Optogenetics: development and application

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In 1979, Francis Crick delineated the major challenges facing neuroscience and called for a technology by which all neurons of just one type could be controlled, "leaving the others more or less unaltered"[1]. A new set of technologies now called optogenetics, synthesizing microbial opsins and solid-state optics, has achieved the goal of millisecond-precision bidirectional control of defined cell types in freely behaving mammals[2-9]. ChR2 was the first microbial opsin brought to neurobiology, where we initially found that ChR2-expressing neurons can fire blue light-triggered action potentials with millisecond precision, as a result of depolarizing cation flux, without addition of chemical cofactors[3]; this approach has since proven versatile across a variety of preparations. Second, in work stimulated by the finding that the all-*trans* retinal chromophore required by microbial opsins appears already present within mammalian brains, so that no chemical cofactor need be supplied[4], we found that neurons targeted to express the light-activated chloride pump halorhodopsin from *Natronomonas pharaonis* (NpHR) can be hyperpolarized and inhibited from firing action potentials when exposed to yellow light in intact tissue and behaving animals; because of the excitation wavelength difference, the two optical gates can be simultaneously used in the same cells even *in vivo*[5]. Third, we employed genomic strategies to discover and adapt for neuroscience a third major optogenetic tool, namely a cation channel (VChR1) with action spectrum significantly redshifted relative to ChR2, to allow tests of the combinatorial interaction of cell types in circuit computation or behavior[6]. Fourth, we have developed genetic targeting tools for versatile use of microbial opsins with existing resources including cell type-specific promoter fragments or Cre-LoxP mouse driver lines suitable for a wide variety of neuroscience investigations[7-9]. Finally, we have developed integrated fiberoptic and solid-state optical approaches to provide the complementary technology to allow specific cell types, even deep within the brain, to be controlled in freely behaving mammals[8,10]. We have used this approach for depth targeting of hypothalamic cells (in this case, the hypocretin/orexin cells in the lateral hypothalamus)[8], establishing for the first time a causal relationship between frequency-dependent activity of genetically defined neurons important in clinical neuropsychiatric disease and complex orchestrated mammalian behaviors.

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