

“Kindling”: Origin of Epilepsy?



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Aside from the triggers that may potentially induce an epileptic seizure, very little is actually understood about the origin of the disorder. As a matter of fact, for 70% of all seizure cases, there is no discernable cause even with the most sophisticated equipment (Wikipedia, n.d.). In addition, approximately 20-30% of those who suffer from epilepsy are resistant to drug treatment (Epilepsy Foundation, n.d.). Yet, there is hope in the form of the many dedicated researchers across the globe who are attempting to decipher, through extensive empirical inquiry, the possible mechanisms of causation.

Here at McMaster, Dr. Gautam Ullal is currently researching the kindling phenomenon along with Dr. Ron Racine and Dr. Margaret Fahnstock. Dr. Ullal has spent over a decade in Bangalore investigating the causes of epileptic seizures in manipulating their onset by “kindling”, and how this relates to a unique form of epilepsy: “hot water epilepsy” (HWE) – a potential model for how epilepsy originates. Kindling is the repeated chemical or electrical stimulation of the brain or a particular brain region that eventually leads to seizures. Along with many others, Dr. Ullal believes that “kindling” provides a mechanism by which the actual origins of epilepsy can be viewed. He has also tried to explain the possible mechanism of kindling by using a paradigm of neural-network modelling.

Epilepsy is generally characterized as the suffering of recurrent seizures, temporary or prolonged alterations in electrical brain activity that cause dysfunction in cerebral structures (Wikipedia, n.d.). Seizures come in two forms – focal and generalized. Focal seizures are local to a neural region and may cause abnormal perception (e.g. flashes of light) or aberrant muscle movements. In contrast, generalized seizures actually disrupt cerebral activity in the whole of the cortex. Seizures are further classified as being either simple or complex. Simple seizures are those that do not undermine one’s consciousness, whereas complex seizures directly interrupt it. This does not necessarily mean that a complex seizure will result in fainting and loss of consciousness. A partial complex seizure may simply manifest in the unconscious repetition of speech or motor movements. The terms petit mal and grand mal are used in describing generalized seizures. Petit mal generalized seizures are characterized by a loss

The Truth About Epilepsy

- 181 000 new cases of epilepsy are diagnosed each year
- Incidence is highest under the age of 2 and over 65
- 45 000 children under the age of 15 develop epilepsy each year
- Prevalence of active epilepsy (history of the disorder plus a seizure or use of antiepileptic medicine within the past five years) is estimated as approximately 3 million in the United States
- Prevalence tends to increase with age
- Trend shows decreased incidence in children, but increased incidence in the elderly 50 percent of people with new cases of epilepsy will have generalized onset seizures
(Epilepsy Foundation, n.d.)

of consciousness for up to 30 seconds, along with muscle twitching. Grand mal seizures (or tonic-clonic) involve an initial contraction of the muscles (tonic phase), which may involve tongue biting, urinary incontinence, and the absence of breathing. This is followed by rhythmic muscle contractions (clonic phase). These are also seemingly accompanied by intense visions or hallucinations, often of a mystical or religious nature (Wikipedia, n.d.).

HWE is a type of reflex epilepsy distinguished by seizures that are triggered by stimuli (in contrast to spontaneous seizures). In HWE, seizures are induced by the pouring of hot water within the range of 35 to 50 degrees Celsius over the head during bathing (in many parts of the world, bathing is done by pouring hot water over one’s body rather than bathing in a tub). What is peculiar about this kind of epilepsy is that although cases have been described in the United States, Australia, Canada, UK, Japan, and other places, the majority of HWE are reported in South India (Satishchandra et al., 1998). The significance of this class of seizures is that they initially start as reflex seizures, but ultimately progress into generalized non-reflex (spontaneous) seizures (Satishchandra et al., 1998). Therefore, studying such seizures as precursors to chronic epilepsy have proven quite useful.

Kindling was originally discovered by G.V. Goddard in 1967 at the University of Waterloo. Short electrical bursts were supplied to the brain’s limbic system once a day for a period of time, and though initially no activity was seen, partial focal seizures were the eventual result, followed by clonic seizures (Goddard et al., 1969).

Since then, much work has been done in utilizing kindling and its proposed effects on neural plasticity (the ability of the brain to adapt to change, which provides the foundation for learning and memory), one of the fundamental properties of neurophysiology. Since neural plasticity is a feature considered universal throughout the central nervous system, this suggests that changes

prompted by kindling within one part of the central nervous system may occur throughout the body as well (Sutula, 2004). With this in mind, many have viewed kindling as most notably affecting the neuronal cells of the hippocampus and via a Hebbian Learning mechanism (synaptic strength is increased the more frequently it is active), these cells become altered permanently. This may be the mechanism by which spontaneous seizures are generated. Although kindling-induced alterations are seen most strikingly in the hippocampus and the limbic system, repeated stimulation of the pathways of the limbic, cortex, subcortical and brain stem regions (either chemically or electrically) induces a progressive sequence of long-lasting cellular and molecular alterations at all levels of biological organization in neural circuits, from gene transcription to patterns of neuronal connectivity (Sutula, 2004). Therefore, it can be assumed that seizures have an effect on the entire body, commensurate with the idea of neural plasticity.

For the last ten years Dr. Ullal conducted empirical studies with animal models for HWE- rats that were seizure-prone. In one experiment, he studied the relationship of varying the inter-stimulus interval on progression of seizure (kindling). This progression appeared to be coupled with a rapid increase in temperature within the organism. Ullal and his colleagues suggested that this form of seizure induction was the result of "hyperthermic kindling" (Satishchandra et al., 1998). When comparing this trend in human epileptics, temperature recordings taken from the auditory canal also showed a rapid temperature increase. Furthermore, autopsy studies of patients with HWE also demonstrated pathological changes in the hypothalamus that could be related to a disturbed thermostat mechanism. According to Dr. Ullal, these results were "very exciting", and have since led to further study biochemical and genetic investigations.

The findings of Dr. Ullal and his collaborators are being further validated through other research. Regarding the functional changes Ullal proposes in the temporal lobe, a recurrent pattern in HWE patients' MRIs shows infolding heterotopic gray matter along a cleft in the left temporo-parietal region, as well as other regions where focal seizures occur (Diehl et al., 2003; Lee et al., 2000; Oshiro & Fukushima, 2003). The idea of hyperthermic kindling and the observation that temperature increase is altered in those with HWE have been extrapolated to the function of the blood-brain barrier, where increased permeability to certain proteins, like GLUT-1 (a glucose transporter protein), loss of permeability to other serial proteins, and altered transport of certain ions has been noted in HWE rats (Ilbay et al., 2003). Finally, Dr. Ullal's manipulation of the intervals between seizure induction is proving to be quite valid in terms of whether seizures will progress to

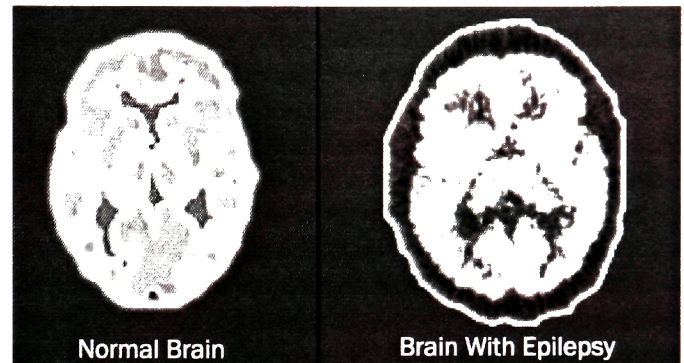


Figure 1: Comparison of a normal brain scan with that of a person with epilepsy (Source: ADEAR)

more complex, spontaneous ones. Though HWE is only one specific type of epilepsy, greater insight will ultimately aid the scientific community in understanding epilepsy in general.

Sutula (2004) notes that inducing seizures with increased frequency actually reduces later seizure activity, something he calls the 'neuroprotective' effect of kindling. Although Goddard (as cited in Sutula, 2004) observed a similar effect. Kindling is only now being understood through complex neural computational models. In a set of collaborated studies, Ullal's group formulates for the first time a computational model for kindling phenomenon (Mehta et al., 1993).

There are still many obstacles to comprehending the "kindling" phenomenon. One of the most perplexing facets of this neurological disorder, as mentioned previously, is that roughly 20-30% of epileptics are drug-resistant. Dr. Ullal believes that this is part of epilepsy's elusive nature, and it is also confirmed in many other studies (Malagon-Valdez, 2004; Stefan, 2004). Even when some researchers believe that they can account for the drug-resistance, their findings prove invalid. A very good example is a paper published by Zimprich and colleagues (2004), claiming to have discovered a gene locus, ABCB1, responsible for the apparent pharmacoresistance many epileptics exhibit. Specifically, they believe that the homozygous halotype of ABCB1 encodes P-glycoprotein, a protein responsible for transporting drugs in the central nervous system, and ultimately leads to a diminished response to epilepsy drug treatment. However, Tan and colleagues (2000) conducted a similar study yielding results inconsistent with Zimprich's findings.

Despite the debate that continues, much more is now known regarding the origins of epilepsy in comparison to the late 1960s when Goddard first uncovered the phenomenon of kindling. While epilepsy remains pharmaceutically untreatable in many patients, with researchers like Dr. Ullal, it is only a matter of time before the origins of this mysterious neurological disorder are revealed, and effective treatments can be administered. **M**