NATURE|Vol 458|23 April 2009

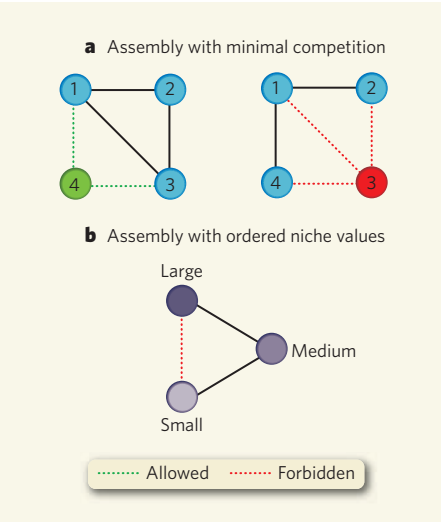

Figure 2 | Minimal assembly rules can explain structure. a, An assembly rule that minimizes competition by adding specialists along paths of least resistance[1]; solid lines denote existing connections. The left-hand sequence minimizes competition by adding species 4 to a single guild of competing species (1 and 3). Because it is easier for species 4 to join the network as a specialist, this is a path of least resistance. In the right-hand 'forbidden' sequence, the new species (3) must compete with two guilds of species — (4 and 1), (2 and 1) — and is not entering as a specialist. **b**, Another common minimal assembly constraint is a natural ordering in the resource set[7], as might result from evolution[6]. The nodes are resources used by each species (here, seed sizes), and each species is represented as a line joining two resource classes. Adding a species that eats small and large seeds, but ignores middle-sized ones, violates the niche ordering (a common minimal assembly constraint)[1,5–7]. (Graphic modified from ref. 7.)

of large-scale failures in cooperative networks[8]. Mutualism facilitates greater biodiversity. But it also creates the potential for many contingent species to go extinct, particularly if large, well-connected generalists (for example, certain large banks) disappear.

Moreover, as reported by Bastolla *et al.*[1], a strong mutualistic interaction between two species (excessively favourable selective terms) can move the system into a strong mutualistic regime; this will destabilize other weakly mutualistic species groups whose interaction strength falls below some threshold. Over time, only the strong cooperators survive, and the weakly cooperating species groups go extinct. This stylized behaviour of simple mutualistic networks possibly applies to other domains, in which strong cooperation between two agents may cause the demise of all other agents — or where, in less-stylized cases, uneven cooperative subsidy or advantage in global networks can be dangerous unless the mutually beneficial effects propagate more or less evenly throughout the network.

As a specific speculative example, consider the interdependence of the Internet auction site eBay and the payment system PayPal. PayPal was the dominant method of payment for eBay auctions when it was bought by eBay in 2002, strengthening cooperative links between the two companies. Insofar as this simplified model applies, this duopolistic partnership would have encouraged the demise of alternative competing payment systems, such as eBay's Billpoint (phased out after the purchase of PayPal), Citibank's c2it (closed in 2003) and Yahoo!'s PayDirect (closed in 2004).

Whether Bastolla and colleagues' model[1] of structured cooperation performs the same role in other domains is intriguing but unclear. In particular, the extent to which the topology of cooperative linkages in payment networks — or more importantly, in networks of balance sheets — may increase systemic risk in the financial sector remains an open question[9]. Tackling such questions will no doubt require mutualistic cooperation between researchers linking different competitive fields. ■

George Sugihara and Hao Ye are at the Scripps Institution of Oceanography, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093-0202, USA.
e-mail: gsugihara@ucsd.edu

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NEUROSCIENCE

Optical control of reward

David E. Moorman and Gary Aston-Jones

Is it wishful thinking that the behaviour of an organism as complex as a mouse might be controlled by modulating its intracellular signalling with light? No: this is just what researchers have achieved with an elegant technique.

Ever since the Italian physician Luigi Galvani discovered that frogs' muscles twitch when stimulated electrically, the integral role of electricity in the functioning of the nervous system has seemed clear. But there is also a growing appreciation that intracellular signalling pathways — which can interact with the extracellular environment through G proteins and G-protein-coupled receptors (GPCRs) — play an essential part in the processing of information by neurons. Deisseroth and colleagues[1] (Airan *et al.*, page 1025 of this issue) now describe a powerful technique that allows intracellular signalling pathways to be controlled through the activation of GPCRs by light. Intriguingly, by modulating specific signalling cascades in this way, the authors can control behaviour in mice.

Deisseroth and colleagues[2] had previously shown that naturally occurring light-activated ion channels, such as channelrhodopsin-2 (ChR2) and halorhodopsin, could be integrated into neuronal cell membranes to drive the respective activation or inhibition of electrical impulses using light. By means of this and other similar techniques[3,4], neuronal impulses can be regulated with unprecedented temporal, spatial and cell-type specificity. In the latest development, Airan *et al.*[1] have created chimaeric GPCR molecules that they call optoXRs. The extracellular and transmembrane portions of optoXRs (opsin) consist of the light-activated rhodopsin protein, but their intracellular components are those of specific GPCRs. The authors focused on two main receptors for the neurotransmitters adrenaline and noradrenaline: the β_2 receptor, which couples to G_s proteins, and the α_{1a} receptor, which couples to G_q proteins. As these two classes of G protein activate signalling pathways that are mediated by different effector molecules[5], the authors could control a wide range of intracellular signalling pathways.

Airan *et al.* first expressed optoXRs in cell lines to test the molecules' basic functionality. Depending on the optoXR expressed, they observed a robust light-driven increase in the levels of the cellular signalling molecules calcium, cAMP and Ins(1,4,5)P_3 — effects that are associated with activation of the corresponding native GPCRs. What's more, the levels of increase were similar to those that occurred after activation of the native receptors, demonstrating that optoXRs can potentially regulate intracellular signalling in a physiologically relevant yet precise manner via specific G proteins.

The authors next investigated light activation of optoXRs in brain slices containing neurons from the nucleus accumbens region. They report an increase in the levels of phosphorylated CREB, a protein that functions downstream of G_s- and G_q-mediated pathways. So it seems that even downstream components of these pathways can be activated by light without the need for additional cofactors, a requirement that would have limited this technology's applicability

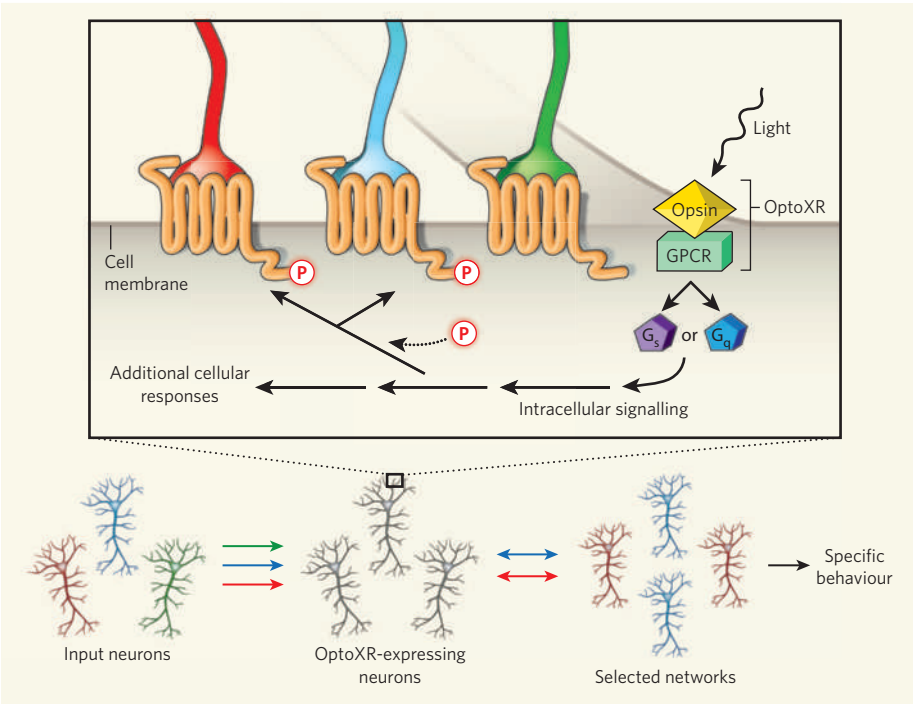

Figure 1 | Light stimulation, intracellular signalling and regulation of function in neural networks. Airan and colleagues' data[1] suggest that light stimulation of chimaeric GPCRs (optoXRs) activates intracellular signalling pathways and is involved in regulating the function of neural networks. Light stimulation of optoXRs can activate intracellular signalling pathways to produce various responses, including phosphorylation (P) of specific receptors (inset). Potentiation of receptors in this way could select a subset of input neurons (red and blue) to influence the optoXR-expressing neurons. Thus, neuromodulation by intracellular signalling can bias network output signals that produce distinct behaviours depending on the GPCR activated.

in vivo. Moreover, illumination of individual neurons either increased or decreased impulse activity, depending on the type of GPCR they expressed. The kinetics of activation or inhibition matched that expected for signalling molecules acting downstream of GPCRs, as opposed to that due to a direct electrical effect.

Notably, light stimulation of optoXRs in the nucleus accumbens influenced reward-related behaviour in mice more reliably than did stimulation of ChR2 that simply increased impulse activity. This behaviour was assessed using a 'place-preference test' in which the strength of the association an animal makes between a pleasant stimulus (such as a drug or food) and a specific location is determined by the time the animal spends in that location in the absence of the stimulus[6].

Airan *et al.*[1] implanted optical fibres in mice expressing optoXR in their accumbens neurons. In this way, they could activate specific G proteins with light pulsed into the accumbens whenever the animals entered a specific location. On a subsequent test day (in the absence of light stimulation), these mice showed a strong preference for the location previously paired with stimulation of the α_{1a} optoXR, weaker preference if the β_2 optoXR had been stimulated, and virtually no preference when ChR2 had been stimulated. Thus, whereas simply increasing electrical-impulse activity in accumbens neurons (using ChR2) does not produce preference, activation of distinct intracellular signalling pathways is effective in generating this behavioural response.

The idea that the coding of information in the nervous system, as reflected in responses such as learning and behaviour, is mediated by factors other than the impulse activity of neurons is conceptually new, and the authors' technique could lead to substantial insights into nervous-system function. But one question, which is not addressed in this paper, arises immediately: how can the behavioural output of the nervous system be mediated by intracellular signalling rather than by electrical impulses?

The answer may lie in the fact that G proteins and GPCRs are involved in neuronal modulation mediated by neurotransmitters such as dopamine and noradrenaline. Neuromodulation is different from neuronal activation or inhibition, because it affects the activity of target neurons by regulating their responses to inputs from other neurons, rather than by simply increasing or decreasing their electrical activity[7,8]. Light stimulation of ChR2 electrically activates a neuron, but has no modulatory effect on the neuron's response to other inputs. Light activation of optoXRs, however, activates specific signalling cascades, which can alter the neuron's response to other inputs, in effect creating a context for the target neuron's responses so that it becomes more sensitive to some inputs than to others (Fig. 1). This effect allows more subtle but complex manipulation of impulse activity in a neuron in response to its multiple networks of inputs, thereby potentiating (or de-potentiating) throughput for selected networks. The associated effects would be more than simply increasing or reducing impulse activity, and could include both short-term[8] and long-term[9] changes in various cellular processes.

Other questions stemming from this report relate to similarities or differences between light-mediated and normal chemical control of G proteins. For example, how flexible is Airan and colleagues' method in mimicking physiological signalling *in vivo*, given that the duration, frequency and temporal pattern of light stimulation used by the authors[1] were optimal for the effects they report? Also, was the light activation of G proteins generally reinforcing or rewarding, or did it have some other effect that resulted in conditioned place preference? And would this technique be useful for specifically modulating other behaviours? The last question is salient, given that the authors expressed optoXRs non-selectively — potentially in all types of accumbens neuron. This concern could be readily addressed by including cell-type-specific promoter sequences upstream of the genes encoding optoXRs[10].

Despite these questions, Airan *et al.*[1] have undoubtedly developed an important technique. Whereas neuroscientists will rightly be enthusiastic about its uses in basic research, it could also potentially be used to develop new treatments for mental disorders, in which GPCR-mediated signalling is often affected[5]. ■

David E. Moorman and Gary Aston-Jones are in the Department of Neurosciences, Medical University of South Carolina, Charleston, South Carolina 29425, USA.
e-mail: astong@musc.edu

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