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Critical review

Interactions of bioactive molecules & nanomaterials with Langmuir monolayers as cell membrane models

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ABSTRACT

Langmuir monolayers at the air/water interface have been used for decades to mimic cell membranes in attempts to determine the mechanisms behind the physiological action of biologically-relevant molecules. In this review, we analyze the vast literature in the area, with the contents organized according to the type of molecules and materials, including peptides, proteins, polysaccharides, a variety of pharmaceuticals, and nanomaterials. The focus is placed on the correlation between the effects induced on the monolayers and the biological activity of the molecules and nanomaterials. Effects observed from these interactions can be coupling or adsorption and penetration of the molecules into the monolayer, which can be expanded, condensed or even disrupted. Changes in monolayer mechanical properties, for example, may be crucial for the biological activity. Whenever possible, we try to identify the forces prevailing in the interaction, which has been made possible with a combination of experimental techniques, including surface-specific spectroscopies, microscopies and rheological techniques, in addition to the traditional surface pressure and surface potential measurements. Overall, the mechanisms are governed by ionic electrostatic forces and hydrophobic interactions. Correlation may be straightforward, as in the cases of positively charged peptides and polymers whose antimicrobial activity is ascribed to electrostatic attraction with the negatively charged microbial membranes. Also general is the importance of hydrophobic interactions for the penetration into the membrane, which can be required for the biological action of, for example, polysaccharides. In other cases, correlation between monolayer properties and the physiological activity cannot be established precisely, as the latter may depend on a multitude of parameters that have not been possible to simulate with a simplified model such as that of a Langmuir monolayer. For nanomaterials, the emphasis is in relating interaction with the monolayers and their possible toxicity. Owing to the relevance of electrostatic and hydrophobic interactions, the effects on monolayers (and indeed toxicity) are found to depend largely on the coating or functionalization of the nanomaterials.

Contents

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1. Introduction

Biological cell membranes are usually described by a bilayer of lipids mixed with other components, mainly proteins and polysaccharides. Interest in the interactions of external agents such as drugs, peptides, and proteins that act in the external membrane, has grown over the last decades, with the membrane being modeled with monolayers at the air–water interface [1]. The thermodynamics of these so-called Langmuir monolayers was described in the 1960s by Gaines and Roberts [2], with parameters such as free energy, compressibility, two-dimensional phases, and transition from 2D to 3D structures (collapse) being investigated. Lipid monolayers are in fact considered as a model for half a membrane [3], being valuable to characterize protein–membrane interactions, which is crucial for several biological functions, including signaling, biomineralization and active and passive transport through the membrane.

The Langmuir technique has been useful to determine the mechanism of action of antimicrobial and membrane lytic peptides in cell membranes [4], in addition to a variety of other biologically-relevant materials. Advantages of using Langmuir monolayers include the possible fine control over the composition and packing of the membrane being mimicked. On the other hand, they are not adequate for studying transport across the membrane, for which other types of models need to be used, such as vesicles. The properties of such monolayers are now investigated with a variety of methods, including surface pressure, surface potential [5,6], fluorescence microscopy [7], Brewster angle microscopy [8], X-ray diffraction [9], light scattering [10], and vibrational spectroscopies [11].

In this review paper, we provide an overview of the use of Langmuir monolayers to model cell membranes. Owing to the vast amount of literature in the topic, we do not intend to cover all contributions exhaustively. Instead, we chose some classes of biologically-relevant materials whose action on cell membranes have been investigated using Langmuir monolayers. We do not describe the experimental methods used for film fabrication and characterization, for they are routinely used in many laboratories around the world and the interested reader is referred to the literature cited in the paper. Whenever possible, we try to correlate the physicochemical properties of the monolayers with the biological action reported for the materials.

2. Interaction of Biomolecules with Langmuir monolayers

2.1. Peptides

Many peptides act as drugs whose mechanism of action may be studied by analyzing their interaction with lipid Langmuir monolayers. Some of these peptides are built to correspond to specific regions of proteins of interest, with the aim of probing the role of each part of the protein and evaluate its interaction with the membrane [12]. Investigations have been made to assess antimicrobial peptides with regard to disrupting microbe membranes [13] and to understand how peptides are translocated across a neural cell membrane. In addition, the way anti-cancer peptides attack cancer cells without disrupting normal cells has also been studied.

2.1.1. β-Amyloid peptides

Studies with the amyloid precursor protein (APP) are aimed at identifying the origin of Alzheimer's disease (AD), for which three main hypotheses exist. The first is related to deposits of amyloid-β (Aβ), which are "APP protein pieces", on the brain of AD patients with oxidative stress caused by free radical damage. The second one is related to formation of Aβ insoluble fibrils in the brain, while the third is associated with inefficiency of macrophages from AD patients in phagocyting Aβ plaques. It is clear therefore that β-amyloid is a primary factor in inducing AD. Monolayer studies are normally made using Aβ peptides or truncated Aβ fragments, which are believed to be key regions of the protein to elucidate Aβ adsorption and aggregation on the neural cell membranes.

Small hydrophobic Aβ segments can initiate fibrillization, which has been corroborated by aggregation of Aβ(31 − 35) fragments at the air/water interface upon film compression [14]. This fibrillization process was further studied with the fragment IIGLM (Aβ(31 − 35)) with a long aliphatic C_{18} chain attached to its N-terminal region [15]. Two peptides were synthesized, with carboxyl acid and amide functionalities. Their interfacial behavior differed, but both peptidolipids formed aggregates at the air–water interface, as seen with epifluorescence data. The peptidolipid (C18 chain) Aβ(25–35) acquired a typical β-sheet structure in a Langmuir film [16]. The fragment known as LSFD (LSFDNSGAITIG-NH_2) peptide is widely studied as a model peptide for Aβ(1–40). Surface pressure isotherms of LSFD peptide showed a lift-off value of 150 $Å^2$/molecule, which matches the molecular area of a β-sheet lying flat on the water interface [17]. Infrared reflection absorption spectroscopy (IRRAS) experiments revealed a β-sheet structure at the interface, with amide I and amide II bands at 1624 cm^{-1} and 1540 cm^{-1}, respectively. The peak at 1690 cm^{-1} is indicative of an anti-parallel β-sheet for the peptide. The grazing incidence X-ray diffraction (GIXD) data for the LSFD Langmuir monolayer, on the other hand, displayed a Bragg peak at $q_{xy} = 1.31\ A^{-1}$, corresponding to the repeat distance of 4.8 Å and a coherence length larger than 575 Å. From these GIXD data, the LSFD peptide was inferred to adopt a single β-strand structure that can assemble into a well-ordered domain.

The fragments Aβ(1–40) and Aβ(1–42) have been studied as they are major constituents of senile plaques, a hallmark in AD patients.