Brainstem spreading depolarization: rapid descent into the shadow of SUDEP

This scientific commentary refers to 'Brainstem spreading depolarization and cortical dynamics during fatal seizures in *Cacna1a* S218L mice' by Loonen *et al.* (doi:10.1093/brain/awy325).

In less than a decade, sudden unexpected death in epilepsy (SUDEP) has risen from a mysterious fate awaiting nearly 5% of persons with uncontrolled epilepsy to an individually diagnosable risk with known genes and a convincing mechanism, at least in animal models. SUDEP is the most common cause of premature mortality in a disease affecting nearly 50 million people of all ages worldwide, and second only to stroke in the number of life years lost (Thurman *et al.*, 2017). Increasing public awareness and a research consortium (Lhatoo *et al.*, 2015) have fuelled a race to move beyond epidemiological studies to understand precisely who is at risk and whether effective interventions can be developed. In this issue of *Brain*, Loonen and co-workers add a new mouse model to the growing genetic landscape of SUDEP and, through MRI, provide further evidence to support a convergent mechanism that centres on pathological depolarization in the brainstem (Loonen *et al.*, 2019).

An early breakthrough in identifying a biomarker of SUDEP risk came from discoveries linking long QT interval cardiac arrhythmias and sudden nocturnal death—then presumed to be of purely coronary origin—to a mutation in the 'cardiac' voltage-gated sodium ion channel SCN5A responsible for Brugada syndrome. The link between brain and heart became clear when *SCN5A* transcripts were detected in limbic circuitry of the temporal lobe, a site vulnerable to seizures (Hartmann *et al.*, 1999). Goldman *et al.* (2009) then developed the first monogenic mouse model of SUDEP by showing that *Kcnq1*, a potassium channel gene implicated in the most common and potentially fatal human long QT syndrome (LQT1), is widely expressed in mouse brain, and that mice with human LQT1 mutations in *Kcnq1* are vulnerable to seizures and sudden death. The realization that a substantial proportion of human carriers of LQT syndrome genes show co-existing epilepsy (Anderson *et al.*, 2014), and that channels for a variety of other cardiac arrhythmias are also expressed in the brain, opened the door to a trove of genes with comorbid brain-heart excitability phenotypes as novel gene candidates for ascertaining personal SUDEP risk.

Nevertheless, a major dilemma remained. How do carriers of lethal SUDEP mutations survive many years of seizures, and what prompts the final seizure to be the last? This question focused attention on events surrounding the actual moment of death. In comparison to 'ictal asystole', the sudden but reversible cessation of the heartbeat during a seizure (Cole *et al.*, 2013), SUDEP is more complicated. Death in monitored cases predictably occurs between 2–15 min after cortical seizure activity has terminated. It follows a brief, reproducible pattern of progressive autonomic collapse, featuring apnoeas and asystoles, descending rapidly into profound slowing of respiratory and heart rate, and finally cardiorespiratory arrest (Ryvlin *et al.*, 2013). Channel gene defects that impair baseline respiratory and cardiac pacemaking function between and even during seizures may therefore abet, but not directly explain, the lethality of the final seizure. Furthermore, in both humans and mice, not all SUDEP mutation carriers die prematurely, suggesting a second conditional threshold must be crossed.

The evidence for this 'second hit' hypothesis came from an unrelated pathogenic event linked not to cardiac rhythms but to the aura of migraine, based on the known ability of spreading depolarization to abruptly silence neural circuits (Pietrobon and Moskowitz, 2014). Aiba and colleagues found that mice with SUDEP mutations displayed spreading depolarization in the dorsal medulla within minutes following a terminal cortical seizure. All SUDEP mice that developed post-seizure spreading depolarization in the medulla died, whereas seizures in wild-type mice did not trigger brainstem spreading depolarization and the mice always recovered. In addition, the threshold for triggering spreading depolarization in *ex vivo* slices of medulla by reducing oxygen and glucose in the bath solution was dramatically lower in three mouse SUDEP models compared with their unaffected littermates (Aiba and Noebels, 2015; Aiba *et al.*, 2016). The genes involved were *KCNA1*, a potassium channel implicated in temporal lobe epilepsy; *SCN1A*, the sodium channel gene linked to Dravet syndrome epileptic encephalopathy; and *RYR2*, the 'leaky' ryanodine receptor linked to catecholaminergic polymorphic ventricular tachycardia: three disorders with risk of premature mortality.

Loonen *et al.* are part of the Leiden group, who pioneered genetic identification of the migraine with aura syndrome, familial hemiplegic migraine (FHM1). The first gene implicated in FHM proved to be *CACNA1A*, which encodes the pore-forming subunit of the P/Q voltage-gated calcium channel, and the results support brainstem spreading depolarization as a convergent proximate cause of SUDEP in the current gene model.

In previous work, several labs demonstrated that a gain of function mutation (S218L) in *CACNA1A*

enhances calcium current related to synaptic glutamate release, and lowers the threshold to trigger cortical spreading depolarization. Once initiated, spreading depolarization may descend subcortically into basal ganglia circuitry, provoking transient hemiparesis. Behavioural seizures with atypical cortical EEG suppression and premature death are also features of this model. Here, Loonen *et al.* add indirect but convincing evidence that pathological depolarization appears in the lower brainstem following a seizure using a rapid diffusion weighted imaging (DWI) protocol (Cain *et al.*, 2017). This signal tracks the slowly propagating abnormal haemodynamics and cellular oedema that correlate with neural silencing during spreading depolarization both in human and mouse migraine aura. As in the prior SUDEP models, death followed a seizure with the expected pattern of respiratory and central autonomic cardiac shutdown. Following electrical stimulation of sensorimotor cortex, the DWI signal spread transversely away from the stimulation site; in four mice, spreading depolarization descended into subcortical brain regions and appeared in lower brainstem, resulting in death. In contrast, 15 mice showing spreading depolarization only in cortex and subcortical forebrain, but not brainstem, all survived.

The precise origin of spreading depolarization onset within the brainstem could not be precisely ascertained by MRI. Loonen *et al.* point out that the 8-s time resolution of image capture precludes tracking the exact spatiotemporal sequence of spreading depolarization spread and serial functional silencing of cardiorespiratory nuclei in the small mouse brainstem. The appearance of brainstem spreading depolarization was rapid (34 s) compared with the standard propagation speed of spreading depolarization in brain tissue (~2–5 mm/min). Thus, it remains unclear whether the malignant depolarization propagated caudally from forebrain in a continuous manner or arose *de novo* in multifocal networks driven by corticofugal synaptic activation, vascular insufficiency or regional metabolic differences. As previously noted in other mouse models, respiratory rhythmicity failed slightly before the final heartbeat, suggesting that pontine respiratory nuclei might be the first to succumb to the depolarizing wave, followed by depolarization of vagal output in the lower medulla. This clinical pattern mirrors that reported in human SUDEP cases during in hospital epilepsy monitoring, although respirations were only detected by inspection of chest wall movements in supine patients videorecorded from a distance, which may not reveal shallow breathing. While the low threshold for brainstem depolarization is similar across the mouse models, the P/Q gain of function mutation model, like every genetic model of epilepsy, shows its own idiosyncrasies. For example, fatal behavioural seizures were marked by electrographical depression of cortical EEG rhythms and reduced neuronal firing, rather than high amplitude hypersynchronous network activity seen in human SUDEP seizures. The behavioural clonic motor seizure is also at odds with the pathognomonic hemiplegia characteristic of spreading depolarization in FHM1.

The importance of the Loonen study lies in the continuing convergence of FHM and SUDEP genes with brainstem spreading depolarization and sudden death. What we now appreciate is that different risk genes for SUDEP carry different comorbid phenotypes. Given their distinct underlying biology, gene-specific intervention strategies may ultimately require personalized seizure therapies. However, if brainstem spreading depolarization threshold proves to be a final common path to the sudden death phenotype, raising this threshold or abbreviating the depolarizing wave may be effective strategies regardless of molecular aetiology. More research on prophylactic and abortive spreading depolarization interventions is needed, and may lead to life-saving measures in persons with epilepsy and potentially other conditions associated with sudden death.

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Competing interests

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Remyelination: a good neuroprotective strategy for preventing axonal degeneration?

This scientific commentary refers to 'Demyelination precedes axonal loss in the transneuronal spread of human neurodegenerative disease', by You *et al.* (doi:10.1093/brain/awy338).

Although the study of neurodegenerative disease has traditionally focused on neuronal damage, over the past decade there has been an explosion of interest in glial cells, among them the oligodendrocytes that produce the myelin sheath. Myelin, in addition to its role in increasing action potential conduction velocity, is critical for establishing proper connections within neural circuits. It also provides trophic support to the axon—as part of the axon-myelin unit (Stassart *et al.*, 2018)—and contributes to brain plasticity and learning (Nave and Werner, 2014). However, myelin is highly susceptible to damage as a result of ischaemic, toxic and inflammatory insults, or secondary to axonal damage (Ferrer, 2018). In this issue of *Brain*, You and co-workers provide further evidence of demyelination in patients with glaucoma or multiple sclerosis, as well as evidence to support the role of trans-synaptic degeneration as a mechanism driving neurodegeneration, both concepts with strong therapeutic implications (You *et al.*, 2019).

You *et al.* conducted quantitative brain MRI and visual evoked potential (VEP) studies to assess the integrity of the posterior visual pathway (optic radiations) by monitoring the presence of demyelination (defined by the combination of delayed VEP latencies and increased radial diffusivity on MRI) and/or axonal loss (amplitude reduction of VEP or increased axial diffusivity on MRI). They analysed the contribution of trans-synaptic axonal degeneration to the degenerative process and the balance between myelin and axonal damage. Trans-synaptic degeneration is a process that spreads damage from the site of injury to the projecting neurons, in a domino-like cascade (Gabilondo *et al.*, 2014). It contributes to the damage to the visual pathway observed in association with various aetiologies, including multiple sclerosis and glaucoma. By focusing on the visual pathway, You *et al.* were able to take advantage of its retinotopic organization and of its close, monosynaptic, relationship to the retina, which allowed them to disentangle the different biological processes. They reported the presence of demyelination prior to trans-synaptic degeneration in the visual pathway, and validated this finding in a longitudinal cohort of patients with multiple sclerosis using diffusion tensor imaging (DTI). Finally, in a rodent model of traumatic optic neuropathy, they revealed demyelination and the presence of macrophages phagocytizing myelin in the optic radiations, again before axonal degeneration—as revealed by accumulation of axonal amyloid precursor protein—was established.

You *et al.* propose that myelin is sensitive to axonal degeneration, and that when the axon-myelin unit is disturbed by the spread of neurodegeneration, damage to myelin occurs before the axons are entirely disrupted. This sequence of events has long been anticipated in multiple sclerosis, a prototypical demyelinating disease, but it was unexpected in a neurodegenerative disease like glaucoma (although the extension of damage from the retina to the cortex has been recognized for years). Moreover, demyelination has also been observed in neurodegenerative diseases such as Alzheimer's disease, in the form of diffuse white matter damage, and in multiple system atrophy as revealed by the accumulation of toxic α-synuclein deposits in oligodendrocytes (Ferrer, 2018).

Demyelination is a dynamic process, which can be efficiently reversed—at least in young adults—through remyelination by surviving oligodendrocytes or by new oligodendrocytes formed by the differentiation of oligodendrocyte precursors (Kutzelnigg and Lassmann, 2014; Plemel *et al.*, 2017). Therefore, the critical question for neurology is whether preventing demyelination or promoting remyelination might be a feasible neuroprotective strategy to