Parkinson's disease power switch located

Harvard-led study says existing drugs may offer future treatment

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Health Reporter

In a transformative new study, U.S. researchers have uncovered both the key cause and a promising treatment for Parkinson's disease.

The degenerative movement disorder occurs when the tiny power plants that fuel afflicted brain cells are turned off, the Harvard University-led study has found.

This power outage may well be reversed by medications that throw a master switch gene controlling the energy-producing cell structures back on, the paper suggests.

"It's all very exciting . . . because I think it is potentially a breakthrough in Parkinson's disease," says Dr. Anthony Phillips, head of neurosciences with the Canadian Institutes of Health Research.

"It's really coming together nicely. I think it is very, very promising and I think it will get a lot of interest."

Dr. Clemens Scherzer, the senior paper author, likens the key gene he has identified – known as PGC-1alpha — to the main breaker in a basement electrical console.

"This would be the main power switch that turns everything back on," says Scherzer, a Harvard neurologist.

Importantly, Scherzer says, there are already approved drugs available that are turning the same genetic master switch on in other diseases like diabetes.

If these drugs can hit the switch in brain cells, as Phillips says is likely, it could provide a treatment that would ward off or reverse the ailment's crippling onslaught in its earliest stages.

Scherzer says that all the genes that control the energy-producing machinery of a cell – churning structures known as mitochondria – are turned off in Parkinson's disease.

These mitochondria are divided into five power cells, each of which is genetically inactivated in the disease. But all five centres can be reactivated by targeting the master PGC-1alpha

gene, Scherzer says.

"You can think of it like a power switch that, if you turn on this master regulator you can turn the activity of this energy-producing machinery back on," he says.

Dr. Timothy Greenamyre, vice chair of neurology at the University of Pittsburgh, calls the identification of a mitochondrial cause a "sea change" in the understanding of the ailment.

"This study was really a tour-de-force and Scherzer brought together a lot of groups and their data sets to do this," says Greenamyre, a movement disorder expert.

"I think he really has to be complimented. This is a very, very solid study."

Parkinson's, which affects some 100,000 Canadians and more than 6 million globally, is an attack on dopamine cells in the brain stem, which control motor movements.

In the study, Scherzer's team actually turned tissue samples of these dopamine cells back on by inducing high levels of the master gene into a cultured mix.

"But (the gene) is a very exciting target for medicines because pharmaceutical companies have realized its importance before in diseases that are much more common than Parkinson's, such as diabetes," he says.

Indeed, there are approved diabetes drugs, and several promising medications now being screened, that appear able to throw the PGC-1alpha switch.

"Pharmaceutical companies can now go back and see whether these drugs or tested compounds can cross into the brain of Parkinson's patients," Scherzer says.

Phillips says the likelihood that some of these drugs would cross into the brain is high.

Adds Greenamyre: "I agree there's that potential and it's very exciting."

The study appears in the first anniversary issue of the journal *Science Translational Medicine*, which features research making the jump from the laboratory to practical usage.

Scherzer thinks a combination of environmental chemicals, like pesticides and manganese, plus a variety of genetic risk factors for the disease combine to cause the ailment.

Yet the afflicted, dopamine-producing cells appear to be able to ward these risk factors off when their mitochondria are robust.

Greenamyre's only caution is that the paper does not definitively show that PGC-1alpha has itself gone off in Parkinson's disease.

"They show that everything that's controlled by (it) is down, but they don't show there's anything wrong with the breaker switch," he says.

He says it could be imagined the electrical wiring coming out of the main switch is bad, but that the switch itself is working.

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