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PRIMARY eyecare

Low Blood Sugar, Diet, and Circadian Rhythms

Episodes of Low Blood Sugar Worsen Eye Disease in People with Diabetes - But Why?

People with diabetes who experience periods of low blood sugar — a common occurrence in those new to blood sugar management — are more likely to have worsening diabetic eye disease. Now, researchers at Johns Hopkins Medicine say they have linked such low blood sugar levels with a molecular pathway that is turned on in oxygen-starved cells in the eye.

Temporary episodes of low glucose which happen once or twice a day in people with insulin-dependent diabetes and often among people newly diagnosed with the condition, can also occur during sleep in people with non- insulin dependent diabetes. The results of this study show that these periodic low glucose levels cause an increase in certain retinal cell proteins, resulting in an overgrowth of blood vessels and worsening diabetic eye disease.

The researchers analyzed protein levels in human and mouse retinal cells and intact retinas grown in an environment of low glucose in the laboratory, as well as in mice that had occasional low blood sugar. They found that low glucose levels in human and mouse retinal cells caused a cascade of molecular changes that can lead to blood vessel overgrowth.

First, the researchers saw that low glucose caused a decrease in retinal cells' ability to break down glucose for energy. Then looking specifically at so-called Müller glial cells, which are supportive cells for neurons in the retina and rely primarily on glucose for energy production, they found that in response to low glucose, these cells increased levels of a transcription factor, called hypoxia-inducible factor (HIF)-1α.

In low-oxygen environments, as occurs in the retinas of patients with diabetic eye disease, the response to low glucose triggered a flood of HIF-1α protein into the cells' nucleus, which resulted in an increase in the production of proteins such as VEGF and ANGPTL4. It is these proteins which cause the growth of abnormal, leaky blood vessels — the key culprit of vision loss in people with diabetic eye disease.

An important limitation of the current study is the absence of correlative data in patients. Another limitation is that the researchers were unable to identify the signalling pathway(s) connecting cellular detection of low glucose with the increase in nuclear accumulation of HIF-1a that remains. However, these signalling cascades may ultimately provide new therapeutic targets for the treatment of Diabetic Retinopathy

Citation: Guo C, Deshpande M, Niu Y, Kachwala I, Flores-Bellver M, Megarity H, Nuse T, Babapoor-Farrokhran S, Ramada M, Sanchez J, Inamdar N, Johnson TV, Canto-Soler MV, Montaner S, Sodhi A. HIF-1α accumulation in response to transient hypoglycemia may worsen diabetic eye disease. Cell Rep. 2023 Jan 31;42(1):111976. doi: 10.1016/j.celrep.2022.111976. Epub 2023 Jan 10. PMID: 36640318;*

PMCID: PMC9960808.

*(*Sodhi is a co-founder of and holds equity in HIF Therapeutics Inc. This arrangement was reviewed and approved by The Johns Hopkins University in accordance with its conflict of interest policies.)*

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Study Finds Link Between Diet, Circadian Rhythms, Eye Health and Lifespan

Researchers from the Buck Institute have demonstrated for the first time a link between diet, circadian rhythms, eye health and lifespan. Admittedly this was in Drosophila, but as explained in their paper published in Nature Communications, they unexpectedly found that processes in the fly eye are actually driving the aging process.

Previous studies have shown in humans that there is an association between eye disorders and poor health. This study argues that it is more than correlation: dysfunction of the eye can actually drive problems in other tissues," said senior author and Buck Institute Professor Pankaj Kapahi, PhD, "We are now showing that not only does fasting improve eyesight, but the eye actually plays a role in influencing lifespan." "The finding that the eye itself, at least in the fruit fly, can directly regulate lifespan was a surprise to us," said lead author, Brian Hodge, PhD.

Circadian rhythms affect complex animal behaviors, such as predator-prey interactions and sleep/wake cycles, down to fine-tuning the temporal regulation of molecular functions of gene transcription and protein translation. In 2016 Kapahi's lab published a study in Cell Metabolism showing that fruit flies on a restricted diet had significant changes in their circadian rhythms in addition to extending lifespan. This new study digs deeper to better understand which processes that enhance circadian functions were altered by the diet change, and whether circadian processes were required for the longer lifespan seen with dietary restriction.

The study began with a broad survey to see what genes oscillate in a circadian fashion when flies on an unrestricted diet were compared with those fed just 10 percent of the protein of the unrestricted diet.

It was immediately noticed numerous genes that were both diet-responsive and also exhibiting ups and downs at different time points (rhythmic). The rhythmic genes that were activated the most with dietary restriction all seemed to be coming from the eye, specifically from photoreceptors, the specialized neurons in the retina of the eye that respond to light. Further experiments showed genes in the eye that are also rhythmic and responsive to dietary restriction do influence lifespan.

Since the eyes are exposed to the outside world, Kapahi noted, the immune defenses there are critically active, which can lead to inflammation, which, when present for long periods of time, can cause or worsen a variety of common chronic diseases. Additionally, light in itself can cause photoreceptor degeneration which can cause inflammation. "Staring at computer and phone screens, and being exposed to light pollution well into the night are conditions very disturbing for circadian clocks," Kapahi said. "It messes up protection for the eye and that could have consequences beyond just the vision, damaging the rest of the body and the brain."

The biggest question raised by this work as it might apply to humans is, simply, do photoreceptors in mammals affect longevity? Probably not as much as in fruit flies, since the majority of energy in a fruit fly is devoted to the eye. But photoreceptors are just specialized neurons and once researchers understand more fully how these processes work, they can begin to target the molecular clock to decelerate aging, whether this be through diet, drugs, lifestyle changes… A lot of really interesting research lies ahead.

Citation: Hodge, B.A., Meyerhof, G.T., Katewa, S.D. et al. Dietary restriction and the transcription factor clock delay eye aging to extend lifespan in Drosophila Melanogaster. Nat Commun 13, 3156 (2022). https://doi.org/10.1038/s41467-022-30975-4

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