Potential drug therapy for diabetic retinopathy under study

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Drs. Sylvia Smith and Alan Saul want to know more about how a drug known for its pain-relieving ability appears to improve the health of retinas damaged by diabetes. Credit: Phil Jones, Campus Photographer

One drug's startling ability to restore retinal health in the eyes of diabetic mice has researchers wanting to learn more about how it works and whether it might do the same for people.

"We want to know if this drug has the potential to block the visual devastation that can occur with diabetes," said Dr. Sylvia Smith, retinal cell biologist and co-director of the Vision Discovery Institute at the Medical College of Georgia. "That means we need to know more about

how and when it is effective."

Diabetic retinopathy, the leading cause of blindness in working-age Americans, results from the destruction of the retina, a thin layer at the back of the eyeball that converts lights to signals that the brain can interpret as images. The retina, which deals with daily assaults from the sun and other external forces, is slowly injured by the high glucose levels of diabetes then further injured when it grows more blood vessels in an attempt to get more blood and oxygen to dying cells.

At least in the early stage of diabetes in mice, MCG researchers appear to have interrupted the first wave of cell destruction with the drug (+)-pentazocine – known for its pain-relieving power – by reducing cell stress. A new $1.5 million grant from the National Eye Institute will enable scientists to test their cell stress theory and fill in missing pieces about how and when the drug works.

Smith and her colleagues have evidence that oxidative stress, believed to be a key player in the cell damage resulting from diabetes, increases the binding of sigma receptors to BiP, a stress protein. Sigma receptors are believed to help cells cope with stress.

While some results of the union are unclear, it is clear that in the mice, (+)- pentazocine reduces binding between the two to a more usual, non-stressed level and restores the typically well-stratified retina to a more healthy state. Smith termed the result "phenomenal" when it was published in *Investigative Ophthalmology & Visual Science* in 2008. In fact, subsequent research has shown, (+)- pentazocine improves the look of the multi-layer retina in a healthy mouse.

"We know (+)- pentazocine binds to sigma receptors, but one of the things we don't know is if the binding blocks or promotes sigma receptor action," Smith said. Working with Dr. Eric Zorilla at The Scripps

Research Institute in California, Smith now has mice with sigma receptors deleted that will help her better determine their role and how (+)- pentazocine intervenes.

Dr. Alan Saul, MCG electrophysiologist skilled in measuring the response of the retina to light, is helping her objectively measure the impact on mouse vision. Much like an EEG measures the electrical activity of the brain, Saul, a faculty member in the MCG Department of Ophthalmology, helps measure the electrical response of the retina – which is part of the brain – to light as an objective vision test to accompany the more common vision chart.

Without a mouse vision chart, it's hard to be certain that a better-looking retina translates to better vision, Smith said. In fact, Saul has seen it go both ways in patients: an eye exam indicates good vision while the retinal test shows differently, and vice versa. "You are surprised a lot of the time," Saul said. In fact, they are beginning to find some surprises in mice with a related problem. Diabetes essentially doubles the glaucoma risk and as their mice with glaucoma reach the equivalent of their 20s and 30s in human years. Saul's electrical exams show early changes in their optic nerves – which extend from the retina to the brain – even though they look normal on microscopic exam.

To help fill in the knowledge gaps, the scientists are inducing diabetes in the mice missing sigma receptors, comparing them to healthy mice and applying non-diabetic stressors to the sigma receptor knockouts. They suspect that other stressors, including age, also cause retinal damage.

Goals include determining if retinal appearance improves as a result of the interaction between the sigma receptors and (+)- pentazocine and consequent reduction of cell stress. To help explore the therapeutic potential, they also want to see whether the drug is effective if given later in the disease process. In their earlier studies, the drug was given

immediately after mice became diabetic, an unlikely stage of diagnosis for most human diabetics.

"If we can get answers to these questions we'll know better whether (+)-pentazocine has the potential to help patients, which is our ultimate goal," Smith said.

To help prevent progression of diabetic retinopathy, patients are encouraged to control glucose and cholesterol levels as well as blood pressure. Laser treatment can help destroy excessive blood vessels that hinder vision and reduce swelling often associated with the condition.

Provided by Medical College of Georgia