Published in final edited form as:

Brain Res. 2019 January 15; 1703: 1–2. doi:10.1016/j.brainres.2018.09.035.

Challenging spontaneity: Do seizures really arise out of thin air?

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Many examples in the literature underscore the link between ion channels and epilepsy, a disease characterized by excessive, hypersynchronous neural activity. Indeed, the term *channelopathy* is closely associated with many epilepsy syndromes. In most cases, however, a dysregulated and invariable state of heightened membrane excitability, as might result from an ion channel mutation, likely does not by itself directly translate into seizures. If such mutations provided the sole precipitating, seizure-generating cause, then one might expect the epileptic brain to exist in a perpetual state of seizure; in reality, seizures are often relatively rare events that appear to spontaneously arise. What, then, defines when the brain seizes?

Herein we challenge the notion of spontaneous. We advance the argument that seizures are probabilistic events that are dictated by factors – many of them *not* directly associated with ion channels – that are in constant flux in the brain. These factors are often sufficient to sway the fine balance of neural network excitability towards seizure generation or seizure abatement. This is not a new concept. Nonetheless, we attempt to provide support for this argument by reviewing several examples by which seizure probability appears to be strongly modulated by mechanisms not immediately associated with ion channels.

We begin with a clinical perspective on seizure occurrence from Amengual-Gual et al. The authors explain that our need to provide order and understanding to apparently randomly occurring seizures dates as far back as the Babylonians and their attempts to classify epilepsy according to the time of day. In the ensuing 4000 years, we have learned quite a bit more regarding the capacity of environmental cues to modulate the occurrence of seizures. Amengual-Gual et al. review several of these modulating factors, as well as describe how mathematical models are beginning to shed light on the apparent nonrandomness of seizures. As our understanding of such non-randomness becomes more sophisticated, the authors further suggest that we may find ourselves in a better position to optimize chronotherapeutic approaches that aim to synchronize seizure treatment to biological rhythms and disease patterns.

Next, Carl Bazil turns our attention towards the relationship between sleep and epilepsy. Many epilepsy subtypes are regulated by sleep-wake patterns. However, we learn that there exist several seizure syndromes that occur nearly exclusively during sleep, or during sleepwake transitions. The inverse can also be true. For example, focal seizure occurrence is rare during sleep associated with rapid eye movement (REM), suggesting that the REM sleep state can be seizure protective. Thus, in aggregate it is clear that the brain cycles

through seizure-resistant and seizure-permissive states, and that sleep can exert a powerful gate for these state transitions.

Then, Padmanaban et al. review our current understanding of light-triggered seizures. Photosensitive epilepsy, the most common form of reflex epilepsy, is found in 10% of all epileptic adolescents. Indeed, photic stimulation is a well-established trigger of paroxysmal events in the EEG of patients with the genetic generalized epilepsies, and even in a small number of patients with no prior seizure history. Interestingly, this photoparoxysmal response, or PPR, is strongly associated with disorders of GABA inhibition. Padmanaban et al. further describe that the transcranial magnetic stimulation (TMS) threshold to evoke a phosphene, the perception of light in the absence of external stimuli, is significantly reduced in patients with genetic generalized epilepsy. As such PPR is currently being used as a predictable and stable biomarker for anti-epileptic drug screening strategies.

Metabolism can be a powerful regulator of seizures. Masino and Rho provide us with a current understanding of how the ketogenic diet can suppress seizures – even in medically intractable epilepsy patients. Evidence is accumulating that the ketogenic diet promotes metabolic homeostasis and thus lowers the probability (i.e., raises the threshold) of spontaneous seizures arising from an inherently unstable metabolic and neuronal/glia/microvascular network. While the seizure-abating properties of the ketogenic diet are well-established, the mechanism(s) by which seizures are controlled remains a very active area of investigation. Masino and Rho review several current hypotheses regarding the diet's efficacy. The hope remains that identification of one or a few key players in this otherwise demanding therapeutic approach will open the door to treatment strategies with improved patient adherence.

Next, Joshi and Kapur review our current understanding of catamenial epilepsy, a well-established phenomenon in which seizure occurrence is strongly regulated by the female reproductive hormones progesterone and estrogen. Such regulation often results in seizure clustering during specific periods of the menstrual cycle and is most commonly associated with temporal lobe epilepsy. We learn that progesterone is a powerful anticonvulsant, but that tapping into this property to combat seizures is not straightforward; indeed, progesterone-based epilepsy treatments have largely failed in recent, multicenter clinical trials. A better understanding of catamenial epilepsy will likely require a firmer understanding of how progesterone withdrawal triggers seizures.

Finally, Salvati and Beenhakker highlight a well-established, enigmatic connection between respiration and a generalized epilepsy syndrome commonly observed in children. For nearly 100 years, clinicians have reported that seizures are reliably triggered by hyperventilation in an overwhelming majority of patients with absence epilepsy. But how? In their review, Salvati and Beenhakker begin by describing several of the physiological changes that occur in response to hyperventilation. Next, the authors review current models that provide an explanation of how circuits in the brain, particularly those in the cortex and thalamus, generate absence seizures. Finally, the authors seek to identify critical nodes within such circuits that may be sensitive to hyperventilation-induced changes in brain chemistry.

In sum, in this special issue of *Brain Research* we turn our attention towards factors that appear to regulate the timing of seizures. Clearly, in most of the aforementioned examples the conditions are such that by virtue of trauma and/or genetics the brain already has the propensity to seize. But what precipitating events transform propensity into actuality. In some cases, principally photosensitive epilepsy and hyperventilation-associated seizures, the seizure-triggering event is clear. That is, it seems as if these triggers are capable of rapidly and momentarily altering the state of the brain such that seizure-generating circuits are promptly provoked. In other cases, however, the precipitating circumstances are less clear; the brain undoubtedly transitions from seizure-resistant to seizure-permissive states, and back again, but such changes in state occur more slowly and are therefore perhaps more difficult to decipher. Nonetheless, the literature reviews presented herein illustrate that seizures are not strictly spontaneous – external circumstances can regulate their occurrence. Clearly, an underlying epileptic condition must exist, and working to better understand how genetics and/or trauma can cause epilepsy should remain a primary objective of epilepsy research. But to fully understand seizures, it appears equally important to understand how additional factors – sleep, diet, light, menstrual cycle, respiration – have the profound capacity to incite or temper seizure-generating circuits.