Light up your life: Optogenetics for depression?

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In the last year, several new studies have shown the potential of optogenetic stimulation to rapidly modify depression- and anxiety-related behaviours in animal models. Optogenetic technology, as described in a previous editorial,[1] gives a whole new meaning to "light therapy" that is potentially more effective and rapid and has fewer adverse effects than classic light therapy or pharmacological approaches to treat mental illness.

Unlike classic light therapy, which involves a generalized effect of photic stimulation of the visual system to mediate its effects,[2] optogenetics involves the activation by light of engineered light-sensitive ion channel proteins expressed in cells of interest.[3] These light-sensitive channels respond to different colors: channelrhodopsin is activated by blue light and depolarizes to activate neurons, while halorhodopsin is activated by yellow light and hyperpolarizes, inhibiting neuronal activity. Viruses have been generated that can express the light-sensitive channel directly or that express the Cre recombinase to trigger its expression in transgenic animals. For in vivo studies the virus is injected into the brain region of interest, and the channel is activated by light fibres implanted at the region of interest in live behaving animals. Recent studies using optogenetic approaches in mice suggest that stimulation by either laser- or LED light at wavelengths to activate channelrhodopsin expressed in transgenically targeted dopamine neurons in the ventral tegmental area (VTA) can mediate an immediate effect in 2 models of depression.[4,5] Importantly, the pattern of stimulation was critical, with phasic but not tonic light stimulation mediating the effect. Interestingly, in the social defeat model phasic stimulation resulted in increased susceptibility to depression-like behaviour, while inhibition of the same neurons conferred resilience.[4] By contrast, in a chronic mild stress model of depression, phasic stimulation conferred resistance and inhibition induced depression-like behaviour in forced swim, tail suspension and sucrose preference tests.[5] Why these results of stimulating or inhibiting VTA dopamine neurons are opposite is unclear, but it could relate to differences between the models: social defeat is an acute high-stress treatment that induces social isolation and anhedonia-like behaviour and may model posttraumatic stress disorder.[6] Chronic mild stress subjects mice to a repeated low level of inescapable stress that is more akin to depression in humans. Phasic activation of the VTA, while considered a reward pathway, is more accurately a salience monitor for both positive and negative events.[7] Its activation is induced by social defeat, and optogenetic activation triggers the negative salience behavioural response.[4] While in chronic mild stress, phasic VTA activation may trigger motivated behaviour, counteracting the demotivating effects of this paradigm.

Several studies have shown the importance of region- and cell-specific activation of channelrhodopsin in triggering anxiety-like behaviours. Perhaps most strikingly, by viral injection of channelrhodopsin in the basolateral amygdala and stimulation of the central amygdala using bevelled light fibres, it was possible to selectively stimulate basolateral projections in the central amygdala to elicit anxiolytic behavioural effects.[8] Kheirbek and colleagues[9] used a nonviral transgenic approach to show that activation of ventral hippocampal granule cells elicits antianxiety responses in open field or elevated plus maze tests, while activation of the dorsal hippocampus enhances context-dependent fear memory. Interestingly these studies found that either dorsal hippocampus inhibition or stimulation prevented context-dependent fear memory, consistent with an ablation of the memory by block or noise due to excess cells activated, respectively. In yet another example of cell specificity, Liu and colleagues[10] specifically labelled cells participating in the fear response using a transgenic mouse containing the event-inducible c-Fos promoter to express the doxycycline-inducible tTA protein and then injected into the hippocampus a viral construct with a tTA response element driving expression of channelrhodpsin. When placed in a conditioned fear environment and treated with doxycycline, only the few fear-activated hippocampal neurons expressed the ChR2; subsequently, light activation of these cells was sufficient to induce the fear response under innocuous conditions.

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In contrast to the immediate actions of optogenetic stimulation described above, other studies show region-specific effects of chronic stimulation on behaviour. For example, chronic, but not acute, stimulation of 5 min/d over 5–6 days of medial orbitofrontal, but not adjacent prelimbic cortical, glutamate neurons can elicit obsessive–compulsive grooming behaviour in mice.[11] On the other hand, activation of adjacent lateral orbitofrontal cortex reduced compulsive grooming in a genetic model of obsessive–compulsive disorder.[12] The chronic studies are important because they show that in addition to immediate effects, optogenetic stimulation can be used to modify long-term behaviour and further broaden the ability of light-activated channels to modify behaviour. However, the studies in mice are extremely invasive and involve microinjection of virus into deep brain regions, implantation of light fibres in the brain above the injected brain areas and attachment to laser or LED devices. Is it possible to overcome these obstacles and envisage a clinical use for optogenetics? If the answer is yes, optogenetics might provide an effective new clinical paradigm for treatment of depression that is a more refined version of deep brain stimulation, but the obstacles must be solved.

Viral targeting

The first obstacle is the expression of channelrhodopsin in the brain. Unlike in mice, germline expression of channelrhodopsin in specific subsets of cells is not feasible in humans. To bypass this, viruses such as adeno-associated virus or lentivirus, have been used to express channelrhodopsin in primate studies. These viral approaches are safe since the viruses are recombinant, nonreplicating and provide relatively stable long-term protein expression. While invasive, the microinjection of virus into humans has been used in the retina and in the brain for treatment of Parkinson disease and Alzheimer disease and appears safe and effective to express proteins.[13,14] However, assuring dosage, safety and reversibility of the viral approach will be important to its success in humans. Potentially newer technologies, such as TAT-mediated protein transduction or liposome-mediated plasmid transfection, may evolve for nonviral delivery of channelrhodopsin to neurons.

Cell specificity

As illustrated in the examples in mice, targeting specific neuronal cell types (e.g., dopaminergic, glutamatergic, GABAergic) is critical to observe robust behavioural effects of optogenetic stimulation since interneurons and pyramidal neurons generally have opposing effects. A limitation with using viruses to deliver channelrhodopsin is that only a small promoter sequence can be incorporated, and such mini-promoters may have limited cell specificity and activity. However, mini-promoters can show some cell specificity (e.g., the calcium/calmodulin-dependent kinase II promoter to express channelrhodopsin in pyramidal neurons in mice[12]). Studies in primates provide some promise that incorporation of small, targeted promoters may yield sufficient cell specificity. In addition, the virus can be injected into discrete brain regions, such as the VTA, and the light fibre can be similarly targeted to specific regions providing spatial specificity.

Targeting illumination

The problem of target illumination is normally solved by implantation of a light fibre with an adaptor to interface with a laser. The recent success of LED to activate channelrhodopsin suggests a much smaller, cheaper and readily available light activation system that nevertheless requires implantation. Practically, implantation could be done immediately after viral injection; however, this still involves a permanently implanted fibre. Permanent implantation is feasible as done for deep brain stimulation, and a light fibre could be considered less invasive than an electrode, but may be less desirable than noninvasive delivery. For example, subcallosal cingulate deep brain stimulation is seen as a last resort for treatment-resistant patients due to its invasiveness and potential adverse events, including suicide.[15,16] It is possible that approaches used for classic light therapy, such as visual stimulation or light stimulation via the aural canal, could provide sufficient light entry to activate channelrhodopsin noninvasively. The use of LED to emit light would greatly enhance the practicality of the approaches. Alternatively, use of near-infrared transcranial stimulation, which appears to mediate some benefit following brain injury, could be used as a light source, but would require engineering a channelrhodopsin that is responsive to this light wavelength.

Once these technical problems have been overcome, one could envisage a biofeedback approach as is being developed for deep brain stimulation,[17] where at the onset of depressive symptoms, a patient could activate the light pack and tune it to a beneficial frequency. The maximum response and remission of treatment-resistant depression appears with chronic (> 1 yr) deep brain stimulation, and optogenetic stimulation may also require a chronic course for remission of clinical depression. However, the results from animal models of depression discussed previously suggest that an immediate improvement is also highly likely. The main advantage of optogenetic stimulation over deep brain stimulation would be the cell specificity and the ability to either stimulate or inhibit activity that should produce fewer adverse effects and a more robust response if correctly targeted.

Of course, each of the obstacles mentioned presents considerable challenges that may take years to overcome, and yet a relatively short time has elapsed since the development of channelrhodopsins, which has led to a revolution in addressing brain circuitry in individuals with mental illness.[3] Optogenetic approaches are revealing the circuitry and firing patterns that may elicit and stabilize depressive behaviour and could be targeted for pharmacological or behavioural intervention. Given the progression of invasive deep brain stimulation as a therapy for major depression,[16] there is promise that optogenetic approaches may find their way into the clinic.

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