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A unified hypothesis of SUDEP: Seizure-induced respiratory depression induced by adenosine may lead to SUDEP but can be prevented by autoresuscitation and other restorative respiratory response mechanisms mediated by the action of serotonin on the periaqueductal gray

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Abstract

Sudden unexpected death in epilepsy (SUDEP) is a major cause of death in people with epilepsy (PWE). Postictal apnea leading to cardiac arrest is the most common sequence of terminal events in witnessed cases of SUDEP, and post-convulsive central apnea has been proposed as a potential biomarker of SUDEP susceptibility. Research in SUDEP animal models has led to the serotonin and adenosine hypotheses of SUDEP. These neurotransmitters influence respiration, seizures, and lethality in animal models of SUDEP and are implicated in human SUDEP cases. Adenosine released during seizures is proposed to be an important seizure termination mechanism. However, adenosine also depresses respiration, and this effect is mediated, in part, by inhibition of neuronal activity in subcortical structures that modulate respiration, including the periaqueductal gray (PAG). Drugs that enhance the action of adenosine increase postictal death in SUDEP models. Serotonin is also released during seizures, but enhances respiration in response to elevated carbon dioxide level that often occur postictally. This effect of serotonin can potentially compensate, in part, for the adenosine-mediated respiratory depression, acting to facilitate autoresuscitation and other restorative respiratory response mechanisms. A number of drugs that enhance the action of serotonin prevent postictal death in several SUDEP models and reduce postictal respiratory depression in PWE. This effect of serotonin-enhancing drugs may be mediated, in part, by actions on brainstem sites that modulate respiration, including the PAG. Enhanced activity in the PAG

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increases respiration in response to hypoxia and other exigent conditions and can be activated by electrical stimulation. Thus, we propose the unifying hypothesis that seizure-induced adenosine release leads to respiratory depression. This can be reversed by serotonergic enhancement of autoresuscitation and other restorative respiratory responses acting, in part, via the PAG. Therefore, we hypothesize that serotonergic or direct activation of this brainstem site may be a useful approach for SUDEP prevention.

Keywords

SUDEP; serotonin; adenosine; periaqueductal gray; amygdala

1. Introduction

Sudden unexpected death in epilepsy (SUDEP) is a devastating concern for people with epilepsy (PWE) and their families, and it ranks second only to stroke among neurologic diseases, in years of potential life lost.[1–6] The risk of sudden death is estimated to be over 20 times greater in PWE than the general population of the same age. [2, 7, 8] The landmark international MORTEMUS study[9] (study of the incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units) documented the temporal sequence of cardiac and respiratory events of the witnessed SUDEP cases that occurred in epilepsy monitoring units and published a compilation of the terminal events that led to death in these cases. In most cases SUDEP occurred following generalized tonic-clonic (GTC) seizures,[9–11] although SUDEP has also been observed interictally.[12] Postictal generalized EEG suppression (PGES), observed in several SUDEP cases, is also proposed to be a contributing factor, but there is a lack of consensus on this.[13, 14]

2. Cardiac versus respiratory mechanisms in SUDEP

The relative importance of cardiac vs. respiratory events in triggering SUDEP has been controversial. Asystole, which is a critical event in many other forms of sudden death and has been reported in SUDEP.[15] Periictal tachycardia is also observed commonly in both focal and GTC seizures.[16] In addition, arrhythmias are also observed in a study of PWE, several of whom subsequently died of SUDEP.[17] Arrhythmias are also seen prior to death in a widely used SUDEP model,[18, 19] but they can be blocked by atropine in doses that do not prevent seizure-induced respiratory arrest.[20] Reductions in heart rate variability (HRV) in PWE has been suggested to be a risk factor and biomarker for SUDEP.[21, 22] However, other studies do not confirm this.[10, 23]

Cardiac and respiratory function are inextricably linked physiologically. Central regulation of cardiac and respiratory function is controlled by brain structures in specific regions of the hypothalamus and brainstem, including rostral medullary nuclei, which are also involved in arousal.[24, 25] In most witnessed cases, SUDEP followed a GTC seizure, and the risk of SUDEP increases with GTC seizure frequency.[26] The terminal event in the Mortemus study is apnea in 67% of cases, which is followed, after a significant time delay often minutes-long, by asystole.[9, 10] Thus, the timing of the terminal apnea preceded asystole, although earlier non-terminal cardiac rate and rhythm changes are also observed in the majority of

witnessed SUDEP cases[9, 10, 27–29] and in many models of SUDEP (see Li and Buchanan, 2019 for review)[30]. A key physiological difference in control of the heart and the lungs that may explain why asystole lags in time after apnea in SUDEP is that the heart, unlike the lungs, has intrinsic pacemaker mechanisms that are independent of central control. As discussed in detail below, there is evidence that seizures can disrupt the function of the brainstem structures that control both cardiac and respiratory activity in certain genetic SUDEP models,[31] which may be mediated, in part, by the release of specific neuroactive substances, including adenosine.[32] Thus, seizures may disrupt the function of brainstem structures that control both cardiac and respiratory activity. However, the intrinsic cardiac pacemaker activity may initially compensate, creating a greater safety margin for cardiac function, whereas there is no comparable lung pacemaker system to maintain respiration, resulting in apnea. The resilience of cardiac function despite disordered central influences is illustrated by the phenomenon of "vagal escape" wherein electrical stimulation of the vagus nerve, releases acetylcholine that slows and eventually stops heart activity. However, despite continued vagal stimulation, the heart will escape from this effect, due to intrinsic pacemaker activity and begin beating again. This clear temporal separation of respiratory and cardiac failure in most witnessed cases of SUDEP may be vital with respect to SUDEP prevention, highlighting the potential importance of compensating for terminal apnea as most critical for preventing death in most potential cases of SUDEP.

Significant degrees of periictal respiratory depression are also well-documented in human primary and secondary GTC seizures that do not result in SUDEP [33–41] and can trigger vigorous intrinsic respiratory-enhancing efforts.[42] Prolonged postictal apnea leads to severe hypoxemia, which is suggested to be an indicator of possible susceptibility to SUDEP.[43, 44] The severity of periictal oxygen desaturation was directly correlated with how many years the patient had experienced seizures and the age of epilepsy onset, suggesting that a progressive increase in respiratory depression is occurring.[27] Based on epidemiological data, a recent SUDEP review by Thijs and colleagues (2021)[28] stated that "no case has yet been reported with asystole but no apnoea." Importantly, prospective data from a recent multi-center clinical study suggest that post-convulsive central apnea may be important in the pathophysiology of SUDEP, since it occurred in near-SUDEP cases as well as in probable SUDEP cases, suggesting this phenomenon may be a clinical biomarker for SUDEP susceptibility.[45] Postictal (brainstem-driven) posturing may be a behavioral indicator and surrogate biomarker for post-convulsive central apnea.[46] An additional measure of seizure-related respiratory deficiency, low interictal hypercapnic ventilatory response is observed in certain PWE and has been suggested to increase the risk of severe respiratory depression and SUDEP after GTC seizures.[47] Other factors that can compromise respiration are localized environmental issues, including being in a prone position and physical respiratory impediments caused by bed clothes.[13, 28, 48, 49] Thus, clinical observations indicate that most cases of SUDEP involve apnea, but a minority of cases appear to have disparate or unclear causation.

GTC seizures in PWE and animal models can lead to central and/or peripheral causes of hypoxemia, including, most prominently, central apnea, as well as obstructive apnea, pulmonary edema, and laryngospasm, which are also reported in PWE and animal models of SUDEP.[11, 36, 50–60] Drugs that depress respiration, such as alcohol, may also contribute to

SUDEP.[61] Spreading depolarization in the brainstem, leading to cardiorespiratory collapse, is proposed as a critical postictal event in certain genetic models of SUDEP,[31, 62, 63] which would trigger hypoxia.

Intrinsic restorative respiratory response mechanisms, including autoresuscitation, are critical to overcome any of these causes of respiratory deficiency. Autoresuscitation, defined as enhancement of respiration in response to elevated blood levels of CO_2, is a critical protective mechanism that acts to reverse severe hypoxia induced by various causes.[64–66] Autoresuscitation involves the triggering of gasping behavior in response to apnea that acts to increase blood oxygen levels to facilitate restoration of normal respiration and is mediated by serotonin (5-HT) involving specific raphe nuclei.[67] The hypercapnic ventilatory response is another important restorative physiological mechanism triggered by apnea that is mediated by the rise in CO_2 due to inadequate ventilation and enhances respiration, involving certain raphe neurons, and is also mediated by 5-HT.[68] Another restorative mechanism is the hypoxic ventilatory response that can increase respiration in response to hypoxia, and one of several elements of this phenomenon also involves 5-HT.[69] Thus, all three of these restorative respiratory responses (RRRs) may be triggered by apnea and involve the action of 5-HT. Note, autoresuscitation has also been used to apply to the “Lazarus” phenomenon, the return of spontaneous circulation following the termination of resuscitation after cardiac arrest,[70] but the usage here does not include this phenomenon. Thus, these RRRs would be activated by any seizure-related cause of hypoxia. Based on this concept, terminal apnea in SUDEP could be viewed as failure of autoresuscitation and the other RRRs. It is noteworthy that there is substantial evidence supporting a major role of serotonin in these physiological mechanisms that are critical for correcting respiratory deficits,[71] as discussed below.

3. Animal models of SUDEP

Although epilepsy is a very common neurologic disorder with a high incidence of GTC seizures in PWE, fortunately, SUDEP is relatively rare, and severe cardiorespiratory post-seizure sequelae seen in SUDEP cases do not often occur.[41] Therefore, the use of consistent SUDEP animal models is vital for systematically establishing mechanisms and developing potential methods for prevention. Despite the fact that postictal “asphyxia“ was noted more than a century ago[72] and that SUDEP was identified as an entity over 50 years ago[73], the lack of useful animal models prevented effective research until relatively recently. Animal models that exhibit seizure-induced death due to cardiorespiratory failure have been developed that may shed light on the pathophysiology mechanisms involved in SUDEP. The animal models of SUDEP include inherited, naturally-occurring models and models induced by genetic manipulation, convulsant drug or electroshock (see Li and Buchanan, 2019 for review)[30]. These models have generated a number of testable hypotheses relating to SUDEP mechanisms, including altered neurotransmitter mechanisms, and several of them have yielded ideas that can be potentially applied as preventative treatment for SUDEP. The most useful models for developing potential preventative treatments are arguably those that consistently and reliably yield a seizure-induced death and are widely available. We propose that an important feature of a SUDEP model is that the death of the animal can be prevented by resuscitation, allowing each animal to serve as its own control. Use of this approach would technically classify such a model as demonstrating “near-SUDEP” in which PWE can

be successfully resuscitated after showing cardiorespiratory deficiencies that would likely cause SUDEP if not corrected.[4] Since a review of SUDEP models has been published recently,[30] the following discussion will focus primarily on the inherited DBA/1 and DBA/2 mouse SUDEP models which meet the criteria noted above[74] and are used by the authors. The DBA/1 mouse model is a widely used SUDEP model[18, 19] and has been studied in more than a dozen labs in several countries, appearing in more than 30 SUDEP-related publications. DBA/1 mice are subject to sound-induced (audiogenic) seizures (AGSz) that are consistently lethal due to seizure-induced respiratory arrest (S-IRA).[18, 19, 75] DBA/1 mice also exhibit an elevated incidence of death due to S-IRA following convulsant drug, hyperthermia, or electroshock-induced seizures.[76–78] A closely related model, the DBA/2 mouse has been extensively used as an epilepsy model and has also been used in SUDEP research.[79, 80] A very useful feature of both DBA models is that death can be prevented in the vast majority of these animals if mechanical resuscitation is instituted promptly during the postictal period.[18, 19, 79] Although DBA/2 mice have a relatively brief (~10 day) period of consistent S-IRA susceptibility in ~75% of animals,[74, 79] susceptibility to S-IRA in DBA/1 mice is observed in up to 100% of the animals and lasts for up to several months. However, it is critical that DBA/1 mice are first subjected to a “priming” protocol, consisting of AGSz evoked daily for 3-4 days in the period between postnatal day 21-30.[18, 19] This priming protocol is a requirement to see this consistently high incidence of S-IRA susceptibility.[18, 19, 81, 82] The mechanisms that mediate priming may involve neurotransmitter-related and/or excitotoxic mechanisms,[78, 83] as discussed below. DBA/1 mice exhibit respiratory failure that always precedes cardiac arrest and yields insights into terminal apnea, the most commonly observed cause of SUDEP clinically.

The neurons in the brain regions that control cardiorespiratory function are modulated by a number of neurotransmitters. Elevated levels in the plasma and brain of a number of neurotransmitters are observed postictally after GTC seizures in animals and PWE.[84, 85] Studies on SUDEP models have focused largely on two of these neurotransmitters, leading to the serotonin and adenosine hypotheses of SUDEP, which are main topics discussed in this review. Other elements that have been implicated in SUDEP include norepinephrine, galanin, somatostatin, and orexin, as well as aberrant ion channels.[86–94]. The changes in plasma levels of certain of these substances may be relevant to brain levels, despite not normally passing the blood brain barrier, because chronic epilepsy can cause disruption of this barrier.[95, 96]

4. The adenosine hypothesis of SUDEP

The adenosine hypothesis of SUDEP, originally proposed by Shen and co-workers (2010)[97] posits that seizure-induced increases in adenosine levels in the brain can lead to SUDEP. This hypothesis is based on extensive findings in animal models and studies on PWE. Adenosine is a purine ribonucleoside that functions as a classical neurotransmitter in certain brain regions.[98] In addition, greatly elevated levels of adenosine are produced by the breakdown of ATP particularly during periods of high energy expenditure that occur during seizures,[99] which are detectable in plasma and the brain postictally.[84, 100–108] Adenosine exerts its effects via interaction with four G-protein coupled receptors, which exert a number of effects on neurons, and drugs that act on these receptors have been developed.[109]

Adenosine is known to exert significant inhibitory effects on respiration, and this action contributed importantly to the adenosine hypothesis of SUDEP.[41, 49, 97, 108, 110–113] Adenosine is proposed to make a major contribution to postictal respiratory depression that occurs commonly after generalized seizures in animals [108] and in PWE.[38, 39] This effect of adenosine is proposed to be mediated, in large part, on brainstem sites, including the rostroventral lateral medulla (RVLM), that controls the rhythm and rate of respiration.[114–116]

Adenosine is also known to exert inhibitory effects on seizures. The greatly elevated levels of adenosine occurring periictally in the plasma and brains of PWE and seizure models are proposed to play a critical role as an endogenous anticonvulsant that acts to terminate ongoing seizures.[97, 99, 103, 108, 117] Adenosine is distributed widely in the brain via volume (paracrine) transmission, indicating that it exerts effects locally and at a distance.[118] Activation of hyperpolarizing presynaptic A_1 receptors by adenosine suppresses seizures, but activation of A_{2A} receptors exerts mostly pro-convulsive effects.[119] Recently, it has been reported that an A_{2A} antagonist reduces the incidence of death in the kainate model of SUDEP.[120] Activation of A_{2A} receptors increases blood-brain barrier permeability, which occurs in chronic epilepsy.[96, 121-123]

Adenosine is known to exert major effects in animal models of SUDEP. Pharmacological blockade of adenosine breakdown in several SUDEP models, including DBA mice, resulted in a significant elevation of post-seizure respiratory depression and mortality.[97, 112, 124] A non-selective adenosine receptor antagonist (caffeine) or a selective A_{2A}, but not a selective A_1 receptor antagonist, significantly reduces S-IRA in DBA/2 mice.[112] Higher doses of adenosine antagonists can actually induce seizures.[112, 125-129] High brain levels of adenosine can contribute to spreading depolarization,[32] a phenomenon implicated as a causal mechanism in certain SUDEP models.[31, 62] Adenosine can also contribute to PGES.[108] Mice with a genetic defect in adenosine breakdown die a few days after birth, and death is due to lethal apnea in most cases.[130]

Physiological elevation of adenosine levels, which trigger NREM sleep,[131, 132] may also contribute to SUDEP by exerting an additive effect with seizure-induced release of adenosine, since SUDEP in PWE occurs most commonly during NREM sleep.[9, 11, 111, 133, 134] If the respiratory depression is too severe, it is proposed to induce apnea,[108] the terminal event in most observed human SUDEP cases.[9, 10] In certain SUDEP models sleep deprivation, which would tend to increase adenosine levels also increase seizure-induced mortality.[135] The post-ictal respiratory depressant effect of adenosine may be mediated, in part, by direct or indirect effects on neurons in the RVLM, periaqueductal gray, amygdala, and raphe nuclei among other brain sites.[98, 136, 137] These subcortical sites are proposed to play significant roles in seizure-induced respiratory changes and SUDEP.

Clinical evidence for a role of adenosine in SUDEP includes the abnormal distribution and density of adenosine receptors in the brains of PWE as well as abnormal adenosine-related findings in certain epilepsy models.[138, 139] In surgical specimens from PWE at high risk for SUDEP and chronic epilepsy, significant alterations of adenosine receptors are seen in multiple brain sites, including the RVLM and amygdala.[90, 113, 140, 141] In addition,

upregulation of adenosine kinase (ADK), which is major degradative enzyme for adenosine, is also observed in PWE with temporal lobe epilepsy.[142] Both the adenosine receptor and ADK changes may occur primarily and/or secondarily as adaptive reactions to the repetitive exposure to high adenosine levels during seizures. These changes may eventually lead to an adenosine deficiency and contribute to increased seizure severity.[139, 142–145] Increased A_1 receptor expression may contribute to periictal amygdala dysfunction involved in SUDEP susceptibility.[90, 113] In a group of PWE increased consumption of coffee, which contains the non-selective adenosine antagonist, caffeine, correlated with a lower degree of periictal hypoxemia.[146] Importantly, levels of adenosine in the brains of PWE have been shown to significantly increase in real time during seizures.[100] These data support the hypothesis that the extensive release of adenosine during seizure contributes importantly to postictal respiratory depression that leads to SUDEP.

5. Serotonin hypothesis of SUDEP

The serotonin hypothesis of SUDEP posits that enhancing the action of the biogenic amine, serotonin (5-hyroxytryptamine, 5-HT), can prevent SUDEP was originally proposed by Tupal and Faingold.[79] This hypothesis is supported by a growing body of evidence in animal research that treatments which modify serotonergic neurotransmission in the brain significantly alter the susceptibility to respiratory dysfunction and seizure-induced sudden death in SUDEP models.[18, 19, 41, 147, 148] This hypothesis has received recent support in clinical studies, as discussed below.

5a. Serotonin Neurotransmission

Serotonin is an important and widely studied neurotransmitter in brain neurons and is synthesized from dietary tryptophan by tryptophan hydroxylase 2 (TPH2) primarily by neurons in the brainstem raphe nuclei, which synthesize, store, and release 5-HT.[149] A recent review presents the receptor nomenclature and a detailed understanding for each of 14 5-HT receptor subtypes, and evidence for two additional receptor subtypes has been presented.[150] All of these receptors are G-protein coupled except for the 5-HT_3 receptor. The raphe nuclei are midline structures in the brainstem throughout the midbrain, pons, and medulla, which contain primarily serotonergic neurons.[151] There are several subpopulations of raphe nuclei, including the rostral group (dorsal and median raphe) and caudal group (raphe magnus, obscurus, and pallidus), as well as the pontine raphe, and these different nuclei may play differential roles in the actions of 5-HT.[152] The more rostral nuclei located in the midbrain and rostral pons – caudal linear nucleus, dorsal raphe, and median raphe – have projections which extend to forebrain structures. The caudal nuclei of the caudal pons and medulla– raphe magnus, raphe obscurus, and raphe pallidus – primarily project to spinal cord structures; this occurs via parallel projections to ventral, intermediate, and dorsal columns.[151] Raphe neurons play major roles in a variety of normal brain functions, including respiration and mood, as well as in epilepsy.[153] Serotonin, like adenosine, also exerts its effects both synaptically and via volume transmission.[154] A number of clinically useful serotonergic drugs exert effects on seizure-induced respiratory dysfunction. These include subtype-selective pre- and post-synaptic 5-HT receptor agonists and antagonists, as well as agents that enhance the availability of 5-HT, including the anticonvulsant,

fenfluramine, and the selective serotonin re-uptake inhibitors (SSRIs), which are used primarily in treating mood disorders, as discussed below.

Serotonin is known to exert major effects in the central control of respiration by actions in the brainstem.[155] Studies in the RVLM have established a critical role of nuclei in this region in control of respiration.[156, 157] Effects of 5-HT, particularly on 5-HT_{1A} receptors, on neurons in these brain regions enhances respiration in response to elevated blood CO_2 levels.[155, 158–160] Neonatal mice in which 5-HT neurons have been genetically deleted exhibit severe and sometimes fatal apnea, and the animals that survive show greatly reduced respiratory enhancement in response to elevated blood CO_2.[161] These findings and other data strongly support a significant role of 5-HT in autoresuscitation and the other RRRs that compensate for respiratory deficits, as noted above,[71] which include those seen during periictal respiratory depression.

5b. Serotonin in Epilepsy

The involvement of serotonin in epilepsy has been extensively studied. Seizure-induced alterations in 5-HT receptors and the 5-HT transporter as well as serotonergic drug alterations of seizure susceptibility have been widely observed in animal models and PWE.[148] Although pro-convulsant effects of enhancing 5-HT availability with SSRIs and other antidepressants were reported in animals and patients, but these anecdotal reports involve toxic doses. [162] The majority of animal and human data indicates that enhancing 5-HT exerts anticonvulsant effects.[148, 163–167] Therapeutic doses of SSRIs used to treat co-morbid depression are well-tolerated in PWE.[168, 254] Increased seizure susceptibility is observed in mice in which 5-HT neurons have been genetically-deleted and mice in which 5-HT has been chemically depleted, as well as genetic deletion of a specific 5-HT receptors.[169, 170] Enhancement of 5-HT neurotransmission plays a major role in the action of the recently approved anticonvulsant drug, fenfluramine.[171–173]

Significant effects of serotonergic agents have been observed in animal models of SUDEP, which support the serotonin hypothesis of SUDEP. The effects of serotonin on respiration and seizures suggest that drugs that enhance the effects of 5-HT might be useful in SUDEP prevention. This led to the treatment of DBA/2 mice with an SSRI, fluoxetine, which selectively blocked S-IRA in doses that did not block tonic hindlimb extension (TLE) convulsions, the most severe seizure behavior seen in AGSz.[79] Thus, despite the finding that the severity of the convulsion was unchanged, respiratory arrest was selectively blocked. Similar doses of fluoxetine had been shown to induce significant elevations in serotonin levels in the rodent brain.[174] Furthermore, a non-selective 5-HT receptor antagonist induces reversible susceptibility to S-IRA in the ~15% of DBA/2 mice that previously exhibited TLE convulsions without S-IRA.[79] These findings in DBA/2 mice were followed by the discovery that a related mouse strain, primed DBA/1 mice, was an even more useful SUDEP model.[18, 19, 74] S-IRA susceptibility in DBA/1 mice is also selectively prevented by SSRIs and enhanced by a non-selective 5-HT antagonist.[18, 19, 175] The ability of the SSRIs to inhibit S-IRA in DBA/1 and DBA/2 mice is likely due to increased availability of 5-HT, since respiratory stimulant drugs that do not affect 5-HT availability also do not block S-IRA in DBA/1 mice.[176]

Susceptibility of DBA mice to S-IRA may be due, in part, to a genetic deficiency in the 5-HT system, including specific 5-HT receptor subtypes expression abnormalities and reduced levels of the 5-HT synthesizing enzyme tryptophan hydroxylase (2 (TPH2).[177–179] A reduced level of TPH2 can be induced in DBA/1 mice by priming.[78] The precursor of 5-HT biosynthesis (5-hydroxytryptamine, 5-HTP) or a high tryptophan diet have also been shown to reduce S-IRA susceptibility in DBA/1 mice.[78, 180] The idea that seizure and S-IRA susceptibility are related to deficits in the action of 5-HT is supported by the 5-HT_{2c} knockout mice, which develop susceptibility to AGSz and S-IRA, following repeated auditory stimulation.[169, 181] A number of drugs that enhance the action of 5-HT have been shown to selectively block S-IRA in the DBA/1 mouse model of SUDEP. These drugs include several other SSRIs and the 5-HT releasing drug, fenfluramine, as well as a selective 5-HT_4 agonist.[75, 172, 175, 182–184] Mice in which 5-HT neurons were genetically deleted exhibit increased seizure-induced mortality following drug- and electroshock (ES)-induced GTC seizures, and administration of agents that enhance 5-HT action prior to ES prevents death in these mice.[148] Pharmacologically-induced depletion of 5-HT in normal mice results in elevated ES-induced death due to respiratory depression, whereas an SSRI and a selective 5-HT agonist increases ES seizure survival.[148] Dravet syndrome is a rare form of epilepsy mediated by genetic abnormalities of the sodium channel that has a very high incidence of SUDEP,[185] and a 5-HT_{1D} agonist increases the threshold of hyperthermia-induced seizure and lowers seizure severity in a Dravet mouse model of SUDEP.[186] The effect of the 5-HT releasing drug, fenfluramine, on S-IRA is primarily on 5-HT_4 receptors, and a selective 5-HT_4 agonist (BIMU-8) also blocks S-IRA in DBA/1 mice.[184] On the other hand, the effect of the SSRI, fluoxetine, appears to involve an action on 5-HT_3 receptors.[187] This difference may be due to the differential localization in the synapse of the 5-HT receptors on which these drugs act. There is also evidence for the involvement of the raphe nuclei, the main neuronal source of 5-HT, in SUDEP as discussed below. The prevention of seizure-induced death by serotonergic agents in DBA mice and other SUDEP models has been proposed to involve a selective dose-related action on the brainstem structures that control respiration and initiate the RRRs.[188] These restorative mechanisms are critical in reversing hypoxia, and serotonin plays an important role in this process.[64–66, 71] Taken together, these findings in animal models support that 5-HT and administration of drugs that enhance its action can potentially contribute to SUDEP prevention.

Clinical evidence supporting the serotonin hypothesis of SUDEP has been developed recently. As noted above, postictal respiratory depression is a common event in PWE, and death was precipitated by respiratory failure in most witnessed cases of human SUDEP. Co-morbid major depressive disorder is commonly observed in PWE, and a number of PWE have been treated with antidepressant drugs that enhance the action of 5-HT.[189] These findings led to the evaluation of clinical evidence regarding the effects of modifying 5-HT action on post-ictal depression in PWE. The retrospective clinical study of Bateman and colleagues[190] showed that the degree of postictal respiratory depression in PWE who were taking SSRIs was significantly less than that in PWE who were not taking these drugs. Importantly, this effect was subsequently observed in prospective studies.[191] In addition, significant postictal increases in plasma 5-HT levels in PWE are observed, and the level of 5-HT increase is negatively correlated with the duration of post-convulsive central apnea

and PGES.[192, 193] These findings indicate an inverse relationship between plasma 5-HT levels and seizure-induced respiratory depression. Reduced numbers of serotonergic neurons in the brainstem and diminished levels of the 5-HT synthesizing enzyme in the raphe nuclei are observed postmortem in SUDEP cases.[89, 194] Elevations of specific 5-HT receptor proteins were recently observed to correlate with the duration of PGES in PWE.[195] These clinical findings continue to support the serotonin hypothesis of SUDEP. Specific subcortical structures are implicated as being involved in the effect of 5-HT on respiration, including the raphe nuclei, amygdala, and periaqueductal gray, as discussed below.

6. Brain structures implicated in SUDEP

Brain structures involved in SUDEP have been investigated in animal models and to a lesser extent in clinical cases. As noted above, normal central control of respiratory function involves brain structures, including specific nuclei in the brainstem and hypothalamus.[24, 25, 28] Neurochemical, anatomical and neuroimaging studies implicate the RVLM and certain cortical sites as potentially playing roles in SUDEP.[196–198] Certain other structures, including the amygdala, raphe nuclei and periaqueductal gray (PAG), exert significant influences on respiration, especially under exigent conditions, including seizures, and abnormal function of these structures may be critical in SUDEP. A recent proteomic study observed differential expression of several proteins in the RVLM and raphe in SUDEP cases as compared to non-SUDEP cases.[199] Since the RVLM is an essential structure in the central control of respiration under normal conditions,[156] these other structures may affect respiration via actions on the brainstem respiratory network, including the RVLM.[200]

AMYGDALA

Evidence for a role of the amygdala in respiratory control has been observed in animals and PWE. In mice the RVLM receives direct input from the amygdala, supporting a potential role of this structure in control of breathing.[157, 201, 202] A study in rats indicated that inhibition of the amygdala suppresses respiratory rate increases induced by alerting stimuli.[203] Functional neuroimaging using manganese-enhanced magnetic resonance imaging (MEMRI) in DBA/1 mice show that significant increases in amygdala neural activity occurs in association with S-IRA.[197] Electrolytic lesions of the amygdala in DBA/1 mice significantly reduces the incidence of S-IRA without altering seizures, baseline breathing, or the hypercapnic ventilatory response,[204] suggesting that activation of the amygdala may be involved in triggering S-IRA. A recent study in DBA/1 mice also implicated an extended amygdalar structure, the dorsal bed nucleus of the stria terminalis, in S-IRA, and disruption of this region reduces S-IRA and also results in changes in the balance of excitatory/inhibitory synaptic events of specific brainstem areas, including the PAG.[205] Human studies have provided evidence for a role of the amygdala in seizure-related apnea in PWE. Thus, spread of ictal activity to the amygdala is associated with the onset of apnea, and stimulation of the amygdala induces apnea in PWE.[206–212] These findings suggest a possible role of the amygdala in inducing apnea in SUDEP cases. However, seizure-related apneas are also reported to have an inconsistent linkage to amygdala seizure spread in a recent patient study.[213] Clearly, more research is needed to clarify the role of the amygdala in SUDEP.

RAPHE NUCLEI

As noted above, the brainstem raphe nuclei synthesize, store, and release 5-HT, and during seizures this release is greatly increased. These brainstem serotonergic neurons are involved in response to external stressors, including elevated blood CO_2 levels.[25] Increases in blood CO_2 lead to increased release of 5-HT by the raphe nuclei, which enhances respiratory network activity and arousal both of which act to stimulate breathing postictally, contributing to the restorative respiratory mechanisms.[41, 214] Functional neuroimaging studies in DBA/1 mice observed significant increases in neural activity following S-IRA in several raphe nuclei.[197] The increased activation of these raphe nuclei provides evidence for increased central release of 5-HT due to seizures. Optogenetic stimulation of the dorsal or magnus raphe nuclei in DBA/1 mice selectively activates 5-HT neurons and significantly and reversibly reduces the incidence of S-IRA induced by AGSz.[215, 216] This stimulation approach also reduces S-IRA induced by a convulsant drug (pentylenetetrazol). The S-IRA-suppressing effect of optogenetic stimulation is facilitated by administration of the 5-HT precursor (5-HTP) and is reversed by a selective 5-HT_3 receptor antagonist, indicating that reduction of S-IRA by this optogenetic stimulation is specifically mediated by enhanced 5-HT neurotransmission.[215, 216] Optogenetic stimulation of the dorsal raphe or administration of an SSRI in electrically kindled mice also reduces PGES.[217] As noted above, the raphe nuclei provide the major 5-HT input to the brain, which is mediated via both synaptic and volume transmission onto many brain structures, importantly including the adjacent periaqueductal gray.

Periaqueductal Gray

The periaqueductal gray (PAG) is strongly implicated in enhancement of respiratory function and arousal in humans and animals[218–220] and has been suggested to function as a central “suffocation alarm.”[221] This action is mediated by its projections to the hypothalamus and RVLM that are involved in control of respiration.[157, 210, 218, 219, 222, 223] The PAG plays an important restorative role to compensate for respiratory distress and in other exigent behavioral situations that require enhanced respiration and arousal; electrical or glutamatergic stimulation of the PAG will result in increases in respiration.[220, 224–227] There are anatomical connections between the PAG, amygdala and dorsal raphe, and PAG neurons express several 5-HT receptor subtypes.[228, 229] Functional neuroimaging studies show significantly elevated postictal PAG neural activity in DBA/1 mice.[197] A recent study in DBA/1 mice also found elevated seizure-induced c-Fos expression in the PAG.[205] This evidence of increased seizure-induced PAG activation is consistent with the high frequency PAG neuronal firing seen during seizures in rat AGSz models.[230, 231] This increase in PAG neuronal firing undergoes an additional significant firing increase after repetitive seizures in an AGSz kindling protocol.[232] These rat AGSz models also exhibit non-lethal postictal respiratory deficits.[124, 233] However, in DBA/1 mice the putative PAG-mediated autoresuscitation and the other RRRs triggered by S-IRA are clearly unsuccessful, since these seizures are lethal.[197] Support for this hypothesis is the reduced effectiveness of PAG stimulation to enhance respiration in DBA/1 mice.[83] Thus, electrical stimulation in the PAG of anesthetized DBA/1 and non-epileptic mice induces significant post-stimulus intensity-related increases in respiration. However, the effectiveness of this stimulation is significantly reduced in DBA/1 mice as compared to non-epileptic mice. The increase in

respiration remained significant for at least 10 seconds,[83] which is the critical period during which mechanical resuscitation can readily reverse S-IRA and prevent seizure-induced death in DBA/1 mice.[18, 19] 5-HT-mediated or electrical stimulation approaches that enhance PAG activity may be able to trigger the RRRs and overcome the apnea.[83, 188] In another form of sudden death, sudden infant death syndrome, hypoplasia of the PAG is observed that is suggested to contribute to this syndrome.[234] Thus, research to date suggests that the amygdala may contribute to induction of seizure-induced respiratory depression, the raphe nuclei release 5-HT in response to the resulting elevated blood CO_2 levels, and the 5-HT enhances PAG activity making a critical contribution to autoresuscitation and the other RRRs.

Human neuroimaging changes in SUDEP

Retrospective analyses of human neuroimaging studies suggests the involvement of subcortical structures in PWE who subsequently succumb to SUDEP. These studies observed MRI evidence of atrophy of the PAG and raphe nuclei among other sites in PWE, who died from SUDEP.[235–240] A recent PET scan study in PWE who exhibited a high frequency of focal to bilateral tonic-clonic seizures and are proposed to be at high risk for SUDEP, observed that several structures, including the PAG, exhibited significant metabolism increases interictally, as compared to a low risk patient group.[241] The authors suggest that these findings may actually be indicative of loss of neuronal function, gliosis and/or active inflammatory responses.

7. SUDEP and Brainstem Atrophy

The atrophy observed in specific brainstem sites, including the PAG, in SUDEP cases is hypothesized to involve cellular damage due, in part, to excitotoxicity that results from the frequent seizures that pre-dispose to SUDEP.[235, 236] Intense PAG neuronal firing is seen during audiogenic seizures in other rodent models[230, 231] and during S-IRA in DBA/1 mice.[188, 197] We hypothesize that respiratory deficits induced by frequent intractable seizures associated with SUDEP[3, 4, 49] trigger frequent RRRs that involve the repeated release of glutamate[242–244] onto PAG neurons, and this can result in cellular excitotoxicity. The excitotoxic damage leads to neuronal loss in the PAG and the other brain sites at which atrophy is seen in SUDEP cases.[90, 91, 235, 236, 240, 245] Atrophy in the PAG may, in turn, result in diminished subsequent effectiveness of the RRRs initiated by this structure and predispose to SUDEP susceptibility. Support for the hypothesis of diminished PAG effectiveness in SUDEP is the reduced effectiveness of electrical stimulation in PAG to enhance respiration in DBA/1 mice that had experienced repetitive seizures, as compared to non-epileptic mice.[83]

8. Brain structures critical to serotonergic prevention of seizure-induced death

Functional neuroimaging in DBA/1 mice has shed further light on the brain structures important to serotonergic prevention of seizure-induced death. This approach provided further evidence that specific brain structures may play critical roles in the terminal

respiratory depression in this animal model of SUDEP.[197] The effects on neural activity of an SSRI (fluoxetine) were also evaluated in DBA/1 mice using neuroimaging.[188] The fluoxetine dose used blocked seizure-induced S-IRA, but did not block TLE convulsions.[18] Extensive fluoxetine-mediated changes are observed in several brain structures, including the amygdala, specific raphe nuclei and PAG. The activity in these structures was significantly increased in SSRI-treated mice that exhibit seizure, without S-IRA, as compared to vehicle-treated mice which exhibit both seizure0 and S-IRA. However, SSRI treatment without seizure induction do not significantly increase neural activity in the PAG or the pontine raphe nucleus, suggesting that these structures are critical targets for fluoxetine prevention of S-IRA. This hypothesis is consistent with the role played by the PAG in the restorative respiratory response mechanisms, discussed above. These findings are also consistent with previous observations that an SSRI enhanced respiration in DBA/1 mice but only after seizure was induced.[246] In light of the significantly reduced effectiveness of PAG electrical stimulation in DBA/1 mice to enhance respiration,[83] the ability of fluoxetine to enhance PAG neural activity may make a critical contribution to the ability of this 5-HT-enhancing agent to block S-IRA. These changes in PAG and pontine raphe neural activity contrast with the amygdala changes. Although amygdala neural activity is increased by fluoxetine, no significant SSRI-induced differences were observed in mice that undergo seizures and those that do not. These findings suggest that the effect of the drug on amygdala may not be related to blockade of S-IRA, and the SSRI-induced increases may be related to the role of serotonin in emotion processing by this structure.[247]

9. Unified hypothesis of SUDEP

This review proposes a unifying hypothesis of SUDEP is as follows. Seizure-induced respiratory depression that results in apnea, which is mediated, in part, by elevated adenosine levels normally triggers autoresuscitation and the other restorative respiratory responses that are mediated by elevated serotonin release, which activates the PAG. If these restorative response mechanisms are not sufficient to overcome the apnea, it results in SUDEP. This hypothesis is based on the findings outlined above that many seizures induce respiratory depression, and the witnessed SUDEP cases have identified seizure-induced respiratory failure as the major mechanism of pathogenesis, which led to the proposal that postictal respiratory depression may actually be a biomarker for SUDEP risk.[44, 45] This unified hypothesis is based on the large increase in adenosine release during seizures that makes a major contribution to the postictal respiratory depression, which occurs in an estimated ~50% of seizures.[41] Fortunately, SUDEP occurs only once out of thousands of seizures, and the reason for this fortuitously low incidence of SUDEP may be due to innate restorative response mechanisms. These mechanisms include the postictal rise of serotonin levels, which acts to enhance respiration in response to hypoxia and activation of the PAG and enhances respiration in this exigent situation. If these restorative response mechanisms are not sufficient due, in part, to previous neuronal loss in critical brain regions, which act to restore normal breathing, especially the PAG, and/or physical impediments to respiration, it will result in SUDEP. This hypothesis suggests potential therapeutic approaches to SUDEP prevention.

10. Future SUDEP preventative approaches

The main purpose of this review is to propose preventative measures for SUDEP based on the unifying hypothesis. Improving antiepileptic treatment, nocturnal supervision, and use of nocturnal listening device are all proposed to be protective measures,[10] but additional approaches are urgently needed to reduce SUDEP mortality. Since SUDEP is unexpected, the development of bio-markers is critical. A recent proposal has been made to evaluate the risk called the SUDEP-3, which is a revised version of the SUDEP-7 list, and is based, in part, on seizure frequency and intellectual disability.[248] Biomarkers for SUDEP susceptibility have been proposed based on the degree of postictal respiratory depression or cardiac abnormalities or duration of PGES.[21, 39, 43–45, 249, 250] Genomic biomarkers have also been proposed.[251] Another recent criterion for SUDEP susceptibility based on the relatively high frequency of focal to bilateral tonic-clonic seizure occurrence in PWE.[241] An automated approach to SUDEP prevention, involving medical intervention to be administered via an implanted device automatically delivering electrical stimulation or medication, has recently been proposed,[252] and a peripheral approach using diaphragmatic pacing in a sudden model has recently been published.[253]

Once criteria for SUDEP susceptibility are validated, preventative approaches should be employed. In specific forms of epilepsy that have a high incidence of SUDEP, preventative measures should be strongly considered currently. Based on the adenosine hypothesis, adenosine antagonists, which reduce seizure-induced deaths in certain animal models could be considered. However, these agents may be counterproductive, because the postictal adenosine rise exerts anticonvulsant effects and in higher doses these antagonists are pro-convulsant. A recent report suggests that an A_{2A} antagonist might be useful.[120] Based on the serotonin hypothesis, drugs that enhance the action of serotonin should be strongly considered. SSRIs, such as fluoxetine, work well in SUDEP models, and PWE treated with these drugs for comorbid depression have a lower degree of postictal respiratory depression than PWE not taking these agents.[191] A pilot study for a clinical trial to evaluate the action of fluoxetine on respiratory function in patients with epilepsy has recently been published.[254] Fenfluramine is a recently approved anticonvulsant drug for Lennox-Gastaut and Dravet syndrome that enhances serotonin availability by a different mechanism and may be worthy of consideration.[172, 184] Another possible approach to SUDEP prevention would involve electrical stimulation of the PAG, which plays such an important role in autoresuscitation and the other RRRs. Thus, implantation of a stimulating electrode into the PAG, which is known to enhance respiration, coupled with a seizure-reactive stimulation device may be a worthwhile possibility. Electrode implantation and stimulation in the human PAG is currently used to treat certain conditions, including chronic pain, and it has been reported to increase respiratory rate as well as increase heart rate variability in patients,[255–260] as it does in normal and epileptic animals.[83]

Based on the loss of volume of brain structures in SUDEP cases, another possible approach to SUDEP prevention may be the postictal administration of drugs that reduce excitotoxicity, which may contribute to these atrophic changes. Glutamate receptor antagonists have been shown to reduce the deleterious consequences of spreading depolarization and block excitotoxicity.[261, 262] In light of the progressive increase in duration of periictal

respiratory dysfunction in PWE,[27] an intervention to block this increase, based on inhibiting excitotoxicity may be useful. Thus, in PWE who frequently exhibit a SUDEP biomarker, such as postictal apnea,[45] the postictal administration by the patient or a caregiver of an agent that blocks excitatory amino acid receptors soon after an apnea might be able to reduce or prevent further excitotoxic damage and reduce SUDEP susceptibility. For example, a wearable pulse oximeter could potentially be programmed to detect a low oxygen saturation level and sound an alarm, and this would signal the caregiver to administer a nasal solution of an excitatory amino antagonist, much like the approach currently available to treat serial seizures in PWE. This approach will require validation in animal models first.

Hopefully, one or more of these approaches individually or in combination will help to reduce the loss of life to SUDEP. Some of these approaches, such as evaluating the SUDEP rates in Dravet syndrome PWE, who have a high incidence of SUDEP, as noted above, could be evaluated currently. Fenfluramine is approved to treat this syndrome, and a comparison of the incidence of post-ictal apnea and the incidence of SUDEP in PWE treated with this drug as compared to other treatments may be instructive. Studies in other PWE who exhibit a biomarker indicative of an elevated susceptibility to SUDEP, such as a high incidence of post-ictal apnea,[45] may also be warranted. Specific patient characteristics, such as age, environment and other co-morbidities, may indicate that one or more of the preventative measures, suggested above, may be more useful in an individual PWE to prevent premature death from SUDEP.

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Key Points

- Most human SUDEP cases exhibit terminal postictal apnea, and useful SUDEP models, including DBA/1 mice, exhibit this phenomenon
- Adenosine released by seizures is implicated in apnea induction
- Seizure-induced release of serotonin is implicated in autoresuscitation and reversal of apnea
- Drugs that enhance serotoninergic activity have the potential to prevent SUDEP
- Specific brain structures, including the periaqueductal gray, modulate apnea cessation and PAG activation may prevent SUDEP

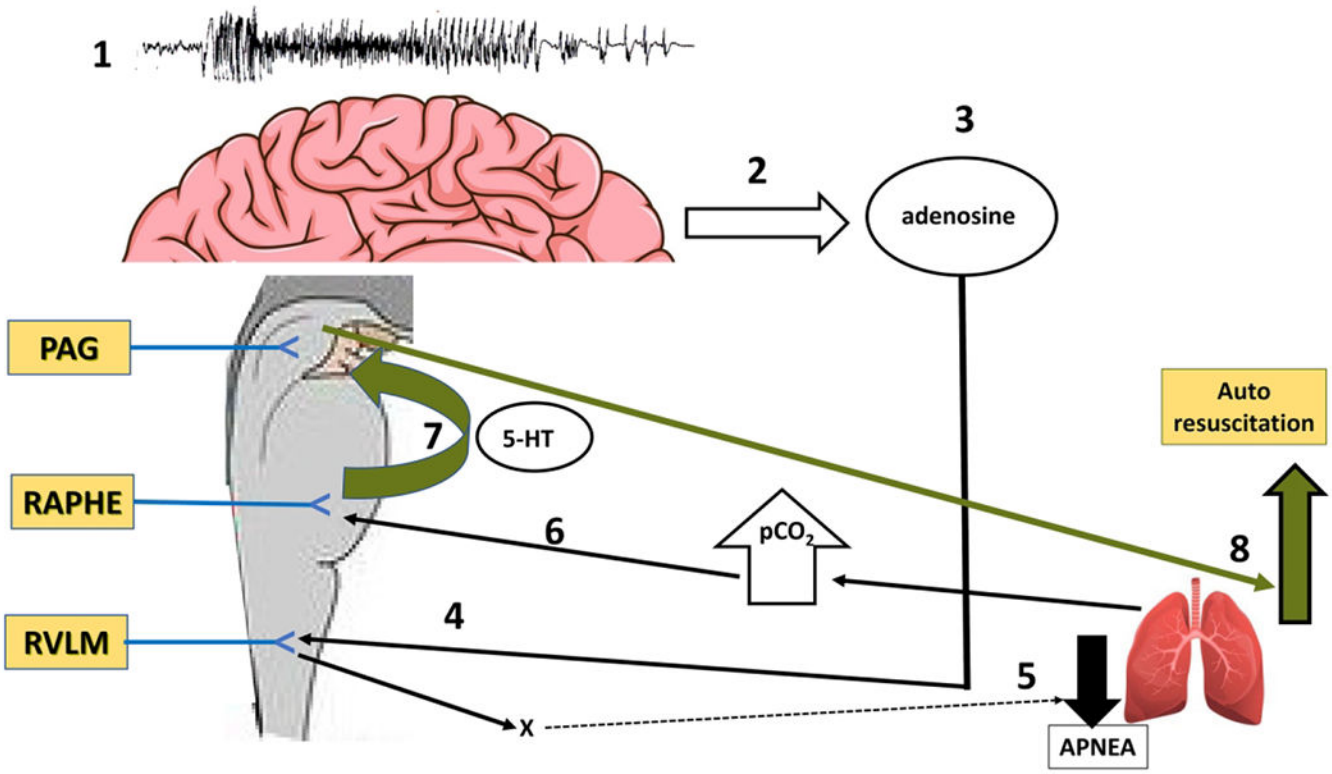

Fig. 1.

A generalized tonic-clonic seizure (1) causes release of neuroactive substances (2), including adenosine (3). Adenosine induces respiratory depression by actions on the neurons in the rostral ventral lateral medulla (RVLM) (4), which in turn diminishes the central drive to the lungs and causes apnea (5). The apnea causes elevated pCO_2, which activates raphe neurons (6) to increase the release of serotonin (5-HT), which activates periaqueductal gray (PAG) neurons (7). PAG activation triggers autoresuscitation and other restorative respiratory responses mechanisms (8). If these mechanisms are not sufficient to overcome the apnea, it results in SUDEP. Enhancement of PAG neuronal activation by exogenous agents that increase the action of 5-HT may prevent SUDEP.