Available online at www.sciencedirect.com
ScienceDirect
Biochimica et Biophysica Acta 1778 (2008) 811–823
Biochimica et Biophysica Acta
BBA
www.elsevier.com/locate/bbamem

Review

Guanidinium group: A versatile moiety inducing transport and multicompartmentalization in complementary membranes

Alexandros Pantos [a,b], Ioannis Tsogas [a], Constantinos M. Paleos [a,b,*]

[a] *Institute of Physical Chemistry, NCSR "Demokritos", 15310 Aghia Paraskevi, Attiki, Greece*
[b] *Dendrigen SA, 7 Afxentiou Street, 17455 Alimos, Athens, Greece*

Received 7 June 2007; received in revised form 6 December 2007; accepted 7 December 2007
Available online 12 December 2007

Abstract

Guanidinium groups present in peptides and dendritic polymers induce their efficient transport through liposomal and cell membranes. Transmembrane crossing of these polymers is affected by their structural features and is critically dependent on the number of guanidinium groups present. Furthermore, the interaction of the guanidinium groups with phosphate groups, both located on liposomal surfaces, triggers a series of processes involving a reorganization of the self-assembled lipids and inducing the formation of multicompartment systems. These observations consistent throughout a diversity of interacting complementary liposomes, support a hypothesis that molecular recognition of liposomes induces the formation of multicompartment structures.

Keywords: Guanidinium; Membrane transport; Multicompartmentalization; Molecular recognition; Dendrimer

Contents

1. Introduction

The role of molecular transporters [1–4] and in particular of drug transporters [5–7] in enhancing membrane transport is an issue of great scientific and practical interest and has recently been addressed employing either cells or model liposomal systems. In both cases the role of an appended guanidinium group, which is the strongest organic base (pK_a 13.65) [8], is crucial due to its interaction with the phosphate or other anionic moieties on the liposomal or cell surface. This is the first stage in the process of molecular transporting in which strong binding between the interacting parties is achieved due to combined hydrogen-bonding and electrostatic forces (Fig. 1). In this connection, it should be noted that strong binding of guanidinium to acidic groups is further amplified as the organization of the interacting substrate is enhanced i.e. as one proceeds from isotropic conditions to liposomal and finally to macroscopic interfaces [9] (Fig. 2). These results clearly indicate that molecular recognition is more effective at interfaces and this binding enhancement is taken advantage of in the liposomal interactions discussed in this review.

* Corresponding author. Institute of Physical Chemistry, NCSR "Demokritos", 15310 Aghia Paraskevi, Attiki, Greece.
E-mail address: paleos@chem.demokritos.gr (C.M. Paleos).

0005-2736/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbamem.2007.12.003

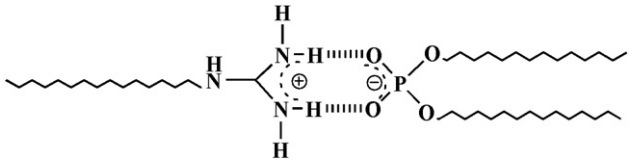

Fig. 1. Complex formed between guanidinium and phosphate groups through combined electrostatic forces and bidentate hydrogen-bonding.

The idea of extending the application of molecular transporters to guanidinylated poly(propylene imine) dendrimers [10] or other dendritic polymers has stemmed from the analogous application of arginine-rich peptides [1,2,11] which also bear a multiplicity of guanidinium moieties. These peptides proved to exhibit enhanced translocation properties, due to the presence of an appropriate number of guanidinium groups. On the other hand, guanidinylated poly(propylene imine) dendrimers having the possibility to bear a varying number of guanidinium moieties also exhibit the so-called adaptive solubility behaviour [12], rendering the dendrimer either hydrophobic or hydrophilic depending on the environment. This is irrespective of the anion effect which tunes hydrophobicity in peptides [13,14]. In the present case, following the binding of the guanidinium to the phosphate groups, guanidinylated dendrimers lie in close proximity to the membrane while they simultaneously adopt a more hydrophobic conformation. This is due to the fact that the guanidinylated derivatives bound to the liposomal surface become less polar through charge neutralization, and therefore more prone to enter the hydrophobic bilayer. In addition to charge neutralization, the adaptive solubility behaviour of dendrimers, i.e. "chameleon behaviour", as for the first time coined by Paleos et al. [12] begins to function, changing conformation and exposing their hydrophobic interior to the bilayer medium. Due to these processes the guanidinylated derivatives become appreciably hydrophobic and consequently appropriate for transport through the hydrophobic liposomal membrane.

In addition it has recently been established that interaction of guanidinium and phosphate groups, located on the surfaces of complementary liposomes, results in the formation of giant liposomes incorporating inside their interior smaller liposomes [15]. These structures are reminiscent of the multicompartment character of eukaryote cells, hypothesized to result from a symbiotic association of prokaryotes, which have analogous structures to unilamellar liposomes [16]. This so-called Serial Endosymbiosis Theory of Eukaryotic Evolution is supported by studies on mitochondria and chloroplasts which are considered to be evolved from prokaryotes (bacteria) living in large cells [17–19]. Thus, it is worth exploring this phenomenon associated with molecular recognition of complementary liposomes and formation of multicompartment systems. It seems that the role of lipids is crucial, self-assembling and organizing in membranes which may lead in the formation of either single compartment prokaryotes or multicompartment eukaryote cells [20–22].

In fact, it has to be noted that due to the organization of lipids into liposomal bilayers, the well-established organizational [9,23,24] and multivalent effects [25,26] are exercised during liposome interaction and adhesion. These effects are beneficial in obtaining enhanced initial liposomal or cell binding as previously mentioned and established by the work of Kunitake et al. [9,24]. The presence of recognizable groups in close proximity, at the relatively small external liposomal or cell surface, induces effective association between the interacting parties.

In this review we will address two processes, both of which are triggered by the presence of guanidinium moiety in appro-

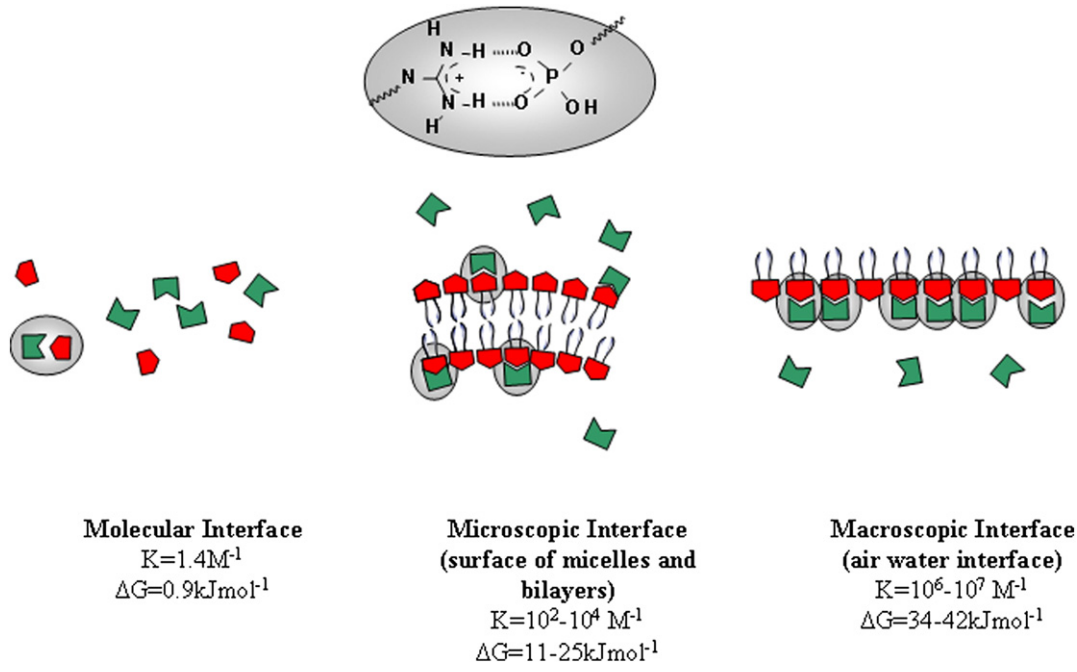

Fig. 2. Binding constants of guanidinium and phosphate groups at isotropic and other organized interfaces.