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Review

Mucus as a barrier to lipophilic drugs

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ABSTRACT

Mucus is a complex hydrogel, comprising glycoproteins, lipids, salts, DNA, enzymes and cellular debris, covering many epithelial surfaces in the human body. Once secreted, mucin forms a barrier to protect the underlying tissues against the extracellular environment. Mucus can therefore adversely affect the absorption or action of drugs administered by the oral, pulmonary, vaginal, nasal or other routes. Solubility and lipophilicity are key factors determining drug absorption, as a drug has to be soluble in the body fluids at the site of absorption and must also possess enough lipophilicity to permeate the biological membrane. Evidence has accumulated over the past 40 years indicating that poorly soluble drugs will interact with mucus glycoprotein. Studies of the permeability of native or purified mucous gels are important when it comes to understanding the relative importance of hindered diffusion versus drug binding in mucous layers. This review highlights the current understanding of the drug–mucin interaction and also examines briefly the interaction of polymers and particles with the mucus matrix. While the concept of mucoadhesion was thought to provide an intensified and prolonged contact to mucosal absorption sites, mucopenetrating properties are nowadays being discussed for (nano)particulate carriers to overcome the mucus as a barrier and enhance drug delivery through mucus.

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1. Introduction

Mucus covers most sites of application for drug delivery. Mucus is a heterogeneous aqueous mixture of glycoproteins. The major glycoprotein components of mucus are called mucin-type glycoproteins, or mucins for abbreviation (Dekker et al., 2002). Mucins can be defined as glycoproteins containing heavily *O*-glycosylated serine/threonine-rich tandem repeat domains (Evans and Koo, 2009). Mucins have great differences in glycosylation and their multimeric complex formation implies that they have a specific physiological role within the environment in which they are expressed. Mucins can be divided into two classes: the membrane bound mucins and the secreted mucins. Mucus thickness and structure depends both on the site of the, and on pathological

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and physiological conditions. A number of excellent reviews about mucin-type glycoproteins have been published (Carlstedt et al., 1985; Hounsell et al., 1996; Rose and Voynow, 2006; Roussel et al., 1988; Strous and Dekker, 1992). Solubility and lipophilicity are key factors when looking at drug absorption. The drug has to be soluble at the site of absorption and must also possess enough lipophilicity to permeate the biological membrane. In the middle of the nineteenth century, Harley, followed by Pavlov, stated that mucus protects the stomach from the chemical action of its own gastric juice (Jerzy Glass, 1964). Almost a century later, Heatley published a mathematical model of the mucus barrier to acid–pepsin attack (Rees, 1987) and many studies followed that focused on the barrier function of gastric mucus to acid, ions, enzymes and various drugs (Crowther and Marriott, 1984; Davenport, 1976; Deguchi et al., 1978; Desai et al., 1992, 1991; Desai and Vadgama, 1991; Niibuchi et al., 1986; Sarosiek et al., 1984; Williams and Turnberg, 1980, 1981; Winne and Verheyen, 1990).

This review will focus on the barrier function of mucus in general with special emphasis on poorly soluble drugs and their binding to mucus, both as solubilized molecules and as particles in any form. Most of these studies utilize gastrointestinal mucus, but there are also a few studies on respiratory and reproductive mucus. It should be noted, however, that the mucus at these sites has different properties. The concept of mucopenetration and mucolytic particles will be addressed at the end of this review as a possible strategy to overcome the mucus as a barrier.

2. Mucus–structure of mucins

Mucus is a complex viscous adherent secretion synthesized by specialized goblet cells in the columnar epithelium that lines all of the organs exposed to the external environment (Bansil and Turner, 2006). The major constituents of mucus are water (95–99.5%) and high molecular weight glycoproteins, called mucins. Other components of mucus include other proteins (immunoglobulins), lipids, DNA, electrolytes, inorganic salts, enzymes and mucopolysaccharides (Bansil and Turner, 2006; Larhed et al., 1998; Smart, 2005). The mucin molecules differ structurally and chemically from other groups of glycoproteins. They are made up of a polypeptide backbone containing high levels of serine, threonine, alanine, glycine, proline and low amounts of aromatic amino acids. The attached oligosaccharide side chains may count for 50–80% of the weight of the glycoprotein (500–800 chains). On average, each oligosaccharide unit consists of eight to ten (from 1 to 20) (Bromberg and Barr, 2000; Peppas and Huang, 2004) monosaccharide residues such as galactose, fucose, *N*-acetylglucosamine, *N*-acetylgalactosamine and *N*-acetylneuraminic acid (sialic acid) (Bansil and Turner, 2006; Hang and Bertozzi, 2005; Rose and Voynow, 2006). These oligosaccharides are covalently linked with alkali labile *O*-glycosidic bonds to the hydroxyamino acids, serine and threonine, along the polypeptide backbone with sialic acids or L-fucose located at the terminal ends of the oligosaccharide side chain. *N*-glycosylation (oligosaccharide covalently linked to the amide nitrogen on the side chain of asparagine) is also a feature common to most mucins (Gu et al., 1988; Strous and Dekker, 1992). There are also domains within the mucin backbone that are devoid of saccharide residues and these naked proteins segments behave like other proteins in solutions and are susceptible to proteolytic attack (Bromberg and Barr, 2000). The ionic constant (pK_a) of sialic acid is around 2.6 and hence, the mucin molecules behave as anionic polyelectrolytes at neutral pH (Johnson et al., 1972; Kharenko et al., 2009).

The molecular weight of the mucins varies from 0.5 MDa to over 50 MDa (Bansil and Turner, 2006; Berry et al., 1996; Dodd et al., 1998; Harding et al., 1999). Molecules of a given species of mucin show great polydispersity (Allen, 1983). Their physical properties such as molecular weight, density and charge per molecule will vary about a mean due to the different number of carbohydrate chains per molecule. Samples of ocular mucin investigated using Atomic force microscopy (AFM) have shown fibrillar structures with dimensions ranging from hundreds of nanometers up to microns in length (Round et al., 2002). An analogy is often made between the mucin structure and that of the "bottle brush", where the carbohydrate chains represent the bristles and the protein core represents the central wire support. Mucins interact very strongly, but non-specifically with other proteins and hydrophobic surfaces (Bromberg and Barr, 2000; Shi and Caldwell, 2000). With the isolation of the pure, undegraded mucin it has come to the recognition that (i) these molecules are covalent polymers of, on an average, four glycoprotein subunits joined together by disulfide bridges, and (ii) the protein core consists of glycosylated regions which are resistant to proteolysis, and non-glycosylated regions, which are susceptible to attack by proteases. These non-glycosylated regions of peptide are the sites of interchain disulfide bridges joining the glycoprotein subunits together to form the polymer (Svensson and Arnebrant, 2010).

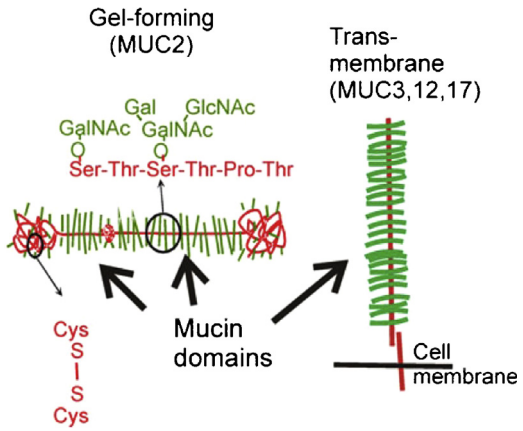

Fig. 1. Schematic presentation of intestinal gel-forming (MUC2) and transmembrane mucins (MUC3, 12 and 17) with their highly *O*-glycosylated mucin domains. Red, protein core; Green, oligosaccharides. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

More than 20 mucin-type glycoproteins have been assigned to the *MUC* gene family approved by the Human Genome Organization (HUGO) Gene Nomenclature Committee (http://www.hugo-international.org/comm_genenomenclaturecommittee.php). This number has been growing for the last few years and it has been questioned that this is a true gene family since the classification is based on function instead of primary structure (Dekker et al., 2002). Based on sequence homology, two major families of mucins can be distinguished; the classical gel-forming secretory mucins (MUC2, MUC5AC, MUC5B, and MUC6) and the membrane bound mucins (MUC1, MUC3, MUC4, MUC12, MUC13, MUC16, and MUC17) (Fig. 1) (Johansson et al., 2011). Membrane-bound mucins differ from secretory mucins in that they contain a hydrophobic domain anchoring the molecules in the plasma membrane. They also lack intermolecular associations through disulfide bridges (Hicks et al., 1998).

3. Function of mucus

Mucins have great differences in glycosylation and their multimeric complex formation implies that they have specific physiologic roles within the environment in which they are expressed. In general, biological function of mucin is to form a