shapes for implementation in imagers. This technology heralds the advent of new classes of imaging devices with wide-angle fields of view, low distortion and compact size.

The recent developments[3] in compressible–stretchable electronics provide the prospect of many new applications such as long-term bionic implants, robotic sensory skins[4], ambient displays embedded in (for example) wallpaper, and intelligent surfaces that are chemically or electronically functionalized and can interact with people, objects or their environment. One of the most difficult requirements is to achieve excellent mechanical robustness and good electronic performance while satisfying basic electrical requirements — the materials and circuit architecture used in conformable and stretchable electronics must be designed such that their mechanical integrity and electrical functionality are preserved during the fabrication and use of the resulting products. In recent years, Rogers and his colleagues[5] have developed one- and two-dimensional stretchable ribbons and circuits for this purpose; the two-dimensional compressible components used in the electronic eye camera represent a natural extension of this line of research.

The promise of this technology extends well beyond the hemispheric configuration demonstrated by Ko *et al.*[2]. For instance, it could be applied to integrate optoelectronics onto complex, curvilinear surfaces for use in health-monitoring devices that optically detect concentrations of oxygen and other constituents in blood. The new possibilities in optics design should lead to a further reduction in the imaging distortion of ultra-compact camera systems in which photodetector surface geometries can be carefully optimized. Furthermore, distortion-free, adaptive focusing mechanisms might be feasible if the stretchable imager of these camera systems can be developed on actively deformable substrate surfaces. Such simplified systems should have much improved optical transparency — that is, have much reduced optical loss compared with that arising from the use of multiple lenses. This beneficial feature will not only generate more industrial applications for these systems, it will also benefit fundamental research at wavelengths for which existing materials cannot ensure sufficient optical transparency.

In addition to the further development of concave photodetector systems, we can expect to see advances in creating convex imagers — for use in, for example, artificial insect-like compound eyes with exceptional dynamic visual acuity, and in fish eyes that have a 360° field of view. These and other types of biologically inspired device should become feasible given the advances in optical engineering made possible by the advent of geometrically transformable and stretchable–compressible electronics and optoelectronics. All in all, with their electronic eye camera, Rogers and colleagues have delivered an outstanding contribution by showing how progress in electronics can be made by overcoming the constraints of flat silicon wafers. ■

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PHARMACOLOGY

Unready for action

Joe Henry Steinbach

Boy scouts recognize that the key to success is to be prepared. The same is true of molecules that bind to and open ion channels — the least effective ones are slower to prepare the channel to be ready for opening.

Some drugs, known collectively as agonists, can be thought of as molecular switches — if the molecule fits the active site of the receptor, the biological response is switched on. But so-called partial agonists pose a problem for this simple model. A partial agonist is a compound that elicits less than a full biological response on binding to its target, even when it occupies all the available binding sites. How can this be?

Reporting on page 722 of this issue, Lape *et al.*[1] provide an answer for partial agonists that bind to two structurally related channels — the glycine receptor and the muscle nicotinic receptor. The binding of a full agonist to these receptors causes the channels to be open almost constantly, so that the maximum possible current in the channel is observed as ions flow through. But when partial agonists bind, the channel is open for a smaller proportion of the time, and only a fraction of the maximum current flows. Lape *et al.* show that this is because the partial agonists often fail to trigger a conformational change in the receptor that precedes the actual opening of the channel.

The classic view of drug action is known as the occupancy model, and proposes that, when a drug binds to an effector (a receptor or an enzyme), the drug–effector complex constitutes the signal that generates a biological effect (Fig. 1a). The discovery of partial agonists posed a problem for this simple model, so an additional step was added[2]: binding creates an inert drug–effector complex, which then undergoes a conformational change to yield an active state. In this scheme, partial agonists binding to ion-channel receptors were thought to cause those channels to open slowly (Fig. 1b). This idea has dominated thinking about the nature of partial agonism for the past 50 years.

But a third model for receptor activation has also been proposed, in which an intermediate state exists between the initial, inert drug–effector complex and the receptor with the channel open (Fig. 1c). This intervening state has been called the flip state[3]. Readers of a military bent might prefer to think of it as a cocked state.

The flip-state theory certainly makes sense for ion channels. These large proteins consist of several subunits, and their activation involves a considerable conformational change that probably takes place in a series of steps. Thermodynamic analyses of kinetic experiments have been used to infer the relative times at which individual amino acids in muscle nicotinic acetylcholine receptors are perturbed during activation[4,5]. The results suggest that five distinct sets of residues exist, with those near the agonist binding site moving first, and those near the channel's gate moving later. This kind of analysis has also been used to compare a range of molecules that bind to acetylcholine receptors, from weak partial agonists to full agonists[6]. The differences between agonists appeared near the start of the activation process, at the same time as the movements of amino acids close to the agonist binding site.

The best way to study receptor states as agonists bind is by the kinetic analysis of currents through a single ion channel. Lape *et al.*[1] adopted this approach, analysing the actions of partial agonists using high-resolution, single-channel recordings. They examined the durations of the brief periods in which a channel is closed while an agonist or a partial agonist is bound, and confirm the existence of a flip state. Their results also show why partial agonists fail to maximally activate these ion channels. It seems that partial agonists do not have an intrinsically low channel-opening rate. In fact, they are just as good at opening channels as full agonists — that is, the rate of conversion of the flip state to the open state is as high as for full agonists. The difference is that partial agonists are ineffective at converting the inert drug–receptor complex to the flip state, so their overall ability to produce open channels is low.

It would be grand to know what the flip state looks like. Crystallography can provide satisfying pictures of proteins, although it can be difficult to relate the resulting static images to

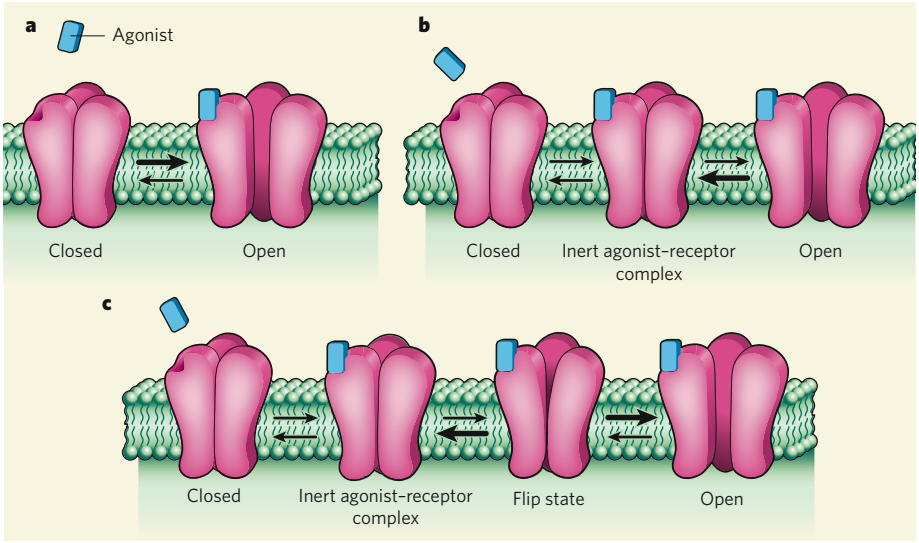

Figure 1 | Models for partial agonism. Agonists bind to receptors to produce an effect, such as the opening of an ion channel. **a**, The occupancy model proposes that agonist binding opens the channel immediately. But this model does not explain how a so-called partial agonist can bind to produce a complex in which the probability of channel opening is low. **b**, A two-step mechanism has therefore been proposed[2] in which an inert receptor–agonist complex forms first, after which the channel opens. Partial agonists were thought to be less effective than full agonists in the channel-opening step. **c**, Lape *et al.*[1] show that another step is required, in which the inert complex enters a state of readiness — the flip state — before channel opening. Partial agonists are less effective than full agonists at inducing the flip state, but bring about channel opening just as quickly.

functional states. Unfortunately, no complete high-resolution structures have been determined for these receptors in known functional states. The crystal structures of putative flip states will be even more difficult to obtain, as such states are necessarily short-lived so that the protein can respond rapidly to transient changes in agonist concentration. Optical or resonance techniques (such as nuclear magnetic resonance) might fill this gap in the future.

The authors' insight[1] into the mechanistic basis of partial agonism will quell some angst among pharmacologists, but it also generates ideas about other consequences of the flip state. For example, it has been reported that mutations in the glycine receptors of mice reduce the ability of glycine to open the associated ion channels, because the receptor is less able to 'flip' after binding the agonist[7]. It is also known that some compounds enhance the effects of partial agonists, and can even sometimes convert them to full agonists. Perhaps these compounds affect the entry of the channel to the flip state. Similarly, certain inhibitors of agonists might work by reducing the stability of the flip state.

Lape *et al.*[1] have answered a long-standing question by showing that the flip state can explain partial agonism. Future research will reveal what other aspects of receptor function are shaped by the properties of this state. ■

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MATERIALS SCIENCE

Protein gels on the move

April M. Kloxin and Kristi S. Anseth

Light-induced reactions enable three-dimensional objects to be built from simple compounds. Proteins have been added to the list of building blocks, and the resulting gels move in response to environmental cues.

The ancient Egyptians were arguably among the first photochemists, because they used light-induced reactions as part of their mummification process. They wrapped bodies in linens that had been dipped in a substance called bitumen of Judea. On exposure to sunlight, the molecules in the bitumen reacted to form crosslinks with each other, yielding a hard, protective coating that preserved the mummy for centuries[1]. Variations of this crude polymerization process are still in use today. Latter-day scientists can choose from thousands of different light-reactive monomers, and use sophisticated laser techniques to turn them into polymers that have diverse applications — for forming printing plates for newspapers, for example, or for dental restoration.

Reporting in *Proceedings of the National Academy of Sciences*, Kaehr and Shear[2] describe a fresh twist to this technique. They have generated complex materials by using lasers to induce crosslinking reactions in proteins. Remarkably, the resulting three-dimensional objects change shape in response to their environment. Such systems might find use as moving parts in miniaturized devices, with applications in medical diagnostics or remote environmental sensing.

The authors' approach relies on advances in a technique known as three-dimensional light patterning. Traditionally, this involves 'drawing' a pattern with a narrow laser beam across liquid monomers on a surface. The monomers react to form solid polymers at the places where the laser strikes, so that three-dimensional objects can be built up one layer at a time. A faster process is also now used, in which an entire layer of polymer is made at once by passing light through a stencil — known as a mask to those in the trade — of the desired pattern.

Kaehr and Shear combine these two approaches by raster-scanning a narrow laser beam across a mask on a protein solution, to create solid, three-dimensional structures. This allows complex macroscopic structures to be made without the elaborate and expensive apparatus required to raster-scan precise shapes with a laser. Using their technique, the authors can expeditiously generate objects with dimensions as small as 100 nanometres, and of any desired shape.

To date, proteins have not found much use as building blocks for three-dimensional photofabrication processes, because commonly used photochemical reactions typically denature or destroy the molecules. An unexpected breakthrough came from studies of photodynamic therapy, a medical procedure that uses molecules called photosensitizers to absorb light and so destroy tumours. The mechanism of action was thought to involve photochemical reactions that created covalent links between proteins (or between proteins and other molecules) in tumour cells, leading to cell damage. The crosslinking was generally considered to be uncontrolled, occurring randomly between the various kinds of amino acid. But studies on proteins[3], and on synthetic macromolecules