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Biochemistry

Membrane lipid phase as catalyst for peptide–receptor interactions

(electrostatic accumulation/sequential binding steps/macroscopic binding characteristics/catalysis by micelles/reconstitution criteria)

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ABSTRACT **Catalysis of ligand–receptor interactions is proposed as an important function of the lipid phase of the cell membrane. The catalytic mechanism is deduced from observed specific interactions of amphiphilic peptides with artificial lipid bilayers. In our model a direct ligand–receptor reaction is replaced by multiple sequential steps including surface accumulation of charged ligands, ligand–membrane interactions, and ultimately binding to the receptor itself. By dividing the total free energy of binding among several steps, the energy per step, including the intrinsic receptor interaction energy, is kept to moderate values. The model thereby yields simple explanations for the large apparent association constants, the high association and dissociation rates, and the heterogeneity of binding sites so frequently found with pharmacological and biochemical ligand–receptor interactions. Furthermore, the measured apparent association constant is a function of the whole system rather than just the receptor. The same, fully functional receptor may show different binding characteristics in different surroundings, such as in another tissue or in a reconstituted system.**

Although the receptor concept was introduced early in the 20th century and has been the subject of ever more intense research, the mechanisms by which polypeptide hormones bind to cells and trigger biological responses still presents many enigmas. In this paper we will address some fundamental questions about the mechanism of hormone–receptor interactions raised by the concentration dependence of the binding and response data.

The form of receptor binding curves, which often show nonlinearities in the Scatchard plot, has led to various interpretations, such as high- and low-affinity binding sites or cooperativity between sites. While undoubtedly relevant in certain cases, such explanations do not supply a satisfying general rationale for the complex behavior that is often observed.

Dose–response curves often indicate EC_{50} values in the nanomolar range or lower, in contrast to the K_ms of enzyme–substrate reactions in solution, for which 1 μM (e.g., arginine-tRNA ligase/arginine) represents an extremely low value. Part of the difference could lie in different proportionation of the intrinsic binding energy between "productive" and "nonproductive" binding energy (1), but other basic factors may also be involved.

The kinetic aspects of the hormone–receptor reaction must also be considered, especially if the low EC_{50} values are rationalized as reflecting a lower proportion of productive binding energy— i.e, less rate enhancement due to reactant destabilization. Reaction rate theory predicts rate constants proportional to $\exp(-\Delta G_b/RT)$, where ΔG_b represents the height of the reaction barrier. If 1000 sec^{-1} can be taken as a reasonable rate constant for the forward reaction (1), then, given an overall $\Delta G_b = -12$ kcal/mol ($EC_{50} \approx 1$ nM), the off reaction would have a rate constant on the order of 10^{-7} sec^{-1}. This corresponds to a time constant of about a year, which is clearly unrealistic for practical metabolic control systems. Again, while completely unrelated schemes can be proposed to explain a rapid turn-off following hormonal stimulation, it is worth considering alternative mechanisms of receptor binding.

Our studies with adrenocorticotropin-(1–24)-tetracosapeptide ($ACTH_{1-24}$) and dynorphin-(1–13)-tridecapeptide ($dynorphin_{1-13}$) show that these polypeptide hormones interact strongly and specifically with pure lipid bilayers. The reactions display regional, conformational, and orientational selectivity of binding to model lipid bilayer membranes (2–11) and thus display structural characteristics closely resembling those held responsible for the catalysis of bimolecular chemical reactions by detergent micelles (12). This similarity suggested influences of the lipid bilayer of target cell membranes on rate and equilibria of peptide–receptor interactions. We have been developing this thesis for several years (3, 13, 14) and other authors have published work in a similar vein (15–17). In this report we derive a model of membrane-mediated peptide–receptor interaction and consider the quantitative implications for macroscopic ligand binding characteristics.

Basic Considerations

Our model is derived from two sets of observations. One comprises structural and binding data describing interactions of $ACTH_{1-24}$ and $dynorphin_{1-13}$ with neutral model membranes or liposomes comprised of 10% (wt/vol) anionic lipid (2–11). The other consists of pharmacological and binding data on the reactions of these peptides with receptors (18, 19). The two elements are connected by the assumption that conformations and orientations imposed on the peptides by the membrane meet receptor requirements better than the random structures in solution. This appears justified by correlations between membrane binding and biological potency (2–11, 20).

The free energy of binding to uncharged lecithin bilayers was found to be about -5.7 kcal/mol for $ACTH_{1-24}$ (21) and -6.7 kcal/mol for $dynorphin_{1-13}$ (11), with binding saturating at about 2×10^{-2} molecules per nm^2 for $ACTH_{1-24}$ and 0.9×10^{-2} molecules per nm^2 for $dynorphin_{1-13}$. The net effect of these interactions is 2-fold: the bound hormone is concentrated at the surface and has a conformation and orientation presumably suited for reaction with the receptor (34). A further concentrating effect will occur for charged species in biological systems due to a Boltzmann distribution between the bulk phase and the charged membrane surface, e.g., ref. 5. For $ACTH_{1-24}$ (net charge +6) reacting with a cell having a fixed charge surface potential (V_{gc}) of some -40 mV, this would amount to a surface concentration of $\exp(-zFV_{gc}/RT) \approx 15{,}000$ times higher than the bulk concentration. For $dynorphin_{1-13}^{5+}$ an enhancement by a factor of 3000 could be expected.

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Abbreviations: $ACTH_{1-24}$, adrenocorticotropin-(1–24)-tetracosapeptide; $dynorphin_{1-13}$, dynorphin A-(1–13)-tridecapeptide.

Pharmacological and binding studies with $ACTH_{1-24}$ have yielded an $EC_{50} \approx 0.9$ nM for lipolysis and a K_d of 1.2 nM for binding to isolated rat lipocytes (18). $Dynorphin_{1-9}$, which behaves very similarly to $dynorphin_{1-13}$, has an EC_{50} of 6.1 nM for the inhibition of electrically induced contractions of rabbit *vasa deferentia* (mainly κ sites) and a K_d of 0.23 nM for binding to κ sites in guinea pig brain homogenates (22). Thus, in these representative assays, both peptides have apparent receptor-binding energies, ΔG°, of about -12 to -14 kcal/mol. $ACTH_{1-24}$ binding to adipocytes has been found to saturate at about 250 sites per μm^2 or 2.5×10^{-4} sites per nm^2 (18).

The Model

Hormone receptors occupy only a small fraction of the total cell surface, so that when a hormone molecule approaches a cell the first contact is much more likely to be with the lipid phase than with one of its own receptors. The interactions found with the lipid bilayer model membranes will thus represent the initial steps of the hormone–cell contact. Furthermore, the binding parameters for $ACTH_{1-24}$ and $dynorphin_{1-13}$ to neutral lipid bilayers are such that the receptor will react predominantly with membrane-associated hormone molecules rather than those free in solution (21).

The hormone–receptor reaction thus proceeds in stages rather than in a single step (lock-and-key model), and the observed binding energy is the resultant of the binding energies of the individual steps.

The simplest binding model based on these considerations is electrostatic accumulation at the surface (Boltzmann distribution) followed by membrane binding (3, 4) and ultimately the receptor interaction itself. The accumulation is described by

$$H_a = H_f \exp(-z_h FV/RT), \qquad [1]$$

where H_a is the hormone concentration in the accumulation layer, H_f is the free hormone concentration in solution, V is the surface potential, z_h is the hormone charge, F is the Faraday constant, and R and T have their usual meanings (see ref. 5). The equation for the membrane binding reaction is

$$H_a + B_m \rightleftharpoons H\text{–}B_m, \qquad [I]$$

where B_m represents the surface binding sites and $H\text{–}B_m$ is the surface-bound hormone. Defining k^+ and k^- as the forward and reverse rate constants for reaction I and using the equation for the conservation of mass, $B_m = B^\circ - H\text{–}B_m$, where the symbols now refer to concentrations, equilibrium of reaction I implies that

$$H\text{–}B_m = \frac{B^\circ}{1 + k^-/(k^+ H_a)}, \qquad [2]$$

where B° is the maximum binding concentration. Substituting for H_a from Eq. 1, and using $k^-/k^+ = \exp(\Delta G_m/RT)$, where ΔG_m is the change in standard free energy for the membrane binding, Eq. 2 is equivalent to the Langmuir adsorption isotherm as modified by Stern for charged species (e.g., ref. 23).

The equation for the hormone–receptor interaction is

$$H\text{–}B_m + R_m \rightleftharpoons H\text{–}R_m + B_m. \qquad [II]$$

Again defining rate constants, k^+ and k^-, total receptor concentration R°, and the change in standard free energy, $\Delta G_r = RT \ln(k^-/k^+)$, and substituting for $H\text{–}B_m$ and H_a, one finds that

$$H\text{–}R_m = \frac{R^\circ}{1 + (1/H_f)\exp[(\Delta G_m + \Delta G_r + z_h FV)/RT]}. \qquad [3]$$

Using $\Delta G^\circ(\text{measured}) = RT \ln K_d(\text{apparent})$, one has the equality

$$\Delta G^\circ(\text{measured}) = \Delta G_m + \Delta G_r + z_h FV. \qquad [4]$$

The value of V, the surface potential, is assumed to be given by the Gouy–Chapman fixed-charge surface potential, which depends on the ionic strength and the total surface charge [$\sigma = \sigma^\circ + z_h(H\text{–}B_m + H\text{–}R_m)$, where σ° refers to the native membrane and the second term gives the charge of the total bound hormone]. From the lipid composition of the target cell membranes (24), σ° appears to be about 1 $e^-/4$ nm^2. The bathing electrolyte (physiological fluid) is assumed to have an ionic strength equivalent to a 145 mM solution of a uni-univalent electrolyte. The Gouy–Chapman potential, V_{gc}, of the system is calculated iteratively using the Graham equation

$$\sigma = (1/2.72)\Sigma c_i[\exp(-z_i FV_{gc}/RT) - 1], \qquad [5]$$

where σ = surface charge density (e^-/nm^2), and c_i = bulk concentration (M) of the ith species, of valence z_i.

One can now solve for $H\text{–}B_m$ and $H\text{–}R_m$ as a function of H_f. Because V_{gc} is an implicit function of σ (Eq. 5), and also depends on H_f, a numerical solution is necessary. The procedure is easiest by choosing $H\text{–}B_m$ as the independent variable, calculating $H\text{–}R_m$ and hence σ, from which in turn V_{gc} and H_f can be determined by iteration.

Results

Plots of $H\text{–}R_m$ vs. H_f for three binding models are presented in Fig. 1 and, in the Scatchard transformation, Fig. 2. Curve A in Fig. 1 and Fig. 2*A* show the results for the model discussed above. To achieve an EC_{50} of 1 nM, a ΔG_r° of -1.07 kcal/mol is necessary. The binding energy of the hormone–receptor interaction is thus very modest, allowing considerable latitude for productive (rate enhancing) binding effects. The Scatchard plot is clearly nonlinear, resulting from a reduction of the surface potential with increasing membrane-

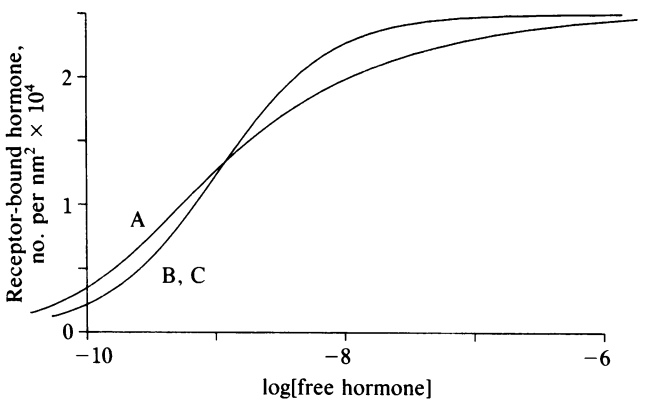

FIG. 1. Logarithmic dose-binding curves for various binding models. (Curve A) Binding of a charged ligand to a receptor on an oppositely charged membrane, the receptor binding being mediated by ligand bound to the membrane itself as follows: $z_h = +6$, $\sigma^\circ = 0.25$ e^-/nm^2, $\Delta G_m^\circ = -5.7$ kcal/mol, $B^\circ = 2 \times 10^{-2}$ sites per nm^2, $R^\circ = 2.5 \times 10^{-4}$ sites per nm^2 (e.g., $ACTH_{1-24}$), $\Delta G_r^\circ = -1.07$ kcal/mol to yield an $EC_{50} = 1$ nM. (Curve B) Binding of neutral ligand to its receptor, the binding being mediated by the membrane matrix as in curve A: $\Delta G_m^\circ = -5.7$ kcal/mol, $\Delta G_r^\circ = -6.3$ kcal/mol ($EC_{50} = 1$ nM). The difference between curves A and B results from the reduction of surface potential due to the nonspecific ligand binding to the membrane in curve A. (Curve C) Binding of a charged hormone to a receptor on an oppositely charged membrane, as in curve A. No nonspecific binding: $\Delta G_r^\circ = -6.44$ kcal/mol ($EC_{50} = 1$ nM). The shapes of curves B and C are identical.

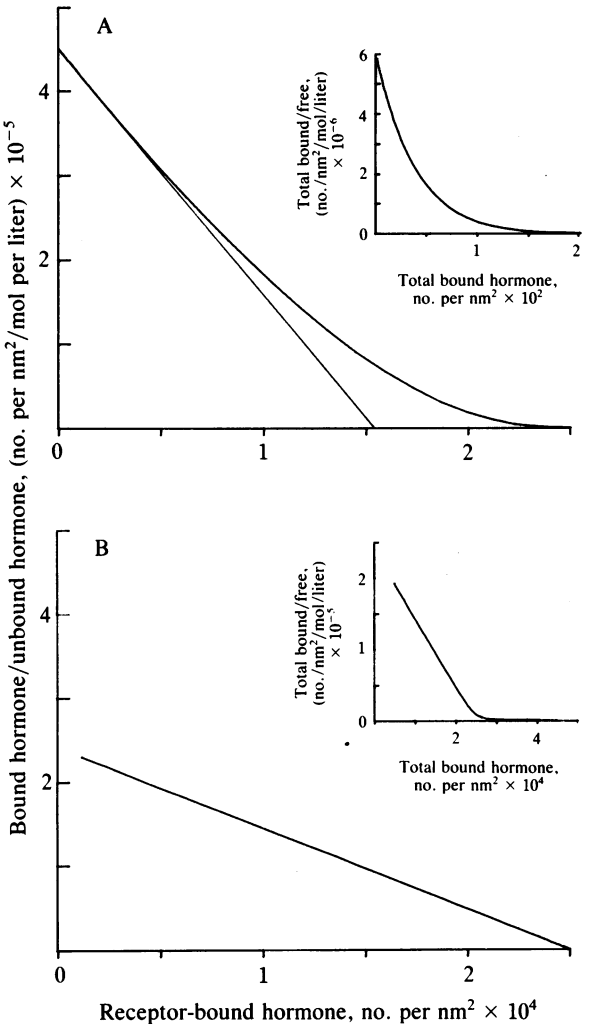

FIG. 2. Modified Scatchard plots of the binding models. *A* and *B* are as described for curves A and B in Fig. 1. An extrapolation of the low concentration section of curve in *A* (straight line) yields apparent parameters of $K_d' = 0.36$ nM, $R^{o'} = 1.6 \times 10^{-4}$ nm^{-2}. The curve in *B* is identical with that of a single-step binding with a $\Delta G_r^o = -12$ kcal/mol. (*Insets*) Scatchard plots for the total bound ligand (nonspecific plus receptor bound) for each situation.

bound hormone. (At $H_f = 1$ nM the original surface potential of −40 mV is reduced by less than 2 mV, but at $H_f = 100$ nM the reduction is already about 12 mV.) If one attempted a linearization at low hormone concentration, as indicated in Fig. 2*A*, apparent K_d and R^o values of about 0.36 nM and 1.6 $\times 10^{-4}$ nm^{-2} would be derived. The lower K_d reflects the smaller electrostatic perturbation at low bound concentration.

For comparison it is interesting to consider two other cases: (*i*) membrane-mediated binding of a neutral hormone and (*ii*) the direct binding of the charged hormone to the membrane receptor.

Case (*i*) is described by the preceding equations, with $z_h = 0$. Using the same parameters for the membrane binding and maximum receptor concentration as before, Eq. **4** shows that a ΔG_r^o of −6.3 kcal/mol is necessary to achieve an EC_{50} of 1 nM (Fig. 1, curve B). The Scatchard plot for the receptor binding is linear (Fig. 2*B*) and indistinguishable from that for a direct hormone–receptor interaction with a K_d of 1 nM.

Case (*ii*), the direct binding of a charged hormone to its receptor taking the electrostatic accumulation into account, is described by Eqs. **1** and **2**, whereby B^o and ΔG^o now both refer to the hormone–receptor interaction. A $\Delta G^o \approx -6.5$ kcal/mol is necessary to reach the same EC_{50} (1 nM) as before (Fig. 1). The Scatchard plot is essentially linear (indistinguishable from the curve in Fig. 2*B*) as the change of surface potential caused by the receptor-bound hormone alone is less than 0.6 mV at saturation. The Scatchard plot would normally be interpreted as that of a single-step reaction with an apparent K_d of 1 nM.

Depending on the technique used for the binding assay, one might measure both receptor-bound and membrane-bound hormone. In this case the Scatchard plots would appear as shown in the insets of Fig. 2. In Fig. 2*A* the membrane binding sites are noticeable even at the lowest concentrations (40 pM hormone) whereas in Fig. 2*B* the membrane binding sites appear as a tail at high hormone concentration.

Reaction Kinetics

A simple, reversible binding reaction of ligand and hormone has a time constant given by $\tau = 1/(k^- + H^o k^+)$, where k^+ and k^- are the forward and reverse rate constants and H^o is the free hormone concentration. A rough comparison of the characteristic time constants for the various reaction mechanisms discussed can be made on the basis of the Eyring rate theory. This theory predicts a rate constant proportional to $\exp(-\Delta G_b/RT)$, where ΔG_b is the height of the energy barrier (including the activation energy) between the two states. The proportionality constant is called the frequency factor, and in the following, is assumed to be constant, and is set equal to unity. A total activation energy of 3 kcal/mol is assumed and partitioned more or less proportionally between the various steps for reasons argued in "zipper" models of direct peptide–receptor interaction (25, 26).

For a single-step binding reaction with an $EC_{50} = 1$ nM ($\Delta G^o = -12$ kcal/mol) one finds $k^+ = \exp(-3/RT) \approx 6 \times 10^{-3}$ and $k^- = \exp(-15/RT) = 6 \times 10^{-12}$, thus at $H^o = 1$ nM we have $\tau = 8 \times 10^{10}$.

For the two-step process preceded by an electrostatic accumulation, as discussed in this paper, three rates must be considered. The setting up of the Boltzmann distribution at the membrane/solution interface is diffusion limited. The accumulation layer itself has a thickness on the order of the Debye–Hückel length which, for a 145 mM 1:1 electrolyte, is about 1 nm. A more relevant length parameter is probably the thickness of the unstirred layer, which would be on the order of 0.1 mm. A process on this scale has a characteristic time on the order of $t = x^2/D$ which, for $D \approx 10^{-6}$ cm^2/sec, is equal to about 50 sec. This is comparable to systemic circulation times and can thus be disregarded. The next step of the reaction chain, the membrane binding itself, has a $\Delta G^o = -5.7$ kcal/mol. Assuming an activation energy of 1.5 kcal/mol yields $k^+ = 7.5 \times 10^{-2}$ and $k^- = 4 \times 10^{-6}$. With a concentration in the accumulation layer of 8.8 μM, corresponding to 1 nM in the bulk solution, one finds $\tau \approx 2 \times 10^5$. With a $\Delta G_r^o = -1.07$ kcal/mol for the binding to the receptor and an activation energy of 0.5 kcal/mol, we have $k^+ = 4 \times 10^{-1}$ and $k^- = 6.7 \times 10^{-2}$, yielding a maximal $\tau \leq 1/k^- = 15$. The membrane binding step is thus rate limiting, and the reaction kinetics will be some 10^5 times faster than for the single-step process without electrostatic accumulation.

For the direct binding of hormone to receptor, but allowing for the electrostatic accumulation, we found that a $\Delta G^o \approx -6.5$ kcal/mol was necessary to achieve an apparent K_d of 1 nM. This is only slightly larger than the ΔG for the hormone–membrane interaction, implying a similar reaction time constant. A reduced frequency factor is to be expected, however, as the number of unfavorable collision geometries between the conformationally and orientationally less restricted hormone molecules in solution is much greater than for the membrane-selected hormone, so that considerably slower reaction kinetics would be expected.

For the electrically neutral, membrane-mediated hormone–

receptor interaction the $\Delta G_r^o = -6.3$ kcal/mol yields a $k^- \approx 1.4 \times 10^{-6}$ and a $\tau \approx 7 \times 10^5$. Thus we have two sequential reactions of approximately equal time constant, which will again yield a significant increase in the overall reaction rate compared to a single-step reaction with an equivalent total ΔG.

Discussion

The surface accumulation due to electrostatic attraction is already a very effective method of enhancing receptor binding of multiply charged molecules. When this is combined with binding to membrane lipid, the final binding to the receptor need only add a small energetic contribution.

The effects of this situation, for which we use the term membrane catalysis, on both macroscopic binding characteristics and reaction kinetics have been investigated.

There are several rate-enhancing factors for ligands like $ACTH_{1-24}$ and $dynorphin_{1-13}$, which show both electrostatic accumulation and direct agonist–membrane interactions. Dividing the total binding energy between several steps reduces the reaction time constants. Compared to the one-step model, dissociation times are reduced by five orders of magnitude, which may account for the observed dissociation in the minute range. Secondly, by reducing the energetic requirements of the individual steps the possibility of rate enhancement by productive binding energy is increased. Finally, the free energy of binding to the membrane is about double that necessary for converting three-dimensional diffusion of the agonist on the membrane surface to a two-dimensional process (21, 27). Accelerated "receptor tracking by reduction of dimensionality" (28) will, therefore, also play a role.

Receptor occupancy, measured either with low concentrations of highly radioactive ligands or with pharmacological assays, is an estimate of the apparent affinity at the final stage (receptor). The observed association constants sometimes exceed 10^{10} M^{-1} (29, 30). Such "high-affinity low-capacity" binding need not be due to an exceptionally strong intrinsic affinity of the receptor for its agonist, but may merely be the consequence of preceding stages that effectively increase the agonist concentration at the receptor. Low-affinity high-capacity binding is also observed (18, 19, 29, 30). Combinations of the two or more types of sites leads to "curvilinear" Scatchard plots that have been explained by inhomogeneous receptor populations or by negative cooperativity between receptors (31). A succession of steps produces similar plots (e.g., Fig. 2, *Insets*) and yields a natural explanation of low-affinity sites. The origin of a "negative cooperativity" in the binding of charged species (Fig. 2*A*) is also clear. Theuvenet *et al.* (32) have discussed similar effects in the transport of ions across biological membranes.

Membrane catalysis thus offers simple alternative explanations for these effects, but it also implies that the specific contribution of the agonist–receptor interaction cannot be determined from the dose–response or binding curves alone. The contributions of the ligand–membrane interactions form an integral part of the measured apparent association constant and must be determined by independent means.

A pictorial representation of our model is given in Fig. 3. In it the flexible amphiphilic peptide agonists (A^0) are assumed to have little, if any, order in the intercellular fluid, as in water. In step 1, A^0 collide with the membrane, and the surface activity of A^0 is enhanced by diffusion (27) and electrostatic (9) phenomena (A^1). Step 2 involves peptide internal rotations and insertions between lipids (loss of translational, conformational, and rotational entropy) and release of bound water (entropy gain) to produce the peptide agonist in its observed membrane-bound conformation and orientation, A^m. Step 3 is the formation of complexes (A^m–R^m) between A^m and the receptor in its unstimulated

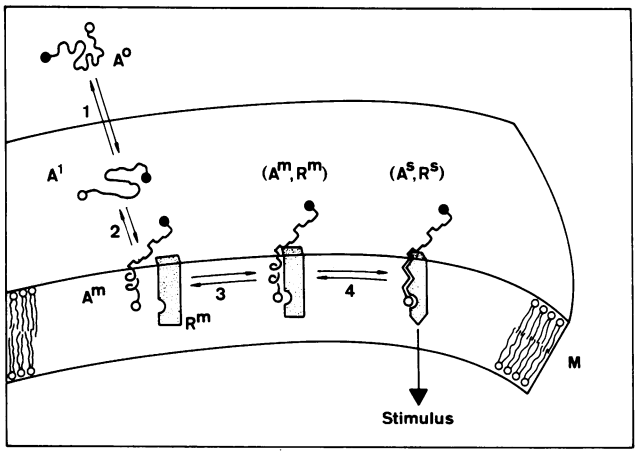

FIG. 3. Physical model of membrane-catalyzed peptide–receptor interactions. Schematic cross section through a lipid bilayer membrane (M) with its outer lipid–water interphase extending up- and backward and showing the peptide agonist (A) and its receptor. The first two steps are based on the observed electrostatic and hydrophobic interactions of the flexible, amphiphilic peptides $ACTH_{1-24}$ and $dynorphin_{1-13}$ with model lipid membranes (2–11). The amino-terminal (○) message segments, $ACTH_{1-10}$ (11) and $dynorphin_{1-13}$ (33), interact with the membrane hydrophobic layers, but the carboxyl-terminal (●) address segments remain in the aqueous head group region (8, 9). In the lipid–water interphase, the peptides assume preferred conformations and orientations, in these cases short helices with their axes perpendicular to the membrane surface (6, 7, 11). The third and fourth steps are based on concepts postulating concerted conformation changes of the agonist and its receptor for stimulation (1, 26). Note that the details of the peptide–membrane and peptide–receptor interactions, such as which section of the ligand interacts hydrophobically or electrostatically, will depend on the local properties of the particular molecule considered.

conformation (R^m) (1, 25). Step 4 is the concerted rearrangement of agonist and receptor conformations (1, 25) to produce the complex (A^s–R^s) between the agonist in its stimulative (A^s) and the receptor in its stimulated (R^s) form. The structural and energetic features are strongly reminiscent of micelle-catalyzed chemical reactions (12). The binding energy between the peptide and the membrane is utilized to overcome the entropy requirements involved in bringing the reacting groups, A^0 and R^m, together (catalysis by induced association). The membrane interaction induces preferred conformations and orientations of the peptides and most probably forces charged amino-terminal groups of $ACTH_{1-24}$ and $dynorphin_{1-13}$ into a hydrophobic environment. This may amount to an agonist destabilization akin to the substrate destabilization in micellar catalysis described by Jencks (12). There is reason to believe that the helically destabilized message segment of A^m (in $ACTH_{1-24}$) meets receptor requirements better than the random segment of A^0 (14) and can, therefore, reach the transition state for receptor interaction more easily.

The numerical results in this paper were based on the assumption of a receptor embedded in a uniformly charged surface, and irregularities in the charge distribution, including on the receptor itself, could affect the results. In a similar way, inhomogeneities in the charge distribution of the adsorbing molecules will modulate the final reaction with the receptor. The differences will be only a matter of degree, however, and the general aspects of the phenomena we have described will remain valid.

Similar effects are potentially important for all substances acting at membranes or other surfaces. The electrostatic accumulation factor is relevant for any charged species, such as substrates of membrane-bound enzymes, charged drugs, etc. Interactions with the lipid phase, be they at the interface

or in the hydrophobic core, are probably more widespread than has been realized. It is obvious that in reconstitution studies more attention must be paid to these effects, especially when proposing criteria for "successful" reconstitutions. The apparent K_d in the reconstituted system will depend strongly on surface charge density, ionic composition of the aqueous phase (multivalent counterions shield much more effectively than univalent ions), perhaps the stereochemistry of the lipid head group (8), etc. Deviations from the physiological values are to be expected and even large differences may not reflect on the integrity of the receptor itself. Similarly, the same receptor might have a different affinity for the same ligand in different tissues, again depending on the properties of its surroundings. More detailed knowledge of the surface potentials and lipid composition of the target cells will be necessary in elucidating such effects.

The importance of the membrane as an antenna for and modifier of ligand–receptor interactions has often been underestimated if not completely ignored. We hope that our ideas will stimulate new studies to elucidate molecular mechanisms governing receptor specificity, recognition, and stimulation. In particular, the concept of surface activity (amphiphilicity) combined with amphiphilic moment (34) may prove more valuable in the study of quantitative structure–activity relationships than the simpler concepts of partition coefficient and hydrophobicity. Conformation studies of membrane-bound peptides (6, 11) may also become useful for predicting new biologically active peptide analogues and drugs.

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