Non-genetic neuronal stimulation with photochromic interfaces: application to retinal degeneration

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Optical technologies allowing modulation of neuronal activity at high spatial-temporal resolution are becoming paramount in neuroscience. We engineered a novel photoswitchable membrane interface made of an azobenzene-based compound (Ziapin2) that stably partitions into the plasma membrane and modulates its capacitance in a light-dependent fashion. Millisecond pulses of visible light induce a transient hyperpolarization followed by a delayed depolarization that triggers action potential firing. These effects are persistent and can be evoked in vivo up to 7 days. Given its sensitivity to visible light we studied its ability to restore light sensitivity in retinal degeneration.
We showed that Ziapin2 is capable of reinstating, in degenerate retinas, the complexity of the physiological responses to light stimuli that are implemented by a healthy retina. Thanks to its dual effect on intrinsic excitability, Ziapin2 reinstated brisk and sluggish ON, OFF, and ON-OFF responses in RGCs evoked by full-field or patterned stimuli, accompanied by the reactivation of excitatory and inhibitory conductances impinging on RGCs. Pharmacological dissection of retinal processing revealed that the light-dependent effects of Ziapin2 occurred at the bipolar cell level, followed by reactivation of light computation in the entire retinal network. When tested *in vivo*, a single intravitreal injection of Ziapin2 in fully blind 6-month-old rd10 mice restored light-driven behavior and optomotor reflexes, with a concomitant activation of RGC populations similar to sighted animals. The results indicate that Ziapin2 is a promising molecule for visual restoration in retinal degeneration, irrespective of the mutation causing degenerative blindness.