Biophysical Chemistry 146 (2010) 60–64

Contents lists available at ScienceDirect

Biophysical Chemistry

journal homepage: http://www.elsevier.com/locate/biophyschem

Protein adsorption and desorption on lipid bilayers

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ARTICLE INFO

Article history:
Received 20 September 2009
Received in revised form 18 October 2009
Accepted 20 October 2009
Available online 27 October 2009

Keywords:
Proteins
Lipids
Adsorption and desorption kinetics
Lipid redistribution
Electrostatic interactions

ABSTRACT

The protein surface usually exhibits one or a few charged spots. If a lipid bilayer contains a significant amount of lipids with oppositely charged head groups, protein adsorption on a bilayer may be energetically favourable due to the protein–lipid electrostatic interaction. The specifics of this case are that the lipids are highly mobile and the protein adsorption is accompanied by the redistribution of lipids between the areas covered and not covered by protein. We present a kinetic model illustrating that this effect is especially interesting if the fraction of the surface covered by charged lipids is relatively low. In this situation, with increasing protein coverage, the protein desorption rate constant rapidly increases while the adsorption rate constant drops, so that there is critical fraction of the area covered by protein. Adsorption above this fraction is hindered both kinetically and thermodynamically.

1. Introduction

Protein adsorption on solid surfaces has long attracted the attention of researchers working in the natural sciences, medicine and industry [1–5], because it plays an important role in biology and in numerous applications, e.g., for biosensors and protein chips, medical implants and in the food industry. The kinetics of protein adsorption are often apparently simple, but in reality very complex, due to multiple binding sites on the protein surface, many nearly isoenergetic conformational states of proteins, adsorption-induced conformational changes, diffusion limitations in the bulk phase, surface diffusion, ordering or aggregation of adsorbed proteins, surface roughness, and a multitude of related microscopic factors. Protein adsorption on soft matter in general and lipid bilayers in particular has attracted much less attention although it is also of interest from various perspectives. Maybe the most important one is protein interaction with cell membranes. In this case, specific binding sites are usually involved, like membrane proteins or peptides, but the interaction (non-specific binding) with the plane membrane is also of interest, e.g., as a possible precursor for the specific binding. Another case where protein binding to lipid bilayers is of interest is biosensors based on supported lipid membranes. A unique new ingredient in adsorption on lipid membranes, compared to solid surfaces, is the fluidity of the bilayer which opens up for rapid adjustment of the lipids to optimize the interaction energy (see Ref. [6], focused on diffusion of lipids in bilayers, and more general related reviews [7,8]).

In the past decades, supported lipid membranes have received rapidly increasing attention [9,10], and are today established model systems to mimic various aspects of cell membranes both for diagnostics (sensors, biochips [11]) and, e.g., as interesting surfaces for (stem) cell cultures [12] and also as protein-resistant surfaces [13]. This situation motivates to look into the protein adsorption on lipid bilayers in more detail and especially on the adsorption and desorption kinetics. Such adsorption is expected to be negligible if the lipids are neutral, because in this case the protein–lipid interaction is weak (for peptids or, more specifically, for antimicrobial peptides, the situation is often different [14], because their size is relatively small and they can easily be incorporated into the bilayers near the hydrophilic lipid head groups). *In vivo*, i.e., in real cells, the bilayers contain however both neutral and charged lipids, and such mixtures are also of interest for basic studies. The fraction of the charged lipids is usually relatively low but not negligible. As model systems, charged lipid bilayers may be formed on solid surfaces by adsorption and rupture of vesicles composed of mixtures of zwitterionic, negatively charged, and/or positively charged lipids [15,16]. All proteins are to some extent charged as well except at the isoelectric point but even there a protein is likely to have local charges. If the charges of the bilayer and protein are opposite, protein adsorption on a bilayer may therefore be favourable even in the absence of specific binding sites. As already noted, this type of adsorption is peculiar, because the lipids forming a bilayer are very mobile [6] and can easily change their spatial distribution in a bilayer in order to increase the interaction with a protein.

The amount of protein adsorbed is determined by the balance of the rates of adsorption and desorption. The activation energy for protein adsorption is usually relatively low. To be adsorbed, a protein should

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doi:10.1016/j.bpc.2009.10.005

however come in contact with charged lipids. For this reason, the protein adsorption rate should strongly depend on the concentration of charged lipids (globally, it can be limited by diffusion). The activation energy for protein desorption should be appreciable in order to observe measurable amount of adsorption. In the case under consideration, the latter activation energy is determined primarily by the Coulomb interaction between charged amino-acid residues of a protein, charged lipids, and electrolyte. Using the conventional Poisson–Boltzmann theory (the relevant studies are numerous [17–23]), one can estimate that the contribution of electrostatic interactions to the protein adsorption energy is about 4–6 kcal/mol per charged amino-acid–lipid pair ("charged" means here that the charges of an amino-acid residue and lipid are opposite while globally a pair is neutral), and accordingly a few (4–5) pairs are sufficient for nearly irreversible adsorption at ambient or body temperature. The statistics of the formation of these binding pairs is expected to be fairly sensitive to the fraction of charged lipids. Our goal here is to illustrate how the rate constants of protein adsorption and desorption can depend on this fraction.

Concerning the subject under consideration, we may notice that various aspects of adsorption of flexible unfolded charged macromolecules on mixed lipid membranes were earlier analyzed in Refs. [24,25] (for the experiment, see e.g. Ref. [14]). The applicability of the results obtained there to proteins is however limited, because, despite partial denaturation, adsorbed proteins usually remain in a folded state.

A few available treatments [26–29] of adsorption of charged proteins on charged lipid bilayers (with emphasis on the electrostatic interaction [27,28], adsorption isotherms [27,29] and aggregation [29]) implicitly assume that a protein is spherical and does not change its shape during adsorption.

In reality, proteins are usually not fully spherical. In addition, proteins are fairly flexible, have a multiplicity of almost isoenergetic states, and can easily change their shape after adsorption. The corresponding conformational changes may range from local reconfiguration near the protein-surface contact to complete denaturation (see, e.g., Refs. [30–34]). For these reasons, a protein is expected to form a flat contact with a lipid bilayer. This case was treated in Refs. [35–37] with emphasis on the adsorption isotherms.

Our analysis below also implies a flat contact between a protein and bilayer. The main novel ingredient of our work compared to Refs. [35–37] is that we focus on the protein adsorption and desorption kinetics or, more specifically, on the dependence of the rate constants of protein adsorption and desorption on the fraction of charged lipids. There are also more specific differences. In Refs. [35–37], for example, the charged amino-acid–lipid pairs forming a protein-bilayer contact are considered to be independent so that the contact energy is linearly proportional to the number of pairs. In our model, the number of protein charges in the contact area is considered to be constant, and the total binding energy is assumed to be maximum when the screening of these charges by charged lipids located in that area is perfect. With decreasing the number of charged lipids there (i.e., with decreasing the number of charged amino-acid–lipid pairs), the total binding energy is considered to decrease rapidly (due to the lack of screening and the corresponding Coulomb repulsion) so that the adsorption becomes energetically unfavourable before breaking the last bond.

2. Model

In our model (Fig. 1), the charged amino-acid residues are assumed to form one or a few spots near or on the surface of a protein (the location of charges near the surface is usually energetically favourable). After (in reality during) adsorption, a protein slightly changes its shape so that one of the spots, containing m charged amino-acid residues, forms a flat contact with n oppositely charged lipid heads on the surface of the lipid bilayer. The

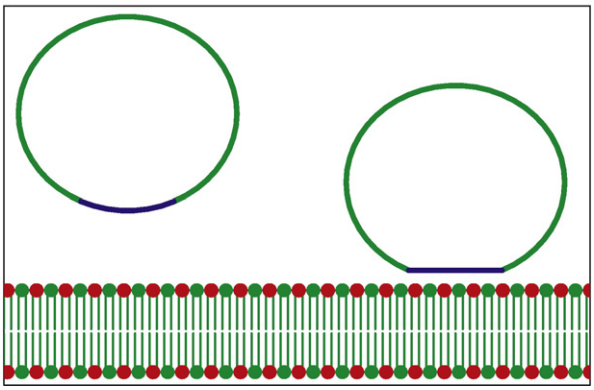

Fig. 1. Scheme of protein adsorption on a bilayer composed of lipids with neutral and charged heads. The charged amino-acid residues form a spot on the surface of a protein. After adsorption, a protein changes its shape so that the charged spot forms a flat contact with the oppositely charged lipid heads of the lipid bilayer.

corresponding protein–lipid-bilayer interaction energy is designated to be E_n. Strictly speaking, E_n is the free energy difference, because it contains entropic contributions. By definition, $E_n<0$ for the bound states. To specify E_n, we notice that the protein- and lipid-bilayer dielectric constants are low, the protein–lipid-bilayer interface is expected to narrow (a few Å), and the corresponding dielectric constant is low as well. In this case, $|E_n|$ is maximum for perfect charge screening, i.e., for $n=m$. This state is the most probable if the fraction of charged lipids, θ, is not too low. With decreasing θ, the states with $n<m$ may become more probable than that with $n=m$.

With decreasing n, $|E_n|$ rapidly decreases and eventually the protein adsorption becomes energetically unfavourable. It happens at $n<l$, where l ($l<m$) is the number of bonds in the bound state with the minimum binding energy. At first sight, one could postulate that $l=1$. In reality, however, as already noted in the Introduction, the protein energy is expected (due to the lack of screening) to become higher than that in the bulk (i.e., $E_n>0$) at $n>1$, and accordingly we should have $l>1$. Thus, the desorption process can be viewed as a set of reversible steps of association of an adsorbed protein, P_a, with charged lipids, L,

$$P_aL_n + L \rightleftharpoons P_aL_{n+1}, \tag{1}$$

combined with the desorption steps,

$$P_aL_n \rightarrow P_u + nL, \tag{2}$$

where P_u is an unbound protein, and n is in the range from l to $m-1$ in Eq. (1) and from l to m in Eq. (2).

According to the scheme above, the apparent rate constant of protein desorption is represented as

$$k_d = \sum_{n=l}^{n=m} k_n p_n, \tag{3}$$

where k_n is the rate constant of step (2), and p_n is the probability that a protein has n bonds with charged lipids.

The probability p_n depends on the details of the charge distribution on the protein surface and may depend on the interplay of steps (1) and (2). In our model, in analogy with the transition-state theory, we assume, that steps (1) are rapid [compared to steps (2)] and close to equilibrium, and use the simplest mean-field approximation in order to calculate p_n. Specifically, we consider that for a given n the protein–lipid interaction energy, E_n, is the same irrespective of the mutual arrangement of the lipids, and the number of the corresponding

configurations of the charged lipids is C_n^m ($C_n^m = m!/[n!\,(m-n)!]$ is the binomial coefficient). In this case, the grand canonical distribution yields

$$p_n = C_n^m \exp\left(\frac{n\mu - E_n}{k_B T}\right) \Big/ \sum_{n=l}^{m} C_n^m \exp\left(\frac{n\mu - E_n}{k_B T}\right), \tag{4}$$

where μ is the chemical potential of charged lipids, defined under the condition that in the absence of the protein–lipid interaction the energy of a single charged lipid is zero.

The rate constant k_n depends on E_n and also on the protein–lipid interaction in the activated state for desorption. The latter interaction contributes to the activation energy for protein adsorption. As already noted, the activation energy for protein adsorption is usually relatively low, and accordingly we neglect the protein–lipid interaction in the activated state. In this approximation, we have

$$k_n = \kappa_d \exp(E_n / k_B T), \tag{5}$$

where κ_d is a constant independent of n.

Substituting Eqs. (4) and (5) into Eq. (3), we obtain

$$k_d = \kappa_d \sum_{n=l}^{m} C_n^m \exp\left(\frac{n\mu}{k_B T}\right) \Big/ \sum_{n=l}^{m} C_n^m \exp\left(\frac{n\mu - E_n}{k_B T}\right). \tag{6}$$

With decreasing n, $|E_n|$ rapidly decreases, and if the fraction of charged lipids is not too low, we can take only two terms (with $n = m$ and $m-1$) in the denominator of expression (6), i.e.,

$$\sum_{n=l}^{m} C_n^m \exp\left(\frac{n\mu - E_n}{k_B T}\right) \simeq \exp\left(\frac{m\mu - E_m}{k_B T}\right)\left[1 + m\exp\left(-\frac{\mu + \Delta E}{k_B T}\right)\right],$$

where $\Delta E = E_{m-1} - E_m$. In this case, expression (6) is represented as

$$k_d \simeq k_m \sum_{n=l}^{m} C_n^m \exp\left(\frac{(n-m)\mu}{k_B T}\right) \Big/ \left[1 + m\exp\left(-\frac{\mu + \Delta E}{k_B T}\right)\right]. \tag{7}$$

To describe the process of protein adsorption, we consider that it happens provided that a protein contacts m lipids and at least l of them are charged. Specifically, the protein adsorption rate constant, k_a, is assumed to depend only on the corresponding probabilities to contact at least l charged lipids, because as already noted we neglect the protein–lipid interaction in the activated state. In this case, we have

$$k_a = \kappa_a \sum_{n=l}^{m} C_n^m \exp\left(\frac{n\mu}{k_B T}\right) \Big/ \sum_{n=0}^{m} C_n^m \exp\left(\frac{n\mu}{k_B T}\right), \tag{8}$$

where κ_a is a constant independent of n. Taking into account that

$$\sum_{n=0}^{m} C_n^m \exp\left(\frac{n\mu}{k_B T}\right) = \left[\exp\left(\frac{\mu}{k_B T}\right) + 1\right]^m,$$

we rewrite expression (8) as

$$k_a = \kappa_a \sum_{n=l}^{m} C_n^m \exp\left(\frac{n\mu}{k_B T}\right) \Big/ \left[\exp\left(\frac{\mu}{k_B T}\right) + 1\right]^m. \tag{9}$$

Eq. (9) describes the effect of the protein–lipid interaction on the rate constant of protein adsorption. If the bilayer is partly covered by protein, this rate constant depends also on the hardcore interaction between proteins. The latter effect can be included into the rate constant κ_a in analogy with numerous earlier studies of protein adsorption on solid surfaces (see reviews [1–5] and, e.g., Refs. [38–42]). This conventional aspect is beyond the scope of our present study and we do not specify κ_a in more detail.

To use the equations presented, we need the relation between μ and θ. In general, this relation is complex. In our examples below, we consider that θ is relatively low (this is the case *in vivo* and expected often to be the case *in vitro*), neglect lateral lipid–lipid interaction, and employ the standard mean-field expression,

$$\mu = k_B T \ln[\theta / (1-\theta)], \tag{10}$$

derived in analogy with that corresponding to the ideal lattice gas.

In our equations above, θ represents the fraction of charged lipids in the area not covered by protein. If the amount of adsorbed protein is low, θ is the same as in the absence of protein, and the equations can be directly used to describe experiments. With increasing protein coverage, the proteins may trap appreciable part of charged lipids, θ may be lower than that in the absence of protein, and accordingly the protein coverage, θ and μ should be calculated consistently. In particular, θ and μ remain to be related as [cf. Eq. (10)]

$$\theta = \exp(\mu / k_B T) / [1 + \exp(\mu / k_B T)]. \tag{11}$$

If for example we consider that the adsorbed proteins are primarily in the states with $n = m$ and $m-1$ [cf. Eq. (7)], the average number of charged lipids per protein is given by $<n> = mp_m + (m-1)p_{m-1}$ or, more explicitly [with the use of Eq. (4)], by

$$\langle n \rangle = \frac{m + (m-1)\exp[-(\mu + \Delta E)/k_B T]}{1 + m\exp[-(\mu + \Delta E)/k_B T]}. \tag{12}$$

The balance of charged lipids is described as

$$\frac{\theta(1-f)}{a} + \frac{\langle n \rangle f}{b} = \frac{\theta_0}{a}, \tag{13}$$

where θ_0 is the fraction of charged lipids in the absence of protein, f is the fraction of the bilayer covered by protein, a is the area per lipid, and b is the protein-bilayer contact area.

Eqs. (6), (7) and (9) alone or in combination with Eqs. (11)–(13) allow one to calculate the protein desorption and adsorption rate constants under various conditions.

3. Results of calculations

To illustrate the dependence of the protein desorption rate constant on θ (at $T = 300$ K), we use expression (7). It shows that the normalized rate constant, k_d/k_m, depends on three parameters, m, l, and ΔE. To be specific, we employ $\Delta E = 6$ kcal/mol, $m = 5$, and $l = 2$, 3 and 4. With these parameters, the desorption rate constant rapidly increases with decreasing θ (Fig. 2), because the protein state with $n = m$ becomes less

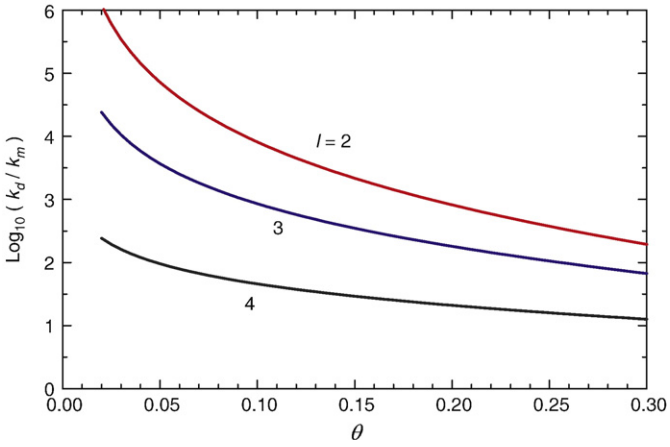

Fig. 2. Rate constant of protein desorption as a function of the fraction of charged lipids for $\Delta E = 6$ kcal/mol, $m = 5$, and $l = 2$, 3 and 4.

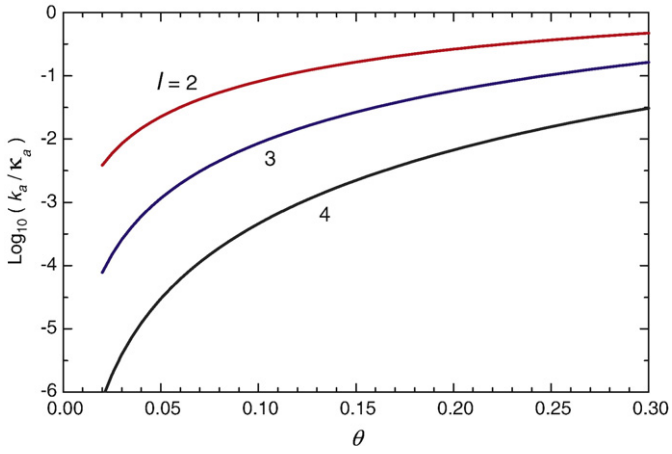

Fig. 3. Rate constant of protein adsorption as a function of the fraction of charged lipids for $m=5$ and $l=2$, 3 and 4.

probable. This effect is especially strong for $l=2$. With increasing l, it becomes weaker. Concerning ΔE, we may notice that for physically reasonable values of the latter parameters the results are fairly insensitive to its variation. For example, the results for $\Delta E=4$ kcal/mol (not shown) nearly coincide with those presented in Fig. 2.

According to expression (9), the normalized adsorption rate constant, k_a/κ_a, depends only on two parameters, m and l. With decreasing θ, this rate constant rapidly decreases (Fig. 3), because the contacts with $n \geq l$ become less probable.

During adsorption, θ may decrease. If θ_0 is high (about 0.5 or higher), Eqs. (11)–(13) predict that θ remains to be high with increasing f up to saturation of the surface by protein. This means that the protein desorption rate constant remains to be close to minimum, i.e., $k_d \simeq k_m$, while the adsorption rate constant is close to maximum, i.e., $k_a \simeq \kappa_a$. This situation is close to the case of adsorption on a surface with fixed uniformly distributed charges.

If θ_0 is relatively low, Eqs. (11)–(13) predict (see, e.g., Fig. 4 for $\theta_0=0.1$) that $\theta \simeq \theta_0$ only if f is low. With increasing f, θ decreases nearly linearly down to negligible values at $f \simeq b\theta_0/(ma)$. This means that with increasing f the protein desorption rate constant increases, while the adsorption rate constant drops. At $f > b\theta_0/(ma)$, the decrease and increase of these rate constants become dramatic. For these reasons, we can introduce the critical parameter, $f_c = b\theta_0/(ma)$. Kinetically, the state with $f > f_c$ can hardly be reached even if at $f < f_c$ the adsorption is easily feasible.

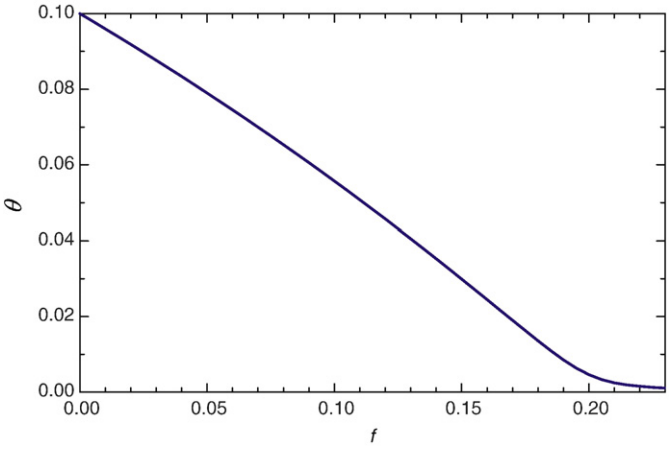

Fig. 4. Fraction of charged lipids in the area not covered by protein as a function of the fraction of the area covered by protein (according to Eqs. (11)–(13)) for $\theta_0=0.1$, $m=5$, $\Delta E=6$ kcal/mol, and $b=10a$.

4. Conclusion

We have proposed a model describing the likely dependences of the rate constants of protein adsorption and desorption on the fraction of charged lipids in a lipid bilayer. Our analysis shows that the redistribution of charged lipids in the bilayer during protein adsorption results in interesting features of adsorption and desorption quite different from those on a surface with immobile charges and binding sites. In particular, our model indicates that there is critical fraction of the area covered by protein. Adsorption above this fraction is hindered.

Concerning the limitations of our model, it is appropriate to articulate that we have assumed that although a protein is deformable its adsorption is not accompanied by denaturation. In reality, the protein–lipid electrostatic interaction may of course result in protein denaturation and it may change the kinetics of adsorption and especially desorption.

Finally, we may notice that the protein adsorption on a lipid bilayer represents the first step of the incorporation of a protein into a bilayer. For this reason, our results are of interest from the latter perspective as well.

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