

Lay summary about the Liraglutide Paper (<https://www.nature.com/articles/s41598-019-52295-2.pdf>):

We know that in Wolfram syndrome, there is a gradual loss of brain cells, including cells in the optic nerve that supply the eyes. This process is often called neurodegeneration, and is seen in some common diseases such as Alzheimer's and Parkinson's disease. The most obvious result of this in Wolfram is the gradual loss of vision experienced by most affected people. We have struggled for many years to understand this as there has not been a good animal model to study. The group led by Anton Tersamaa and Mario Plaas, in University of Tartu, have developed a rat model that seems to have most of the features of Wolfram that are seen in people. This has allowed them to study the rat brains and show that there is loss of brain cells in selected areas of the rat brain. This latest publication looks at the effects of treating these 'Wolfram' rats with a drug called Liraglutide. Liraglutide belongs to a class of drugs called GLP-1 receptor agonists. They are licensed for use in adults with type 2 diabetes, and now for children with type 2 diabetes. They are not licensed to treat neurodegeneration in humans, as the evidence is inconclusive.

In this study, the research group treated 'Wolfram' rats, and healthy rats, with the drug Liraglutide, or saline as control, given by injection, for up to 6 months. Wolfram rats treated with Liraglutide still had diabetes, but there was some delay in the worsening of blood glucose compared with those treated with saline. The Wolfram rats treated with Liraglutide lost weight, and did not grow so well as Wolfram rats treated with saline.

Treatment with Liraglutide in the Wolfram rats was associated with more brain cells compared to saline treated rats, in selected areas of the brain studied; however in other areas, there was no difference. Similarly, there was some reduction in endoplasmic reticulum stress and inflammation (mechanisms of disease in Wolfram) in some areas of the brain but no difference in others. Finally, Wolfram rats treated with Liraglutide had more retinal ganglion cells (eye cells) than those treated with saline. The report does not include any visual function tests to know if treatment had any effect on vision.

Overall this is an excellent paper showing that Liraglutide is a good candidate for a clinical treatment trial in patients with Wolfram. There are some more questions that need answering:

- a) Does Liraglutide get into the human brain in big enough amounts to have an effect on neurodegeneration?
- b) Is there any new data on how well Liraglutide protects brain cells in other neurodegenerative diseases?

c) Is the effect of Liraglutide in the brain localised to just a few areas, or does it help the whole brain?

d) Would treatment with Liraglutide in humans slow or stop the progression of loss of vision or other brain features?

Nolwen Le Floche from the French WS Association has invited the research team to the international Wolfram meeting for Doctors, Researchers and CEO's of WS Patient Groups in Paris in March 2020; and it will be really interesting to talk with them and hear some more of their results.