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Microglia PACAP and glutamate: Friends or foes in seizure-induced autonomic dysfunction and SUDEP?

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ABSTRACT

Seizure-induced cardiorespiratory autonomic dysfunction is a major cause of sudden unexpected death in epilepsy (SUDEP), and the underlying mechanism is unclear. Seizures lead to increased synthesis, and release of glutamate, pituitary adenylate cyclase activating polypeptide (PACAP), and other neurotransmitters, and cause extensive activation of microglia at multiple regions in the brain including central autonomic cardiorespiratory brainstem nuclei. Glutamate contributes to neurodegeneration, and inflammation in epilepsy. PACAP has neuroprotective, and anti-inflammatory properties, whereas microglia are key players in inflammatory responses in CNS. Seizure-induced increase in PACAP is neuroprotective. PACAP produces neuroprotective effects acting on microglial PAC1 and VPAC1 receptors. Microglia also express glutamate transporters, and their expression can be increased by PACAP in response to harmful or stressful situations such as seizures. Here we discuss the mechanism of autonomic cardiorespiratory dysfunction in seizure, and the role of PACAP, glutamate and microglia in regulating cardiorespiratory brainstem neurons in their physiological state that could provide future therapeutic options for SUDEP.

1. Introduction

Epilepsy affects about 50 million people worldwide (WHO, 2005). Sudden unexpected death in epilepsy (SUDEP) is an important but poorly-appreciated disorder (Massey et al., 2014) that accounts for 5–17% of deaths in people with epilepsy, and 50% in refractory epilepsy (Ficker et al., 1998; Holst et al., 2013). The first evidence of SUDEP was published nearly 50 years ago (Hirsch and Martin, 1971), but the underlying mechanism remains obscure. The classical mechanism of SUDEP is extensively studied, and accounts for seizure-induced central autonomic and cardiorespiratory dysfunction (Figs. 1–2). Maximal electroshock applied by two ear electrodes, in freely moving rats, leads to seizure causing cardiac arrhythmia that is precisely correlated with the ictal period (Darbin et al., 2002). In human, seizure is commonly associated with profound apnoea and oxygen desaturation (Bateman et al., 2008; Dlouhy et al., 2015). Here we survey new data and propose a role for microglia (innate immune cells of the CNS), and the neurotransmitters, pituitary adenylate cyclase activating polypeptide (PACAP), and glutamate in the context of seizure induced cardiorespiratory dysfunction (Fig. 3). These novel findings suggest probable mechanisms of cardiorespiratory dysfunction in seizure, and point to future therapeutic strategies that may help in the management, and prevention of SUDEP.

Cardiorespiratory disturbances such as arrhythmia and apnoea that occur during, and after seizures are the leading cause of SUDEP in both humans, and animals (Fig. 1) (Dlouhy et al., 2015; Johnston et al., 1997; Metcalf et al., 2009; Naggar et al., 2014). Cardiac sympathovagal imbalances with sympathetic dominance, baroreflex dysfunction, tachycardia or bradycardia with severe ictal ECG abnormalities are common in patients and animals (Bhandare et al., 2015; Nei et al., 2000; Opherk et al., 2002; Ponnusamy et al., 2012; Sakamoto et al., 2008). Seizure-related respiratory dysfunction, with associated hypoxaemia, is common, as seen in video-electroencephalogram (EEG) telemetry (Fig. 4), from patients in epilepsy monitoring units (Bateman et al., 2008; Dlouhy et al., 2015; Seyal et al., 2010).

Recent studies have uncovered a novel mechanism of seizure-induced cardiorespiratory dysfunction in animal models of seizure and epilepsy that involves three important mediators: microglia, which are immune cells in the CNS, PACAP, a pleiotropic neuropeptide, and glutamate, a major excitatory neurotransmitter in the brain (Fig. 3).

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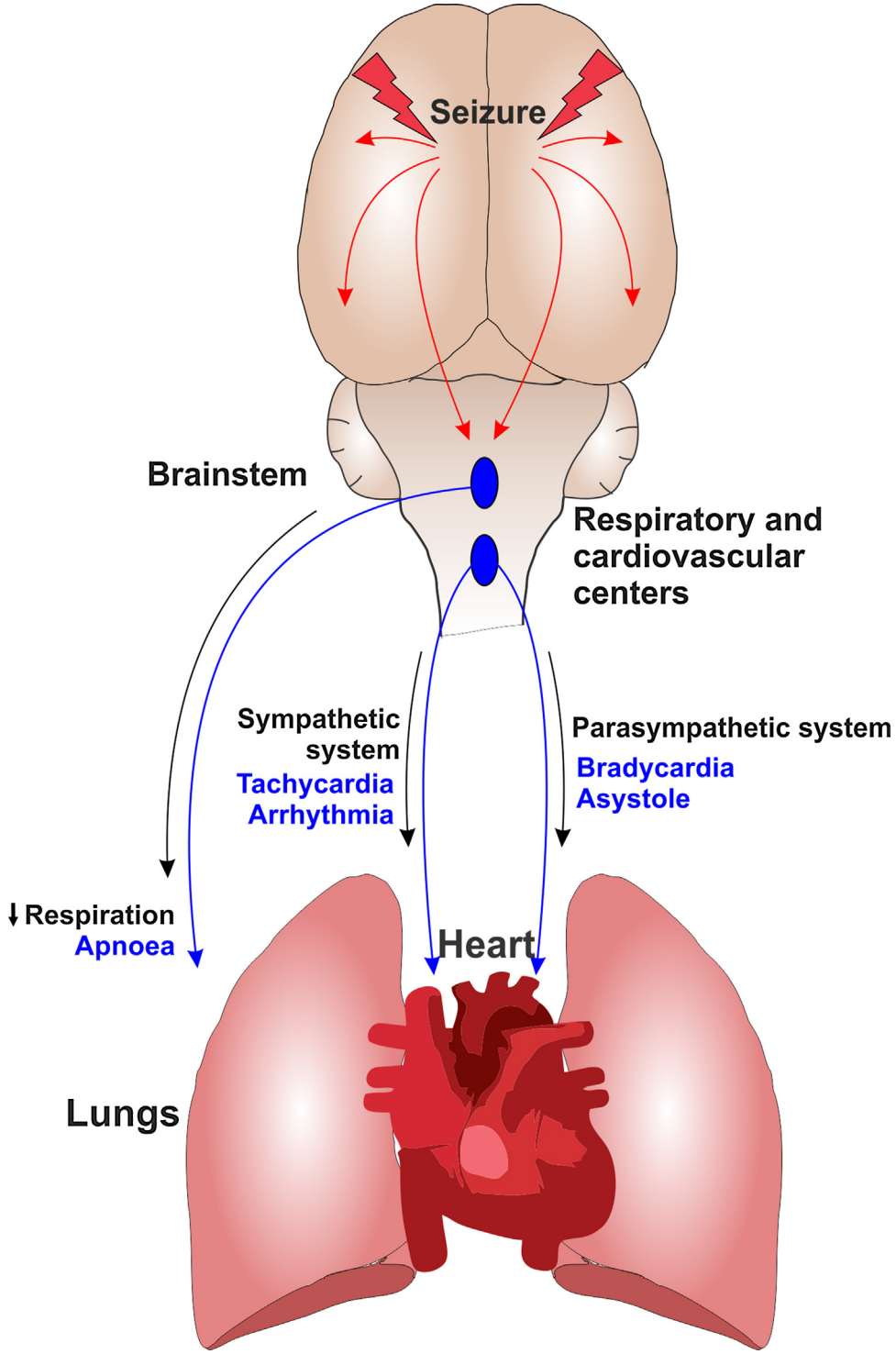

Fig. 1. A schematic diagram of mechanism of seizure-induced central autonomic cardiorespiratory dysfunction. Seizures propagate from higher brain region into the cardiorespiratory brainstem autonomic nuclei, and disturb the normal cardiorespiratory activity and reflexes. Seizure-induced excitation of sympathetic neurons leads to tachycardia and arrhythmia, whereas activation of parasympathetic system causes bradycardia and asystole. Moreover, spread of seizures could results in postictal coma, and loss of protective airway reflexes eventually causing decreased respiratory drive, apnoea and hypoventilation.

Microglia are ubiquitously distributed throughout the CNS, including in the vicinity of sympathetic premotor rostral ventrolateral medullary (RVLM) neurons (Fig. 5) (Kapoor et al., 2016). Microglia can be either neuroprotective or neurodegenerative, depending on circumstances (Li et al., 2007; Vinet et al., 2012). Extensive microglial activation is evident in animal models of seizure (Beach et al., 1995; Drage et al., 2002; Shapiro et al., 2008). During the acute phase of seizure, preconditioning of hippocampal microglia reduces the seizure score in mice (Mirrione et al., 2010). Moreover, antagonism of microglia activation, with intrathecal administration of minocycline, during acute phase seizures in rats produces more sympathoexcitation (Bhandare et al., 2015).

PACAP expression increases in the paraventricular nucleus (PVN) of the hypothalamus, after kainic acid-induced seizure in