

Transcript of Cerebrum Podcast: A New Approach for Epilepsy

Guest: **Raymond Dingledine**, Ph.D., is professor and chair of the Department of Pharmacology at Emory University School of Medicine. Ray received his Ph.D. in pharmacology under Avram Goldstein at Stanford and postdoctoral training from Leslie Iversen and John Kelly at Cambridge, UK, then Per Andersen at Oslo. His research focuses on the pharmacology of glutamate receptors and on the causes of epilepsy. He serves on the scientific advisory boards of the Epilepsy Project and NeurOp, a biotech start-up he co-founded. He is also chair of the investment committee of the Society for Neuroscience and a member of the National Academy of Medicine.

Guest: **Bjørnar Hassel**, M.D., Ph.D., is a neurologist and a biochemist. He is professor and senior consultant at the University of Oslo, Department of Neurohabilitation. The department serves adults with developmental disabilities, both intellectual and physical. Hassel works with persons who have severe cerebral palsy or profound intellectual disability and autism, and who are restricted in their ability to communicate. He explores the use of sensors for physiological parameters (pulse, plasma glucose, etc.) as a means by which they can communicate their needs and their degree of well-being. His preclinical research centers on cerebral energy metabolism, including how it is affected by anti-epileptic drugs.

Host: **Bill Glovin** serves as editor of *Cerebrum* and the *Cerebrum Anthology: Emerging Issues in Brain Science*. He is also executive editor of the Dana Press and *Brain in the News*. Prior to joining the Dana Foundation, Mr. Glovin was senior editor of *Rutgers Magazine* and editor of *Rutgers Focus*. He has served as managing editor of *New Jersey Success*, editor of *New Jersey Business* magazine, and as a staff writer at *The Record* newspaper in Hackensack, NJ. Mr. Glovin has won 20 writing awards from the Society of Professional Journalists of New Jersey and the Council for Advancement and Support of Education. He has a B.A. in Journalism from George Washington University.

Bill Glovin: Hello and welcome to our first *Cerebrum* podcast. *Cerebrum* is the Dana Foundation's research-based publication, and all articles can be found at dana.org. I'm editor Bill Glovin, and today on the phone with us are research collaborators and the authors of our new *Cerebrum* article, "[A New Approach for Epilepsy](#)," Ray Dingledine in Atlanta and Bjornar Hassel in Norway.

65 million people worldwide suffer from some form of epilepsy, and many use drugs to alleviate their seizures; but, for a full one-third of those people, over 20 million, more than the entire population of New York City and state, there is no treatment. For some of those people, especially young children, a high-fat diet that mimics the effects of fasting has been shown to be effective, but this diet, called the ketogenic diet is very difficult to maintain for any number of reasons.

A promising new study, one that may someday be able to transform some of the principles of the ketogenic diet into pill form, is the focus of their article.

Ray is professor and chair in the Department of Pharmacology at Emory University, and Bjornar is a professor and senior consultant in the Department of Neurohabilitation at the University of Oslo. It's nice to have you, gentlemen. Let's begin with how you met and why you decided to collaborate.

Ray Dingledine: Well, we've worked together off and on for more than a decade. I used to live in Oslo long ago in the mid-70s, and Bjornar and I met during one of my trips back to Oslo. In my mind, I think we hit it off. Bjornar has an unusually lively mind and even more lively personality, and so we've ended up working together on, I think, four projects so far, this being the fifth.

Bjornar Hassel: You were very early to look at gene regulation and how it's affected by anti-epileptic drugs, and that was one of our first projects together, which was very fruitful, I think, and taught us a lot about the way anti-epileptic drugs affect the way our genes are read in the brain.

Bill Glovin: Can you provide an explanation as to what happens in the brain to cause epilepsy?

Ray Dingledine: Well, that's an important question, obviously. Epilepsy is one of the oldest known medical conditions. It's been recognized for thousands of years. After an event like a severe head injury, the brain undergoes a rewiring, and that rewiring is the process of developing epilepsy. Sometimes the checks and balances that usually keep things in your brain under control go awry during the rewiring so that normally innocuous stimuli can occasionally cause a large group of nerve cells to become active all at once. This is called a seizure. When the brain is predisposed to developing seizures, you have the condition known as epilepsy. There are a number of causes, and it takes a while, anywhere from months to decades to develop epilepsy, but it's generally a rewiring of the brain.

Bill Glovin: Is there any age group that is more particularly vulnerable?

Ray Dingledine: Well, the most vulnerable times, if you look at the incidence, are between zero and two-years-old, when you find most of the genetic epilepsies revealing themselves, and then in older life. When you're 60 years old and older, the incidence begins going up. Probably one of the main reasons for that is that elderly folks have a larger chance of developing strokes, and stroke is a very high-risk factor for developing epilepsy.

Bill Glovin: Progress in eliminating or slowing down a brain disorder is usually very slow. Is epilepsy a disorder where drugs have made a major difference?

Ray Dingledine: Definitely. Drugs have made a huge difference in the economically developed regions like North America, Europe, and Japan. There are now 34 FDA-approved

medications for epilepsy, and they work well in about two-thirds of patients; but, unfortunately, the other third are drug-resistant, and their lifestyles are severely impacted by continued seizures that occur at unpredictable times. They make it difficult to hold a job. Legally, you're not allowed to drive in states if you have a diagnosis of epilepsy and have not been seizure-free for a period of time. So, it really does a number on your lifestyle.

Bill Glovin: Bjornar, can you explain to people what the ketogenic diet is all about?

Bjornar Hassel: I'd say that the ketogenic diet may be very efficient, especially in children, and maybe especially in the people suffering from intellectual disability, maybe, again, especially those that can be fed through a tube, who are severely disabled, who don't have to worry about the taste of the ketogenic diet. That would be my first response, that it's very good in children with epilepsy that is difficult to manage and in some other cases. I don't know. In trials, it has been useful also for adults with epilepsy, but I don't think that the long-term effect is all that encouraging, simply because it's very hard to adhere to the diet. It's also very hard for families to adhere to the diet, families with children with epilepsy, because it's so demanding to keep up.

Ray Dingleline: Yeah. So, the diet works both in children and adults, but you have problems with compliance with adults. They can't handle the high-fat diet.

Bill Glovin: If you are suffering from epilepsy and you're not on the ketogenic diet, does what you eat factor into your level of seizures or affect the disorder in any way?

Bjornar Hassel: In general, I would say, "No." Being regular in your meals, as being regular in everything else in life, is something that may help people with epilepsy to control their seizures a bit better. For instance, sleeping during nighttime and ... How do you say that, Ray, when you sort of turn day into night?

Ray Dingleline: Yeah. You don't want to burn the candle at both ends. It causes pretty high stress in your body, and that can trigger a seizure.

Bill Glovin: How about alcohol use?

Bjornar Hassel: Of course, alcohol is very detrimental to people with epilepsy. After they have drunk, they will be at greater risk of having a seizure, actually, for the next week; but, for a day or two, that renders them vulnerable. We tend to explain that with GABAA receptors being withdrawn or internalized fairly rapidly during drinking. I don't know whether it's true, but that's an explanation that we often turn to and that for the cells to put the GABA receptors back into place takes longer time. So, that's the base. The next day, after having drunk, when the liver has done away with the alcohol, they'll find themselves under the normal barrage of excitatory inputs, but have fewer GABAA receptors to sort of protect them with.

Ray Dingleline: Yeah, I think that sounds right. It's a convenient explanation that you're losing these inhibitory transmitter receptors in the brain; but, like Bjornar mentions, it's the extent to which that actually happens isn't clear.

Bill Glovin: Can endocannabinoids or cannabis play a role in alleviating seizures?

Ray Dingleline: Well, a lot of attention has been devoted to this question in the US, especially for treating some of the really devastating epilepsies of childhood, such as Dravet's syndrome. Parents are desperate for any new remedy in these cases, and medical marijuana or cannabis oil, which is enriched in what might be an anti-seizure drug, cannabidiol, these things are legal in over half the state for compassionate use treatment of a number of disorders, including epilepsy. On the other hand, the gold standard demonstration of effectiveness, which is a well-controlled, double-blind clinical trials, are just now ongoing in one form of childhood epilepsy.

The mechanisms by which cannabis might be effective in the treatment of epilepsy are unclear. Of course, we all look forward to the results of these clinical trials, but there's a lot of anecdotal and more or less offline use of cannabis oil and marijuana in the states for epilepsy. How about in Norway, Bjornar?

Bjornar Hassel: We don't treat epilepsy with cannabidiol, even though it doesn't give a high like cannabis does. It's a lot of attention around the possibility, of course, but so far we haven't started treating patients with it yet.

Ray Dingleline: Yeah. I wonder if it's common throughout Europe, that it's more of a wait-and-see attitude.

Bill Glovin: Can you explain why the Sada study is such an important breakthrough?

Ray Dingleline: These authors, they've made a really excellent start to developing the first line of anti-seizure medications since the early 2000s. The epilepsy community hopes that these lactate dehydrogenase inhibitors, or LDH inhibitors, will eventually take their place among other anti-seizure medications and particularly address some of the need in the 33 percent of patients who are unresponsive to current medication.

Bill Glovin: Okay. How closely aligned is your own research to this groundbreaking study by the Sada group? Does the group's finding change the research landscape for epilepsy?

Ray Dingleline: Well, Bjornar and I worked together 10 years ago on a study that showed a mitochondrial link to the ketogenic diet. Mitochondria are the main energy-producing factories in nerve cells and, really, all cells in your body. Most of the work that I'm doing today centers on the question of how inflammation in the

brain influences seizures. The Sada group, their work really opened a new avenue for developing new anti-seizure drugs.

Bill Glovin: How about your work, Dr. Hassel?

Bjornar Hassel: Well, as a clinician, I was faced with the problems of how brain abscesses cause seizures. Worldwide, infections in the brain is a leading cause of epilepsy, and we really don't know why that happens. Of course, this ties in very nicely with your interest, Ray, namely that infections in the brain always entail a traumatic inflammatory response. So, when they get that to a degree that inflammatory mechanisms are involved in most forms of epilepsy, they must be very important in epilepsies that derive from brain infections, both encephalitis and meningitis and also the focal infections in the brain known as brain abscesses.

Bill Glovin: How close do you think we are to a clinical trial for a drug?

Ray Dingledine: Bjornar might have a different thought about this, but I think the next step, really, is to replicate that finding in another laboratory. That's important, because although the finding appears secure, there may be little circumstances that even the authors themselves were not aware of that might influence how effective their drugs were in their own laboratory. So, before putting hundreds of millions of dollars into a clinical program, it's important to replicate.

Once that's done and a pharma picked up on this project, I think the Phase I clinical trials could begin within 18-24 months, assuming no glitches, a glitch like an unexpected toxic effect in animals that would sideline these drugs. On the other hand, there's already a weak LDH inhibitor on the market, stiripentol, which is available from Europe for treatment of Dravet's syndrome, although it's, as I understand it, not FDA-approved yet. To me, that's the way forward and, perhaps, even increasing the use of stiripentol.

Bill Glovin: At the end of the article, you hint that a drug for weight control could come out of this research. Can you elaborate on that?

Ray Dingledine: Well, many anti-seizure drugs have found uses in psychiatry and neurology for treating other disorders, like migraine pain, bipolar disorder. The ketogenic diet consists of a very high fat, very low carbohydrate diet. It's still unclear whether the high fat or the near absence of carbohydrates is the necessary ingredient for the anti-seizure effect.

The LDH inhibitor identified in this paper clearly acts by interrupting the metabolism of glucose, which could in some way mimic a starvation-like diet. So, maybe the LDH inhibitor by itself, if taken as a pill, would reduce glucose metabolism and thereby help one to lose some weight. Now, having said that, I suspect that that's an over-simplification of the consequences of blocking the metabolism of glucose. Bjornar may have a more informed opinion about that.

Bjornar Hassel: It's a very good point, that drugs that are efficient for one condition are often efficient for other conditions as well. So, we have to keep an open mind as to what other conditions may be treated with new drugs. Of course, overweight being such a big problem worldwide with very few drugs available to do something about it, we shall always be on the lookout for new uses of drugs that are approved for other conditions.

Bill Glovin: Is there anything that I've left out that you think might be important?

Ray Dingedine: It's useful to recognize that the group that identified the LDH inhibitor as an anti-seizure drug is working in Japan. Over the past decade, in particular, quite a number of national and international research consortia and global planning efforts have appeared, which increasingly ... to me, they emphasize the research-without-borders nature of epilepsy research. Going forward, I think, harmonizing efforts across national boundaries should accelerate progress toward the day when epilepsy no longer limits human potential.

Bill Glovin: Anything from you, Dr. Hassel?

Bjornar Hassel: No. I quite agree. That was very well put.

Bill Glovin: Well, that was an unbelievable update on the state of epilepsy research. Thank you, Ray and Bjornar, for sharing your insights and perspectives on a topic that is of great interest to millions of people and their families from around the globe. Thanks, again, for your wonderful article, which is available by linking to [dana.org\cerebrum](http://dana.org/cerebrum). Join us next time when we [talk to Harry Tracy](#), president and co-founder of NI Research, about the state of private equity funding for neuroscience. That's all for now. See you next time.