A challenge ahead – improved treatments for epilepsy.

The brain is an amazing organ – billions of individual neurons in constant electrical and chemical communication via trillions of minute connections or synapses. We have discovered much about the repertoire of neurotransmitters and receptors that mediate this nerve communication. We have lists of the ion channel proteins that generate and modulate electrical activity in nerve cells of the brain. We have extensively characterised the intricate properties of many of these ion channels. These are significant accomplishments, 30-40 years of patience and perseverance of many talented and dedicated neuroscientists and biophysicists, and at least 5 Nobel prizes along the way. As a cellular neuroscientist new to epilepsy research, I have been thinking about what all this knowledge about the cellular mechanisms of brain function means for people with epilepsy?

Why do 50 million people worldwide still suffer from the seizures that characterise the disease? People[1] like TColvin (diagnosed age 6, now 21 years old) who laments … " My personal view is that epilepsy is my enemy and I want it blown to smithereens". Or people like Danielle who has been having 2-3 grand mal seizures for the past 6 years and naturally worries about the next one … "I can't remember the last time I fell asleep before 3 a.m (I think this has a little to do with my anxiety? but i'm not sure) and I always wake up in the middle of the night, sometimes with severe anxiety, thinking I am going to have a seizure."

Why can't we develop a drug to free people from seizures once and for all? Why is it, that every ne of the fifty two brands of drugs used for treatment of epileptic seizures has half a dozen side effects[2]. Side effects include dizziness, sedation, sleep disturbance, confusion, nausea, vomiting. Side effects that apparently subside but that still terrify people like KateK … "I am really really scared… I started on a 500 mg dose of Keppra … and I just don't feel right. I'm nauseous all the time, I get night sweats, and don't have any appetite at all...I don't know what to do! My next appt with my doc is in 2 weeks and I don't think I can hold out much longer. This might be worse than the seizures.". Or the continual side effects experienced by "juicy" during a four year treatment protocol "..horribly sore tummy, I couldn't sleep with it, eat with it, I was literally bent over with it……. itchiness, bruising and rash…. but it did eventually go away. They used to make me so tired… Anyway I am now getting double vision which is reallyyy bothering me ….. I have gotten side effects from every tablet I have ever, everrr, taken. What is that about? Am I doomed..If anyone can help I would reeeeeeeeeeeeeally appreciate it.." For some people like "juicy" there may be no side-effect free medications. Furthermore for 30% of epileptics, no medications can completely control seizures. Clearly this is not adequate. We need better medications. Despite intense

efforts by pharmaceutical companies and scientists around the world – we're not there yet. But why not?

The answers lie in the complexity of the brain. The feats the brain can achieve are amazing – somehow co-ordinating the electrical activity of nerves and synapses into networks that enable us not only to see, touch, taste and talk, but also to laugh, to cry, to learn, and the many other behaviours we do throughout our day to day lives. But it's a double edged sword. When these neurons are not correctly co-ordinated, or when they respond inappropriately to some event, then seizures can occur–and this excessive electrical activity may even spread out uncontrolled throughout the whole brain. We just don't know enough about how electrical activity in nerve cells throughout the brain all comes together to mediate these wonderful feats of living, and equally we don't know what exactly goes wrong in these neurons and connections to alter the epileptic brain. The same processes of neuroplasticity that changes our brain chemicals and nerve connections so as to enable us to learn and refine our senses, must surely also cause some of the adaptations in epileptic brains to make it hyperexcitable and prone to seizures. We need to somehow identify underlying mechanisms that cause these plastic changes in response to events that precipitate epilepsy, and figure out how to reverse the changes in the hyperexcitable brain. The current drugs vaguely target (we don't even know their precise actions in most cases) the basics of the building blocks – the ion channels and receptors – and turn them on or off like a sledgehammer. But subtle fine adjustments to and hopefully reverse the mechanisms that cause the hyperexcitability may be more successful.

So a challenge to neuroscientists to continue to investigate the mechanisms of hyperexcitability and to propose new treatment targets. Our current application to the Brain Foundation suggests one such new target. I don't know if this will be the "holy grail", - a better treatments and ultimately a drug that reverses the cause of seizures. But I know we will try our best, and am confident that science, one day, will reach this goal.

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Footnotes:

1. The personnel experiences related in this essay come from recent (June 2012) posts on a discussion board about living with epilepsy and the side effects of medication. (see www.epilepsy.com/discussion/: accessed June between 28-31, 2012)
2. From (http://www.epilepsy.com/EPILEPSY/seizure_medicines; accessed June 29, 2012)