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Review article

Antiarrhythmic drugs and epilepsy

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ABSTRACT

For a long time it has been suspected that epilepsy and cardiac arrhythmia may have common molecular background. Furthermore, seizures can affect function of the central autonomic control centers leading to short- and long-term alterations of cardiac rhythm. Sudden unexpected death in epilepsy (SUDEP) has most likely a cardiac mechanism. Common elements of pathogenesis create a basis for the assumption that antiarrhythmic drugs (AADs) may affect seizure phenomena and interact with antiepileptic drugs (AEDs).

Numerous studies have demonstrated anticonvulsant effects of AADs. Among class I AADs (sodium channel blockers), phenytoin is an established antiepileptic drug. Propafenone exerted low anti-electroshock activity in rats. Lidocaine and mexiletine showed the anticonvulsant activity not only in animal models, but also in patients with partial seizures. Among beta-blockers (class II AADs), propranolol was anticonvulsant in models for generalized tonic-clonic and complex partial seizures, but not for myoclonic convulsions. Metoprolol and pindolol antagonized tonic-clonic seizures in DBA/2 mice. Timolol reversed the epileptiform activity of pentylenetetrazol (PTZ) in the brain. Furthermore, amiodarone, the representative of class III AADs, inhibited PTZ- and caffeine-induced convulsions in mice. In the group of class IV AADs, verapamil protected mice against PTZ-induced seizures and inhibited epileptogenesis in amygdala-kindled rats. Verapamil and diltiazem showed moderate anticonvulsant activity in genetically epilepsy prone rats. Additionally, numerous AADs potentiated the anticonvulsant action of AEDs in both experimental and clinical conditions. It should be mentioned, however, that many AADs showed proconvulsant effects in overdose. Moreover, intravenous esmolol and intra-arterial verapamil induced seizures even at therapeutic dose ranges.

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Introduction

Relationships between seizures and arrhythmias are rather complex and should be considered at least in three dimensions, i.e. in the aspect of similarity between: (1) conductive cardiac and neural tissue, (2) cardiac and neural action potential, and (3) Na^+ and K^+ channels located in either the brain or the heart. In a shell, the cardiac conduction system consists of highly specialized cells that histologically resemble nerve tissue. Conductive cells and neurons share two main features: excitability and conductivity. Furthermore, both cardiac and neural action potentials have been divided into five phases. Both of them are related to the sodium inward currents and potassium outward currents [1,2]. This makes it possible for the two disorders to have similar pathogenesis and a common electrical background. In fact, epileptic seizures are triggered by simultaneous activation of a group of nerve cells in the cerebral cortex leading to sudden and excessive bursts of electrical energy [3]. On the other hand, cardiac arrhythmia is any of a heterogeneous group of conditions characterized by abnormal electrical activity in the heart [4]. Similar pathogenesis of the two disturbances may explain why drugs affecting seizures can influence cardiac functions and vice versa. A classic example is phenytoin.

Interestingly, relationship between heart and brain seems to be bidirectional. On one hand, cardiac arrhythmias can provoke seizures – in most cases they are syncopal attacks, but sometimes also true epileptic convulsions. The interplay between heart and brain may also underlie the mechanism of sudden unexpected death in epilepsy (SUDEP). It is closely associated with seizure-induced imbalance of the autonomic nervous system and its effect on cardiac conductivity [5].

Channelopathies and their role in epilepsy and cardiac arrhythmias

Clinical observations indicate that variants and mutations in long QT syndrome (LQTS) and Brugada syndrome genes, which encode Na^+, K^+ and Ca^{2+} ion channels, may predispose for either epilepsy or cardiac arrhythmias. LQTS and Brugada syndrome are inherited cardiac channelopathies, in course of which sudden cardiac death due to epileptic seizures are identified more frequently than in healthy controls [6].

A significant progress was made, when KCNQ 1 potassium channels, $Na_V1.6$ sodium channels and RyR2 (ryanodine receptors, mediating intracellular calcium homeostasis) were localized not only in the heart muscle, but also in the brain [7]. It suggests a possible link between cardiac and cerebral channelopathies [8]. Mutations of aforementioned ionic channels may affect function of both organs, thereby leading to an increased susceptibility to either epilepsy or cardiac arrhythmias [9]. It has been confirmed that voltage-dependent "M-type" KCNQ K^+ channels play a major role in neuronal excitability, affecting generation and propagation of action potential, tuning patterns of neuronal firing, and modulating release of neurotransmitters at synaptic terminals [10]. Brain KCNQ channels have been localized in the primary neurons of nucleus tractus solitarii, a brain structure that controls a variety of autonomic functions, including integration of baroreceptor and chemoreceptor inputs. These afferents are relayed to higher brain centers that adjust heart rate, peripheral resistance, respiration, and other autonomic reactions [11]. It has been observed that kainic acid-induced seizures can lead to SUDEP-like deaths in rats. Simultaneously, a significant loss of GABAergic neurons in the nucleus tractus solitarii was noted in brains of these animals. This, in turn, may impair GABAergic inhibitory regulation of the cardiorespiratory reflex [11].

Hypothesis on the close relationship between heart and brain has been confirmed in experimental studies. For instance, mice with mutated genes KvLQT1 and KCNQ1, encoding voltage-gated delayed rectifier K^+ channels, presented episodes of cardiac arrhythmia, which in many cases were accompanied by seizures. Thus, the two mutations define a candidate mechanism for SUDEP [6]. On the other hand, it was revealed that mutation of gene coding the neuronal sodium channel $Na_V1.6$ impairs action potential propagation and excitation-contraction coupling in the mouse heart [12].

SUDEP

Patients with refractory epilepsy have life-long 1% risk of SUDEP development. Proposed mechanisms of SUDEP include central or obstructive apnea, acute neurogenic pulmonary edema and cardiac arrhythmia. The cardiorespiratory system is regulated tightly by the autonomic nervous system. Imbalance between the parasympathetic and sympathetic activity, dysregulation or hyperactivity of the autonomic nervous system have been reported in SUDEP cases [11]. A nature of autonomic dysregulation seems to be very different. It was reported that epilepsy can be associated with vagal suppression (which is the most potent risk factor for arrhythmias) but also with sympathetic activation, vagal activation, and sympathetic-vagal suppression [13]. SUDEP may develop in three mechanisms: (1) respiratory: (ictal respiratory suppression, central or obstructive apnea), (2) neurogenic: (neurogenic pulmonary edema), and (3) cardiovascular: sudden cardiac arrest (SCA): asystole, ventricular arrhythmia, e.g. torsades de pointes. The incidence of SUDEP has been assessed as 1/1000 of epileptic patients, and the risk seems to be higher in young and female individuals [6].

Postictal apnea, observed in 40% of recorded seizures, can be triggered by inhibitory neurotransmitters released in the seizure self-terminating mechanism. On the other hand, seizure-related sympathetic activation increases pulmonary vascular resistance. In severe cases, it may lead to pulmonary edema observed in 50–86% of patients with SUDEP [14]. However, cardiac arrhythmia is considered as the most frequent reason of SUDEP [14,15]. The probable reason may be that brain centers of autonomic control, like the insula, amygdala, cingulated gyrus, and prefrontal cortex may also play a role of epileptic foci [16]. Autonomically mediated effects modulate vascular tone of coronary arteries and myocardial perfusion. According to some authors thalamic dysfunction and/or autonomic changes can lead to myocardial fibrosis, which may become an anatomical substrate of ventricular arrhythmia or myocardial electrophysiological instability. They, in turn, increase the risk of SUDEP development [14]. Moreover, sympathetic and parasympathetic stimulation may alter duration of action potential and refractoriness, as well as generate early and delayed afterdepolarizations [17]. In patients with chronic epilepsy, a variety of abnormal cardiac repolarization may lead to ventricular tachyarrhythmia and SUDEP development (Fig. 1). Based on these observations, considered ways to reduce the risk of or prevent SUDEP may be antiarrhythmic treatment or implantation of cardiac pacemaker–defibrillator devices [9].

Ictal cardiac changes

Epileptic seizures may provoke either ictal and interictal cardiac disturbances, which pathophysiology is strongly associated with disturbed homeostasis of the central autonomic nervous system. Cardiac ictal changes occur at the same time as seizures and are believed to be the basic pathogenic factor of SUDEP. Simultaneous existence of seizures and cardiac arrhythmias was