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Inhibition of adenosine metabolism induces changes in post-ictal depression, respiration, and mortality in genetically epilepsy prone rats

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ABSTRACT

A major cause of mortality in epilepsy patients is sudden unexpected death in epilepsy (SUDEP). Post-ictal respiratory dysfunction following generalized convulsive seizures is most commonly observed in witnessed cases of human SUDEP. DBA mouse models of SUDEP are induced by audiogenic seizures (AGSz) and show high incidences of seizure-induced death due to respiratory depression. The relatively low incidence of human SUDEP suggests that it may be useful to examine seizure-associated death in an AGSz model that rarely exhibits sudden death, such as genetically epilepsy-prone rats (GEPR-9s). Adenosine is released extensively during seizures and depresses respiration, which may contribute to seizure-induced death. The present study examined the effects of inhibiting adenosine metabolism on the durations of post-ictal depression (PID) and respiratory distress (RD), changes in blood oxygen saturation (% SpO_2), and the incidence of post-seizure mortality in GEPR-9s. Systemic administration of adenosine metabolism inhibitors, erythro-9-(2-hydroxy-3-nonyl) adenine (EHNA, 30 mg/kg) with 5-Iodotubericidin (5-ITU, 3 mg/kg) in GEPR-9s resulted in significant changes in the duration of AGSz-induced PID as compared to vehicle in both genders. These agents also significantly increased the duration of post-seizure RD and significantly decreased the mean% SpO_2 after AGSz, as compared to vehicle but only in females. Subsequently, we observed that the incidences of death in both genders 12–48 h post-seizure were significantly greater in drug vs. vehicle treatment. The incidence of death in females was also significantly higher than in males, which is consistent with the elevated seizure sensitivity of female GEPR-9s developmentally. These results support a potentially important role of elevated adenosine levels following generalized seizures in the increased incidence of death in GEPR-9s induced by adenosine metabolism inhibitors. These findings may also be relevant to human SUDEP, in light of the elevated adenosine levels that occur post-ictally in humans and its respiratory depressant actions.

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Introduction

Patients with epilepsy are at a higher risk of mortality as compared to the general population. Sudden unexpected death in epilepsy (SUDEP) is the leading cause of mortality in refractory epileptic patients, with an estimated risk of 35% over a patient's lifetime (Massey et al., 2014) and occurs in 8–17% of epileptic patients (Nobili et al., 2011). Studies in epilepsy monitoring units suggest potential roles of multiple mechanisms including respiratory, cardiac and cerebral dysfunctions in causing SUDEP (Ryvlin et al., 2013). Respiratory dysfunction was observed as the primary initiating event in most witnessed cases of SUDEP (Ryvlin et al., 2013; Tomson et al., 2008). Most animal models of SUDEP involve mice (Sowers et al., 2013; Wagnon et al., 2015), including DBA/1 and DBA/2 mice which exhibit a high incidence of audiogenic seizure (AGSz)-induced death when tested early in development (Faingold and Randall, 2013; Faingold et al., 2010; Tupal and Faingold, 2006). However, since SUDEP in patients is relatively rare, we evaluated factors governing susceptibility to seizure-induced death in an AGSz model that rarely dies post-ictally, the genetically epilepsy prone rats (GEPR-9s), which are a well-established reflex epilepsy model that also occasionally exhibits spontaneous seizure episodes (Dailey et al., 1989). Generalized seizures in GEPR-9s are blocked by all clinically effective antiepileptic drugs that have been examined. GEPR-9s do not show evidence of other neurological disorders, exhibit a genetic predisposition to seizures, and exhibit seizure susceptibility to stimuli that do not cause seizures in non-epileptic

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animals (Faingold et al., 2014; Jobe et al., 1995). When GEPR-9s are exposed to an intense acoustic stimulus they exhibit a stereotypical seizure pattern, consisting of wild running, tonus, and tonic hind limb extension, which is a seizure score of 9 on the established AGSz severity scale (Dailey and Jobe, 1985). Following the tonic hind limb extension, GEPR-9s exhibit a period of post-ictal depression (PID) characterized by a loss of righting reflex (Jobe et al., 1995). In patients, the post-ictal state is associated with morbidity, including cognitive decline and psychiatric issues (Fisher and Schachter, 2000), and in human cases of SUDEP respiratory depression was the initiating factor that led to death most commonly during PID (Bateman et al., 2010; Ryvlin et al., 2013). Thus, terminal apnea was observed in most witnessed cases of SUDEP following generalized seizures (Ryvlin et al., 2013; So et al., 2000), and a significant degree of respiratory depression is observed in most patients during and/or following this type of seizure (Bateman et al., 2008).

Several neurotransmitters are known to be released during seizures, including serotonin, GABA, opioid peptides, and adenosine (Fisher and Schachter, 2000; Lado and Moshe, 2008), and it has been proposed that these neurotransmitters affect post-ictal respiratory depression and the susceptibility to SUDEP (Faingold et al., 2013; Faingold and Tupal, 2014; Shen et al., 2010; Tupal and Faingold, 2006). Recent clinical studies have shown that most cases of SUDEP, or possible SUDEP, occurred at night with patients found in the prone position in bed (Lamberts et al., 2012; Nashef et al., 1998; Nobili et al., 2011). Adenosine is implicated as an important causative factor in the induction of sleep, since adenosine levels are highest as sleep is initiated and increase greatly during sleep deprivation (Huang et al., 2014; Porkka-Heiskanen et al., 2000), and adenosine antagonists are widely used to maintain wakefulness (Schwartz and Roth, 2008). There are also major increases in extracellular adenosine levels in the brain during seizures in patients with epilepsy, which is proposed to be involved in mechanisms of seizure arrest and post-ictal refractoriness (During and Spencer, 1992). Adenosine is also known to depress breathing in rodents by actions in the brainstem (Gettys et al., 2013; Lagercrantz et al., 1984; Winn et al., 1980; Zwicker et al., 2011). A significant degree of respiratory depression is seen in association with generalized seizures in most patients examined (Bateman et al., 2008; Nadkarni et al., 2012; Seyal et al., 2013). A model of SUDEP has been developed involving administration of adenosine metabolism inhibitors in kainic acid-induced seizures, which shows an increase in incidence of death in mice (Shen et al., 2010). This study also showed that an adenosine antagonist, caffeine, could significantly delay the time of death (Shen et al., 2010). Thus, the roles of adenosine in sleep, respiration, and seizures have been documented previously, but the role of adenosine in mechanisms of seizure-induced death merits further investigation. Since GEPR-9s are a model of AGSz with a very low incidence of post-ictal death, we examined if inhibition of the metabolism of adenosine could alter respiratory function and the incidence of death following seizures in this model. We administered adenosine metabolism inhibitors, adenosine deaminase blocker erythro-9-(2-hydroxy-3-nonyl) adenine (EHNA) and an adenosine kinase blocker 5-iodotubercidin (5-ITU) (Pak et al., 1994) and subsequently exposed GEPR-9s to AGSz. Respiratory function was monitored using blood oxygen saturation (% SpO_2) levels, and the duration of respiratory distress (RD) during post-ictal depression (PID) was evaluated based on polygraphic and video data. The duration of PID was also measured, since it is implicated as a risk factor for SUDEP and morbidity in epileptic patients (Lhatoo et al., 2010; Semmelroch et al., 2012; Seyal et al., 2013). We also monitored the incidence of death subsequent to seizure in GEPR-9s after administration of the adenosine metabolism inhibitors as compared to the vehicle controls.

Methods

Animals

A total of 48 GEPR-9s (males, 22 and females, 26) (150–400 g) from our institutional colony were included in the study. The rats were screened for susceptibility to AGSz in response to an acoustic stimulation paradigm, as noted below, starting at the age of ~7 weeks, once a week for 3 weeks (Dailey et al., 1989). All animals used in this study showed a score of 9 (tonic hind limb extension). Groups of GEPR-9s received either vehicle or active drugs followed by AGSz, while another group received the drugs but was not subjected to AGSz. The durations of PID, and RD, as well as % SpO_2, were examined 30 min after administration of vehicle or drug immediately following AGSz. Surviving GEPR-9s were exposed to acoustic stimulation again at 24 h.

Seizure induction

GEPR-9s were individually placed in a plastic cylinder (43 cm diameter) within a sound-attenuating chamber and subjected to acoustic stimulation (broadband acoustic stimulus at 110 dB SPL; 0.0002 dyne/cm^2) generated by an electrical bell (Foss electric bell, Model No: 4771L, Tecumseh, MI) for a maximum duration of 30 s or until the rat exhibited AGSz. Seizure-related behaviors were recorded on videotape and quantified visually off-line by a blinded observer. Following tonic hind limb extension, GEPR-9s exhibited a period of PID, characterized by loss of the righting reflex, and during this period the % SpO_2 levels and duration of RD were evaluated (as described below). The duration of PID was also evaluated off-line by visual analysis of video recordings based on the loss and subsequent return of the righting reflex. All videos were recorded using a Sony Digital Handycam (Model No: DCR-TRV120/TRV320), which records in normal and low light conditions.

Pulse oximetry

During PID, % SpO_2 levels were recorded with MouseSTAT™ (Kent Scientific) using computer drivers downloaded from www.ftdichip.com/drivers/vcp.htm. Pulse oximeter data was transferred to a computer (Acer Aspire One – D150) with these port settings (Baud rate: 115200; data bits: 8), to a WCOM32 application, which was later exported to Microsoft Excel for analysis. The sensor from the pulse oximeter was clipped to the rat's hind paw, which passed low intensity red light and infrared waves through the tissue to a photo detector. Blood saturated with oxygen absorbs less energy than oxygen-depleted blood, and these changes in absorbed wavelength of light were transduced into % SpO_2 values. We were able to record % SpO_2 levels only from animals that were restrained or in PID after exposure to AGSz, since potentially disruptive movement artifacts occur in awake, behaving animals.

Breathing pattern analysis

During PID, we also attached a piezoelectric pulse transducer (MLT 1010, AD instruments) to record the thoraco-abdominal respiratory movements (Levai et al., 2012; Manzeika and Swanson, 2007). The transducer was connected to a pre-amplifier circuit, which recorded the events onto a chart recorder (Model 7B Polygraph, Grass Instruments Co. MASS, USA). For all the recordings the following parameters were used: pre-amplifier sensitivity of 5 mv/cm, 1/2 amplitude low frequency at 0.03 Hz, DC driver 1/2 amplitude high frequency at 3 Hz, and the chart recorder speed of 3 mm/s. Breathing pattern analysis was done only in animals that exhibited AGSz-induced PID because of movement artifacts. The duration of RD, which included periods of ataxic breathing,

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