involves mass transfer from the primary to the companion.

According to this binary model, during the 20-year Great Eruption, the companion would have accreted matter in the form of gas in an amount equivalent to several times the mass of the Sun. A huge amount of gravitational energy would have been released during this accretion process, which would have been the main energy source of the Great Eruption. Furthermore, some of the mass accreted by the companion would have been blown by the companion itself in two opposing directions, leading to the shaping of the Homunculus bipolar nebula, which is now observed to surround the binary system. Most of the mass in the nebula was blown directly by the primary star. The present masses of the primary and companion may be up to 170 and 80 times that of the Sun, respectively[3].

During the Great Eruption, η Carinae experienced two bright peaks in luminosity, in 1838 and in 1843 (refs 4, 5). Rest *et al.*[1] find that the echoes' light curves — graphs of their intensity as a function of time — are consistent with these peaks. The time difference between the two peaks corresponds to the orbital period of the binary system around 1840; at present, the orbital period is five and a half years[3,4,6]. The peaks themselves occurred when the two stars were closest together in their elliptical orbit around each other. Rest and colleagues' analysis of the echoes' spectra and light curves lends some support to an eruption model in which energy comes from mass transfer that is triggered at the stars' closest approach.

The temperature of about 5,000 K and the occurrence of two strong peaks (two weaker peaks are recorded historically at around 1849 and 1854) are reminiscent of the eruptive event[7] that the star V838 Monocerotis experienced in 2002 (Fig. 1). One popular model for this eruption posits[8] that a low-mass star of about half the mass of the Sun was destroyed in a merger with a star about six times more massive than the Sun. The accretion of gas from the low-mass star onto the surface of the more massive star would have been the energy source of the eruption. As in the case of η Carinae, the star that accreted mass is a non-evolved star such as the Sun: it is at an evolutionary stage during which nuclear-fusion reactions of hydrogen still occur in its centre.

The progenitor of η Carinae's eruption seems to fall into a varied group of systems that undergo eruptions powered by impulsive mass accretion onto non-evolved stars. The accreting stars can be very massive, as for η Carinae; five to eight times as massive as the Sun, as for V838 Monocerotis; or Sun-like stars. This heterogeneous group of progenitors might also include dying red-giant stars. Accretion of mass from a dying red-giant star onto a Sun-like star over a time span of 5–50 years could lead to eruptions and shape some bipolar planetary nebulae. Red-giant stars are Sun-like stars in a late phase of evolution, during which they become very bright and large. Planetary nebulae are the last moment of a Sun-like star's glory: they are beautiful shining clouds of gas and dust that last for 100,000 years. The nebulae are formed from gas that was once part of the outer shells of the red-giant star. Some of these planetary nebulae are known to have been formed over a short period of time, and have a structure that is not unlike that of η Carinae. One example of such nebulae is the bipolar planetary nebula NGC 6302 (ref. 9).

As Rest and colleagues[1] mention, a few more years of data are required to improve the echoes' light curves and to test their consistency with the historical observations. This will definitely help to nail down the origin of the eruption event, to find out whether it was triggered by mass transfer to the companion or by some as-yet-undetermined eruptive event in the primary itself, as proposed by some traditional models. Although it has been studied for more than a century, η Carinae still holds several secrets. In the coming years, it is hoped that observations with modern telescopes will shed more light on this intriguing binary system. ■

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STRUCTURAL BIOLOGY

Ion channel in the spotlight

When expressed in neurons, channelrhodopsin proteins allow the cells' electrical activity to be controlled by light. The structure of one such protein will guide efforts to make better tools for controlling neurons. SEE ARTICLE P.369

OLIVER P. ERNST & THOMAS P. SAKMAR

Imagine taking a pigment from the eyespot (the light-receptive organelle) of a motile, photosynthetic alga and putting it into the neuron of a living mouse. Now imagine exciting the pigment using laser light and seeing a reproducible effect of this stimulus on the behaviour of the mouse. It sounds unbelievable, but this is the basis of optogenetics — the combination of optical techniques and genetic engineering that allows light to control an organism's physiology and behaviour[1].

The algal eyespot pigments that facilitate optogenetics are proteins called channelrhodopsins (ChRs), and they can be thought of as light-activated, nanometre-scale electrodes. When expressed in cells *in vitro* or *in vivo*, ChRs target the cell membrane and are bound to a chromophore — a kind of molecular antenna that absorbs light. Illumination of the ChR rapidly causes a flow of cations across the membrane. The resulting electrical current then gradually turns off and the ChR 'recovers', whereupon the whole process can be repeated. But the precise mechanism for how light opens the channel gate and how the gate closes is not known. On page 369 of this issue, Kato *et al.*[2] report a high-resolution X-ray crystal structure of a genetically engineered ChR, and use it to propose an explanation for how the isomerization of its chromophore causes pore opening.

Although the behaviour of motile algae has been studied for decades, it wasn't until 2002 that an eyespot pigment of the alga *Chlamydomonas reinhardtii* was identified[3] as the light-activated protein channelrhodopsin 1. Three years later, ChRs were expressed in mammalian neurons and used to facilitate the light-induced stimulation of the cells' activity[4]. Subsequent bioengineering of ChRs, enabling optical control of cells on the millisecond timescale, together with the development of systems for delivering genes to specific cell types, boosted the rapidly growing field of optogenetics[5]. Since then, the use of this technology has grown exponentially, with no signs of its popularity waning.

Microbial opsins — the family of light-activated proteins that includes channelrhodopsin — have been the most commonly used protein tools for optogenetics[6]. The light sensitivity and spectral absorption of opsins are due to the fact that the proteins are covalently bound to their chromophore (all-*trans*-retinal, a derivative of vitamin A). These proteins share a common structural plan, which includes seven transmembrane helices and a characteristic bond (known as a Schiff base) that connects retinal to a lysine amino-acid residue in helix 7.

The first microbial opsins to be identified were bacteriorhodopsin and halorhodopsin, both of which were found in halobacteria. Bacteriorhodopsin (BR) uses light energy to pump protons out of cells, whereas halorhodopsin pumps chloride ions in the opposite direction. In halobacteria, a complex of a sensory rhodopsin and a transducer protein mediates phototaxis (the microbe's movement in response to light). But in microalgae, ChR performs this task without a transducer, opening its pore in response to light to generate an ion current. It can do this because the light-sensitive chromophore and the channel reside on the same polypeptide chain.

What puts these molecular channels and pumps in the top drawer of the optogenetics toolbox for neuroscientists is the fact that they allow light to be used as a fairly innocuous method to change the ion gradient across the membrane of a neuron, thereby enabling cell depolarization (neuronal activation) or cell hyperpolarization (neuronal silencing). The latest optogenetic gadgets actually contain two microbial opsins linked in tandem, a system that allows greater control of ion flow compared with previously used individual opsins[7].

Although a wealth of structural and biophysical studies have improved our understanding of the pump processes for BR and halorhodopsin, relatively little is known about the gating process of ChR. What is known is that the ChR process, like those of BR and halorhodopsin, is cyclic, with each cycle lasting tens of milliseconds and involving several intermediates. Experiments that introduced targeted mutations into ChRs, and analysed the proteins' electrophysiological and spectroscopic properties, have also yielded modified ChRs that show altered ion preferences, spectral properties and pore-opening and -closing kinetics.

Kato *et al.*[2] now report that the structure of ChR (Fig. 1), although similar to that of BR in some respects, also brings a few surprises. These unexpected features might explain the properties of some of the commonly used engineered ChR mutants. When the authors superimposed the structure of their ChR on that of BR, they found that the transmembrane domain and position of retinal are similar. But unlike BR, which assembles in trimers in the membrane of halobacteria, ChR forms a dimer in which the two subunits are in close contact, in agreement with a previously proposed structure[8] obtained using electron crystallography.

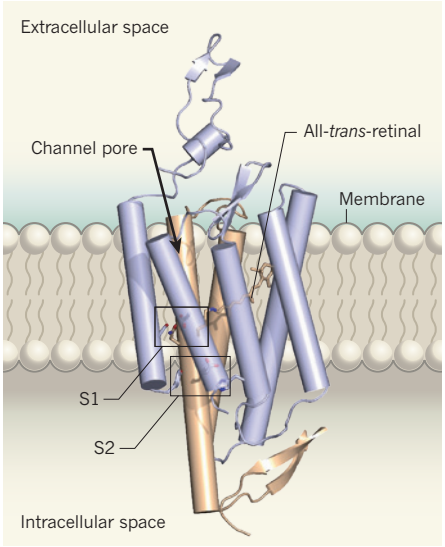

Figure 1 | Structure of a closed light-gated cation channel. Channelrhodopsins (ChRs) are proteins that form channels in microbial cell membranes. The channels form from seven transmembrane helices (shown as cylinders) and open in response to light, allowing cations to pass through the membrane. Their light sensitivity is caused by a molecule, all-*trans*-retinal, that is covalently attached to the protein. Kato *et al.*[2] report the X-ray crystal structure of a chimaeric ChR constructed from two other ChRs, ChR1 and ChR2; the purple parts of the protein are from ChR1 and the brown parts are from ChR2. The chimaeric ChR forms dimeric structures, but only one ChR is depicted. The authors find that a negatively charged pore sits between helices 1, 2, 3 and 7 and is interrupted by two trios of amino acids, which form gates S1 and S2. They propose that light-induced isomerization of the retinal causes the gates to open, extending the pore to the cytoplasm.

Another difference between BR and ChR is that ChR has extended amino-terminal and carboxy-terminal domains. The N-terminal extension contains three cysteine amino-acid residues, which form covalent disulphide bonds with their counterparts in a second ChR molecule, enabling dimerization. The C-terminal extension forms a β-sheet at the end of the long helix 7, which protrudes into the intracellular space. For their study, Kato *et al.* crystallized a truncated version of ChR, which — like ChRs used as optogenetic tools — consists only of the transmembrane part and lacks more than half of the naturally occurring protein. So, the β-sheet observed by the authors may be a part of the large, mostly missing C-terminal domain, which is thought to be involved in subcellular localization and tethering of the ChR to the algal eyespot.

Perhaps the most notable difference between ChR and BR is that the extracellular ends of helices 1 and 2 in ChR are tilted outward by about 3–4 ångströms with respect to the analogous helices in BR. Together with helices 3 and 7, this creates a pore extending halfway through the protein. The authors observe that the inside surface of the pore contains many negatively charged amino-acid residues. Most of these are glutamic acid residues from the extracellular part of helix 2, suggesting that this helix is mainly responsible for defining the pore's conductance and ion selectivity. The negatively charged pore elongates into a slightly positively charged vestibule in the extracellular space.

The pore created by helices 1, 2, 3 and 7 ends in the middle of the protein, where retinal resides. On its intracellular side, the pore is constricted by two gates, each consisting of three residues from different helices. The three residues of the innermost gate form a hydrogen-bonding network next to retinal's attachment site, suggesting that helix movements caused by retinal's isomerization might break the network and open the gate. The movement of helices 1 and 2 might also open a second gate further towards the intracellular side, along the putative cation channel. Although Kato *et al.*[2] argue quite convincingly that the cation-conductance pore comprises helices from a single ChR molecule, an alternative hypothesis is that the ChR dimer assembles to form the pore using elements from each of the two ChRs[8]. Such an arrangement would be reminiscent of the situation reported[9] for two-pore-domain potassium channels.

With this first report[2] of a high-resolution crystal structure of an engineered ChR, are we at the dawn of the age of 'structural optogenetics'? Structure-based design, combined with the discovery of other useful microbial ChRs, might produce optogenetic tools that have highly specific properties tailored for the study of individual cell types and signalling processes. And although it is too early to say "take photons, not drugs", the potential for optogenetics to revolutionize neuroscience and neurology is now even more in the spotlight. ■

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