The million-dollar question in epilepsy research today is whether the condition can be alleviated best by targeting glutamate receptors. The man most likely to be able to answer that is Ray Dingledine, Professor and Chairman of the Department of Pharmacology at Emory University for the past decade. He shared his views with *Nature Medicine*.

Ray Dingledine

In neuropharmacological terms, Dingledine's experience is second to none. He did his PhD with drug addiction specialist, Avram Goldstein, at Stanford University in 1975, followed by a post-doc with Leslie Iversen at Cambridge. During his professorship at the University of North Carolina, he did a sabbatical in Steve Heinemann's lab at the Salk Institute. He has consulted for three major pharmaceutical companies and is currently on the scientific advisory boards of two small biotech firms. Among other things, he was Editor of *Molecular Pharmacology* and has served on a variety of National Institutes of Health and National Science Foundation review panels, and received far too many awards to mention.

His research accomplishments include the discovery that glycine is a coagonist of NMDA receptors (*Science* **241**, 835; 1988) and characterization of the topology of a glutamate receptor subunit (*Neuron*, **14**, 373; 1995). And for his day job, Dingledine runs the Department of Pharmacology at Emory University where he has an equally hyperactive research lab.

It is no wonder then that Dingledine refutes the suggestion that electrophysiologists—a technique he taught himself—are patient scientists. "On the contrary, we want immediate data!" he says. A practice he tries to apply in his work is deciding when to cut his losses and end a program that will cost too much effort for the reward gained.

Back to the million-dollar question: what are the prospects of developing antiepileptic therapies that attack glutamate systems when this neurotransmitter mediates transmission at almost all of the excitatory synapses in the brain? Specificity is the key, explains Dingledine. "17 glutamate receptor subunits have now been identified—the last two only in the last couple of years. These assemble into groups of four to form functional receptors and each of these different assemblies has its own pharmacology. So we'll need to take advantage of subunit-specific blockers to hone in on pathways involved in propagating seizures."

Dingledine's own laboratory is pursuing this course of investigation. In a brain region undergoing a seizure, the pH drops from around 7.5/7.4 to 7.3/7.2 and certain glutamate receptors are exquisitely sensitive to such small changes in pH. Dingledine's group has identified a new class of compounds whose potency increases greatly as pH drops. "The idea is that this chemical wouldn't block the receptors in healthy brain tissue but as soon as a seizure began, and pH drops, the receptor would be blocked and the seizure truncated." Simple in theory, and the strategy has shown promise in the maximal electroshock animal model, a tool that is highly predictive for anticonvulsant drug efficacy in humans.

On the glutamate trail

The paucity of animal models that accurately reflect human epilepsy is a considerable barrier to research in the field, particularly for epilepsy that originates spontaneously in a brain area (epileptogenesis). "If you have a head injury, you have a 50% chance of developing epilepsy within two years. It takes time because a large number of genomic events, neuronal reorganization, apoptotic cell loss, sprouting and other changes occur in brain circuitry to make it hyperexcitable and prone to spontaneous seizure," says Dingledine. Although two animal models yield a similar neuropathology to this condition, both rely on chemical convuslants (pilocarpine and kainic acid) to induce status epilepticus, and their course of effect is compressed into three weeks rather than the years it takes in humans.

Transgenic models fare no better. "There are some animal models that reproduce a rare human genetic epilepsy, called autosomal dominant nocturnal frontal-lobe epilepsy, which is caused in humans by mutations in the nicotinic acetylcholine receptor channel. These have been transferred into animal models but do they have any bearing on garden-variety adult onset? The jury is out on that," says Dingledine. Tinkering with glutamate receptors by knock-in/knock-out techniques also has variable results. "I think this is because human epilepsy is not a single disorder, there are more than 40 different clinical phenotypes."

His team is now using microarray analysis to discover genes that are causal in epileptogenesis and vulnerable to intervention. "And I've started a new collaboration with scientists at Georgia Tech," Dingledine enthuses. "Most available algorithms cluster microarray hits based on similar expression profiles with the hope that genes that are expressed together have some functional relationship with one another. That may be true in yeast, but probably not in mammals. So we are text mining biomedical literature to develop algorithms that will cluster genes based on shared abstract key words and it's working out great!"

The initiative has brought Dingledine "a lot of professional growth in the last year." After 10 years as Pharmacology Professor and Chairman, he says he is entering the second phase of his job. "So far, the road to success has been to make the right decisions on who to hire, and I think I've done a really good job of that. But that's straightforward. Now our laboratory space is pretty full and so the next stage is how do you continue to improve the department without adding new faces? I'm just trying to work that out."

With such a solid reputation in the pharmaceutical industry, wouldn't Dingledine consider a move away from academia? "I have considered it and would do so again if the right situation comes up. A lot of really excellent scientists were recruited to industry over the past 20 years and the level of science done there is outstanding. They are a lot more goal-oriented and timely—something I really don't like is wasting time. But right now I want to be where I make the biggest impact and I think that's what I'm doing at Emory. It's going to be a new job for me over the next few years."

Karen Birmingham, London