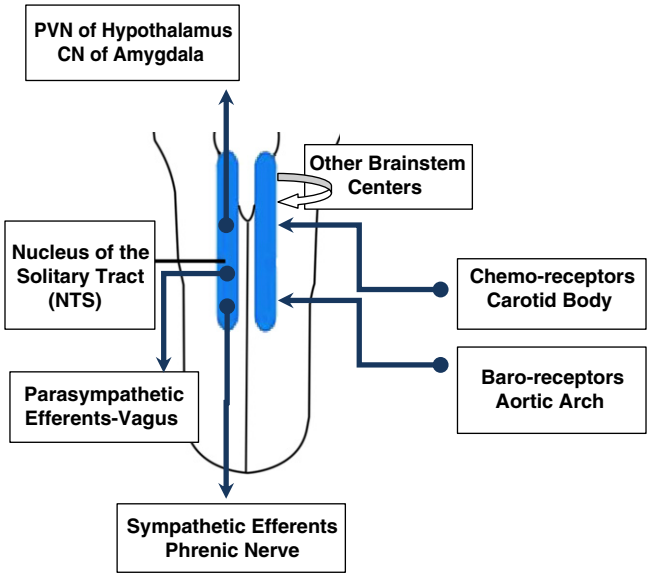

Fig. 1. Afferent projections to the nucleus of the solitary tract in the brainstem.