

The neuroprotective effect of latanoprost acts via klotho-mediated suppression of calpain activation after optic nerve transection

Yamamoto K (1) , Sato K (1,2) , Yukita M (1) , Yasuda M (1) , Omodaka K (1,2) , Ryu M (1) , Fujita K (3) , Nishiguchi KM (4) , Machida S (5,6) , Nakazawa T (1,2,3,4)

Latanoprost was first developed for use in glaucoma therapy as an ocular hypotensive agent targeting the prostaglandin F₂ receptor. Subsequently, latanoprost showed a neuroprotective effect, an additional pharmacological action. However, although it is well known that latanoprost exerts an ocular hypotensive effect via the FP receptor, it is not known whether this is also true of its neuroprotective effect. Klotho was firstly identified as the gene linked to the suppression of ageing phenotype: the defect of klotho gene in mice results ageing phenotype such as hypokinesia, arteriosclerosis and short lifespan.

After that, the function of klotho was also reported to maintain calcium homeostasis and to exert a neuroprotective effect in various models of neurodegenerative disease. However, the function of klotho in eyes including retina is still poorly understood. Here, we show that klotho is a key factor underlying the neuroprotective effect of latanoprost during post-axotomy retinal ganglion cell (RGC) degeneration. Importantly, a quantitative RT-PCR gene expression analysis of klotho in sorted rat retinal cells revealed that the highest expression level of klotho in the retina was in the RGCs. Latanoprost acid (LA), the biologically active form of latanoprost, inhibits post-traumatic calpain activation and concomitantly facilitates the expression and shedding of klotho in axotomized RGCs.

This expression profile is a good match with the localization, not of the FP receptor, but of organic anion transporting polypeptide 2B1 (OATP2B1), known as a prostaglandin transporter, in the ocular tissue. Furthermore, an OATP2B1 inhibitor suppressed LA-mediated klotho shedding *ex vivo*, whereas an FP receptor antagonist did not. The klotho fragments shed from the RGCs reduced the intracellular level of reactive oxygen species (ROS), and a specific klotho inhibitor accelerated and increased RGC death after axotomy. We conclude that the shed klotho fragments might contribute to the attenuation of axonal injury-induced calpain activation and oxidative stress, thereby protecting RGCs from post-traumatic neuronal degeneration.

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