

## News Release

### Title

**Omega-3 Fatty Acid and its Metabolite 18-HEPE Ameliorate Retinal Neuronal Cell Dysfunction by Enhancing Müller BDNF in Diabetic Retinopathy**

### Key Points

- In diabetic retinopathy (DR), which is one of the three major complications of diabetes, irreversible damage to neurons in the retina is an important problem, so neuroprotective treatment from the early stage of DR is important.

- In this study, it was confirmed that retinal dysfunction in DR also involved a decrease in BDNF, a neurotrophic factor produced by Müller cells, and that oral administration of eicosapentaenoic acid (EPA), one of the  $\omega$ 3 fatty acids, significantly increased BDNF expression in the retina.

- This study is the first study to identify that 18-HEPE, one of the metabolites of EPA, can improve BDNF production and neuronal function in the retina specifically, indicating the efficacy of oral EPA for retinal neuropathy in DR and its mechanism.

### Summary

The research group led by Graduate Student Ayana Suzumura, Associate Professor Hiroki Kaneko, Professor Hiroko Terasaki (Ophthalmology) elucidated the mechanism of retinal dysfunction in diabetic retinopathy and clarified the mechanism of retinal damage suppression by oral administration of  $\omega$ 3 fatty acids and its effects.

Diabetic retinopathy (DR), which is one of the three major complications of diabetes, involves irreversible damage to retinal nerve cells, so early neuroprotective treatment is important. It has been already known that retinal dysfunction has occurred before the appearance of fundus abnormal findings which is used for diagnostic criteria. In this study, they focused on BDNF, a neurotrophic factor that is reported to decrease in diabetes. According to the recent study which suggested that oral administration of eicosapentaenoic acid (EPA), one of the  $\omega$ 3 fatty acids, improves BDNF production in the hypothalamus, they investigated the effect of oral EPA administration to improve BDNF production in the eye and retinal function.

It was confirmed that inhibition of Müller cells that produce BDNF in DR and a decrease in BDNF production leads to a decrease in the activity of Amacrine cells, which are neurons in the retina. It was also revealed that oral administration of EPA improved electroretinogram results and EPA was metabolized in the body and worked in the form of 18-HEPE, suggesting that oral administration of EPA may suppress retinal neuropathy in early DR.

The study has been published online in Diabetes on Feb 6th, 2020.

### Research Background

Diabetic retinopathy (DR) is one of the three major complications of diabetes, and prevention

of blindness by DR is an important issue that directly reduces social loss. Since DR involves irreversible damage to neurons in the retina, neuroprotective treatment from the early stage of DR is important. It has been already known that retinal dysfunction has occurred before the appearance of fundus abnormal findings which is used for diagnostic criteria. The importance of detecting neuroretinal dysfunction is supported by the concept of “neurovascular unit impairment,” which is characterized by the neuronal, glial, and vascular cells mutually influencing each other to cause subclinical changes during the early stages of DR. Therefore, they focused on the fact that one of the neurotrophic factors, BDNF, was reduced in patients with DR, and decided to investigate the possibility of suppressing retinal neuropathy through improved BDNF expression. Previous studies have shown that BDNF neuroprotective role in the eyes, they used subretinal transplantation of the transfected cells that can express BDNF or BDNF intravitreal injection. On the other hand, it has been reported that oral administration of eicosapentaenoic acid (EPA), one of the  $\omega$ 3 fatty acids, improves the production of BDNF in the hypothalamus. Based on this, they examined the possibility of improving BDNF production and retinal function in the eye by using a less invasive method rather than taking EPA and examined the mechanism.

## **Research Results**

Based on the result that the levels of reactive oxygen species (ROS) in the vitreous of DR patients was significantly higher and the fact that oxidative stress is involved in the onset of DR, a DR model was created by administering hydrogen peroxide as oxidative stress. MIO-M1 cells were used as Müller cells to produce BDNF, and PC12D cells were used as Amacrine cells. When hydrogen peroxide was administered to each of them, the decrease in their cell viability decreased, and BDNF production of MIO-M1 cells decreased. On the other hand, when BDNF was administered to PC12D cells, suppression of neurite shortening was observed, and cell viability was improved depending on the concentration of BDNF administered to PC12D cells under oxidative stress.

Eight-week-old female Sprague–Dawley rats were used for these studies and divided into three categories: [a] control group without streptozocin (STZ) injections and fed standard chow without fishmeal but with sunflower oil (5%); [b] STZ group with intraperitoneal (i.p.) injections of STZ and fed the same chow as the control group; and [c] EPA group with i.p. injections of STZ and fed the standard chow without fishmeal but supplemented with 5% EPA. After feeding each of these diets for 8 weeks, the general condition was evaluated and the electroretinogram (ERG) and the choroid samples were analyzed. The STZ group and the EPA group showed a decrease in body weight and an increase in blood glucose level compared with the control group, resulting in ketosis, but there was no significant difference between these two groups. Regarding the oscillatory potentials (OPs) in ERG, which are widely used to evaluate the function of Amacrine cells, the amplitude of the OP wave was clearly improved in the EPA group compared with the STZ group (Figure 1). Analysis of retinal choroidal samples showed that oxidative stress markers increased in the STZ group but decreased in the EPA

group, and that BDNF production decreased in the STZ group but clearly improved in the EPA group. These results indicated that oral administration of EPA did not improve the general condition, but improved oxidative stress in the retina, as well as BDNF production, and improved the function of Amacrine cells with oral administration of EPA. Additionally, lipid mediators in each retinal choroidal sample were quantified by high-performance liquid chromatography and revealed that several metabolites of EPA in the EPA group. Among these metabolites of EPA, only 18-HEPE improved BDNF production, so they decided to confirm this effect in animal experiments. They injected the same amount of PBS and 18-HEPE into the vitreous respectively and confirmed that the OP wave and BDNF production were improved in the eyes to which 18-HEPE was injected.

These results suggested that oxidative stress produced under hyperglycemia impairs Müller cells and reduces the activity of Amacrine cells by reducing BDNF production. It was also confirmed that oral administration of EPA improved BDNF production and suppressed Amacrine cell damage, and furthermore, it was found that oral EPA was metabolized to 18-HEPE in the body and affected the retina specifically (Figure 2).

Figure 1.

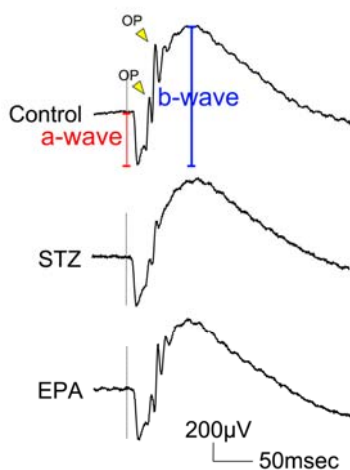
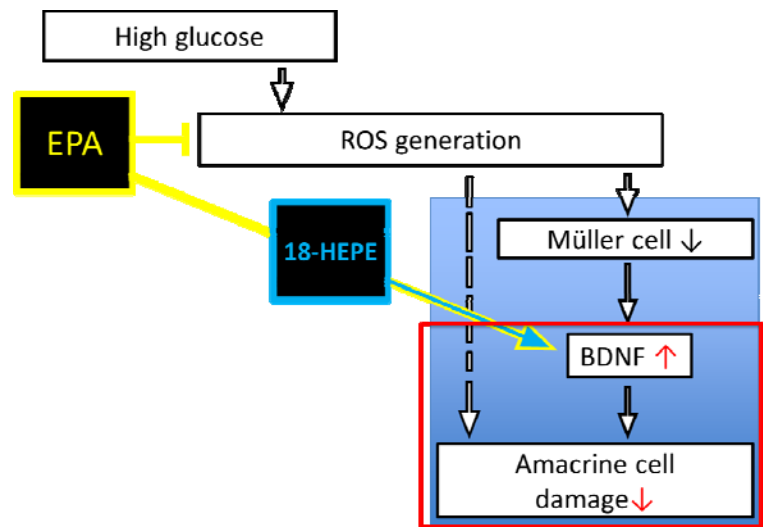


Figure 2.



### Research Summary and Future Perspective

In this study, they found that retinal dysfunction observed in DR involves not only direct damage to Amacrine cells but also a reduction in BDNF produced by Müller cells. In addition, it was also suggested that the specific action of 18-HEPE, a metabolite of EPA, improved BDNF production and intraretinal neuronal function. Therefore, further investigation of the oral EPA intake which has the potential to improve retinal damage in the early stage of DR with neurotrophic factors might contribute to building a new therapeutic strategy.

### Publication

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Diabetes (Feb 6<sup>th</sup>, 2020)

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DOI: 10.2337/db19-0550

Japanese ver.

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