Zinc is a critical regulator of optic nerve regeneration

Lukas Andereggen MD; Yiqing Li; Stephen Lippard PhD; Paul Rosenberg MD, PhD; Larry Benowitz PhD
Department of Neurosurgery and F.M. Kirby Neurobiology Center, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA, USA

Introduction

The inability of neurons to regenerate injured axons in the central nervous system (CNS) results in life-long disabilities in victims of traumatic brain injury, spinal cord injury and other CNS diseases. Like other pathways in the CNS, the optic nerve cannot regenerate if injured (Fig. 2E), resulting in lifelong losses in vision. Recent studies have achieved a moderate level of axon regeneration through the injured optic nerve by combining treatments that synergistically activate the intrinsic growth state of retinal ganglion cells (RGCs), the projection neurons of the eye. Nonetheless, even under optimal conditions, more than 50% of RGCs die after optic nerve injury, and most of the surviving RGCs fail to regenerate axons. These observations point to the existence of additional major suppressors of RGC survival and axon regeneration.

Methods

We used autometallography (AMG; Fig. 1 A-C) and the fluorescent Zn2+ sensor ZinPyr1 (ZP1; Fig. 1 D-F) to detect levels of free Zn2+ in the retina after optic nerve injury; and N,N,N',N'-tetrakis-(2-Pyridylmethyl)ethylenediamine (TPEN) and/or ZX1 to chelate free Zn2+.

Results

Chelating Zn2+ using either TPEN or the highly selective chelator ZX1 eliminated the Zn2+ signal in the inner plexiform layer (IPL) and led to enduring survival of RGCs (Fig. 2C, D) as well as considerable axon regeneration (Fig. 2F). These effects were lost when the chelators were saturated with Zn2+, suggesting that the effects of the chelators are mediated through binding of free Zn2+. Combining Zn2+ chelation with other pro-regenerative treatments enabled some RGCs to regenerate axons the full length of the optic nerve in just 2 weeks.

Conclusions

These studies indicate that Zn2+ is an endogenous suppressor of axon regeneration, and they suggest that Zn2+ chelators may be valuable in promoting recovery after various forms of traumatic CNS damage.

Learning Objectives

By the conclusion of this session, participants should be able to understand the unique role of zinc as an endogenous suppressor of CNS regeneration.

Figure 1: Appearance of Zn2+ in the retina after optic nerve injury

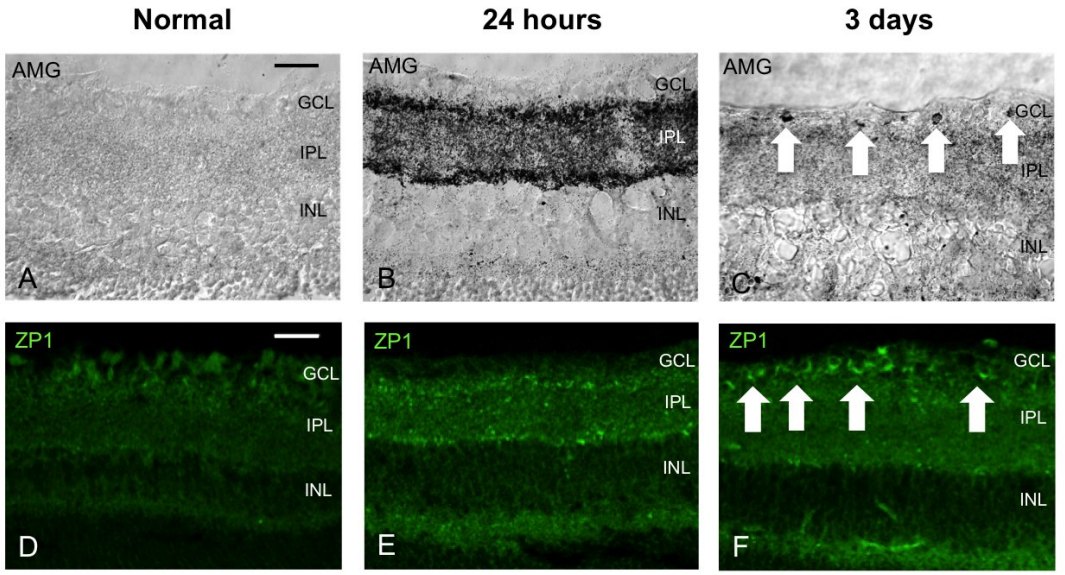
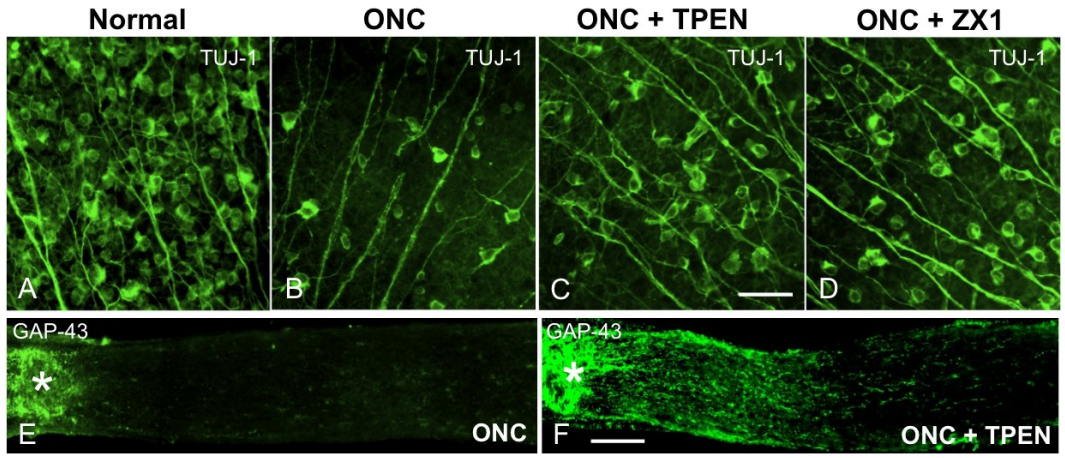


Figure 2: Chelating Zn2+ promotes RGCs survival and optic nerve regeneration



Abbreviations: AMG= autometallography; GAP-43= growth associated protein 43; GCL= ganglion cell layer; INL= inner nuclear layer; IPL= inner plexiform layer; ONC= optic nerve crush; TPEN= N,N,N',N'-tetrakis-2-Pyridylmethyl)ethylenediamine; TuJ-1= tubulin beta III; ZP1= ZinPyr1; asterisks denote the injury site; arrows show RGCs; scale bare= 200µm.