indicating that they are part of an expanding spherical shell. Spread along arcs 0.4–70 AU in size (where 1 AU is the Sun–Earth distance), the masers are expanding at about 9 km s^{-1} and lie on a circle with a radius of about 60 AU. The deviation from a perfect circular fit is less than 0.1%. Because few masers lie away from the circular distribution, it is likely that the shell is quite thin. After determining the position of the centre of the circle, the authors consulted archival radio data and detected a very faint source, probably the young star powering the expanding shell. But the maser circle is not complete, perhaps indicating that other portions of the shell are disrupted by interactions with the surrounding medium or other nearby stars undergoing formation.

The uniform shape and the thinness of the maser arc in Cepheus A strongly suggest that the material originated in a single, short-lived ejection event. If the object associated with this maser distribution is a young star, as Torrelles *et al.* argue, this means that, at the very earliest stages of stellar formation, mass can be ejected in episodic, spherically symmetric and brief events. Further observations, looking for molecules associated with stellar jets such as molecular hydrogen or SiO, would help to prove that the source is young, but the necessary resolution is not yet available. The planned Atacama Large Millimeter Array, a large interferometer to be built through international collaboration in Chile, could help shed light on the exact nature of the source when it is completed.

Existing theories of stellar formation cannot explain this unique source, so there is a chance it could actually be a mature star. The current observations only reveal details about the masers themselves, not their stellar host, and so we cannot be entirely certain of the host star's age. Only time will tell if the source that has formed this symmetric shell of water masers will eject more material, perhaps allowing a sequel to the stunning set of images presented by Torrelles and colleagues. ■

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Neurobiology

Snails, synapses and smokers

Dennis A. Dougherty and Henry A. Lester

The discovery of a protein that controls the transmission of nerve impulses in snails is significant in its own right. It also advances our understanding of the vertebrate neurotransmitter receptor that responds to nicotine.

On pages 261 and 269 of this issue[1,2], Sixma and colleagues describe how they identified a protein, found in snails, that controls communication between nerve cells; how they characterized that protein's properties; and how they analysed its structure on the atomic scale. This comprehensive set of studies is impressive in itself. Even more important, the structure reveals the essential features of a key region of the nicotinic acetylcholine receptor — the prototypical member of a group of proteins with diverse roles in vertebrate and invertebrate nervous systems. How can we be so sure that a small soluble protein from a snail is relevant to a receptor in the vertebrate central nervous system? First, the amino-acid sequences of the snail protein and of the relevant portion of the vertebrate receptor are similar. And second, the new structure rationalizes almost every result from over 40 years of biochemical and electrophysiological studies of the vertebrate receptor.

Communication between neurons occurs at junctions known as synapses. When stimulated, the presynaptic neuron releases a neurotransmitter, such as acetylcholine at 'cholinergic' synapses. The neurotransmitter diffuses away, and some binds to receptors, which are large proteins in the membrane of the postsynaptic neuron. The nicotinic acetylcholine receptor not only has a binding site for the neurotransmitter, but also has a channel portion (Fig. 1a); when the receptor binds acetylcholine or other 'agonists' (including nicotine), the channel opens to allow ions to flow.

Sixma and colleagues[1] started by studying a cholinergic synapse in cultured snail neurons. They detected the new protein —

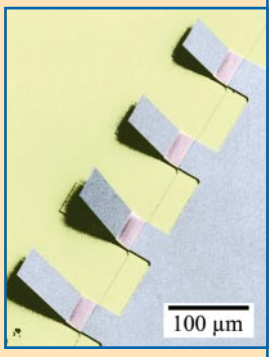
Micromachines

Strain against the machine

The world of micro-electromechanical systems (MEMS) is a tiny one, in which fully functional devices, ranging from electronic circuits to biosensors, operate on micrometre scales. Unfortunately, this world is still mostly a dream, because important elements such as hinges are not only difficult to make but also break easily. P. O. Vaccaro *et al.* address this issue by using elastic strain to make a hinge that moves itself into position (*Applied Physics Letters* **78,** 2852–2854; 2001).

The first generation of MEMS devices was limited to only two dimensions as they were formed by etching techniques. Making devices in three dimensions provides much more flexibility and functionality. This can be done by using hinges that rise above the base layer, known as the substrate. But previous attempts at making hinges involved many steps that required manual or electrostatic intervention. Furthermore, these conventional hinges are prone to defects, tend to stick, and may wear out quickly as sliding parts rub against each other.

Vaccaro *et al.* have taken a simpler approach by bonding two different semiconductors (indium–gallium–arsenide and gallium–arsenide) together to form part of their MEMS device. These materials have different-sized unit cells in their crystal lattices, and the mismatch causes strain. When the semiconductor layers are released from the substrate by etching, they stand up by themselves (see picture). This effect is similar to the way the bimetallic strip works in thermostats — it flexes according to changes in temperature because of the strain between the two metals. The authors also deposited a reflective layer on top of the strain layer to make the hinges into tiny mirrors.



These hinges appear to be fairly robust — they bend with ease and move back to their original position after bending. By creating hinges of different lengths, the authors can change the angle of the mirrors relative to the substrate. More generally, by varying the amount of indium, or by using different materials altogether, the authors can design mirrors with specified angles. And because there aren't any other moving parts, wear and tear shouldn't be a problem. **Josette Chen**

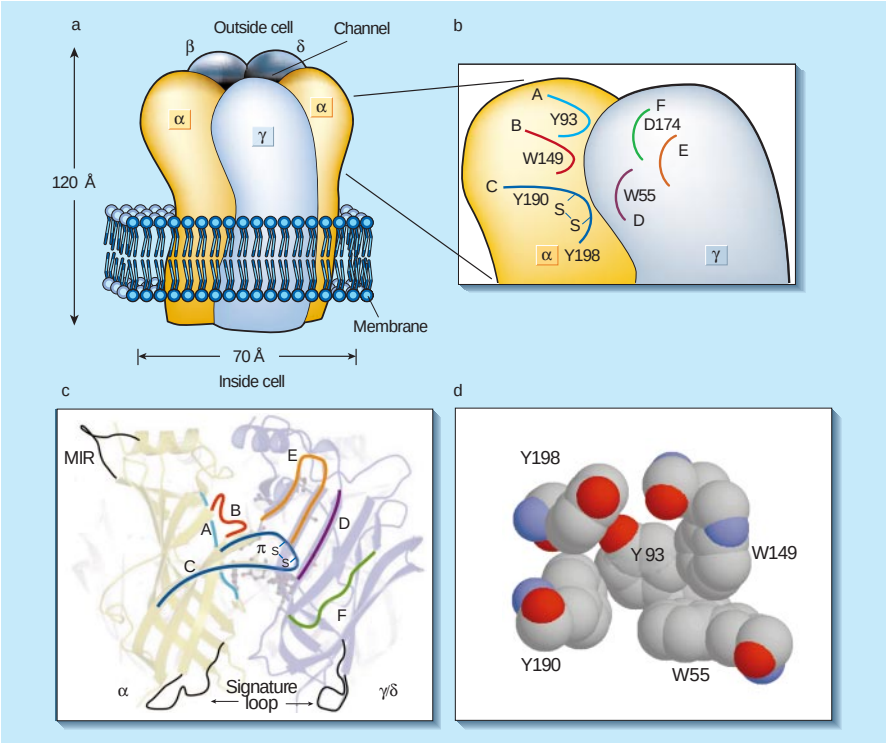


Figure 1 **The nicotinic acetylcholine receptor.** a, **The overall layout of the receptor, based on cryoelectron microscopy studies by Unwin and colleagues[5], showing the α, β, γ and δ subunits. This is the receptor found in postsynaptic muscle cells; some neuronal receptors consist of just one type of subunit.** b, **Biochemical results mapped onto the structure shown in** a. **The agonist-binding site consists of the interface between the α and γ subunits (or the other α and the δ subunit; not shown). One key disulphide bond is shown (labelled S–S), along with the six loops (A–F) that contribute to the agonist-binding site, and the key aromatic residues (Y, tyrosine; W, tryptophan). D174, aspartate residue 174.** c, **The results summarized in** b **are mapped onto Fig. 2b from ref. 2 (page 271). The agonist-binding site is denoted by π, emphasizing the importance of aromatic residues in general and tryptophan 149 in particular. Also highlighted are the signature loops of both subunits, and the main immunogenic region (MIR).** d, **The open box, formed by five aromatic residues, that probably defines much of the agonist-binding site. The view is derived from** c **by a 90° rotation clockwise around the vertical axis.**

which they christen 'acetylcholine-binding protein' — by following the trail of an electrophysiological curiosity. They noticed that postsynaptic neurons at cholinergic synapses show much reduced responses to acetylcholine if glia (non-neuronal cells in the nervous system) are cultured nearby. This led the authors to purify the acetylcholine-binding protein, which they found to be released from vesicles in the glia. They sequenced this protein's amino acids, cloned the gene encoding it, expressed the protein in yeast, and characterized both its effects in yeast and its distribution in snails.

Receptor (number of known subunits)	Drugs and toxins that bind to the ligand-binding domain
Mammalian nicotinic acetylcholine receptor (≥16)	Nicotine, muscle relaxants, ganglionic blockers, possible painkillers, possible cognition enhancers, possible treatments for Parkinson's disease
Mammalian serotonin 5-HT_3 receptor (≥2)	Treatments for nausea, treatment for irritable bowel syndrome
Mammalian $GABA_A$-receptor family (≥19)	Benzodiazepines, muscimol (a toxin found in certain mushrooms), convulsants
Mammalian glycine receptor (≥5)	Strychnine (a convulsant), Zn^{2+}
Invertebrate glutamate chloride receptor (≥2)	Ivermectin (antiparasitic drug)

This protein presumably decreases neurotransmission, but how? We know many quantitative details about the repertoire of molecules and mechanisms that make the nicotinic cholinergic synapse an exquisite electrochemical machine, specialized to function on a timescale of milliseconds and a distance of micrometres. For example, in order to open, the nicotinic acetylcholine receptor must bind at least two molecules of its agonist. Acetylcholine-binding protein might act as a buffer, decreasing the peak concentration of acetylcholine just after its release from the presynaptic neuron.

Figure 2 **Medical notes. The nicotinic acetylcholine receptor belongs to a superfamily that also contains receptors for the neurotransmitters serotonin, γ-aminobutyric acid (GABA), glycine and glutamate. The amino-terminal 230 or so amino acids of each receptor form the agonist-binding domain. This region, as well as binding neurotransmitters, also binds molecules of importance in human and veterinary medicine, as shown here. In addition, in myasthenia gravis (a human autoimmune disease), antibodies bind to the main immunogenic region of the nicotinic acetylcholine receptor. Finally, some naturally occurring mutations in the binding domain prolong the open state of the human nicotinic acetylcholine receptor in muscle. This leads to excessive activation, which damages the synapse and muscle fibre, causing a muscular weakness termed 'slow-channel myasthenic syndrome'[11].**

Acetylcholine would eventually be released from acetylcholine-binding protein, but asynchronously, so its concentration would decrease to the range where the likelihood of two agonist molecules finding the same receptor decreases dramatically. Some neurotransmitter transporters might have related buffering roles at various non-cholinergic synapses[3]. It is also possible that the glia release more acetylcholine-binding protein specifically in response to acetylcholine.

In effect, then, acetylcholine-binding protein would be a 'decoy' receptor for acetylcholine. The idea of decoy receptors is not new; indeed, one of the first artificial decoy receptors involved short peptides from the binding domain of the nicotinic acetylcholine receptor. These peptides sequestered nicotinic toxins, so protecting synapses[4].

Sixma and colleagues[2] also describe the structure of the acetylcholine-binding protein, and this fits beautifully with biochemical and physiological observations of the agonist-binding region of the nicotinic acetylcholine receptor. Some of these earlier results are mapped onto a low-resolution image of the receptor[5] in Fig. 1b. Pioneering work by Karlin and colleagues[6,7] showed that there is an unusual structural feature in the α-subunit of the receptor, namely a disulphide bond between cysteines 192 and 193 (187 and 188 in the acetylcholine-binding protein). Another important advance was the identification by Changeux and colleagues[8] of specific amino acids near the agonist-binding site.

These results, combined with those from mutation analyses[9–11], led to two general

conclusions about the agonist-binding site. First, it is defined by several discontinuous regions of amino-acid sequence, known as loops. The main loops are A–C on the α-subunit and D on the γ- or δ-subunit, so the agonist-binding site spans an interface between subunits. Loops E and F are less important. Second, the agonist-binding site does not appear to contain a negatively charged amino acid to bind the positive acetylcholine, but instead is rich in aromatic residues (tyrosine and tryptophan). Apparently, acetylcholine binds the receptor through an interaction with aromatic residues[1,2], especially tryptophan 149 in the α-subunit (residue 143 in the acetylcholine-binding protein[1,2])[13].

When the earlier results are mapped onto the new structure[2] of the acetylcholine-binding protein, the remarkable image shown in Fig. 1c emerges. Loops A–D do indeed form a binding site, with loops E and especially F more remote. The disulphide bond is right in the middle of the action. The binding site is shaped by the five key aromatic residues, and resembles a box that is open at one end to allow the agonist to enter (Fig. 1d). The crystals of the acetylcholine-binding protein did not contain acetylcholine, but a molecule from the crystallization buffer was present, and an ammonium (positively charged) group from this molecule was positioned directly over tryptophan 143.

Another disulphide bond, between cysteine residues 123 and 136 (128 and 142 in the nicotinic acetylcholine receptor), produces a separate 'signature loop' that defines this group of proteins. But its position — the loop is at the very 'bottom' of the binding domain — is surprising. It means that, in the full receptor, the signature loop is positioned to interact directly with the membrane, or possibly with the transmembrane regions (or the short sequence connecting two of them) of the receptor. The implication is that the signature loop might be involved in 'gating' — the coupling of agonist binding to the opening of the ion-channel portion of the receptor. Intriguingly, the residues of the signature loop in the acetylcholine-binding protein interact more favourably with water than do those of the nicotinic receptors. This may be why this protein could be more easily overexpressed in soluble form for crystallization.

In the wake of these papers[1,2], computational models of the agonist-binding region of the acetylcholine receptor, as well as of those of other members of the group (the serotonin, γ-aminobutyric acid, glycine and glutamate receptors), will no doubt appear soon. Molecules that stimulate or block these receptors are useful in treating several ailments (Fig. 2), and structural information on the binding region will aid the design of even better treatments. Also, the structure of the transmembrane domain and, crucially, the mechanism of gating must be worked out. And it remains to be seen whether the snail acetylcholine-binding protein has counterparts in mammals. ■

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Developmental biology

Making head or tail of Dickkopf

Roel Nusse

Signals that guide embryonic cells through development are often under the control of inhibitors. It now seems that one such inhibitor does not bind to the signal itself, but rather to the receptor that detects the signal.

A typical cell's network of signal-transduction pathways has so many molecular interactions that it looks like a complex wiring diagram. Recently, it has become clear that signalling events outside the cell can be equally elaborate, with many different components that bind to each other and act as positive or negative regulators of signalling. This is particularly true for proteins with key functions in development, such as bone morphogenetic protein[1], Hedgehog and Wnt. Various factors can interact with these proteins outside the cell, modulating their activity[1] or altering their structure. On page 321 of this issue[2], Mao and colleagues describe an interesting twist to the regulation of extracellular signalling through Wnt proteins.

Wnt proteins, which are found in animals from hydra[3] to insects, worms and vertebrates[4], have a wide range of activities during animal development[4]; for example, they are involved in the formation of the head-to-tail axis of the embryo. Extracellular Wnt proteins trigger signalling pathways inside cells that proceed through several protein complexes that interact dynamically with each other.

One protein in these pathways is the

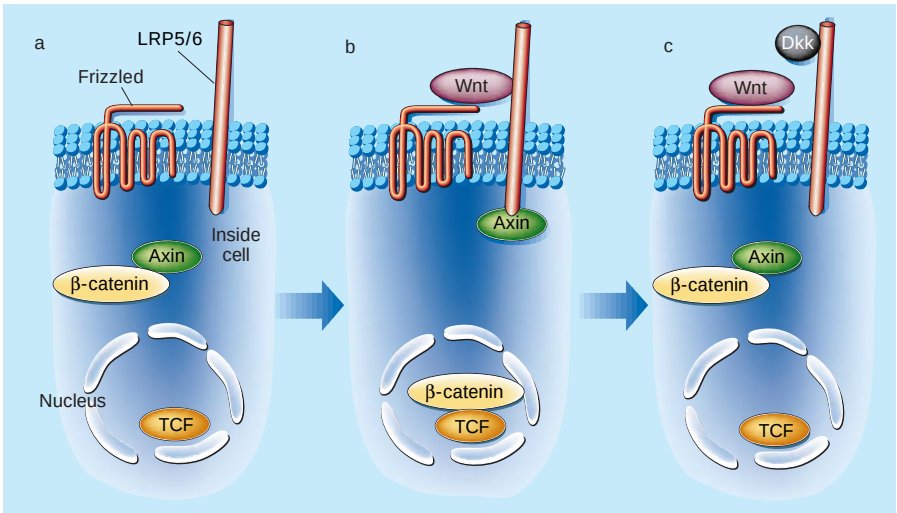

Figure 1 **Events inside and outside the cell during Wnt signalling in development, based on recent results[2,14,15].** a, **In the absence of the Wnt protein, β-catenin is found outside the nucleus, in a complex with several proteins, including Axin. The transcription factor TCF is in the nucleus.** b, **The Wnt protein binds to its two receptors, Frizzled and LRP5/6 (for 'low-density-lipoprotein (LDL)-receptor-like protein 5 or 6'). Axin is then recruited to the intracellular tail of LRP5/6, releasing β-catenin in the process, which enters the nucleus to activate gene expression with TCF.** c, **Dickkopf (Dkk) binds to LRP5/6 and prevents the Wnt–Frizzled complex from interacting with LRP5/6. Axin is released and once more forms a complex with β-catenin.**