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*Review*

# Fundamental Mechanisms in Membrane Receptology: Old Paradigms, New Concepts and Perspectives

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**Abstract:** Receptology, the science of receptors, is a multidimensional field of research which can be dissected into biosynthesis, membrane sorting, ligand binding and signal transduction. Plasma membrane receptors connect the cells with their environment and transmit signals that are translated into biological information. The historical paradigm of ligand–receptor interactions is the lock-and-key model. This model presupposes that both partners have a precise 3D shape that perfectly fits together to form the ligand–receptor complex. However, this simple model suffers from severe limitations due to several levels of simplifications: (i) water molecules and membrane lipids are not considered; (ii) not all ligands have a stable 3D structure; (iii) the ligand-binding pocket of the receptor is often flexible and conformationally rearranged after the initial binding step (induced fit mechanism) and/or subjected to conformational selection by the ligand; (iv) there are signal transduction mechanisms which can be either purely mechanical (conformational change of the receptor induced after binding of the ligand), lipid-assisted (e.g., by raft lipids such as cholesterol or gangliosides), or in some instances of quantic nature (detection of odorant molecules). The aim of the present review is to challenge the old paradigms and present new concepts of membrane receptology that consider the impact of critical parameters such as water molecules, membrane lipids, electrostatic surface potential and quantum mechanisms.

**Keywords:** receptor; ligand; membrane; lipid raft; cholesterol; ganglioside; signal transduction; quantum mechanisms



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## 1. Introduction

A receptor is a biomolecule whose primary biological function is to be recognized by a ligand and thereafter to transmit biological information [1]. In this context, the notion of receptor is closely linked to the concept of selectivity [2]. In other words, each biological ligand has a receptor that is specific to it. Thus, receptology is traditionally based on selectivity. At first glance, this dogma seems correct, and at least in agreement with the way of classifying receptors. We thus define the insulin receptor, the glucagon receptor, the acetylcholine receptor, etc. as the unique proteins devoted to selectively binding their ligand at the cell surface. This means that insulin recognizes the insulin receptor, but not any other receptors that could be present in the same plasma membrane. This is why high selectivity seemed, in the first days of receptology, to be a major property of each receptor. It turned out that this notion is in fact far from being universal (for instance in the case of the human chemokine-receptor network, which has evolved into a highly degenerate receptor–ligand recognition code [3]). However, taking this parameter into account will make it possible to present the historical model of formation of a receptor–ligand complex, which will be referred to throughout this review as the "old paradigm".

## 2. The Old Paradigm

If two molecules interact and form a complex it is because they possess two essential properties: (i) geometric complementarity and (ii) chemical compatibility [4]. In the initial

formulation of the old paradigm, only geometric complementarity is considered, which naturally led to the analogy of the key in the lock [5]. This analogy is entirely legitimate and evocative of this notion of specificity which applies to key–lock pairs and, by analogy, to ligand–receptor pairs (Figure 1). We are in a static mechanical world, governed by precise connections which perfectly determine which ligand binds to which receptor. The keys may look similar, the locks may have similarities, but the selectivity remains absolute: a key for each lock, a ligand for each receptor.

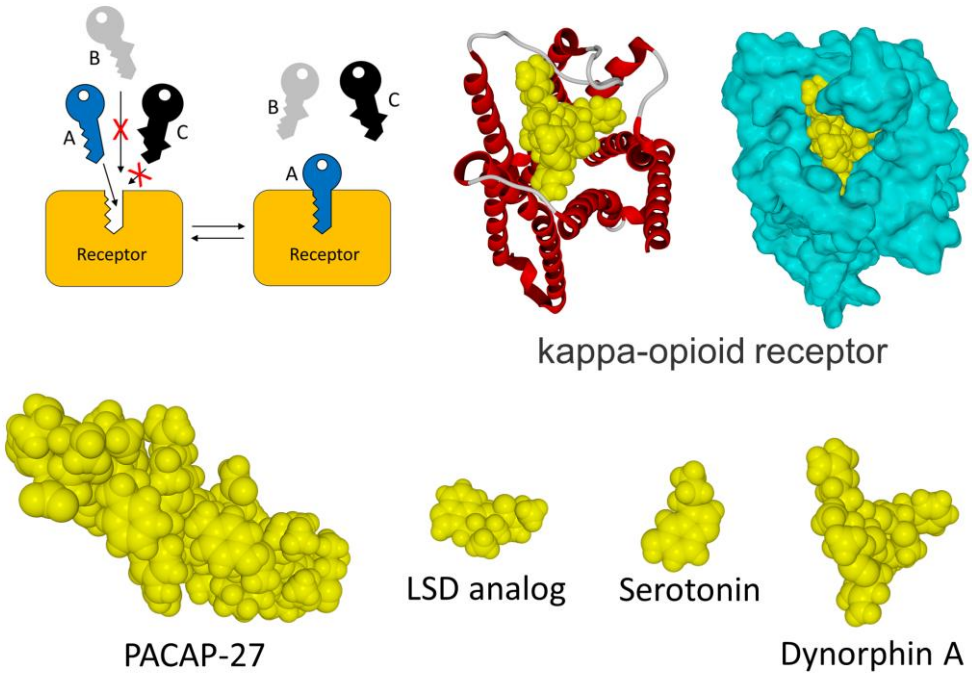


**Figure 1.** The old paradigm: a simple world of keys and locks that fit (or not) geometrically. In the example (upper left) three distinct keys (A, B, and C) try to fit into the lock, but only key A succeeds, while keys B and C are excluded. One receptor, one ligand. This concept is illustrated with the kappa-opioid receptor (pdb 8F7W) [6] which can easily discriminate its ligand dynorphin A against any other possible ligand (e.g., PACAP-27, an analog of LSD or serotonin).

## 3. Limitations of the Old Paradigm

Despite its apparent effectiveness, the old paradigm suffers from numerous irremediable flaws, so it gives a false image of the molecular mechanisms of ligand–receptor interactions. Indeed, two mechanisms considering the flexibility of membrane receptors are proposed to describe the ligand-binding mechanisms [7]. The first mechanism, referred to as "induced fit", suggests that the initial binding step is followed by a conformational rearrangement of the ligand-binding pocket through an adaptative process that optimizes the ligand–receptor complex [8]. In the second mechanism (referred to as "conformational selection"), the ligand-binding pocket exists in an equilibrium of multiple conformations, one of these conformations being selected by the ligand by a typical Darwinian selection process [9,10]. These two interpretations are not mutually exclusive [11], but they do not consider auxiliary factors bound to the receptor and/or the ligand, i.e., water molecules and membrane lipids.

### *3.1. Water Molecules Bound to Membrane Receptors*

Water is probably the most neglected parameter of biology textbooks [12,13]. This is surprising if we consider that water represents 70% of the composition of living organisms. The structure of proteins is generally described by several orders of structure which are the amino acid sequence (primary structure), the local folding of the peptide chain (alpha or beta secondary structure), the 3D structure (tertiary structure) and the associations

of subunits for the quaternary structure. It is striking to note that the water molecules bound to the protein surface are never mentioned in this description, even though these have a major impact on the stability of proteins and their capacity to bind ligands. For a protein to bind to a ligand, its binding site must first dehydrate, and the same generally also applies to the ligand [14]. Most membrane receptors are affected by this mechanism because the binding site of these membrane proteins is generally accessible to the solvent. The rare exceptions concern ligands of a lipid nature such as endocannabinoids which must first penetrate the plasma membrane of the target cell before being able to reach their receptors [15]. The role of water molecules in protein–ligand interactions has been the subject of an excellent study to which we refer for more details [14]. There is often a competition between the ligand and the water molecules to occupy the binding pocket. The entropic component of the ligand–receptor complex formation is thus a major parameter which also controls ligand binding [16].

The degree of order of the water molecules initially attached to the binding site can finely modulate the selectivity of the ligands for a given receptor (Figure 2). We can metaphorically compare this effect to greasing the lock which, when the fit with the key is not perfect, can facilitate the insertion of the key and the opening of the mechanism. An illustration of this concept is shown in Figure 2. The bacterial sugar binding protein L-Arabinose-binding protein (ABP) can bind either L-arabinose, D-glucose or D-galactose, but not D-fucose [17]. In fact, water molecules frequently establish a link between a ligand functional group and a receptor residue. For this reason, water should be considered as an active partner in ligand–receptor interactions.

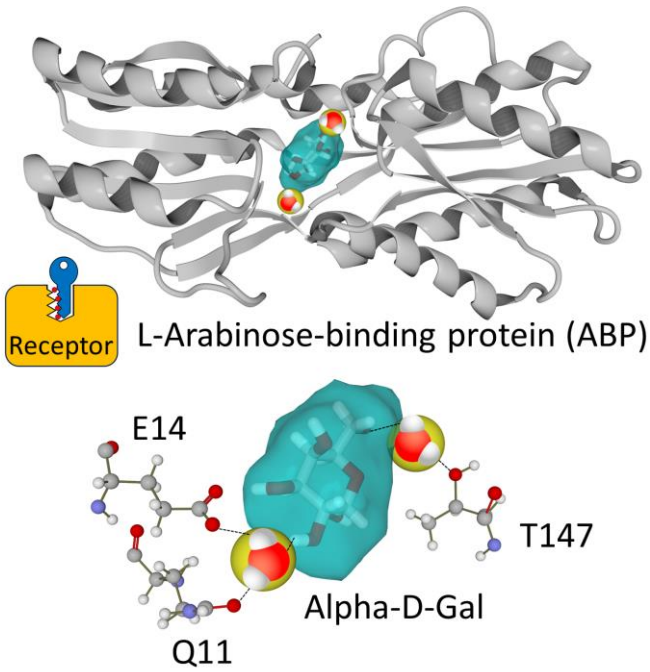


**Figure 2.** Impact of water molecules on ligand binding to a receptor. This concept is illustrated with L-Arabinose-binding protein (ABP) which serves as an initial receptor for the high-affinity active transport in Gram-negative bacteria (pdb 5ABP) [17]. Two hydrogen-bonded water molecules in the sugar binding site interact with alpha-D-galactopyranose (Alpha-D-Gal), creating several bridges between the ligand and the receptor (three amino acid residues involved in such bridges are represented). In this case, water molecules contribute to the molecular recognition of the ligand and contribute to tight binding. Hydrogen bonds are visualized with dashed lines. In the cartoon inset, water molecules are represented as red spheres bridging the ligand and the receptor.

### *3.2. Membrane Receptors Are Surrounded by Lipids*

A second important characteristic of membrane receptors is that their shape is generally controlled by surrounding membrane lipids [18,19]. Among these lipids, those clustered in sphingolipid and cholesterol-rich microdomains, referred to as lipid rafts [20,21], play a critical role in receptor structure and function. Lipid rafts serve as signaling platforms (signalosomes) for a broad range of plasma membrane receptors [22,23]. Membrane lipids allow receptors to accommodate their membrane spanning domains, with the central apolar zone of the membrane containing the hydrocarbon chains of these lipids. This function can be compared to a solvation process analogous to that played by water molecules which surround the polar parts of water-soluble molecules [24]. But the role of lipids is more complex, due to the biochemical diversity of their structures which results in varied physicochemical properties and numerous possibilities of interaction with receptors. Over time, we have realized that membrane lipids do not play a passive role in the function of receptors, but that they can allow very fine regulations of their structure and functions [25]. By combining the actions of cholesterol in the two leaflets of the plasma membrane and of sphingolipids, especially gangliosides, in the extracellular leaflet, lipid rafts provide a privileged environment for transmitting information across the plasma membrane (Figure 3). Membrane lipids refine the structure of the receptors and prepare them to receive the ligand.

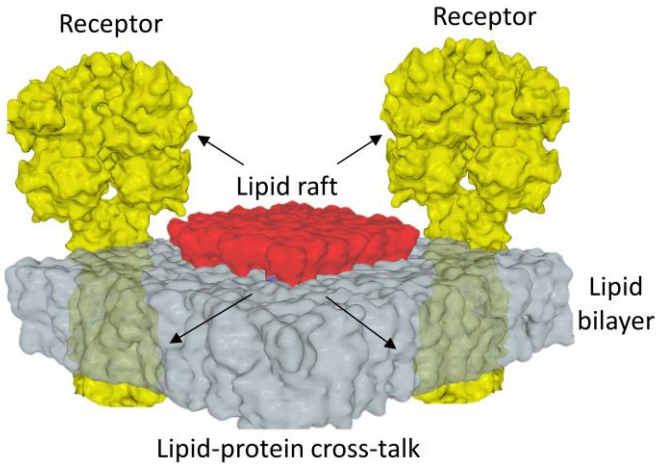


**Figure 3.** Receptology in the lipid world. The receptors (colored in yellow) illustrated in this cartoon are the glutamate receptor mGluR5 which possess extracellular ligand-binding Venus flytrap domains, in the bound conformation (pdb 6N51) [26]. Gangliosides are colored in red, phosphatidylcholine and cholesterol in grey. Lipid rafts have a profound impact on the structure and function of a broad range of receptors. In the key–lock analogy, the rafts correspond to the door. Yet a door is a passive support whereas lipid rafts play an active role in key–lock recognition. The lipid raft structure was reproduced from [27] (published by MDPI under the terms and conditions of the Creative Commons Attribution (CC BY) license).

A characteristic example of the role of lipid rafts in the structuring of membrane proteins is given by the 5-HT1A receptor. In this case, the ligand-binding pocket is shaped by cholesterol molecules that are constitutively bound to this seven transmembrane (7 TM) G-protein coupled receptor (GPCR) [28]. By constraining the TM domains in both the outer and inner leaflets of the plasma membrane, cholesterol molecules have a chaperone activity that determines the structure of the serotonin-binding pocket (Figure 4). The presence of cholesterol molecules associated with GPCR and their impact on GPCR function has been recognized for a long time [29,30]. Two linear consensus motifs allowing cholesterol recognition, referred to as CRAC and CARC [31], are frequently found in these receptors, together with 3D and tilted motifs [32]. All these motifs are based on the same biochemical logic which determines how individual amino acid side chains interact with specific parts

of the cholesterol molecule [33]. Such motifs are located in either the inner or outer leaflet of the plasma membrane and, in some instances, in both. In this latter case, two cholesterol molecules in an opposite orientation can interact with the same TM domain, defining a mirror code of cholesterol recognition by membrane receptors [34]. An illustration of this mirror code is given in Figure 4 (cholesterol molecules colored in cyan for the outer leaflet and in orange for the inner leaflet).

Apart from cholesterol, gangliosides may also specifically interact with membrane receptors [35]. Thus, lipid raft provides a specific environment allowing multiple molecular contacts between membrane receptors and surrounding lipids that act as chaperones [36].

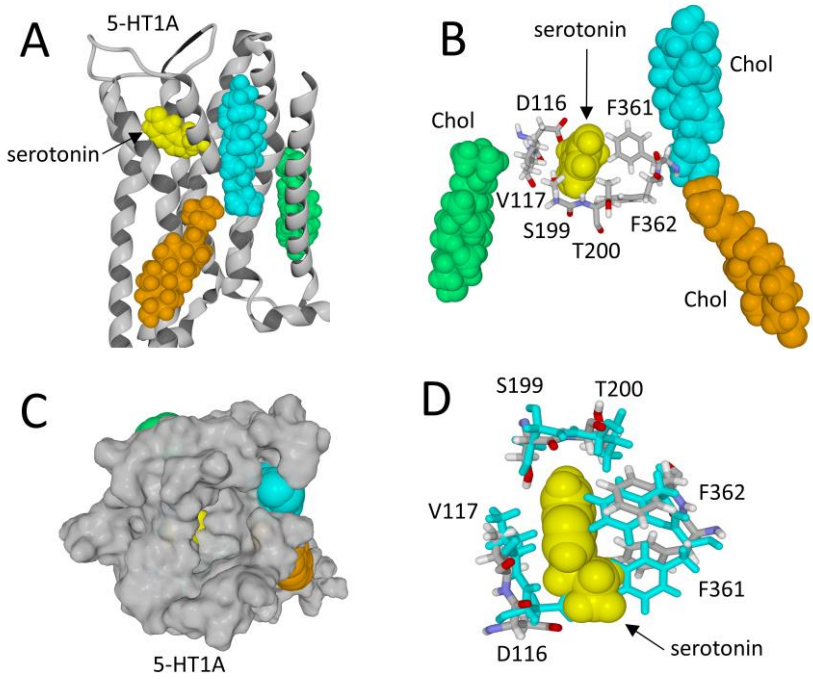


**Figure 4.** Cholesterol molecules act as chaperones for shaping the serotonin-binding pocket of the 5-HT1A receptor. (**A**) TM domains of the 5-HT1A receptor (pdb 7E2Y) [37]. The bound serotonin molecule is colored in yellow. Three cholesterol molecules are shown (colored in cyan, orange and green). Note that the cyan and orange cholesterol molecules are in a typical mirror orientation, one in each leaflet of the plasma membrane. (**B**) Amino acid residues involved in serotonin binding and surrounded by cholesterol molecules. These amino acids define the serotonin-binding pocket of the receptor. (**C**) Surface representation of the 5-HT1A receptor with bound serotonin and cholesterol molecules surrounding the binding pocket. (**D**) Superposition of the amino acid residues forming the serotonin-binding pocket shaped by cholesterol (same colors as in (**B**)) and the same structure minimized without cholesterol (colored in cyan). In absence of cholesterol, the binding pocked is smaller and it cannot accommodate serotonin.

The intricate network of molecular interactions between membrane receptors and raft lipids suggests a co-evolution process involving both partners. This co-evolution process has strongly impacted the nucleotide sequences of the genes encoding receptors. In this respect, the example of Figure 4 is particularly informative. The amino acid sequence of the 5-HT1A receptor can generate a functional receptor only if this receptor is present in a lipid raft environment, where it can find cholesterol molecules able to exert a chaperone activity shaping the serotonin-binding pocket [28]. Molecular modeling of the same receptor without cholesterol leads to a smaller binding site which can no longer accommodate serotonin. This absolute requirement is also demonstrated experimentally in cells treated with cholesterol-depleting agents such as methyl-β-cyclodextrin [38]. As a consequence, an adequate lipid composition often determines the transfer of functional membrane

receptors by DNA transfection. Indeed, the specific lipid requirement of membrane protein is considered a bottleneck for heterologous expression [39]. It is also a major consequence of the epigenetic dimension of protein structure (EDPS) [40–42], a concept developed for explaining the failure of the AlphaFold algorithm [40,43] for correctly predicting the structure of membrane proteins from their amino acid sequence [41,42,44,45].

### *3.3. Intrinsic Disorder in Receptology: The Puzzling Case of Glucagon*

Another intrinsic limitation of the AlphaFold program is that not all proteins have a stable 3D structure. In the traditional interpretation of protein folding, apolar amino acid residues collapse in the center of the structure to avoid any conflict with water molecules, leaving polar residues at the periphery where they can stabilize the structure by a network of hydrogen bonds with water molecules. Although universally accepted, this model does not work for proteins displaying a high polar/apolar balance because in this case there is no reason for the protein to collapse into a globular form. Instead, their polar residues determine a flexible and highly dynamic snake-like shape that oscillates in the aqueous environment between thousands of possible conformations. Such proteins are called "intrinsically disordered proteins" (IDPs) [46–49]. The glucoregulatory peptide hormone glucagon is an IDP [50–52]. We are thus in a case where the key has no particular shape, behaving like a piece of soft material. Under these conditions, how can we conceive of a specific interaction between glucagon and its receptor? The answer was provided by structural studies completed by in silico simulations [53]. When glucagon is near its membrane receptor, it is unstructured and oscillates between different conformations (Figure 5). None of these structures has any particular biological significance. Like all IDPs, glucagon must interact with a ligand to acquire a stable structure. The acquisition of this conformation depends on the presence of a ligand which will literally structure the IDP by molecular molding. This is therefore a typical case of conformational selection.

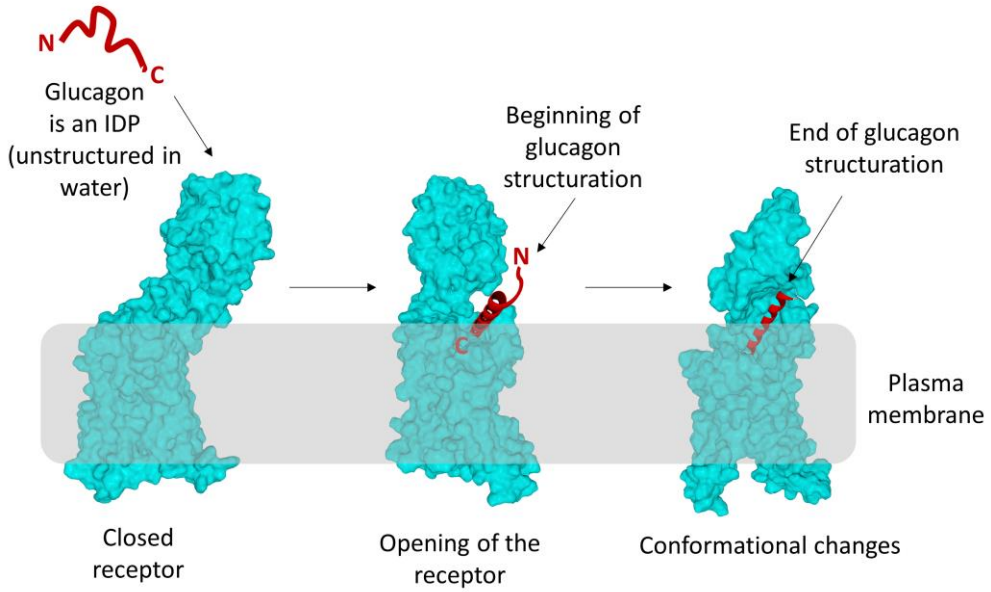


**Figure 5.** Structuration of glucagon during receptor binding. The closed conformation of the glucagon receptor (**left panel**) was retrieved from pdb 5XEZ [53]. The hypothetical docking pose of glucagon on its receptor (**center panel**) and the stabilized glucagon-receptor complex (**right panel**) were retrieved from pdb 5VAI [53].

But in the case of glucagon, this effect is particularly spectacular since the active conformation of the hormone is a helical structure which pre-exists only very transiently in an aqueous environment. It is only when glucagon penetrates inside a cavity of the receptor that glucagon is forced to acquire this helical structure, which is then locked inside

the receptor itself as shown in Figure 5. This mechanism is very intriguing, and one can legitimately wonder whether or not the glucagon amino acid sequence is predisposed to form an alpha helix. This type of analysis was initiated by Chou and Fasman by determining for each amino acid its probability of being found in an alpha helix, in a beta strand, or in a region of the protein without any particular secondary structure (random coil) [54]. The results of such an analysis with the glucagon sequence is given in Figure 6.

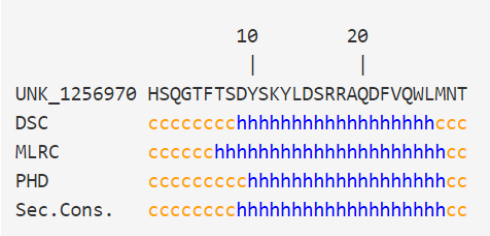


**Figure 6.** Secondary structure predictions of glucagon. Amino acids denoted **h** (in blue) have a high probability of forming an alpha helix, amino acids denoted **c** (in orange) do not give a particular secondary structure. Three prediction methods were applied (DSC, MLRC and PHD), and all gave a similar result. The last line (Sec. Cons.) represents the consensus of these three methods (https://npsa-prabi.ibcp.fr/cgi-bin/npsa_automat.pl?page=/NPSA/npsa_seccons.html, accessed on 28 December 2023).

According to this analysis, the amino acids 9–27 of glucagon are expected to be structured as an alpha helix, whether or not the hormone interacts with its receptor. We can therefore conclude that the receptor eventually restores the structure that glucagon should logically adopt. By limiting contact with water molecules and replacing glucagon–water interactions with glucagon–receptor interactions, the alpha helix structure then becomes the unique hormone conformation. A similar phenomemon has also been observed in glucagon crystals: in this case, glucagon trimers adopt a helical conformation stabilised by hydrophobic interactions [55].

It can be noted that the receptor itself undergoes a significant conformational change between the unbound and the bound forms (Figure 5). In this respect, it is also interesting to note that the concept of simultaneous binding and folding is by no means a new idea. A mechanism referred to as "fly-casting mechanism" was proposed more that 20 years ago [56] and subsequently further developped [57]. The underlying idea is that an IDP can have a greater capture radius for a specific binding site than a stably folded protein with its restricted conformational freedom.

### *3.4. Conformational Rearrangements following Ligand Binding*

The notion of conformational change following the formation of a ligand–receptor complex [58] can be interpreted as a subtle refinement of the lock and key model. In some cases, a minimal ligand-induced conformational change as low as 1 Å can induce a conformational wave that propagates along 100 Å across the plasma membrane, functionally linking the ligand binding site to a cytoplasmic activation domain [8,59]. Upon activation by capsaicin (a vanilloid agonist), a conformational wave induces the opening of TRPV1, revealing how the channel transits from the apo to the open state [60]. Yet the situation is more complex than one might first believe. The activation of the TRVP1 channel is controlled by a set of molecular interactions between this channel and selected membrane lipids such as phosphatidylinositol (PI), which control its opening. In fact, phosphatidylinositol initially occupies the vanilloid pocket and maintains the channel in the closed conformation. The vanilloid agonist capsaicin displaces the channel-bound PI, causing a series of conformational changes that induces the opening of the channel. We therefore see once again that the ligand–receptor pair cannot alone explain how signal transduction mechanisms work. We really need to take into consideration the lipids bound

to the receptor to understand how the conformational waves are triggered by the ligands and propagate across the plasma membrane as a long-range chaperone effect.

Another representative example is given by plasmolipin (PLLP), a proteolipid with 4 TM domains involved in myelin sheath formation [61] and signal transduction [62]. PLLP is located in lipid rafts [63], where it can interact simultaneously with cholesterol and ganglioside GM1 [64]. The extracellular loops of PLLP are intrinsically disordered domains that have the freedom to oscillate between several conformers until they interact with the polar headgroups of GM1 gangliosides in the raft environment. Molecular dynamics simulations suggested that GM1 has a chaperone effect on the extracellular loops of PLLP that is transmitted to the TM helices [64]. Cholesterol then controls the conformational flexibility of these TM domains. The conformational wave initiated by GM1 is first transmitted to cholesterol, then it propagates through the TM domains and reaches the intracellular loop, which eventually adopts a stabilized structure (Figure 7). By clustering gangliosides and cholesterol into signaling platforms, lipid rafts play an active role in the propagation of such conformational waves across the plasma membrane.

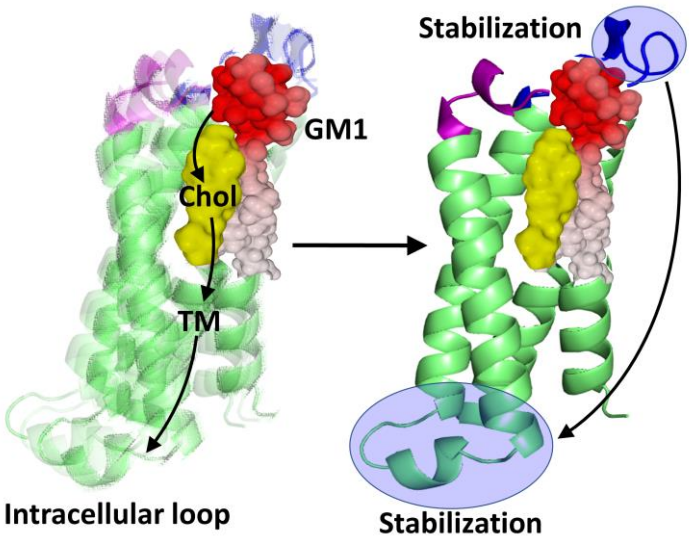


**Figure 7.** Lipid-raft-assisted conformational wave. The ganglioside GM1 interacts with a flexible extracellular loop of plasmolipin (PLLP). This interaction triggers a conformational wave that propagates from cholesterol to the TM domains and eventually reaches the flexible intracellular loop which adopts a stable structure (adapted from [64] published by IMR Press under the CC BY 4.0 license).

It is important to mention that the possible presence of tail-to-tail cholesterol dimers [65] (mirror code [34]) is consistent with a functional coupling of the outer and inner leaflets of the plasma membrane via the TM domains of a membrane receptor [34]. Finally, GPCRs have been suggested to act as scramblases able to mediate phospholipid and cholesterol flip-flop [15,66,67]. The transbilayer transfer of cholesterol may also affect the geometry of TM domains in the membrane core during the propagation of the conformational wave.

## 4. New Concepts

### *4.1. Quantum Mechanims: The Swipe Card Model of Olfaction*

The classic model of recognition of odorant molecules by olfaction receptors is based on a key–lock type geometric adjustment triggering a conformational change responsible for the activation of a G protein (mechanical effect). However, this model is not satisfactory, leading some authors to propose an alternative quantum theory involving an electron transfer from a donor site to an acceptor site, a transfer which is only possible when the energy difference between these sites corresponds to the vibrational energy of the odorant molecule (tunnel effect) [68,69]. In support of this theory, experiments on fruit flies (Drosophila melanogaster) have shown that the shape and size of odor molecules

are insufficient parameters to explain odor detection. Interestingly, the substitution of hydrogen atoms with deuterium atoms in an odorant molecule results in a change in odor despite the fact that the two molecules have the same shape [70]. Clearly, these findings are inconsistent with a shape-only model for smell. Consequently, a new explanatory model of the mechanisms of olfaction has been developed within the framework of Quantum Biology: the "swipe card" model [71].

The key–lock model is based on docking for discrimination (binding of the odorant molecule on the receptor), then on mechanical mechanisms of signal transduction (activation of a G protein by conformational effect). According to the swipe card model, selective docking still plays the same role in the first step of the process (receptor recognition), but the activation of the G protein no longer relies on a conformational mechanism (classical mechanics) but on an electronic transfer involving a tunnel effect, hence a quantum mechanism [72]. This field of research is particularly promising and it warrants further consideration, especially for young biologists. As stated by Brookes et al. [73] "the swipe card paradigm, whether at this stage definitive as a model or not, introduces perhaps more productive ways of thinking that confront interesting observations in nature". In any case, one can already consider that the conformational wave triggered by a ligand binding to plasma membrane receptors can be mecanically driven, lipid-assisted or quantic [64].

### *4.2. Electrostatic Surface Potential*

The electrostatic surface potential [74] is a fundamental parameter governing a broad range of molecular mechanisms including ligand–receptor interactions [12]. The enrichment of lipid rafts in gangliosides possessing sialic acids gives these membrane microdomains an overall negative surface potential [36]. There are other anionic lipids (phosphatidylserine, phosphatidylinsitols, phosphatidic acid), but those lipids are only found in the intracellular leaflet of the plasma membrane and they represent at best less than 25% of membrane lipids [75]. Incidentally, most of these lipids are also enriched in the inner leaflet of lipid rafts [20]. In any case, gangliosides in lipid rafts are the only anionic lipids of the extracellular leaflet. The electronegative surface potential therefore controls all the molecular interactions occurring at the level of lipid rafts, whether physiological [76–79] or pathological [80–83]. The evolution of viruses, for example, largely takes into account the attraction by lipid rafts which are privileged areas of attachment (landing platforms) to host cell membranes [12,27,84,85]. In the case of glutamate, which is negatively charged at physiological pH, the rafts play a role of repellent (electrostatic shield) which maintains this neurotransmitter far from the postsynaptic neuron, thus minimizing its excitotoxicity [4]. In contrast, raft gangliosides attract positively charged neurotransmitters such as serotonin [86]. The gangliosides then control access to the receptor of these neurotransmitters whose binding sites are very close to the plasma membrane, or even slightly inside [4]. Overall, the position of the binding site of neurotransmitters on their receptor is largely determined by the electronegative surface potential of the rafts. Electrostatic vortices are thus created which direct the neurotransmitters towards their binding site.

In this regard, a particularly interesting study was published by Carpenter and Lightstone on the characterization of an electrostatic funnel guiding the neurotransmitter γ-aminobutyric acid (GABA) to its binding site on the GABA type A receptor, a representative member of the pentameric ligand-gated ion channel (pLGIC) superfamily [87]. These authors reasoned that since the GABA molecule is zwitterionic, with charged termini connected by a short hydrocarbon linker, the driving forces controlling its binding pathway must necessarily be electrostatic in nature. Thus they calculated the electrostatic surface potential of the GABA receptor and represented the electrostatic field that surrounds this receptor (Figure 8A). Then they analyzed the pathway by which GABA molecules approach the binding site and concluded that it is far from random. In fact, the electrostatic field of the receptor greatly influences the GABA molecules to become more concentrated at specific positions as they approach the binding site (Figure 8B). This type of analysis, which

highlights the impact of the surface electrostatic potential, should be extended to numerous ligand–receptor pairs.

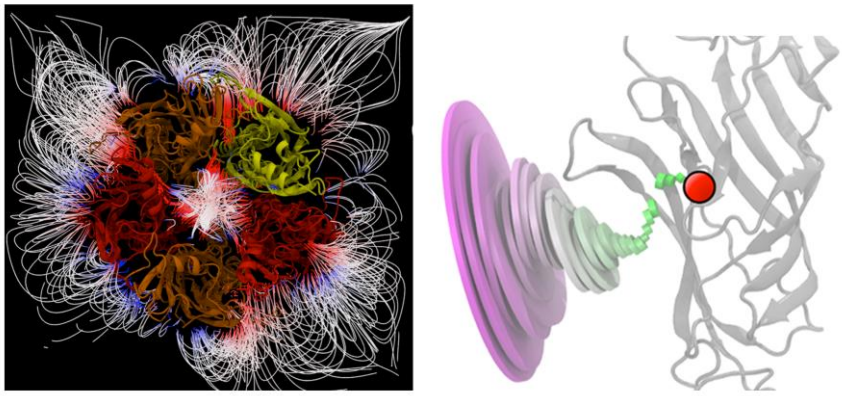


**Figure 8.** Electrostatic vortex in the GABA receptor. (**A**) Top view of the GABA receptor with all the surrounding electrostatic field lines shown (eletropositive areas of the receptor are colored in blue, electronegative regions in red). (**B**) Average binding patwhway of GABA molecules. The GABA molecule positions are 'focused' or 'funneled' once they reach a distance of ~1.9–2.0 nm from the binding site (red circle). Reproduced from ref. [87] (published by PLOS under the terms and conditions of the Creative Commons Attribution (CC BY) license).

## 5. Summary and Perspectives

This brief overview of the molecular mechanisms at work in the field of membrane receptology first led me to challenge the old key–lock paradigm. Then, without entering the still current debate between induced fit and conformational selection mechanisms, I introduced the notion of conformational plasticity of receptors and of certain ligands. Considering the dynamic flexibility of the receptors seems obviously essential, and it is undeniable that this notion has been adopted by most scientists in the field. However, there remain a series of neglected parameters which nevertheless appear to play a major role in ligand–receptor interactions.

(i) Taking water molecules into account should be a systematic reflex for every biologist [13]. The notions of bound water, molecular disorder, hydration/dehydration energy and entropy are likely to modify our vision of ligand–receptor interactions. In addition, the impact of water molecules on the structure—or lack of stable structure—of receptors and ligands is critical.

(ii) The role of membrane lipids, chiefly cholesterol and raft gangliosides [23], remains largely underestimated in receptology. Significantly, numerous studies show that it is possible to annihilate the function of a receptor by modulating the membrane levels of cholesterol and gangliosides that are associated with the receptor [88–90]. These lipids exert a chaperone activity on the receptors, such that in their absence these receptors are no longer functional because they are incapable of recognizing their ligand.

(iii) The consideration of molecular disorder and structuring phenomena resulting from the formation of a ligand–receptor complex was approached using the example of glucagon. However, it is likely that such mechanisms could be operative for many other ligand–receptor pairs [51]. But to undertake research in this context, we must realize that about 50% of proteins of the human proteome are either totally or partially disordered [47]. Furthermore, the case of glucagon demonstrates that even short peptides (with less than 30 amino acid residues) can exhibit such characteristics, which takes us even further away from the original key and lock model.

(iv) If we combine this notion of IDPs with the chaperone activity of membrane lipids, we understand the failure of the AlphaFold program for predicting the structure of

membrane proteins [41]. My personal experience leads me to believe that too many colleagues have a lot of confidence in the protein structures proposed by AlphaFold, whose self-appreciation is probably slightly exaggerated [91]. In fact, although it is usually very good in the prediction of globular proteins, this is unfortunately not the case for membrane proteins. Specific examples of AlphaFold's low reliability in the case of membrane proteins have recently been published [41,42]. We should therefore not overestimate the capabilities of this program.

(v) Conformational waves induced by ligands on membrane receptors are often interpreted as isolated phenomena totally disconnected from membrane lipids [92]. This is clearly not the case. The unique configuration of lipid rafts, functionally associating cholesterol molecules and gangliosides as well as tail-to-tail cholesterol dimers, underlines how these microdomains are adapted to the transmission of conformational information across the plasma membrane [64]. The establishment of these mechanisms required a long co-evolution of receptors and lipids, with cholesterol replacing bacterial hopanoids and gangliosides replacing ancestral glycosylated lipids [93–96]. Concomitantly, bacterial receptors gradually evolved into synaptic receptors, modulating hopanoid recognition patterns to make them even more efficient for raft cholesterol [97].

(vi) If there is one area of receptology that is still very underrated, it is that involving quantum mechanisms [72]. However, the swipe card model of odorant recognition [73] is particularly attractive, and it should inspire vocations among our young researchers. This open field of research is an opportunity which should stimulate the imagination of our students. Incidentally, this should start with a questioning of professors who neglect this promising new dimension of biology. Indeed, quantum biology is not sufficiently taught in university biology courses.

(vii) Finally, I consider the electrostatic surface potential as the most intuitive of fundamental notions [12]. This is perhaps the most important and, in any case, the most accessible parameter for understanding molecular interactions, which is still the basis of receptology.

## 6. Conclusions

The future of membrane receptology will involve both a questioning of old paradigms and the careful consideration of the above-mentioned parameters that are still too neglected, especially by scientists who are not familiar with the field of receptors. This review, necessarily biased by the selection of themes addressed by the author, would achieve its objectives if it could stimulate interest and encourage vocations among our current students.

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