Short-term levodopa treatments ameliorate early stage electroretinogram (ERG) delays in diabetic patients

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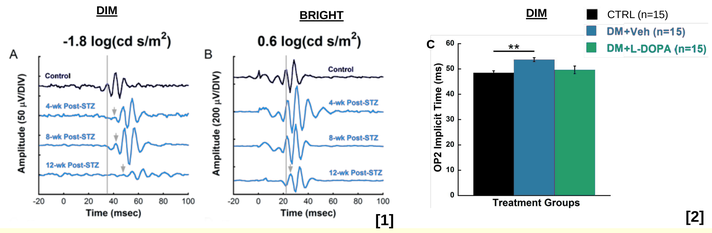
Introduction

- **Diabetic retinopathy (DR)** is one of the leading causes of blindness worldwide
- Currently, it is recognized as a vascular disease and *only detected clinically when it has advanced to the point of being visible on fundus photography*
- Previously, our group demonstrated that diabetic rodents have oscillatory potential (OP) implicit time (IT) delays via a dim, but not bright flash stimuli at 4 wks post hyperglycemia, prior to vascular defects **(Figure A,B)**.
  - We also showed that the dopamine deficiency and OP delay can be reduced via levodopa treatment for 5 weeks after hyperglycemia **(Figure C)**.

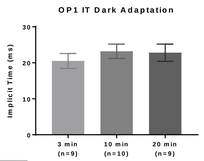


[1] [2]

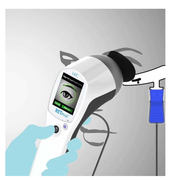
- **Thus, we sought to evaluate if we could detect an OP delay in diabetic patients without retinopathy using dim flash stimuli with a handheld ERG device (the REТeval) and then reduce these OP delays by treating with levodopa for two weeks.**

Methods

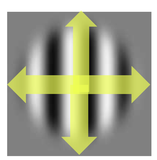
- Non-diabetic controls between the ages of 30-70, without a history of any degenerative retinal disease were recruited first (n=15)
  - We determined optimal dark adaptation time using 3, 10 and 20 minutes dark adaptation
  - Subjects were tested at 0, 2 weeks, and 4 weeks
  - REТeval ERG testing
    - Two scotopic flashes (1.13 & 85 Tds) after being dark adapted 10 minutes
    - Two light adapted (10 minutes) flicker flashes (32 & 85 Tds, 28.3 Hz)
  - Drifting Spatial Contrast Sensitivity (Metropsis)
  - Visual Acuity
- ***All tests were performed on each eye individually***
- Diabetic (DM) participants had received a fundus photo within the last 6 mo and had no signs of retinopathy
  - Participants consented to the study
  - At the first visit, all the tests performed on controls were repeated on diabetics.
  - If either eye showed a delay in the dim flash (1.13 Tds) OP IT, participants qualified for the study and were randomized to one of two doses of oral levodopa (Sinemet) taken twice a day for two weeks
    - Low (25 mg carbidopa/100 mg levodopa)
    - High (50 mg carbidopa/200 mg levodopa)
  - Participants were then re-tested after taking 3 pills (2 days), 28 pills (2 weeks), and then two weeks after they had finished their last dose (4 weeks from start)



Visual Acuity



REТeval [3]

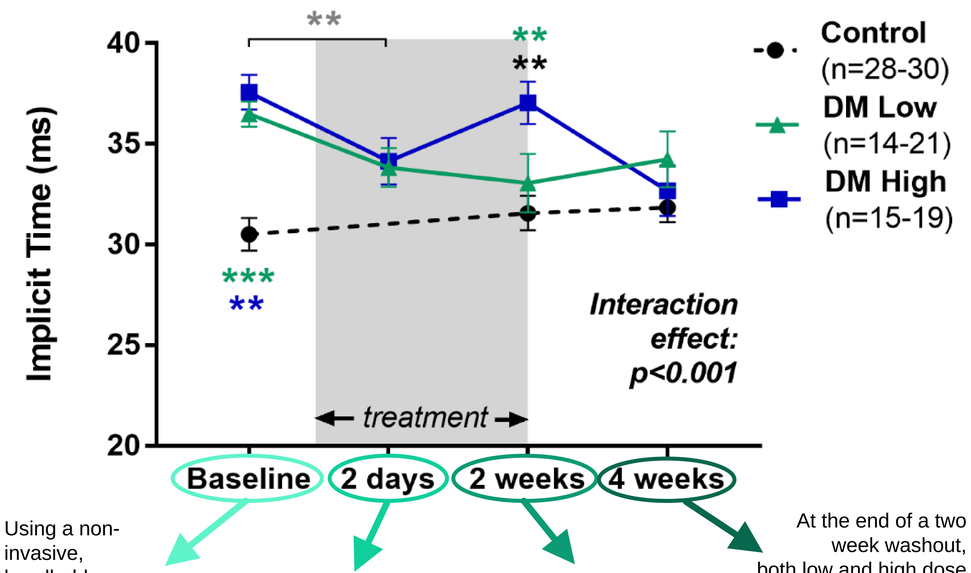


Drifting Spatial Contrast Sensitivity

All graphs are mean +/- SEM and p<0.001 = ***, p<0.01 = **, p<0.05 = ***

Results

Dim Flash (1.13 Tds) OP1 Implicit Time



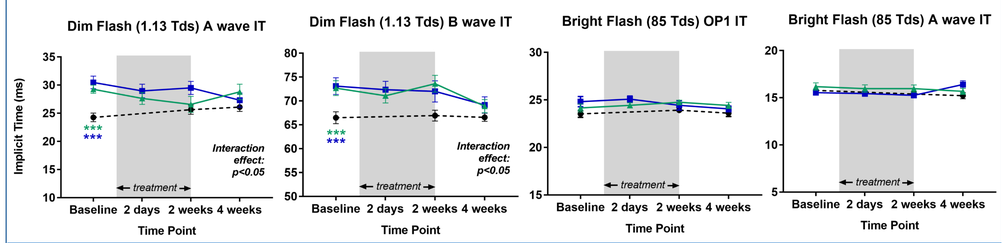
Using a non-invasive, handheld ERG device, significant delays in OPs were found in diabetic patients without retinopathy relative to controls

With only 3 pills of either high or low dose levodopa, the OP implicit time was significantly improved in DM patients

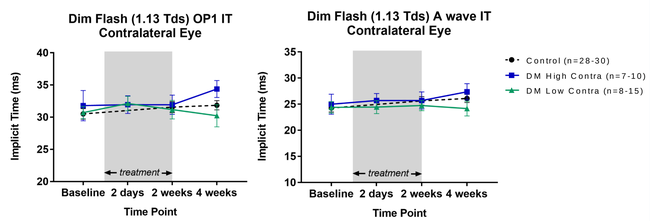
At two weeks, only the low dose levopdopa had a sustained effect on dim flash OP IT of DM patients

At the end of a two week washout, both low and high dose levodopa had a statistically significant improvement in OP IT such that the values were no longer statistically different from controls

Some benefit with treatment was seen in other dim flash ERG parameters, but not with bright flash ERG parameters

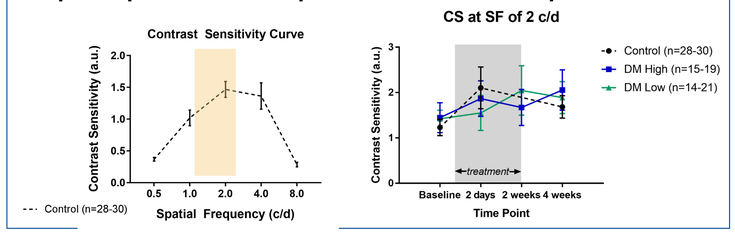


Early neuronal dysfunction is necessary to see improvement with levodopa; contralateral, undelayed eyes of participants did not show any changes



Results

Drifting spatial contrast sensitivity does not show a deficit in DM participants nor an improvement with levodopa treatment



Conclusion & Future Directions

In conclusion:

- Early OP delays in diabetic patients without retinopathy are detectable using a handheld device with dim flash stimuli, no dilating drops and a cheek electrode.
- The detection of OP delays provides a novel treatment window to slow progression of retinopathy.
- Low dose levodopa consistently improved OP implicit times across the treatment period.
- High dose levodopa produced transient benefits, perhaps due to homeostatic changes in retinal dopamine receptors.
- Rod-driven OP delays are a sensitive measure to detect early retinal neuronal changes prior to vascular pathology and could be used to monitor retinopathy over time

In the future:

- Evaluate whether any health factors correlate with OP delays (i.e. BMI, years of diabetes, blood glucose, HgbA1c%, etc.)
- Perform a larger, long-term clinical study with levodopa

References

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