FOOD-ASSOCIATED STIMULI ENHANCE BARRIER PROPERTIES OF MUCUS

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Mucus, a complex network consisting of micro- and nano-scale fluid-filled domains formed via mucin glycoprotein interactions, provides a barrier through which nutrients and orally delivered drugs must penetrate before entering the circulatory system. Mucus provides a significant, yet poorly characterized barrier to particulate, pathogen, and small molecule transport (e.g., nutrient, toxin) to epithelial surfaces. It is important to understand mucus barrier properties as they are significant to drug delivery and potentially disease. The main objective of this project was to examine the impact of physicochemical changes occurring upon food ingestion on gastrointestinal (GI) mucus barrier properties. The motivation for studying these phenomena includes understanding how drug delivery and microbe transport through mucus may change upon food exposure, and how these effects may be exploited to enable more efficient drug delivery or block pathogen transport.

Lipid content associated with fed state intestinal contents significantly enhanced mucus barrier properties, as indicated by 10 – 140-fold reduction in the transport rate of 200 nm microspheres through mucus, depending on surface chemistry. Physiologically relevant increases in \([\text{Ca}^{2+}]\) resulted in 3-fold, 4-fold and 2-fold reduction of amine-, carboxylate- and sulfate modified particle transport rates, respectively, likely due to binding of \([\text{Ca}^{2+}]\) to mucin glycoproteins and thus enhanced cross-linking of the mucus gel network. Reduction of pH from 6.5 to 3.5 also affected mucus viscoelasticity, reducing particle transport rates approximately 5-fold for amine-modified particles and 10-fold for carboxylate- and sulfate modified microspheres.
Macroscopic visual observation and micro-scale lectin staining patterns indicated mucus gel structural changes, including clumping into regions impenetrable by microspheres, correlating with altered transport properties. Histological examination of intestinal tissue indicated food ingestion can prevent microsphere contact with and endocytosis by intestinal epithelium. Furthermore, exposure of mucus to lipids associated with fed state intestinal contents reduced *E. Coli* motility over 6-fold in GI mucus.

Impact of food-associated lipids on transport of molecular species, specifically model drug carriers (<500 Da, 5 Å), in gastrointestinal (GI) mucus was also studied utilizing electron paramagnetic resonance (EPR). Lipid contents associated with fed intestinal state reduced transport rates of nitrooxide spin probes nearly 1.5 fold in mucus. Molecular properties had a considerable influence on small molecule transport in mucus. Positively charged 4-amino tempo was 10-fold slower than negatively charged 3-carboxy proxyl and 4-hydroxy tempo. Additionally, hydrophobic interactions are likely important, as diffusion of hydrophobic 4-hydroxy tempo benzoate spin probe in mucus was slower than negatively charged 3-carboxy proxyl (3-fold) and 4-hydroxy tempo (2-fold).

In summary, these findings could provide meaningful guidance on fundamental understanding of mechanisms behind the “food effect” on intestinal barrier properties. Additionally, these results could guide strategies relevant to oral delivery of drugs, enhancement in nutrient uptake, or modulation of pathogen invasion in diseases such as inflammatory bowel disease, or exposure to bioterrorism agents. A new, relatively facile model for controlling intestinal epithelial exposure could be introduced to the biomedical community.