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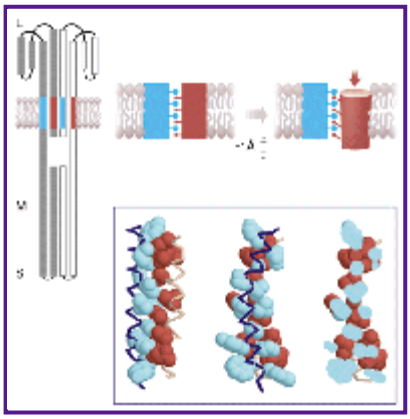
SIGNAL TRANSDUCTION:

Proteins in Motion

Mark Gerstein and Cyrus Chothia*

The aspartate receptor is a protein that spans the inner membrane of some bacteria. It is known that the portion of the receptor on the outside face of the membrane (the periplasmic domain) binds a small molecule, aspartate, that promotes bacterial movement (chemotaxis). Binding of aspartate to its receptor results in a conformational change in the receptor that is transmitted to the cytoplasmic domain. This domain interacts with proteins in a phosphorylation cascade that further transduces the signal, eventually resulting in a change in the swimming behavior of bacteria. Exactly how conformational changes in the aspartate receptor (and in other transmembrane proteins) result in signal transduction is not known, although several models have been proposed. Now on page 1751 of this issue, Ottemann *et al.* (1) describe a sliding motion of two transmembrane helices in the aspartate receptor that suggests a piston-like model of transmembrane signaling.

The structure of the aspartate receptor's periplasmic domain is known, and the location of its two transmembrane helices can be predicted confidently (see the figure) (2). Kim *et al*. recently reported a structure of the cytoplasmic domain of the serine receptor (3), another member of the highly conserved bacterial chemotaxis receptor family. Thus, we now have a fairly complete picture of the whole molecule, which consists entirely of helices (see the figure). The periplasmic domain is a four-helix bundle. The newly solved cytoplasmic domain is composed of two long helices that are coiled together. Pairs of these coiled-coils dimerize to form an extended four-helix bundle. Overall, the receptor is highly elongated: only ~25 Å wide but stretching about 380 Å from the periplasmic domain to the cytoplasmic domain. In the crystal structure, the receptor is a dimer, and there is some disagreement about whether transmembrane signaling involves a monomer or dimer unit. Nevertheless, it is clear that conformational changes in the receptor must somehow be transmitted by the relative motions of the two transmembrane helices. Ottemann *et al*. use electron paramagnetic resonance spectroscopy to estimate changes in distance between selectively labeled residues in the receptor's transmembrane helices, in the absence and presence of aspartate. The distance changes are consistent with the two transmembrane helices sliding relative to each other by 1 Å, in a piston-like motion. This motion presumably affects the geometry at secondary binding sites in the cytoplasmic domain for downstream proteins that are far away from the initial site of aspartate binding.



Sliding helices. (**Top left**) View of a bacterial chemotaxis receptor [adapted from (3)] showing the location of the transmembrane helices (red and blue). Note the separation between ligand-binding sites in the periplasmic domain (L) and the secondary binding sites in the cytoplasmic domain (M and S). (**Top right**) View showing the hypothetical sliding motion of two transmembrane helices. (**Bottom**) Different views of the close-packing in soluble protein helices.

The investigators compare the motion in the aspartate receptor to that observed between sets of packed α helices in soluble proteins. The fundamental constraint underlying motion in soluble proteins is that internal interfaces, such as those between helices, are tightly packed in low-energy conformations. This tight packing has been observed in numerous studies (4). Combined with the interdigitated nature of side chains at protein interfaces, tight packing suggests that if the interface structure is to be preserved throughout a motion, only very small motions are possible.

This constraint on possible motions at interfaces allows many individual movements within proteins to be described in terms of two basic mechanisms--shear and hinge--depending on whether or not they involve sliding over a continuously maintained interface (5). A complete protein motion can be built up from combinations of these mechanisms. Hinge motions, such as those in calmodulin, occur when there is no continuously maintained interface constraining the motion. In contrast, the shear mechanism describes the special kind of sliding motion a protein must undergo if it wants to maintain a well-packed interface (such as that between two helices) throughout the motion. Individual shear motions are very small; their net effect is usually limited to ~2 Å translations and 15° rotations. To produce a large motion, a number of smaller shear motions need to be concatenated. (Imagine each plate in a stack of plates sliding slightly to make the whole stack lean considerably.)

Shear motions are an intrinsic type of flexibility found in well-packed polypeptides. They are the predominant mechanism of motion in proteins such as citrate synthase, insulin, interleukin-5, glyceraldehyde-3-phosphate dehydrogenase, and aspartate amino transferase (6). Hinge motions, in contrast, are "special" in that they require the protein to have sections of the main chain free from the usual packing constraints.

To what degree do the mechanisms of soluble protein motions apply to membrane proteins? Helices in membrane proteins are believed to be as tightly packed as those in soluble proteins. This crucial fact, which implies that the constraints on soluble proteins also apply to membrane proteins, is borne out by calculations showing that the buried atoms in membrane proteins occupy the same (or even less) space as comparable atoms in soluble proteins (7) (see the table). These calculations are, of course, limited to some degree by the current resolution of membrane protein structures. Nevertheless, evidence from mutagenesis experiments also suggests that membrane protein structures are tightly packed (8). It is thus reasonable to assume that the shear mechanisms observed in soluble proteins also occur in membrane proteins. Indeed, they may even be more common in membrane proteins because these proteins consist primarily of nearly parallel helices.

PACKING EFFICIENCY OF BURIED ATOMS IN MEMBRANE PROTEINS (7)

	Atoms	Vol. (3)	Relative packing efficiency (%)
Bacteriorhodopsin	597	7,889	+1.8
Cytochrome bc1 complex	9,963	130,467	+1.8
Cytochrome c oxidase (1ar1)	3,885	55,934	+1.9
Cytochrome c oxidase (2occ)	11,321	157,103	+0.4
Fumarate reductase	6,332	86,085	+2.1
K^+ channel	1,006	12,881	+4.5
Light-harvesting complex	1,383	19,120	+2.2
Reaction center (1prc)	5,851	83,595	+1.4
Reaction center (1aig)	4,488	63,581	+1.6

The membrane protein for which there is the most crystallographic evidence about motion is bacteriorhodopsin (9), a bacterial photoreceptor. This protein consists of seven transmembrane helices packed around a central chromophore. Light interacting with the chromophore drives the protein through a photocycle where the major conformational changes involve small shifts of two of the helices relative to the other five. Thus, the small sliding motions in bacteriorhodopsin, as well as those in the aspartate receptor, appear to be consistent with a shear mechanism.

Low-resolution images of the nicotinic acetylcholine receptor (10) reveal another type of helical motion. This gated ion channel has five subunits, and the channel is lined by a helix from each of them. Binding of acetylcholine leads to substantial rearrangements that switch the channel-lining helices to an alternative association, resulting in opening of the channel. A similar type of motion has also been proposed for the opening of the potassium channel (11). These motions need to be seen at a higher resolution before detailed analyses can be made. Nevertheless, their current descriptions suggest that they involve "high-energy" transitions different in character from the sliding motions in bacteriorhodopsin and the aspartate receptor. It is notable that both of these high-energy motions involve movements of whole subunits rather than of single domains.

It remains to be seen to what degree the movements of other membrane proteins follow either the pattern of small shifts in the aspartate receptor or the large rearrangements in the potassium channel. However, describing the mechanisms for motion in helical membrane proteins has many applications. For example, a number of recent surveys estimate that the fraction of genes encoding proteins with two or more transmembrane helices is between 10 and 15% in prokaryote genomes, and perhaps even more in those of eukaryotes (12). Thus, as genome sequencing efforts power ahead, we may find that the sliding transmembrane helices in the aspartate receptor may be representative of a large number of protein motions in the cell.

References and Notes

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7. In table, relative efficiency is V(ref)/V - 100%, where V is the observed volume of the buried atoms in membrane protein structures and V(ref) is the corresponding standard reference volume of these atoms in soluble proteins. The slightly positive values indicate comparable or even tighter internal packing in membrane proteins. [See (4) and bioinfo.mbb.yale.edu/geometry/membrane)].
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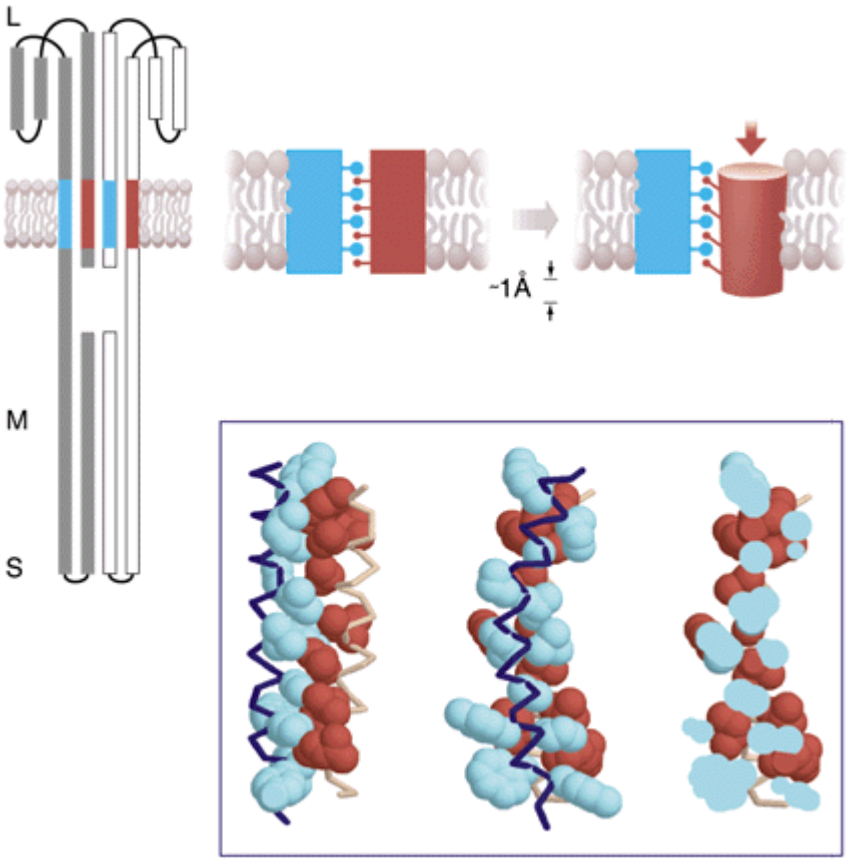

Sliding helices. (**Top left**) View of a bacterial chemotaxis receptor [adapted from (3)] showing the location of the transmembrane helices (red and blue). Note the separation between ligand-binding sites in the periplasmic domain (L) and the secondary binding sites in the cytoplasmic domain (M and S). (**Top right**) View showing the hypothetical sliding motion of two transmembrane helices. (**Bottom**) Different views of the close-packing in soluble protein helices.

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