Research reveals possible reason for cholesterol-drug side effects

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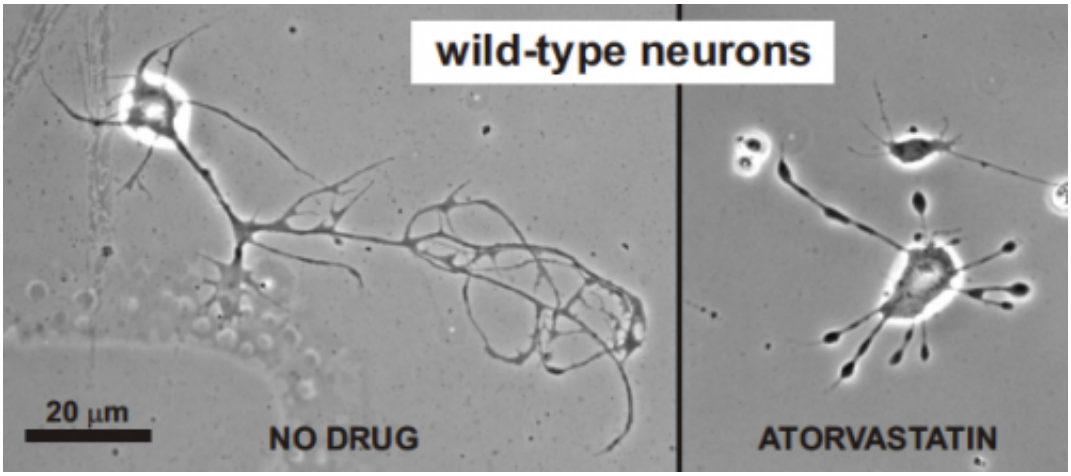


Of 1,040 drugs tested, only four caused nodules to form inside the neurites, resembling beads on a string. All four drugs were statins. Credit: Linda Restifo/University of Arizona

The U.S. Food and Drug Administration and physicians continue to document that some patients experience fuzzy thinking and memory loss while taking statins, a class of global top-selling cholesterol-lowering drugs.

A University of Arizona research team has made a novel discovery in brain cells being treated with statin drugs: unusual swellings within neurons, which the team has termed the "beads-on-a-string" effect.

The team is not entirely sure why the beads form, said UA neuroscientist Linda L. Restifo, who leads the investigation. However, the team believes that further investigation of the beads will help inform why some people experience cognitive declines while taking statins.

"What we think we've found is a laboratory demonstration of a problem in the neuron that is a more severe version for what is happening in some peoples' brains when they take statins," said Restifo, a UA professor of neuroscience, neurology and cellular and molecular medicine, and principal investigator on the project.

Restifo and her team's co-authored study and findings recently were published in *Disease Models & Mechanisms*, a peer-reviewed journal. Robert Kraft, a former research associate in the department of neuroscience, is lead author on the article.

Restifo and Kraft cite clinical reports noting that statin users often are told by physicians that cognitive disturbances experienced while taking statins were likely due to aging or other effects. However, the UA team's research offers additional evidence that the cause for such declines in cognition is likely due to a negative response to statins.

The team also has found that removing statins results in a disappearance of the beads-on-a-string, and also a restoration of normal growth. With research continuing, the UA team intends to investigate how genetics may be involved in the bead formation and, thus, could cause hypersensitivity to the drugs in people. Team members believe that genetic differences could involve neurons directly, or the statin interaction with the blood-brain barrier.

"This is a great first step on the road toward more personalized medication and therapy," said David M. Labiner, who heads the UA department of neurology. "If we can figure out a way to identify patients

who will have certain side effects, we can improve therapeutic outcomes."

For now, the UA team has multiple external grants pending, and researchers carry the hope that future research will greatly inform the medical community and patients.

"If we are able to do genetic studies, the goal will be to come up with a predictive test so that a patient with high cholesterol could be tested first to determine whether they have a sensitivity to statins," Restifo said.

Detecting, Understanding a Drugs' Side Effects

Restifo used the analogy of traffic to explain what she and her colleagues theorize.

The beads indicate a sort of traffic jam, she described. In the presence of statins, neurons undergo a "dramatic change in their morphology," said Restifo, also a BIO5 Institute member.

"Those very, very dramatic and obvious swellings are inside the neurons and act like a traffic pileup that is so bad that it disrupts the function of the neurons," she said.

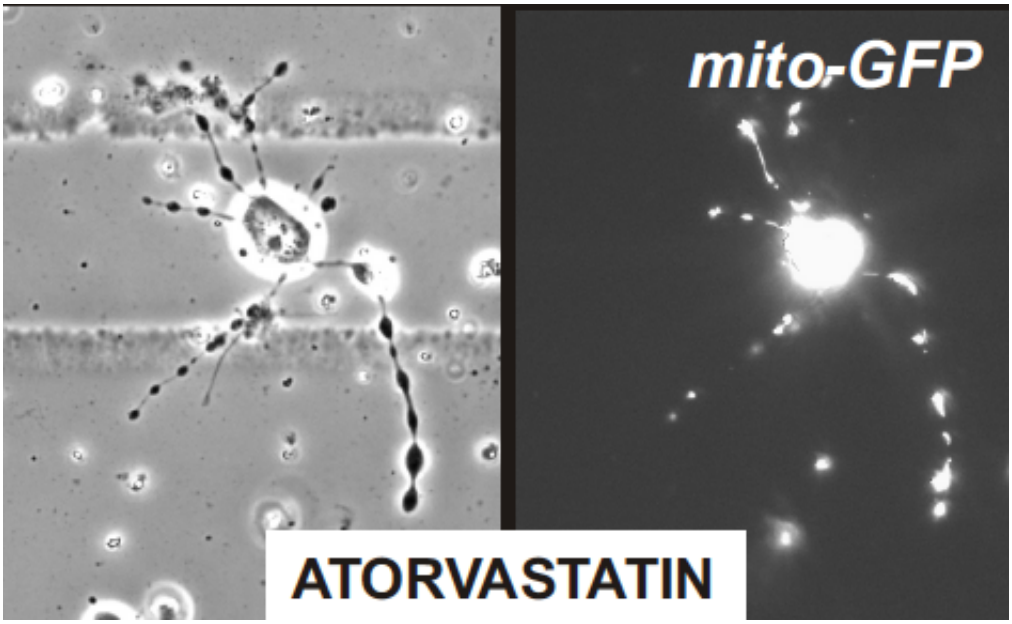
It was Kraft's observations that led to team's novel discovery. Restifo, Kraft and their colleagues had long been investigating mutations in genes, largely for the benefit of advancing discoveries toward the improved treatment of autism and other cognitive disorders.

At the time, and using a blind-screened library of 1,040 drug compounds, the team ran tests on fruit fly neurons, investigating the reduction of defects caused by a mutation when neurons were exposed to different drugs. The team had shown that one mutation caused the

neuron branches to be curly instead of straight, but certain drugs corrected this. The research findings were published in 2006 in the *Journal of Neuroscience*.

Then, something serendipitous occurred: Kraft observed that one compound, then another and then two more all created the same reaction – "these bulges, which we called beads-on-a-string,'" Kraft said. "And they were the only drugs causing this effect."

At the end of the earlier investigation, the team decoded the library and found that the four compounds that resulted in the beads-on-a-string were, in fact, statins.



Neurons whose mitochondria are labeled with green fluorescent protein (GFP) reveal that statins cause mitochondria to pile up inside the branches that neurons use to connect with each other. Credit: Linda Restifo/University of Arizona

"The 'beads' effect of the statins was like a bonus prize from the earlier experiment," Restifo said. "It was so striking, we couldn't ignore it."

In addition to detecting the beads effect, the team came upon yet another major finding: when statins are removed, the beads-on-a-string effect disappears, offering great promise to those being treated with the drugs.

"For some patients, just as much as statins work to save their lives, they can cause impairments," said Monica Chaung, who has been part of the team and is a UA undergraduate researcher studying molecular and cellular biology and physiology.

"It's not a one drug fits all," said Chaung, a UA junior who is also in the Honors College. "We suspect different gene mutations alter how people respond to statins."

Having been trained by Kraft in techniques to investigate cultured neurons, Chuang was testing gene mutations and found variation in sensitivity to statins. It was through the work of Chuang and Kraft that the team would later determine that, after removing the statins, the cells were able to repair themselves; the neurotoxicity was not permanent, Restifo said.

"In the clinical literature, you can read reports on fuzzy thinking, which stops when a patient stops taking statins. So, that was a very important demonstration of a parallel between the clinical reports and the laboratory phenomena," Restifo said.

The finding led the team to further investigate the neurotoxicity of statins.

"There is no question that these are very important and very useful drugs," Restifo said. Statins have been shown to lower cholesterol and

prevent heart attacks and strokes.

But too much remains unknown about how the drugs' effects may contribute to muscular, cognitive and behavioral changes.

"We don't know the implications of the beads, but we have a number of hypotheses to test," Restifo said, adding that further studies should reveal exactly what happens when the transportation system within neurons is disrupted.

Also, given the move toward prescribing statins to children, the need to have an expanded understanding of the effects of statins on cognitive development is critical, Kraft said.

"If statins have an effect on how the nervous system matures, that could be devastating," Kraft said. "Memory loss or any sort of disruption of your memory and cognition can have quite severe effects and negative consequences."

Restifo and her colleagues have multiple grants pending that would enable the team to continue investigating several facets related to the neurotoxicity of statins. Among the major questions is, to what extent does genetics contribute to a person's sensitivity to statins?

"We have no idea who is at risk. That makes us think that we can use this genetic laboratory assay to infer which of the genes make people susceptible," Restifo said.

"This dramatic change in the morphology of the neurons is something we can now use to ask questions and experiment in the laboratory," she said. "Our contribution is to find a way to ask about genetics and what the genetic vulnerability factors are."

The Possibility for Future Research, Advice

The team's findings and future research could have important implications for the medical field and for patients with regard to treatment, communication and improved personalized medicine.

"It's important to look into this to see if people may have some sort of predisposition to the beads effect, and that's where we want to go with this research," Kraft said. "There must be more research into what effects these drugs have other than just controlling a person's elevated cholesterol levels."

And even as additional research is ongoing, suggestions already exist for physicians, patients and families.

"Most physicians assume that if a patient doesn't report side effects, there are no side effects," Labiner said. "The paternalistic days of medication are hopefully behind us. They should be."

"We can treat lots of things, but the problem is if there are side effects that worsen the treatment, the patient is more likely to shy away from the medication. That's a bad outcome," he said. "There's got to be a give and take between the patient and physician."

Patients should feel empowered to ask questions, and deeper questions, about their health and treatment and physicians should be very attentive to any reports of cognitive decline for those patients on statins, she said.

For some, it starts early after starting statins; for others, it takes time. And the signs vary. People may begin losing track of dates, the time or their keys.

"These are not trivial things. This could have a significant impact on

your daily life, your interpersonal relationships, your ability to hold a job," Restifo said.

"This is the part of the brain that allows us to think clearly, to plan, to hold onto memories," she said. "If people are concerned that they are having this problem, patients should ask their physicians."

Restifo said open and direct patient-physician communication is even more important for those on statins who have a family history of side effects from statins.

Also, physicians could work more closely with patients to investigate family history and determine a better dosage plan. Even placing additional questions on the family history questionnaire could be useful, she said.

"There is good clinical data that every-other-day dosing give you most of the benefits, and maybe even prevents some of the accumulation of things that result in side effects," Restifo said, suggesting that physicians should try and get a better longitudinal picture on how people react while on statins.

"Statins have been around now for long enough and are widely prescribed to so many people," she said. "But increased awareness could be very helpful."

Provided by University of Arizona