Lipoxin Mediated Neuroprotection

Published date: May 29, 2017

Technology description

Lipoxins LXA4 and LXB4 as potential treatment for glaucoma and other neuronal injury related pathologies

Neuroprotective agents represent an intensive research field and an area of high interest for pharmaceutical development. Lipoxins are known pro-resolving lipid mediators that act locally in paracrine or autocrine manners to dampen inflammation. A team of researchers from the University Health Network and the University of California at Berkeley have discovered a new role for lipoxin signaling directly on neuronal homeostasis and survival. Both endogenous lipoxins LXA_4 and LXB_4 demonstrate direct neuroprotective effects in a neuronal cell line, primary cortical neurons, and cultured retinal ganglion cells (RGCs). Interestingly, the much less well-studied LXB_4 demonstrates superior neuroprotective action compared to LXA_4 (Fig.1). In an acutein vivoretinal injury model LXB_4 was similarly more potent than LXA_4. Finally, in a challenging 15-week rat model of chronic glaucoma, LXB_4 was therapeutically delivered to the eye and via IP injection starting from week 8. RGC function and survival was significantly better in LXB_4-treated retinas compared to vehicle, as shown in Figs. 1 & 2. Importantly, there was no observed effect of LXB_4 treatment on intraocular pressure, eliminating a potential indirect effect.

Fig. 1. Therapeutic administration of LXB_4 protects RGC function following chronic IOP injury. (a) Schematic of the experimental design showing ERG and OCT readings every 4 weeks following suture induce IOP. LXB_4 administration started at week 8, and retinal flatmounting and RGC counting was performed at week 15.**(b)**Average waveforms for RGC (pSTR) responses at week 15 for LXB_4 and vehicle groups, and**(c)**relative change in RGC function across 15 weeks. Starting at week 12, there was a significant and increasing rescue of LXB_4 treated eyes compared to vehicle (* $p < 0.05$; n=8 per group, bars are S.D., the shaded area indicates the treatment period).

Fig.2. Quantification of RGC density revealed the suture induced loss was significantly rescued by LXB_4 treatment compared to vehicle in both the outer and inner retinas (***$p < 0.001$ compared to vehicle, n=8, bars are S.E.M.).

Publications

Izhar Livne-Bar, Jessica Wei, Hsin-Hua Liu, Samih Alqawlaq, Alessandra Tuccitto, Karsten Gronert, John G. Flanagan, and Jeremy M. Sivak Lipoxin LXB4 mediates direct neuroprotection from acute and chronic retinal injury (submitted)

Application area

Neuroprotection
Treatment for glaucoma

Institution

University Health Network

Inventors

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