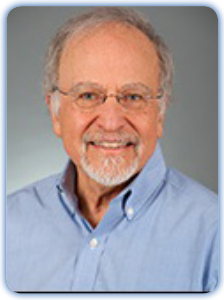
Larry I. Benowitz, J Pediatr Neurol Med 2018, Volume 3
DOI: 10.4172/2472-100X-C1-001



Larry I. Benowitz

Harvard Medical School, USA

Optic nerve regeneration: regulation by amacrine cells, nitric oxide and zinc

Retinal Ganglion Cells (RGCs), the neurons that project visual information from the eye to the brain, cannot regenerate their axons once the optic nerve has been injured and soon begin to die. This failure has dire consequences for victims of traumatic or ischemic nerve damage or degenerative diseases such as glaucoma. Our lab and others have recently identified methods that enable some RGCs to regenerate axons from the eye to the brain, yet most RGCs go on to die and only a small fraction of surviving RGCs regenerate their axons. These findings imply the existence of other major suppressors of RGC survival and axon regeneration. We recently identified mobile zinc (Zn^{2+}) one such factor. Within an hour after optic nerve injury, Zn^{2+} increases dramatically in synaptic vesicles of amacrine cells (ACs), the inhibitory interneurons of the retina, then transfers slowly to injured RGCs. Zn^{2+} chelation leads to the persistent survival of many RGCs and to appreciable axon regeneration, with a therapeutic window of several days. New results show that Zn^{2+} elevation is induced by nitric oxide (NO), a gaseous signal that is generated in a small population of ACs via glutamate-dependent activation of the enzyme NO synthase-1 (NOS1). A novel fluorescent NO sensor reveals that retinal NO levels increase within 30 minutes of optic nerve damage. NO or a derivative thereof probably liberates Zn^{2+} from proteins such as metallothioneins via nitrosylation of Zn^{2+}-binding cysteine residues. Surprisingly, we also find that NO has a second, positive effect on optic nerve regeneration through a cGMP-dependent pathway. Besides eliminating Zn^{2+} accumulation in the retina, AC-specific deletion of NOS1 blocked the regeneration that would otherwise have occurred upon Zn^{2+} chelation. Conversely, elevation of NO with the NO donor DETA-NONOate or prevention of cGMP degradation was sufficient to induce axon regeneration. Thus, NO generated by NOS1 in a small population of ACs is responsible for the deleterious elevation of Zn^{2+} after optic nerve regeneration, but also exerts a positive effect on optic nerve regeneration via cGMP signaling.

Biography

Larry Benowitz is a Professor of Surgery and Ophthalmology. His research interests involve understanding the mechanisms that underlie cell death and regenerative failure after CNS injury, and developing methods to preserve damaged neurons and promote the rewiring of neural circuitry.

larry.benowitz@childrens.harvard.edu

Notes: