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Minireview

The archaeal sensory rhodopsin II/transducer complex: a model for transmembrane signal transfer

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Abstract Archaebacterial photoreceptors mediate phototaxis by regulating cell motility through two-component signalling cascades. Homologs of this sensory pathway occur in all three kingdoms of life, most notably in enteric bacteria in which the chemotaxis has been extensively studied. Recent structural and functional studies on the sensory rhodopsin II/transducer complex mediating the photophobic response of *Natronomonas pharaonis* have yielded new insights into the mechanisms of signal transfer across the membrane. Electron paramagnetic resonance data and the atomic resolution structure of the receptor molecule in complex with the transmembrane segment of its cognate transducer provided a model for signal transfer from the receptor to the cytoplasmic side of the transducer. This mechanism might also be relevant for eubacterial chemoreceptor signalling.
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1. Introduction

The chemotactic receptors of *Escherichia coli*, *Salmonella typhimurium*, and *Halobacterium salinarum* are members of a large superfamily of membrane proteins that modulate a signalling cascade which is known as the 'two-component' phosphor transfer system ubiquitous in prokaryotes and lower eukaryotes [1–3]. The main components of this regulatory network are chemoreceptors, histidine and aspartate kinases, a SH3-like coupling protein, as well as two proteins involved in adaptation to constant stimuli (see Fig. 1a). Over the years considerable structural, kinetic and physiological information has been gathered, mostly by analysing the chemotaxis system of enteric eubacteria. Recently, the elucidation of colour-sensitive phototaxis in *H. salinarum* has revealed a homologous organisation of the signal transduction chain (reviewed in [4,5]). However, in the special case of photoreception the receptors, which belong to the family of microbial rhodopsins, are not directly fused to the transmembrane domain but bound to cognate transducer molecules (halobacterial transducer of rhodopsin, Htr). The cytoplasmic domain of these latter membrane proteins is highly homologous to the corresponding section of the chemotaxis receptors. Additionally to two Htrs, at least 15 other methyl-accepting proteins which resemble their eubacterial relatives have been identified through biochemical experiments and sequence analysis of the *H. salinarum* genome [6–8]. The congruence between the phototaxis and the *E. coli* chemotaxis system has been further established in experiments in which a chimeric protein was expressed in *E. coli* [9]. In this large construct the photophobic receptor (from *Natronomonas pharaonis*, NpSRII) was merged to an N-terminal fragment of its cognate transducer (NpHtrII) fused in turn to cytoplasmic signalling and adaptation domains of *E. coli* chemotaxis receptors. Bacteria expressing these fusion proteins showed phototaxis [9] as well as light-mediated autophosphorylation and transfer reactions [10]. The equivalence of the archaeal and eubacterial 'two-component' signalling cascade combined with the knowledge about these systems provides the means to establish a model for investigating signal transfer across the membrane on a molecular level. The elucidation of the photoreceptor-mediated signal transduction has the further advantage of using light as substrate, which as a physical entity is easier to apply than chemicals.

2. Phototactic signalling chain

The colour sensing of the haloarchaeon *H. salinarum* is mediated by two sensory rhodopsins which differentiate between light below and above 500 nm, respectively [11]. Sensory rhodopsin I (SRI), the first phototaxis receptor discovered, displays a dual function. In an orange light response SRI directs the bacteria towards the light source; however, additional blue light – in a two-photon reaction – induces a photophobic response of the bacteria. The second receptor, sensory rhodopsin II (HsSRII or phoborhodopsin), has an action spectrum with its maximum at 490 nm and enables the bacteria to avoid photooxidative stress under conditions of bright sunlight in the presence of oxygen. The interplay of the two receptors guides the bacteria into environments optimal for the functioning of the two structurally closely related ion pumps bacteriorhodopsin (BR) and halorhodopsin (HR)

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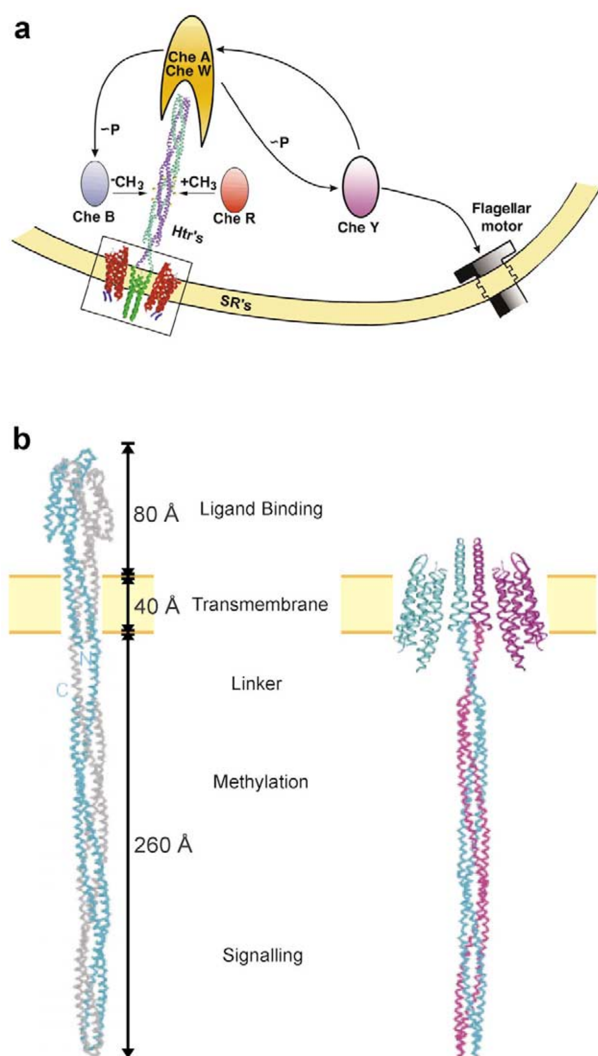

Fig. 1. Phototransducer vs. chemoreceptor. a: The two-component signalling cascade. By activation of the transducer HtrII by SRII the signal is transferred to the cytoplasmic end of the molecule, where, in analogy with the bacterial chemotactic system, the homodimeric histidine kinase CheA is bound together with CheW. The next steps involved in this cascade happen through the response regulators/aspartate kinases CheY and CheB, where phosphorylated CheY functions as a switch for the flagellar motor. The adaptation process is exhibited by the methylesterase CheB and the methyltransferase CheR. This figure is taken from Gordelily et al. [29]. b: Models of a eubacterial chemoreceptor (left) and a SRII/HtrII complex from *N. pharaonis* (right) showing the domain architecture of the protein family (in SRII from *H. salinarum* an additional periplasmic serine binding domain is present). This figure is adapted from Oprian [30].

which are expressed under low oxygen pressure. This latter condition is insufficient for growth of *H. salinarum*; however, the light-activated proton pump BR can supply the energy needs of the cell under such conditions (for recent reviews see [5,12]).

Sensory rhodopsins are seven-helix (A–G) membrane proteins containing as cofactor retinal which is bound to a lysine residue on helix G via a protonated Schiff base. The colour of this complex (λ_{max} = 580 nm for SRI and 490 nm for HsSRII) is regulated by specific protein–retinal interactions [13,14]. On light excitation the all-*trans* chromophore isomerises to a 13-*cis* configuration, thereby triggering conformational changes, which lead to the activation of the cognate transducer. This sequence of events is accompanied by proton transfer steps which are similar to those in BR. Likewise, a vectorial proton transfer is observed although it is not very efficient. Importantly, this proton pump activity is blocked if the transducer is bound [15–17].

The general structure of the transducer molecules is quite similar to that of the chemoreceptors (Fig. 1b). A transmembrane domain consisting of two helices is followed by a cytoplasmic domain, which contains the sub-domains for signal transfer to the histidine kinase CheA and for adaptation by reversible methylation of Glu residues. Between the N-terminal helix (TM1) and the following transmembrane helix (TM2) in the chemoreceptors a periplasmic receptor domain is inserted, which is also present in HsHtrII (a serine receptor [18]) but not in HtrI and NpHtrII. The observation that HsSRII displays a dual functionality is important with respect to a common mechanism of transmembrane signalling in photo- and chemotaxis.

The chemoreceptors form in membranes dimers which aggregate to higher-order complexes [19,20]. Similarly, the transducers constitute a 2:2 complex with their cognate photoreceptors [21,22]. The long rod-shaped cytoplasmic domains are arranged in a four-helix bundle, the X-ray structure of which has been resolved for the serine chemoreceptor [23].

3. Structure of the NpSRII/NpHtrII complex

Since it has been shown that HsSRII is not particularly stable under the conditions of purification [24], most of our knowledge was obtained from the closely related NpSRII/NpHtrII system. Consequently, the first structural information was obtained on NpSRII [25–27], which showed its close structural relationship to that of BR. In a further step the structure of NpSRII in complex with a shortened transducer ($NpHtrII_{1-114}$) was determined. A small fragment of NpHtrII was chosen because of the foreseeable complexity of crystallising the intact complex. In prior experiments it was shown that $NpHtrII_{1-114}$ is tightly bound to NpSRII (K_D = 200 nM) thereby still being able to block the proton pump [28].

The structure of the complex is depicted in Fig. 2 [29]. In accordance with the dimeric organisation of the eubacterial chemoreceptors the transducer crystallises as a dimer with the four transmembrane helices arranged as a four-helix bundle. The resulting super-helical twist is right-handed in the case of $NpHtrII_{1-114}$ but left-handed in the serine receptor Tsr as pointed out earlier [30]. Each of the transducer molecules is bound to a receptor molecule thereby forming the signalling complex with its stoichiometry of 2:2. It should be noted that this arrangement was also demonstrated by gene fusion experiments for the functional SRI/HtrI complex in halobacterial membranes [21] indicating that this arrangement might be a general feature of archaeal photoreceptor/transducer complexes.

The view along the plane of the membrane (Fig. 2a) shows that the eubacterial ligand binding domain (which is present in the case of HsHtrII, see above) is replaced by a short 'stalk' which can be interpreted as a remainder of such a ligand binding domain indicating the evolutionary conversion of a proto-chemoreceptor, which was acquired by a proto-sensor gene, to the transducer proteins. It was not possible to deter-

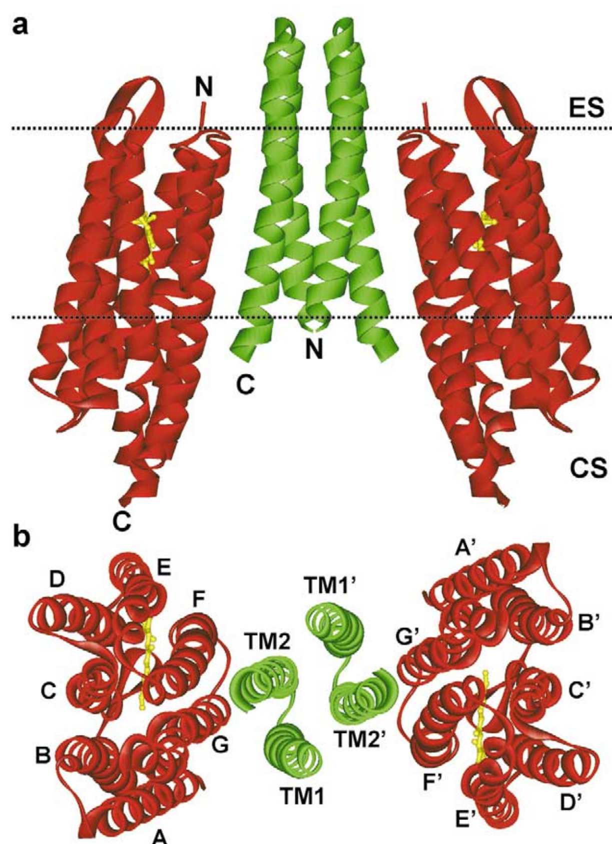

Fig. 2. Ribbon diagrams of the crystal structure of the transmembrane part of the NpSRII/NpHtrII complex structure [29]. NpSRII helices are shown in red, NpHtrII helices in green. a: Side view of the complex. CS, cytoplasmic side; ES, extracellular side. The dotted lines depict the limits of the hydrophobic part of the proteins. b: The complex viewed from the cytoplasm. Both receptor and transducer helices are labelled. The labels of the symmetry-related complex are marked by a prime. This figure was prepared using the program Viewerlite 5.0 from Accelrys.

mine the structure of the complete fragment, only residues 24–82 could be resolved. The lack of electron density for the C-terminus is unfortunate as one can expect this fragment to be crucial for the signal relay from the membrane domain to the cytoplasmic signalling domain. Two reasons could account for the lack of resolution. Either the crystal packing might enforce different conformers or this fragment might be inherently mobile.

The main interactions in the complex are van der Waals contacts, predominantly at TM1-helix G, TM2-helix F, TM1-TM2′ and TM1′-TM2′ (see Fig. 3). Notably, only four hydrogen bonds are formed (Tyr-199_{NpSRII} to Asn-$74_{NpHtrII}$ (1), Thr-189_{NpSRII} to Ser-$62_{NpHtrII}$ (2), Thr-189_{NpSRII} to Glu-$43_{NpHtrII}$ (1)). The importance of Tyr-199 has already been deduced from the X-ray structure of NpSRII [26]. It should be noted that this hydrogen bond is not essential for the thermodynamics of the complex formation [28] although it might be of importance for the receptor transducer signal transfer [31].

4. Receptor activation

The absorption of a photon leads to isomerisation of the retinal chromophore from the all-*trans* to the 13-*cis* conformation, followed by thermal relaxations which finally lead back to the original ground state. The resulting sequence of intermediates has been denoted, in analogy with the BR nomenclature, K, L, M, N, and O states. An important result of the photocycle analysis concerns the identification of a spectrally silent irreversible reaction between two M states ($M_1 \rightarrow M_2$) with a time constant of 3 ms [32]. For BR this transition is correlated with the accessibility switch, which changes the access to the Schiff base from the extracellular channel to the cytoplasmic channel. This key event is thought to be essential for the vectorial proton transfer [33]. The $M_1 \rightarrow M_2$ transition has also been observed in Fourier transform infrared (FTIR) measurements clearly demonstrating amide bond changes but not alteration of the chromophore bands [34]. In vivo experiments using *H. salinarum* [35] are in agreement with the assumption that these conformational changes are an indication for the formation of the photosignalling state. According to these data the active state is reached during the formation of the M intermediate. Deactivation appears to require the decay of O.

A more detailed picture of the conformational changes occurring during the life time of M and the last part of the photocycle was obtained from time-resolved electron paramagnetic resonance (EPR) spectroscopy applying the technique of site-directed spin labelling. The kinetic analysis of the time-resolved EPR signals derived from specifically Cys-mutated NpSRII, which was subsequently modified with a spin label [(1-oxyl-2,2,5,5-tetramethylpyrroline-3-methyl)methanethiosulfonate], revealed a mobilisation of helix F during the $M_1 \rightarrow M_2$ transition which became immobilised again during the decay of O [36]. Contrarily, helix G did not show

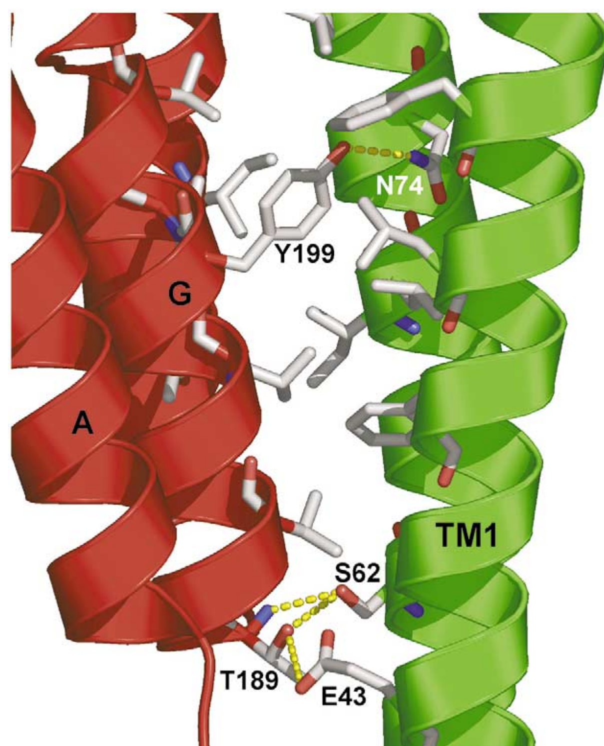

Fig. 3. Interface between receptor (α-helices in red) and transducer (α-helices in green) showing hydrogen bonds and van der Waals contacts. Residues involved in hydrogen bonds (yellow dots) are labelled. This figure was prepared using the program PyMol (DeLano Scientific).

considerable alteration of its mobility. These data were interpreted as a flap-like outwardly directed movement of the cytoplasmic half of helix F, similar to the motion of the corresponding helix in BR which has been demonstrated by various techniques including cryo-electron microscopy [37], X-ray structural analysis [38], and EPR [39,40]. As was proposed for BR [41], the hinge might be located at Pro-175 in the middle of helix F. It was concluded that this tilt of the cytoplasmic portion of the receptor helix F, which occurs during the $M_1 \rightarrow M_2$ transition, triggers the activation of the transducer.

5. Receptor–transducer signal transfer

The structure of the NpSRII/NpHtrII complex (Fig. 2) reveals the transmembrane interaction domain between receptor and transducer. A similar structure was proposed from EPR data [22]. As already mentioned there is a close contact between helix F and TM2 which is depicted in Figs. 3 and 4. It is obvious that an outwardly tilting helix F will collide tangentially with TM2, thereby inducing a rotary motion of this helix as indicated by the arrows in Fig. 4. This reaction was analysed by EPR measurements [22]. The investigation made use of specifically spin-labelled transducer and receptor Cys mutants, positioned on helices F and G as well as on TM1 and TM2. Especially, two observations were central to establish a model for receptor–transducer signal transfer. The first observation concerned the mobility changes of S158R1 (were R1 denotes the spin-modified Cys side chain) and L159R1 after light excitation of NpSRII. Whereas S158R1, which faces TM2, experiences a transient immobilisation the opposite is observed for L159R1, which is oriented towards the interior of NpSRII (see Fig. 5a). In the second set of experiments TM2 was modified at positions 78 and 82 (Fig. 5a). EPR measurements of the complex in detergents revealed relatively mobile unperturbed residues; however, reconstitution of the sample into lipids showed a broadening of the EPR

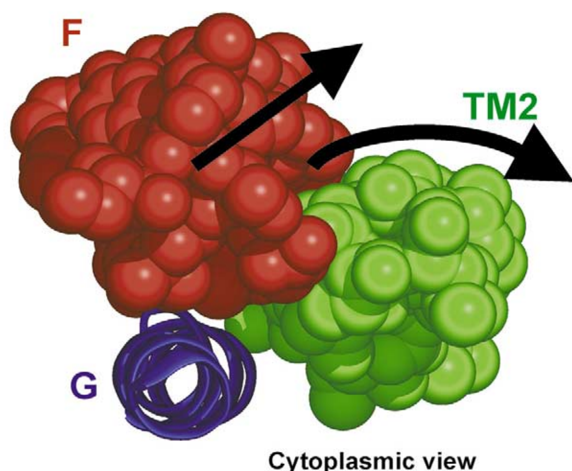

Fig. 4. Illustration of the light-induced conformational changes of the receptor helix F and the transducer helix TM2. The spacefill model shows the tight interaction between F and TM2. The outward movement of helix F (straight arrow) clearly affects TM2 in the way of a clockwise rotary motion (bent arrow). This rotation might be accompanied by a slight (1–2 Å) piston-like movement as predicted for the chemoreceptor activation mechanism.

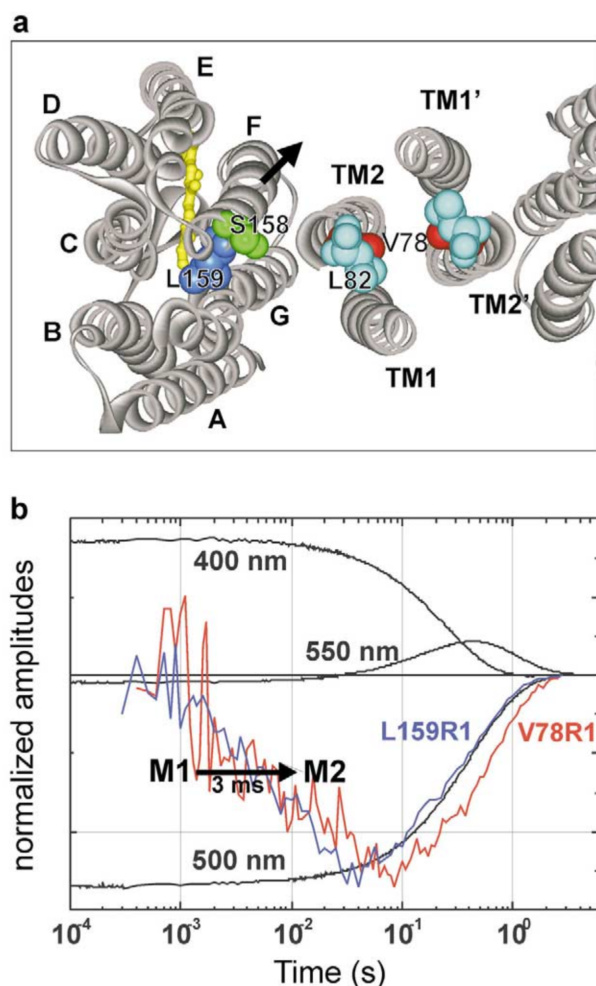

Fig. 5. Conformational changes during the signalling process in the NpSRII/NpHtrII complex. a: Locations of the spin labels used for static and time-resolved EPR measurements. Side chains at position 158 (green) and 159 (blue) on the receptor as well as positions 78 (red) and 82 (cyan) on the transducer helix TM2 were replaced by cysteines and concomitantly labelled with the spin probe. b: EPR transients of the movements of receptor helix F (red) and the transducer helix TM2 (blue) with the corresponding optical traces (400 nm: M intermediate, 500 nm: ground state and 550 nm: O intermediate).

bands due to spin–spin coupling. It should be emphasised that these data prove the formation of a 2:2 complex in membranes, which is disrupted in detergents.

The dipolar coupling allowed determining the distances between the two residues, thereby providing a topology of the transducer helices in the dimer. On light excitation only the distance between V78 and V78′ increases, but not that between L82 and L82′. This result is only compatible with a rotary motion of TM2 as mentioned above. A piston-like movement would change both distances, because V78 and L82 are one helix turn apart. In support of this mechanism are experiments on Cys transducer mutants. Cysteines at positions which face the interior of the four-helix bundle showed an increase in the cross-linking efficiency of TM2 [42]. However, it should be emphasised that a small piston-like movement of about 1 Å cannot be excluded which would – together with the rotation of TM2 – result in a screw-type motion.

The time course of the flap-like tilt and the TM2 rotation

has been determined by time-resolved EPR spectroscopy which was correlated with the optical absorbance changes. The absorbance changes due to the alteration of the protein–chromophore interactions are characteristic for the isomerisation state of retinal, the protonation state of the Schiff base, and changes in the conformation of the protein. The motion of helix F was determined at position L159 which monitors its transient mobilisation. Finally, TM2 rotation was detected by the distance change of V78R1 (see Fig. 5a). The transients are shown in Fig. 5b [43]. For comparison the time domain of the $M_1 \rightarrow M_2$ transition is indicated by an arrow. As is obvious, the helix F movement and the TM2 rotation occur simultaneously with the $M_1 \rightarrow M_2$ transition. On the other hand, the back reactions of receptor and transducer are decoupled as TM2 returns back to its original position delayed by about 200 ms. Taking physiological data into account [44] it appears plausible that the signalling state is reached by the outward movement of helix F concomitantly with the rotation of TM2. This active state is sustained even after the receptor has returned back to the original ground state. This independence from the signalling state of the receptor molecule allows a regulation of the transducer activity according to the cell's own physiological requirements.

6. Pertinent questions

There are two general unanswered questions which relate to the mechanism of receptor activation and the signal transfer from the membrane to the cytoplasmic signalling domain of the transducer molecule.

Concerning the transducer activation two general mechanisms are discussed. In the first model the neutralisation of the Schiff base leads to conformational changes, which subsequently tilt helix F outwardly, thereby opening the cytoplasmic channel. This model has been derived from similar considerations to explain the proton uptake by BR during M decay.

The second possibility takes kinetic arguments into account. In this frame of reasoning the isomerisation of retinal induces rate-determining conformational changes of the protein which occur independent of the charge distribution within the protein. In favour of this model are photocycle measurements, recent FTIR studies and physiological experiments. The photocycle of NpSRII can be described by eight exponentials which are independent of the external pH, although different intermediates are observed at low versus high pH values [32]. Time-resolved FTIR studies on the D75N-NpSRII mutant – whose Schiff base does not deprotonate on light excitation – reveal similar backbone changes of the protein compared to those of the wild-type [45]. In physiological experiments Spudich and coworkers (Spudich, personal communication) showed that bacteria expressing the D75N-NpSRII mutant display wild-type phototaxis responses. These two results indicate that at least a deprotonation of the Schiff base is not mandatory for receptor activation.

The second question, about the signal transfer from the membrane to the CheA activation domain, is of fundamental importance not only for transmembrane signal transfer but also for an understanding of how small conformational alterations such as rotation and/or a piston stroke can be transmitted along large distances. In the case of the transducer or the chemotactic receptors it would be almost 260 Å [23] (recent electron microscopic results indicate a 20% shorter cytoplasmic domain [46]).

For an explanation of this kind of signal transfer only assumptions have been put forward so far. The key role in understanding the mechanism of signal transfer will certainly be played by the linker region which connects the transmembrane helices of the chemoreceptor or phototransducer molecules with the cytoplasmic four-helix bundle (see Fig. 1b). To obtain more structural information about this region, either better crystal structures are needed or the structure has to be determined by other means, e.g. EPR and/or nuclear magnetic resonance spectroscopy. It would also be of advantage if the structures of intermediates became available. These experiments will be more easily performed with the photoreceptor system than with the chemoreceptors, as the structure determination of BR intermediates has already demonstrated (for a recent review see [47]).

In connection with possible signal relay mechanisms two more general models should be discussed. In the first model the small perturbation at the membrane domain, rotation and/or piston stroke, is transmitted to the signalling domain. The rotation could invoke an unwinding of the coiled-coil domain. However, one has to bear in mind that these small alterations might be damped out by the helix dynamics during their way to the tip of the helix bundle. On the other hand, if the linker region was to provide the means for amplification – like e.g. a lever arm – one could envision the transmission of the signal. A second possibility was proposed by Kim and coworkers [48]. In their model the activation of the receptor domain decreases the dynamics of the cytoplasmic domain, thereby increasing phosphorylation of CheA. The adaptation process was also explained in the framework of this model as methylation of Glu residues would modify the dynamics of the transducer.

Finally, one has to consider the supramolecular structure of the chemoreceptors. It has been shown that the receptors form patches which have been proposed to be responsible for the high sensitivity and wide dynamic range of chemoreceptor signalling [48]. These clusters of receptor molecules are thought to consist of trimers of the receptor dimers, which assemble to higher-order patches [48,49]. If the analogy between phototaxis and chemotaxis signalling holds true, the photoreceptor/transducer complexes should also accumulate in such superstructures. A preliminary analysis taking the topology of the HtrII/SRII complex into account indicated that similar clusters can be constructed. However, more experimental evidence for the resulting receptor–receptor contacts for both the chemoreceptors and the photoreceptors is needed for a more detailed description of signalling complexes.

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