Stimulated by hormones and sensory stimuli, serpentine receptors promote the release of GDP that is bound to the α subunit of trimeric G proteins and its replacement by GTP. Recent investigations have begun to define the sizes, shapes, and relative orientations of receptors and G proteins, the surfaces through which they interact with one another, and conformational changes in both sets of molecules that underlie receptor-catalyzed guanine-nucleotide exchange.

How receptors talk to trimeric G proteins
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Abbreviations
2D two-dimensional
3D three-dimensional
AR adrenoceptor
tc loop extracellular loop of serpentine receptors
Gα α subunit of a trimeric GTP-binding protein
GnRHR gonadotropin-releasing hormone receptor
ic loop intracellular loop of serpentine receptors
mAChR muscarinic acetylcholine receptor
NK1R neurokinin-1 receptor
NMR nuclear magnetic resonance
NT amino terminus
SDSL site-directed spin labeling technique
TM transmembrane helix

Introduction
The serpentine receptors transduce extracellular signals into cells by activating heterotrimeric G proteins located on the cytoplasmic face of the plasma membrane. Each of the ∼1000 serpentine receptors in vertebrates responds selectively to a hormone, neurotransmitter, odorant or photon, and in turn selectively activates one or more G-protein (Gαβγ) trimers, which are assembled from the products of three small gene families (there are 16 α, 5 β, and 11 γ genes). The receptor catalyzes the replacement by GTP of GDP bound to the α subunit, followed by the dissociation of GDP, pick up GTP, and separate from βγ.

Here, I present a preview of what promises to be an exciting film, on the basis of details learned in the past few years. I begin with our knowledge of the sizes, shapes, and positions of the three dancers. I then tell what we know about how the leading man moves from one position to another in response to a proper cue—that is, how serpentine receptors change their conformation in response to stimulating ligands —and how he chooses specific Gα and βγ partners from the corps of available ballerinas. Finally, I sketch a blurred but plausible choreography for the pas de trois itself, the intricate arsènbque in which the receptor persuades Gα to release GDP, pick up GTP, and separate from βγ.

Sizes and shapes
Recent evidence tells us a great deal about shapes and sizes of serpentine receptors and Gaβγ, as well as their orientations vis-à-vis one another and the plasma membrane (Fig. 1). In crystal structures of two G-protein trimers, Gα1 [2**,3**] and Gγ [3**], the α subunit cradles GDP in a pocket between an α-helical domain and a domain whose α-helix/β-sheet structure resembles that of p21ras. The Gβ polypeptide is made up of seven β sheets arranged in a propeller-like structure, viewed from the side in Figure 1a; loops on opposite faces of the propeller interact either with the Gγ polypeptide or with the ras-like domain of Gα, respectively. One side of the Gaβγ trimer [2**,3**], shown in Figure 1b, forms the plasma membrane, as inferred [3**,4**] from locations of three structural features that interact with the lipid bilayer, including the 10-residue carboxy-terminal tail of Gα, which is known to interact with serpentine receptors [5,6], plus two lipophilic modifications at the amino terminus of Gα (the amino terminus is myristoylated and/or palmitylated) and the carboxyl terminus of Gγ (the carboxyl terminus is isoprenylated). Thus, the plane of the membrane is perpendicular to the elongated Gγ polypeptide and roughly parallels the β sheets of Gβ. Note that the membrane face of Gaβγ, which must serve as the principal surface for contacting the receptor, is located far (∼30 Å) from the interdomain pocket that encloses GDP (Fig. 1a).

The receptor, a bundle of seven transmembrane α helices (Fig. 2a), displays its amino terminus and three interhelical loops to the extracellular fluid, while three more loops, plus the carboxyl terminus, are exposed to the cytoplasm [7,8]. Two-dimensional (2D) crystals of the light receptors
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Size, shape, and probable membrane orientation of Goβγ, represented by the α-carbon trace of the Gi crystal structure [3**]. (a) A sideview of the G-protein trimer, sitting on the plasma membrane. (b) The trimer as viewed through the membrane, from the receptor’s perspective. Giβ is magenta, Gi is green (in the left-hand part of [a,b]), and Go is orange (α-helical domain), red (carboxy-terminal tail) and gray (ras-like domain). (For other colours relating to Go, see below.) Bound GDP (within Go) is yellow. The trimer’s proposed orientation to the membrane is based on the locations of the carboxy-terminal tail of Go (red) and residues near the amino terminus of Go and the carboxyl terminus of Gi (indicated by the yellow van der Waals representations in the left-hand part of [a,b]), close to sites of lipid modification that are not seen in the crystal structure. Four features of Go that play a role in its response to receptor activation are given specific colors: the α5 helix is black; the carboxyl terminus is red; the β6–α5 loop is green (shown at right-hand side of [a,b]); and the α2 helix is cyan.

(rhodopsins) of cow and frog retinas [9,10*] reveal the seven transmembrane helices (TMs) bundled together, albeit at low resolution (6-9 Å). Projection densities suggest that a cross-section through the TM bundle where it meets the cytoplasm is smaller (40 x 28 Å) than the surface of Goβγ that is postulated to face the membrane (60 x 42 Å).

The seven transmembrane helices (TM1–TM7) almost certainly bundle together in the order shown in Figure 2a, clockwise as viewed from the cytoplasm. A large body of recent evidence (Table 1) supports this arrangement, first inferred by Baldwin [11] from the relative brevity of intracellular loops (ic loops) in many serpentine receptors and from patterns of conserved residues and hydrophobicity in their TMs. Four helices (TMs 1–3 and TM5) probably slant as they cross the membrane; three helices (TMs 4, 6, and 7) orient perpendicular to the plane of the membrane (Fig. 2a), as inferred [9,10*] from their more compact densities in the crystals.

The receptors’ ic loops transmit signals from receptor to G protein. Mutational studies locate the essential signal-transmitting information of these loops in short (6–16 residue) amino acid sequences near the junctions with TMs. Although the rhodopsin crystals tell us little or nothing about the three-dimensional (3D) architecture of ic loops, site-directed mutations, site-directed spin labeling techniques (SDSLs), and nuclear magnetic resonance (NMR) are beginning to define 3D structures for ic loops in several receptors (Table 2). In rhodopsin and in muscarinic receptors, all three approaches indicate that the amino-terminal residues of ic3 form α-helical extensions of TM5; weaker evidence suggests that the carboxy-terminal residues of ic3 (just preceding TM6) are also α helices. Less is known about the 3D structures of ic1 and ic2.

Like the ic loops, carboxy-terminal tails of serpentine receptors vary considerably in amino acid sequence. These regions have been thought to contain a short loop that comes back to the membrane, because conserved cysteines downstream from the TM7 sequence are often covalently attached to palmitate (e.g. [12]), a fatty acid with high affinity for the lipid bilayer. The NMR structure of a 43-residue peptide representing the carboxy-terminal tail of rhodopsin confirms and extends this inference [13]. This NMR structure reveals a compact domain, with an α helix (which would extend TM7) connected by a loop to cysteine residues that would be close to the plane of the membrane, followed by a hydrophilic β sheet.

The serpentine receptor switch
To stimulate the receptor, many agonist peptides bind to extracellular (ec) loops, whereas biogenic amines and retinal, the chromophore of rhodopsin, bind to a helix-lined pocket within the plane of the membrane (for
The seven-helix bundle of serpentine receptors, viewed from the cytoplasm. (a) The sizes and orientations of the transmembrane helices, based on two-dimensional crystal structures of frog and cow rhodopsin [9,10]. Individual helices are identified by number according to the model of Baldwin [11]. Darkly shaded circles indicate the locations of two key amino acid residues (single-letter amino acid code is used) in the TMs of rhodopsin. In the dark, rhodopsin is stabilized in an inactive state by a salt bridge (shaded bar) between a glutamate (El 13) in TM3 and the protonated Schiff's base linkage of retinal (not shown) to a lysine (K296) in TM7 [18,19]. Upon activation, TMs 3, 6, and 7 separate from one another and the salt bridge is broken. (b) An imagined structure for the receptor's active state, in which TMs 6 and 7 lean out of the structure, opening a postulated cleft (shaded ring) in the middle of the bundle. Such a cleft could play a role in G-protein activation (see text).

How does the receptor switch work? Accumulating evidence from studies of rhodopsin suggests that activation causes several TMs in the helix bundle to separate from one another (Fig. 2b). Before discussing this evidence, it is worth emphasizing that the helix bundle slides, moves, and breathes; it is not, as we might have imagined, a motionless and tightly packed domain that strictly excludes water. Indeed, many receptor ligands are hydrophilic molecules, including some, like the catecholamines, that bind to a pocket within the helix bundle. Moreover, a series of recent experiments [16*,17*] revealed an apparent intrabundle crevice by an approach that involved substituting cysteines individually for each of the residues in TMs 3, 5, and 7 of the dopamine2-receptor (D2R). Approximately one third of the mutations in each helix produced a D2R that reacted with charged, hydrophilic, lipophobic, sulfhydryl-specific reagents added from outside the cell; a dopamine agonist protected the cysteines from reacting with these reagents. The water-accessible crevice extended all the way from the extracellular to the intracellular side of the membrane.

**Activation separates TMs**

The first hint that receptor activation can induce TMs to separate from one another came from the constitutive activities (i.e. Gt activation in the absence of retinal) of opsin mutants that have lost a constraining salt bridge between a lysine in TM7 and a highly conserved glutamate in TM3 [18,19]. The lysine residue in TM7 is covalently linked to retinal, via a protonated Schiff's base linkage; the same constraining salt bridge breaks when light isomerizes l-l-cis-retinal to the all-trans form, with transfer of the Schiff's base proton to the glutamate in TM3 [20]. Thus, the salt bridge normally prevents the opsin from taking on an active conformation. Activation could break the salt bridge by causing TM3 or TM7 to rotate on its axis or, as shown in Figure 2b, by separating the two helices from one another in the plane of the membrane.

A series of site-directed spin labeling experiments [21,22*,23*,24**] shows that TMs 3 and 6 are located close to one another in inactive (dark) rhodopsin and that photoactivation induces these two TMs to move apart also, as depicted in Figure 2b. In these studies, every residue in ic2 and ic3 was individually replaced by a cysteine, to furnish sites for labeling by a nitroxide reporter group. Spin label spectra of such modified mutants provide information about the relative constraints imposed upon receptors for glutamate, etc., even though the amino acid sequences of these serpentine receptors are not similar to those of the larger family. Indeed, mammalian receptors can activate the G-protein trimer of *Saccharomyces cerevisiae* [15], replacing a yeast serpentine receptor that shows no similarity of primary structure and that is separated from its mammalian counterpart by more than a billion years of evolution.

**a review, see [14])**. The TMs act as switch cassettes that transmit ligand-induced changes in conformation across the membrane to Gαβγ, which responds by exchanging GDP for GTP. Most of our information about the molecular switch mechanism comes from studying members of the largest and best studied of several serpentine receptor families [7,8], which includes the opsins and receptors for biogenic amines. Signal transmission by this family may be a reasonable model for TM switches in other receptor families (e.g. receptors for secretin and related hormones,
movement of the corresponding amino acid residues and about changes in the relative hydrophobicity of their immediate environments [25]. Spectra of these mutants in the dark indicate that apparently 'inward-facing' side chains in the helical cytoplasmic extensions (see Table 2) of TM6 [23°] and TM3 [22°] are constrained by tertiary contacts with other parts of the protein. Photoisomerization of bound retinal relieves these constraints, more so for TM6 than for TM3; most residues in TMs 4 and 5 show little change. Thus, light appears to induce the juxtacytoplasmic portions of TMs 6 and 3 to move as rigid bodies relative to the rest of the helix bundle. Absorption spectra of mutant opsins show that light also markedly alters the environments of tryptophan residues that are located farther from the cytoplasm in the same two TMs [26]. Light-induced isomerization of retinal, which is bound in a pocket located between the tryptophans, probably initiates movement of TMs 3 and 6.
Another set of spin label experiments [24••] shows that light induces these two TMs to separate from one another, and not just to move relative to other helices. Spectra of double cysteine mutants made it possible to estimate relative distances between a modified residue in TM3 and a second such residue at each of several positions in TM6. The results suggest that light activation causes TM6 to turn by ~30° on its axis (clockwise, as viewed from the cytoplasm) and to lean outwards, away from TM3. Two experiments suggest that these movements are essential for activation of Gt. Oxidative conditions prevent the cysteine double mutants from activating Gt, by promoting formation of disulfide links between TMs 3 and 6 [24••]. Similarly, a Zn2+ bridge between histidine residues substituted at almost the same positions in TMs 3 and 6 also prevents Gt activation [27].

Activation may open a crevice

It is attractive to imagine that separation of the TMs opens a crevice (Fig. 2b) for binding or activating Goβγ. If the seven-helix bundle is readily accessible to water and stimulatory ligands on its extracellular side, it would not be surprising that its cytoplasmic surface could also open to admit a part of the G trimer (see below). Such an opening could allow access of part of the G protein to key residues lining the putative crevice, including specific amino acids in both TM6 and TM3 that play key (albeit undefined) roles in activating G proteins. For instance, the highly conserved glutamate-arginine-tyrosine (ERY) sequence located close to the junction of TM3 with ic2 is intimately involved in G-protein activation. Replacement of the arginine residue at this location by other residues allows mutant rhodopsins to bind to, but not to activate, Gt, because the mutants cannot induce GDP to dissociate from Goβγ [28••, 29]. In contrast, the negative charge of the glutamate side chain (aspartate in some receptors) appears to inhibit activation [29–31]. The inhibition is removed by light, which induces protonation of the glutamate carboxyl group; replacing the glutamate with glutamine enhances the efficiency of Gt activation by photoactivated rhodopsin, probably by reducing the negative charge at this position [32].

The switch mechanism of serpentine receptors is remarkably susceptible to constitutive activation by mutation, especially by point mutations located at the carboxyl termini of ic3, near the junction with TM6 [14,33–35]. Like the mutations in rhodopsin that break a salt bridge between TMs 3 and 7 [18], point mutations in TM6 may create a ‘looser’ seven-helix bundle by relieving constraints that normally hold the receptor switch in an inactive (higher-energy) conformation. Although such constraints have not been localized in the receptor structure, this idea is in keeping with the fact that activation by a point mutation often depends critically on context, as observed in receptor chimeras constructed from receptors for luteinizing hormone and follicle-stimulating hormone [36].

Choosing G-protein partners

By detecting and discriminating among structural features of both βγ [37,38] and Go [6,39–41], the serpentine receptor activates only a subset of the available G proteins (reviewed in [5,42]). Extensive investigation of receptor peptides and chimeras has shown that the ic3 sequence determines Goβγ selectivity more often than does ic2, that ic1 rarely determines specificity, and that loop sequences near TMs are especially determinants of specificity (reviewed in [7,43]). Perhaps surprisingly, ic loop sequences of two receptors that activate the same G protein often show no family resemblance, whereas similarity is the rule in comparing TM to TM or ec loop to ec loop among members of each subfamily that is regulated by a specific class of stimuli (e.g. light, catecholamines, or acetylcholine) [7,43]. Consequently, it has not yet been possible to predict the G-protein specificity of any receptor from primary structure. As genes encoding G-protein subunits duplicated and diverged, ic loops from each agonist-specific receptor subfamily probably co-evolved together with the G proteins. Thus, it is likely that loop sequences in certain receptors from distinct branches of the receptor lineage may have convergently evolved to take on 3D shapes that can selectively activate a single type of G-protein trimer.

Two experiments dramatically illustrate that a single TM cassette can activate many different G proteins, but that isolated stretches of cytoplasmic sequence can restrict activation to only a small subset of G proteins. One experiment [44] assessed G-protein specificities of four splice variants of a prostanoid receptor; these variants differed only in the sequences of their carboxy-terminal tails. The four isoforms were found to activate three different sets of G proteins (Gβγ/Gi in one case and Gβγ/Gβγ/Gq in another; two variants activated Gi only). In the other experiment [45], the ic3 of muscarinic acetylcholine receptor (mACHR) 1 or 2 was replaced with a corresponding sequence from the β1 adrenoceptor (AR). One parent of each chimera (the β1AR) normally activates Gi, whereas the other parent specifically activates either Gq (the m1ACHR) or Gi (the m2ACHR). Surprisingly, all the combinations produce promiscuous chimeras that activate, with comparable efficiencies, three classes of G trimers—Gi, Gi, and Gq—rather than just the G trimers specific for the parent receptors. The promiscuity disappears in m1 or m2 AChRs in which the β1AR sequence replaces ic2 as well as ic3; such chimeras activate Gi exclusively.

These results tell us that the serpentine receptor and G protein do not fit together neatly like a precisely engineered lock with its key, or like an Src homology 2 domain with its phosphotyrosine. Instead, the ic loops of a particular activated receptor probably take on a restricted subset of somewhat plastic conformations that can mold to accommodate certain G-protein trimers, but not others. In this way, ic loops of receptors that activate
the same G protein need not share similar primary structures. Conversely—and even more surprisingly—a single ic loop sequence can activate different G proteins, depending upon changes in a quite separate part of the receptor. Two recent examples include: a point mutation in an extracellular loop of the luteinizing-hormone receptor abolishes its ability to activate Gα in response to bound agonist ligand but preserves its ability to stimulate Gq [46]; and a point mutation in the α3β2AR, located in TM3 at a site distant from the cytoplasm, causes selective (and constitutive) activation of Gq, but not Gi—unlike the native protein, which activates both Gq and Gi in response to stimulatory agonist [47]. Apparently, the specificity of these interactions does not depend on precise contacts between side chains but is encoded more subtly in a selectively flexible repertoire of main-chain conformations. Such selective plasticity may turn out to be a common feature of protein surfaces that have evolved convergently to bind the same target.

**Intimate contacts**

To make a crude sketch or working model (Fig. 3) of the receptor–Gαβγ pas de trois, we must first define surfaces of the G-protein trimer that interact with the receptor, and then identify specific regions of the receptor and Gαβγ that interact directly with one another. The Gα surface that interacts with the receptor is fairly well defined (Fig. 3). The carboxy-terminal tail of Gα, and especially its last five residues, interacts directly with the receptor [6,39–41] (reviewed in [5]); the different short sequences of this carboxy-terminal tail in different G proteins encode much of the specificity of that interaction [5,41]. A more extensive receptor-interacting surface was defined by a recent alanine scanning mutagenesis study [48*] of Gαq, the retinal Gα that is stimulated by rhodopsin. Positions at which alanine substitutions impair Gα activation by rhodopsin map to the carboxy-terminal tail of Gα and to adjacent regions on the protein's membrane-oriented surface, extending up the side of Gα approximately halfway to the GDP-binding pocket.

Four pieces of data (Table 3) begin to define regions of the G-protein trimer that interact directly with short stretches of sequence in the receptor. The most precisely defined contact involves five residues in the carboxy-terminal tail of a Gα and four residues in a receptor [49*]. The key experiment took advantage of a previous observation [41] that substitution of the last five residues from the carboxyl termini of Gα subunits of the αi family for the corresponding residues at the carboxyl terminus of αq produces an αq–αi chimera (and an αq–αiβγ trimer in cells) that can be activated by receptors otherwise selective for Gi proteins. The m3AChR, a Gq-specific receptor, cannot stimulate a G trimer that contains an αq subunit with five carboxy-terminal residues replaced with those of an αi subunit of the αi family. A mutant m3AChR becomes able to mediate agonist stimulation of Gα,i however, when m3AChR contains four noncontiguous residues transplanted from the ic3 region of the m2AChR, a Gi-coupled receptor. The Baldwin model [11] suggests that the key m2AChR residues are located close to one another on the inward-facing surface of the helix at the junction of ic3 and TM6.

Evidence summarized in Table 3 can be used to position the membrane-facing surface of Gαβγ in relation to the helix bundle of the receptor, roughly as shown in Figure 3. This orientation places key parts of the two proteins close to one another, as follows. First, the last five residues of the Gα carboxy-terminal tail point more or less into the middle of the triangle formed by TMs 3, 6, and 7 of the receptor. As described above, these TMs separate from one another upon activation, perhaps creating a crevice that is large enough to accommodate a part of the

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**Table 3**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Regions connected in:</th>
<th>G-protein subunit</th>
<th>Results*</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ic3–TM6 junction (four residues)</td>
<td>Five residues at Gα CT</td>
<td></td>
<td>Functional complementation between an αq–αi chimera and an m2AChR–m3AChR chimera (see text)</td>
<td>[49*]</td>
</tr>
<tr>
<td>CT of ic3 loop (14 residues)</td>
<td>17 residues at Gα NT</td>
<td></td>
<td>A peptide representing this ic3 loop sequence can be photochemically cross-linked to the indicated region of Gα</td>
<td>[63]</td>
</tr>
<tr>
<td>CT of ic3 loop (14 residues)</td>
<td>60 residues at Gβ CT</td>
<td></td>
<td>A peptide representing this ic3 loop sequence can be photochemically cross-linked to the indicated region of Gβ</td>
<td>[63,64]</td>
</tr>
<tr>
<td>CT tail</td>
<td>Gβ</td>
<td></td>
<td>Fluorescence studies show that the peptide representing a sequence in the CT tail of rhodopsin interacts with Gβγ</td>
<td>[65,66]</td>
</tr>
</tbody>
</table>

*Genetic evidence and peptide studies that link specific regions of receptors to specific parts of Gαβγ form the basis of the arrangement depicted in Figure 3. Each individual observation is open to question, however. Although the experiment with receptor and Gα chimeras [49*] appears to show specific interaction between a receptor site and a G-protein site, indirect effects of mutations can never be completely ruled out; moreover, the site-site interaction may not be relevant to other receptors and G proteins. The receptor peptide results [63–66] could represent nonspecific interactions that may not be relevant to interactions of the corresponding peptides.
Gα carboxyl terminus during activation of the trimer; in the unstimulated receptor, presumably, the crevice would be smaller. Such a scenario could explain the striking differences, documented by NMR [40], in conformations of a carboxy-terminal Gα peptide (from αi) interacting with inactive versus activated receptor (dark vs. light rhodopsin). Second, the critically important arginine in the conserved ERY sequence of TM3 (see above) and the ic2 connecting this TM with TM4 are positioned close to Gα residues identified by alanine scan [48*] as important for receptor interaction. Third, the ic3 loop connecting TMs 5 and 6 is located in close proximity to a cavity in the Gαβγ trimer at the interface between Gα and βγ. Although not easy to see in Figure 3, this cavity is readily appreciated in 3D computer models; it is a likely site for contact with the receptor. Fourth, the receptor's carboxy-terminal tail, a substantial and compactly folded mini-domain (see above), is located where it could project into the cytoplasm beside the G-protein trimer and interact with both Gα and βγ. Fifth, as expected from its relative lack of importance in determining G-protein specificity, ic1 (connecting TMs 1 and 2) is located away from known receptor-interacting regions of Gα.

**How does Gαβγ release GDP?**

The short answer is: we don't know. The nucleotide-binding pocket of Gαβγ is found too far from the membrane to be probed open by direct contact with ic loops of the receptor. We have proposed two potential routes for conducting receptor-induced conformational change from the membrane face of the trimer to the nucleotide-binding pocket [4*,48*]. One route is via the α5 helix of Gα, which forms the connecting link between the β6–α5 loop, adjacent to the guanine ring of GDP, and a key receptor-interacting structure, the carboxy-terminal tail of Gα. Mutational perturbation of the α6–β5 loop promotes GDP dissociation [1]. If interacting with this part of Gα, as proposed above, the inter-TM crevice of the activated receptor could perturb the β6–α5 loop in a similar way.

The other route, even less precisely defined, might involve a receptor-induced change in the orientation of βγ and Gα. Such a perturbation could result from interaction of the receptor's ic3 with the cavity between Gα and βγ, leading to conformational changes in Gα structural elements that interact with Gβ and/or the phosphodiester of GDP. One such element in Gα is the α2 helix, which is oriented almost perpendicular to the membrane (Fig. 1), connecting the nucleotide-binding pocket to the membrane face of Gα. The tip of α2 (cyan in Fig. 3) forms the roof of the cavity between Gα and βγ, close to ic3 of the receptor.

**Coming soon, to a theater near you**

Our preview of the receptor-Gαβγ ballet presents an enticing prospect. Scrutiny of the three principal dancers will continue unabated, and parts of the preview will turn out to be misleading, or simply wrong. In the meantime, it is worth emphasizing that this graceful pas de trois forms one brief episode in a huge ballet, choreographed for thousands of principals, in complex arabesques we can only begin to imagine. The movie will be a blockbuster!

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**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest


These papers [2*,3*] present very similar 3D structures of two different Gα–βγ trimers, revealing the structure of Gβγ and defining the Gα–βγ.
binding interface. In addition, the structures define a probable membrane-oriented face of the trimer by identifying the likely locations of lipid modifications of Gα and Gβγ, as well as the carboxyl terminus of Gα.

4. Lichtarge O, Bourne HR, Cohen FE: Evolutionarily conserved cations of Gα and Gβγ, as well as the carboxyl terminus of Gα, oriented face of the trimer by identifying the likely locations of lipid modifications at the binding interface. In addition, the structures define a probable membrane-facing domain of Gα, as shown in the G0-βγ trimer structures. The other, presumably, interacts with serpentine receptors.


At somewhat higher resolution, this structure confirms the seven-helix bundle model inferred from the projection structure of cow rhodopsin [9]. Together, these structures powerfully constrain possible models of mechanisms of receptor activation by ligands and of G-protein activation by receptors.


These papers [16*–17*] show that interstices within the seven-helix bundle are permeable to water-soluble ligands. Other water-soluble ligands (e.g. biogenic amines) had been shown to bind within the seven-helix bundle. The cysteine-accessibility approach has shown that at least in the D2R the potential corex is bordered by at least three helices (TMs 3, 5, and 7) and extends all the way from extracellular fluid to cytoplasm.


24. Farrens DL, Altenbach C, Yang K, Hubbell WL, Khonara HG: A light-activated conformational switch in rhodopsin. Science 1996, 274:678–770. These (and other) papers [22*,23*,24*] from a collaboration between the Khonara and Hubbell laboratories present evidence that the activation of rhodopsin causes TMs 3 and 6 to move, as rigid bodies, relative to the rest of the seven-helix bundle; in addition, activation is associated with movement of these two TMs away from one another.


Using a variety of biophysical and biochemical techniques, the authors of this paper show that receptor-promoted release of GDP from the G-protein trimer requires more than just association of the trimer with a serpentine receptor. Although the mechanism by which the receptor induces GDP release is unknown, it probably requires the ERY (single-letter code for amino acids) sequence located at the junction of IC2 and TM3.


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