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Hope for seizure control blooms from unexpected source

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Aided by former graduate student Nadeem Ashraf, and a Himalayan flower, Robarts Research Institute scientist Michael Poulter may be getting to the root of a solution to epileptic seizures.

Ashraf, a Pakistan native, didn't actually bring the flower itself to Poulter in May 2011, but rather a pure synthesized molecule, identical to the one in the plant's root, which had been studied for almost a decade by scientists at the International Center for Chemical and Biological Sciences at the University of Karachi.

"He showed me that he had this and told me there has already been a publication on its activity. So, I looked at it and saw it seemed to do something," Poulter said. "According to this report, it looks to work. But how it works, we didn't know. So, I said, 'Let's let see how it works.'"

And they did just that. What they discovered shocked even a veteran researcher like Poulter.

"When I could identify what it did, and didn't do," he continued, "what it does makes sense – it suppresses seizures. It was really quite remarkable."

Regular brain rhythms are high frequency and low amplitude. In those with epilepsy, however, the brain synchronizes its activities to the point where brainwaves become high amplitude and low frequency.

"So, you go from fast and small to large and slow, and that is an abnormal brain rhythm, which precipitates and inappropriate behavior or seizure," Poulter said. "The trick in the treatment of epilepsy is to prevent those high-amplitude, hyper-synchronized activities."

All epilepsy medications – with between 15 and 20 currently on the market – aim to do the same thing, and 70 per cent do the job. But there are side effects such as memory loss, rashes and auto-immune reactions.

Drawn from the lavender-coloured delphinium denudatum flower, the root extract molecule blocks the activity of an ion channel, called the sodium channel, responsible for the excitation of nerve cells.

"When a sodium channel activates, it activates the neuron. When you have excess activation, you can try to dampen down that activity a little bit, but not completely, or you would die," Poulter said. "You're trying to dampen down the activity that is inappropriately high due to epilepsy.

"That's what we know (the root) does and that makes sense. What we don't know is why this particular drug prevents the progression of the seizures in the animal model. There are other drugs out there that will block sodium channels, but do not stop the progression of the seizures. We still don't understand that."

While excited around the early findings, Poulter remains cautious.

"Everybody knows it is still a very, very high-risk proposition," he said. "The reason is, in normal progression of a drug to the clinics, you have to show it first works acceptably in animal models, and that costs loads of cash."

In the next phase, which Poulter referred to as "the valley of death," the molecule is sent to a company that does long-term toxicity tests, which

usually makes or breaks a drug's success.

"At the end of all that, you slowly open up the report because you just spent close to a million dollars, and if it passes, then you're ready to put it into people. If not, and you have money left, you go back to the start and reformulate the chemistry," Poulter said, noting he is still a couple of years away from that point.

Poulter has obtained funding from the Ontario Brain Institute, and other private-sector investors, to begin a pharmaceutical company to commercially develop this promising drug when, and if, it gains approval.

Poulter said some of the greatest finds in medicine come from the last place you would think. For example, Amazon jungle locals hunt with poison blow darts with an active ingredient called tubocurarine, an alkaloid found in the bard of a South American vine. That same ingredient has been used as a muscle relaxant during surgery to prevent unwanted movement of the patient.

"There is precedent for natural products having real effects that become mainstay and are in use," Poulter said. "No doubt, there are molecules out there. People spend their careers going through the jungles looking for things that work, called ethnopharamacology."

But while undiscovered remedies remain, Poulter cautions their efficacy is anecdotal until put through the paces.

"Nobody in the Amazon jungle sets up a double-blind, cross-over trial of the local fauna to see whether or not it cures spider bites," he said. "These things kind of, by happenstance, fall into our laps, and basically, that's what happened here."

Provided by University of Western Ontario