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Review

Structural transition in micelles: novel insight into microenvironmental changes in polarity and dynamics

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ABSTRACT

Structural transitions involving shape changes play an important role in cellular physiology. Such transition can be conveniently induced in charged micelles by increasing ionic strength of the medium. Shape changes have recently been shown to result in altered packing and lowering of micellar polarity. As a consequence of reduced polarity, the ionization states of micelle-bound molecules vary in micelles of different shape. The changes in micellar organization and dynamics due to structural transition can be effectively monitored utilizing the red edge excitation shift (REES). These changes are influenced by the position (location) of the probe in the micelle, *i.e.*, the region of the micelle being monitored. Changes in organization and dynamics of probes and peptides upon structural transition are discussed with representative examples. We envisage that the reduction in micellar polarity and tighter packing upon structural transition represent important factors in the incorporation of drugs in micelles (nano-carriers), since micellar polarity plays a crucial role in the incorporation of drugs.

Contents

1. Micelles: organized molecular assemblies suitable for optical spectroscopy

Detergents are important in the context of biological membranes due to their ability to solubilize membrane proteins and receptors (Chattopadhyay et al., 2002; Seddon et al., 2004; Kalipatnapu and Chattopadhyay, 2005). They are soluble amphiphiles and above a critical concentration (strictly speaking, a narrow concentration range), known as the critical micelle concentration (CMC), self-associate to form thermodynamically stable, noncovalent, nano-sized colloidal aggregates called micelles, at temperatures above the critical micelle temperature (CMT) (Helenius and Simons, 1975; Tanford, 1978). Micelles are widely used as membrane-mimetic systems to characterize membrane proteins and peptides (Sham et al., 2003; Raghuraman and Chattopadhyay, 2004; Rajagopalan and Rajarathnam, 2004; Rawat et al., 2005) and as vehicles for drug delivery (Narang et al., 2007; Katragadda et al., 2011). Studies on micellar organization and dynamics assume relevance since the general principle underlying the formation of micelles (*i.e.*, the hydrophobic effect) is common to other related assemblies such as reverse micelles, bilayers, liposomes, and biological membranes (Tanford, 1978; Israelachvili et al., 1980). Micelles are highly cooperative, organized molecular assemblies (nanostructures) of amphiphiles, yet dynamic in nature (Menger, 1979). The organization and dynamics of micellar environments, namely, the core, the interface, and the immediate layers of water on the interface, have been investigated using experimental and theoretical approaches (Sterpone et al., 2006).

Abbreviations: CMC, critical micelle concentration; CMT, critical micelle temperature; ESR, electron spin resonance; NBD, 7-nitrobenz-2-oxa-1,3-diazol-4-yl; NBD-cholesterol, 25-[N-[(7-nitrobenz-2-oxa-1,3-diazol-4-yl)-methyl]amino]-27-norcholesterol; NBD-PE, N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)-1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine); REES, red edge excitation shift; SDS, sodium dodecyl sulfate; TOE, tryptophan octyl ester.

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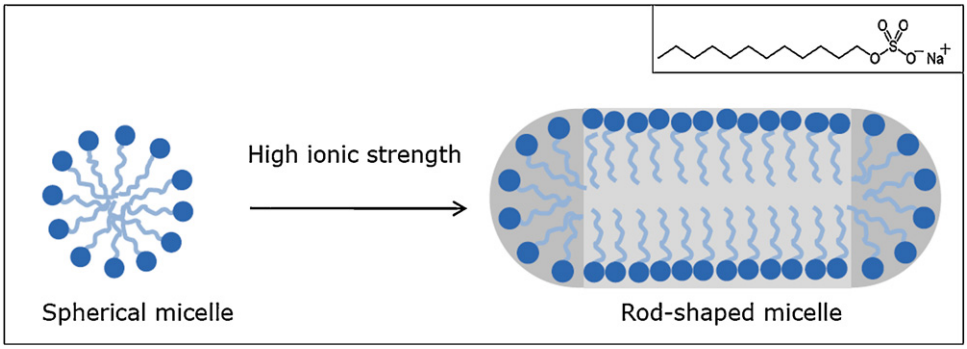

Fig. 1. Structural (sphere-to-rod) transition in charged micelles induced by high ionic strength. The structural transition takes place in charged micelles (such as SDS micelles; inset shows the chemical structure of SDS) at concentrations well above the critical micelle concentration. It should be noted that the microenvironment and packing for micelle-bound molecules in rod-shaped micelles are heterogeneous and are shown as spherical 'end caps' (darker shade) and the cylindrical central part (lighter shade). The headgroup spacing is reduced in the cylindrical part of the rod-shaped micelle due to attenuation of charge interactions at high ionic strength.
Adapted and modified from Chaudhuri et al. (2009).

It is well established that practically all types of molecules have a surface-seeking tendency in micelles due to very large surface area to volume ratio and that the interfacial region is the preferred site for solubilization, even for hydrophobic molecules (Shobha et al., 1989). In addition, they offer certain inherent advantages in fluorescence studies over membranes since micelles are smaller and optically transparent, have well-defined sizes, and are relatively scatter-free. Micelles can be of any desired charge type and can adopt different shapes and internal packing, depending on the chemical structures of the constituent monomers and the ionic strength of the medium (Mazer et al., 1976; Young et al., 1978; Hayashi and Ikeda, 1980; Raghuraman and Chattopadhyay, 2004).

2. Structural transition in charged micelles: change in micellar polarity

Structural transition (shape change) can be induced in charged micelles at a given temperature by increasing ionic strength of the medium or amphiphile concentration (Mazer et al., 1976; Young et al., 1978; Hayashi and Ikeda, 1980; Rawat and Chattopadhyay, 1999; Shobini et al., 2003; Heerklotz et al., 2004; Geng et al., 2005; Rawat et al., 2005; Chaudhuri et al., 2009; Paul and Guchhait, 2011). For example, spherical micelles of sodium dodecyl sulfate (SDS) that exist in water at concentrations higher than CMC assume an elongated rod-like (prolate) structure in presence of high electrolyte (salt) concentrations when interactions among the charged headgroups are attenuated due to the added salt (see Fig. 1). This is known as sphere-to-rod transition (Missel et al., 1984). This shape change induced by increased salt concentration is accompanied by a reduction in CMC (Chattopadhyay and London, 1984). Micellar sphere-to-rod transition can be explained in terms of the packing model described by Israelachvili (1991).

Interestingly, it has been suggested that large and elongated rod-shaped micelles are better models for biomembranes since the orientation of the hydrocarbon chains are more ordered in these micelles (Israelachvili, 1991; Rawat and Chattopadhyay, 1999; Heerklotz et al., 2004), perhaps due to the release of curvature stress encountered in spherical micelles. This was recently supported by monitoring the change in organization and dynamics associated with shape change (sphere-to-rod transition) of SDS micelles utilizing pyrene fluorescence (Chaudhuri et al., 2009). The fluorescence emission spectrum of the hydrophobic probe pyrene is sensitive to environmental polarity (see Fig. 2a; Dong and Winnik, 1982). It has been previously shown that pyrene is localized predominantly in the interfacial region in micelles (Menger, 1979; Shobha et al., 1989; Konuk et al., 1989). Interestingly, this is the region of the micelle that is sensitive to polarity changes due to water penetration. Utilizing changes in the ratio of polarity-sensitive pyrene vibronic peak intensities (I_1/I_3; see Fig. 2b), the apparent dielectric constant experienced by pyrene in spherical SDS micelles (in absence of salt) was found to be ~32, based on a calibration plot of pyrene vibronic peak intensity ratio in solvents of varying polarity. The apparent micellar dielectric constant displayed a reduction with increasing ionic strength and the dielectric constant in rod-shaped micelles of SDS (in presence of 0.5 M NaCl) was estimated to be ~22 (Chaudhuri et al., 2009). The reduction in polarity upon micellar shape change could be attributed to a decrease in micellar water content due to attenuation of the electrostatic repulsion between negatively charged headgroups of SDS (resulting in a reduction in headgroup spacing, see below). Importantly, the apparent dielectric constant for rod-shaped micelles compares well with the apparent polarity of hippocampal (Saxena et al., 2008) and model (Shrivastava et al., 2008) membranes.

In addition, pyrene forms excimers with very different fluorescence characteristics and the ratio of excimer/monomer is known to be dependent on monomer lateral distribution and host dynamics (Vanderkooi and Callis, 1974; Ioffe and Gorbenko, 2005), although the exact mechanism of excimerization is not clear (Blackwell et al., 1986). An analysis of the increase in pyrene excimer/monomer ratio accompanied with micellar shape change (see Fig. 2c) indicated an increase in average number of pyrene molecules per micelle associated with the sphere-to-rod structural transition (Chaudhuri et al., 2009). This is due to a combination of (i) a reduction in CMC (from 8.2 mM in case of spherical SDS micelles to 0.5 mM for rod-like micelles), (ii) an increase in aggregation number (from 62 in spherical SDS micelles to 480 in rod-shaped micelles), and (iii) the accompanying reduction in headgroup spacing which results in tighter packing of detergent monomers in the micellar assembly, enabling more monomers to pack in each micelle that ultimately results in shape change at higher ionic strength.

The reduction in polarity associated with micellar structural transition also influences the ionization state of micelle-bound molecules. This was apparent when the ionization behavior of an amphiphilic tryptophan analogue, tryptophan octyl ester (TOE, see Fig. 3), was monitored in micelles of different shape (Arora-Sharawat and Chattopadhyay, 2007). TOE represents an important model for membrane-bound tryptophan residues. The fluorescence characteristics of TOE incorporated into model membranes and membrane-mimetic systems have been shown to be similar to that of membrane-bound tryptophans (Ladokhin and Holloway, 1995; Chattopadhyay et al., 1997, 2005; de Foresta et al., 1999; Sengupta and Sengupta, 2000). TOE fluorescence is known to be sensitive to