Oct 13th, 12:00 AM

Retinal degeneration in mice devoid of membrane-type frizzled-related proteinor adiponectin receptor 1 results in selective fatty acid synthesis impairments

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Introduction

- Abnormal lipid metabolism is the derivation of multiple retinal degenerative and blinding diseases.
- The omega 3 fatty acids eicosapentaenoic acid (EPA; 20:5) and docosahexaenoic acid (DHA; 22:6) provide substrate for the fatty acid elongase-4 (ELOVL4) to synthetize VLC-PUFAs.
  - These fatty acids then became part of phospholipids of the outer segments of photoreceptors where they tightly interact with rhodopsin.
  - In the retinal pigmented epithelium (RPE), they serve as precursors to the potent neuroprotective molecules known as Elovanoids.
- The membrane-type frizzled-related protein (MFRP), a protein expressed in the RPE and ciliary bodies, and adiponectin receptor 1 (AdipoR1), a protein expressed in the retina and RPE, were shown to be vital to the maintenance of a healthy retinal lipidome.
  - Given that these lipids are essential for proper vision, it is important to compare the amount of the total fatty acids in the ω-3 and ω-6 pathways in *Mfrp*^{rd6} and *Adipor1* $^{-/-}$.

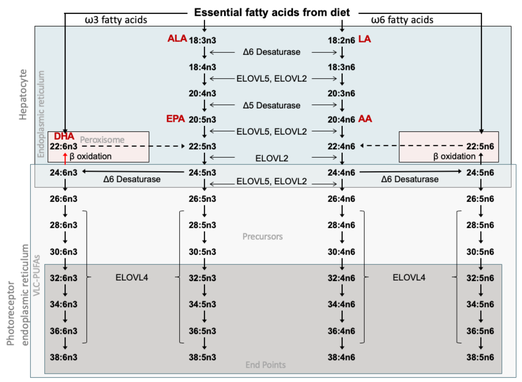
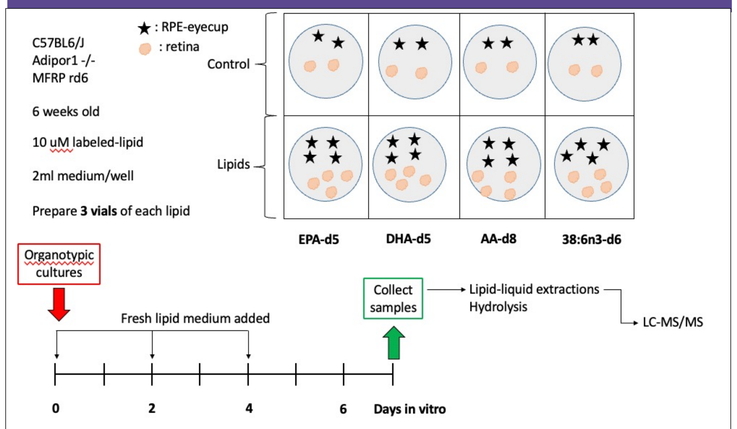


Figure 1: VLC-PUFA lipid metabolism pathway

Methods



Results

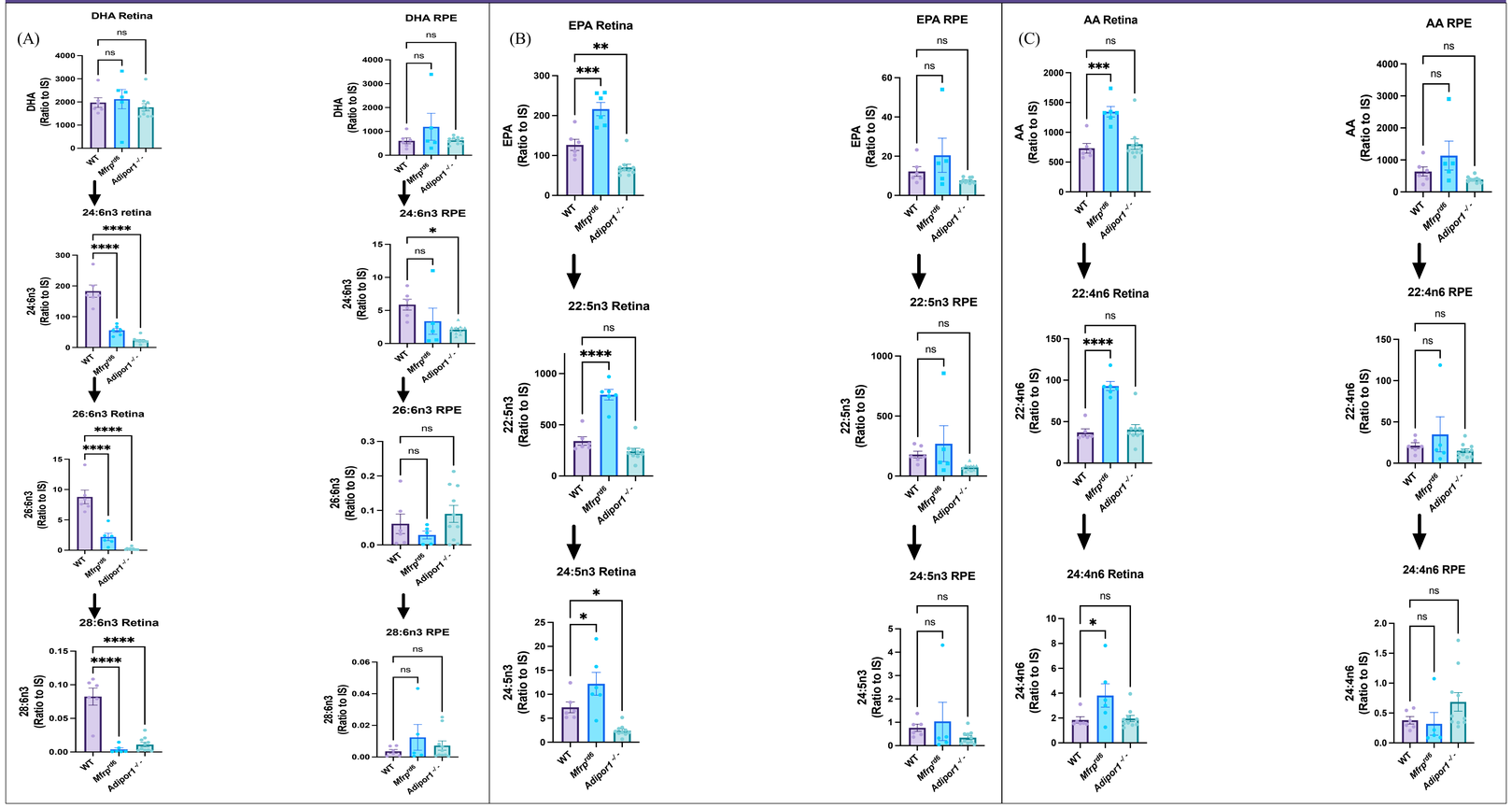


Figure 2. Lipid concentrations in ω-3 and ω-6 pathways relative to the internal standard starting with DHA (A), EPA (B), or AA (C) for WT, *Mfrp*^{rd6} and *Adipor1* $^{-/-}$. $^{*}P \leq .05$, $^{**}P \leq .01$, $^{***}P \leq .001$, $^{****}P \leq .0001$.

Conclusions

- *Mfrp*^{rd6} and *Adipor1* $^{-/-}$ had depleted levels of VLC-PUFAs from 24:6n3 onwards suggesting a decreased ability to synthesize Elovanoids which require the precursors 32:6n3 and 34:6n3.
- Given that there was a buildup of 24:5n3 in *Mfrp*rd retina, the conversion of 24:5n3 to 24:6n3 seems to be impaired in animals with *Mfrp*^{rd6}
- In contrast, the levels of PUFAs in *Adipor1* $^{-/-}$ retina were low from 20:5n3 to 36:6n3.
- In *Mfrp*rd retina, there were increased levels of arachidonic acid and its downstream products, suggesting a compensatory effect.
- The use of deuterium starting products can help unveil the accurate pathway.
- The lipid concentrations of RPE and retina samples from 4 week and 8-week-old mice will be analyzed for developmental comparison.

References

1. Jun B, Mukherjee PK, Asatryan A, et al. Elovanoids are novel cell-specific lipid mediators necessary for neuroprotective signaling for photoreceptor cell integrity. *Sci Rep.* 2017;7:5279-5292.
2. Kautzmann M-AI, Gordon WC, Jun B, et al. Membrane-type frizzled-related protein regulates lipidome and transcription for photoreceptor function. *FASEB BioAdvances*. 2020;34:912-929.
3. Rice DS, Calandria JM, Gordon WC, et al. Adiponectin receptor 1 conserves docosahexaenoic acid and promotes photoreceptor cell survival. *Nat Commun*. 2015;6:6228-6242