Light now in sight: Control of a 'blind' neuroreceptor with an optical switch

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When nerve cells communicate with one another, specialized receptor molecules on their surfaces play a central role in relaying signals between them. A collaborative venture involving teams of chemists based at Ludwig-Maximilians-Universitat (LMU) in Munich, Germany, and the University of California in Berkeley has now succeeded in converting an intrinsically "blind" receptor molecule into a photoreceptor. They achieved this feat by using molecular genetic techniques to attach what amounts to a light-controlled chemical "switch" to a macromolecular receptor that is normally activated by the endogenous neurotransmitter acetylcholine.

Dirk Trauner, Professor of Chemical Biology and Genetics at LMU Munich, who played a leading role in the project, hopes that the synthetic construct will help to elucidate the precise roles of the natural receptor in the brain. Indeed, he says that it might ultimately be possible to use such synthetic photoreceptors to restore sight to patients suffering from certain forms of blindness.

Trauner and his colleagues chose one of the so-called nicotinic acetylcholine receptors for their experiments. These molecular machines transmit nerve impulses essentially by converting an incoming chemical signal into an electrical response, which is propagated along the length of the nerve fiber. They are found in many types of excitable cells in the nervous system, and at the so-called "endplates" which form the functional connections between muscle cells and the motor nerves that control them. Such receptors span the cell membrane, forming a physical

link between the external medium and the interior of the cell. Binding of the neurotransmitter acetylcholine to the external surface of the receptor acts as a switch, opening a tiny pore in the receptor, through which positively charged sodium ions can flow into the cell. The resulting depolarization (change in the balance between positive and negative charges on either side of the membrane) gives rise to the so-called action potential, the basic electrical stimulus that constitutes the neural response.

The functional features of neuroreceptors make them attractive targets for a research strategy that Trauner calls "optochemical genetics." This involves the use of genetic manipulation to modify a receptor protein so that it can bind a synthetic, light-sensitive switching ligand. Compounds known as azobenzenes can serve as the basis for such switching elements. They contain a photosensitive double bond between nitrogen atoms, and can be flipped between bent and extended conformations by illumination with monochromatic light of different wavelengths. In order to ensure that the artificial switch attaches at the correct position, and that the light-induced conformational changes are sufficient to open and close the ion channel, Trauner and his colleagues introduced several targeted modifications into the gene that specifies the amino acid sequence of the receptor. Using electrophysiological techniques, they were able to confirm that cultured cells expressing the mutated gene responded in the expected manner. Following incubation of the cells with the appropriate azobenzene compound, illumination with violet light was shown to activate the modified receptor, while subsequent exposure to green light closed its ion channel.

In 2010 Dirk Trauner received one of the highly endowed Advanced Grants awarded by the European Research Council (ERC) for a project which is also based on a "photopharmacological" approach. Its long-term goal is to find ways of compensating for the loss of dedicated photoreceptors in the eye – the most common cause of blindness. To

achieve this goal, Trauner is working on the development of hybrid photoreceptors. "The basic idea, which has in principle been shown to work in animal models, is to confer light sensitivity on surviving neurons in the eye that do not normally respond to light," he says.

More information: Optochemical control of genetically targeted neuronal nicotinic acetylcholine receptors, I. Tochitsky, M.R. Banghart, A. Mourot, J.Z. Yao, B. Gaub, R.H. Kramer, D. Trauner, *Nature Chemistry*, Jan 8, 2012. doi:10.1038/NCHEM.1234