New model tackles sticky problem of getting drugs past mucus

Mucus acts as friend and foe. On the one hand, this slimy secretion protects body parts such as the lungs, eyes and gastrointestinal tract against bacteria, viruses, allergens and irritants—trapping and rapidly flushing them from the body. On the other hand, this same mucus barrier that limits infection can also prevent the delivery of many beneficial drugs and decrease their effectiveness.

Unfortunately, a review published in March found that drug delivery models rarely take all of the complexity of mucus into account[1]. This oversight could be one reason that experimental medicines fail to work.

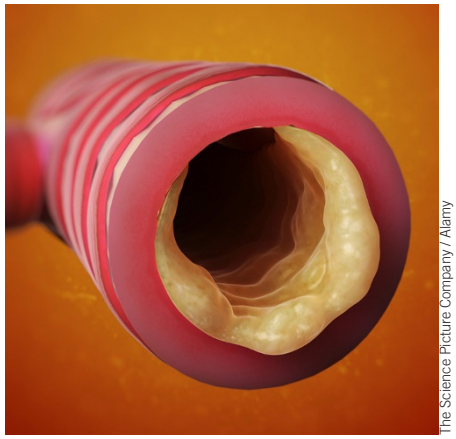
There's growing interest in mucus, according to Hanne Mørck Nielsen, a coauthor of the new paper and a pharmacologist at the University of Copenhagen. "More and more researchers are recognizing that it might be worth considering the presence of mucus in their drug delivery approach," Nielsen says. "It's a black box that's starting to open."

Mucus is made mostly of water and proteins called mucins, which form a highly entangled gel-like network. To further complicate matters, mucus is also dynamic, continuously being shed and secreted. Nearly 10 liters of mucus are secreted into the gastrointestinal tract daily, most of which is reabsorbed[2].

Drug molecules or drug carriers that diffuse poorly in mucus can produce less of a therapeutic effect. This can pose a challenge for drugs that are administered via inhalation, through the eye, or vaginally, for example, as well as those that are administered orally, because they then have to pass through the intestine's mucus. "Any drug that gets delivered at a mucosal surface has to diffuse upstream through a sticky mucus net to get to the underlying cells," says Catherine Taylor Nordgård, a research scientist in the department of biotechnology at the Norwegian University of Science and Technology.

Creating a drug delivery vehicle that can penetrate mucus could expand and improve treatment options for diseases that involve and affect mucosal surfaces. This may be particularly useful for oral drug delivery systems, because these medications offer good patient compliance, are cheaper, have a longer shelf life and are easier to produce compared to injectable intravenous drugs. Many already marketed drugs could also benefit from improved drug delivery systems, as they would be taken up much more efficiently.

"Mucus generally binds delivery systems up and prevents them from evenly spreading on the mucosal surfaces. This leads to nonuniform delivery of the drug to some areas but not others," says Justin Hanes, director of the Center for Nanomedicine at Johns Hopkins University in Baltimore, Maryland. "This lack of uniform delivery is likely to be a major problem in many diseases, including effective gene therapy for cystic fibrosis, effective microbicides designed to prevent sexually transmitted diseases, [and] drug delivery for diseases like inflammatory bowel disease and cancer."



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Oozing answers: Mucus holds the key.

Hanes's lab pioneered the development of mucus-penetrating particles in 2007. They showed that coating drug-loaded nanoparticles with an inexpensive polymer allows the rapid passage of particles through mucus, opening up pharmaceutical possibilities[3] .

Difficult barriers

Part of the reason the barrier properties of mucus aren't yet well understood is that these secretions are hard to handle and study. "There have been few systematic studies done to optimize drug delivery through mucus," says Katharina Ribbeck, an assistant professor in the department of biological engineering at the Massachusetts Institute of Technology in Cambridge, Massachusetts. "The biochemistry of mucus is challenging and mucus is often still considered a waste product."

To this end, Nielsen and her colleagues have developed a model to study the combination of mucus together with an epithelial barrier. They designed a semi-artificial mucus mixture, mimicking what's found in the intestine, that is compatible with the standard cell models[4]. The main challenges, Nielsen says, are to have a mucus gel that mimics intestinal mucus in the body but doesn't damage the cells during the study, which would lead to erroneous results.

"The mucus and epithelium need to be studied in combination; otherwise we may overestimate the beneficial effect of a drug delivery approach as well as overestimate the toxicity risk of such new drug delivery systems," Nielsen says. "We tried to develop a model that can give relatively fast ideas of barrier properties of the complete mucosa—knowledge which can be exploited when designing future drugs."

When combined, the construct could help examine and explain the transport of drugs and particles in this type of biological barrier. The researchers have completed a proof-of-concept study with model compounds representing small-lipophilic-molecule drugs, as well as peptide therapies and small-protein drugs. In as-yet-unpublished research, the team has also investigated the effect on the delivery of desmopressin (a peptide drug used, for example, for treating bed-wetting children) and the antibiotic vancomycin. Although Nielsen's model used purified mucins from pigs, mucins purified from animal or human mucus or those isolated from cell culture can also be reconstituted to form a gel.

However, researchers warn of the limitations of these approaches. Mucus is a complex mixture not only of mucins, but also of various proteins, lipids, salts and cells, says Samuel Lai, who studies how antibodies work with mucus to block infections at the Eshelman School of Pharmacy at the University of North Carolina in Chapel Hill. He previously worked in Hanes's lab when it first developed mucus-penetrating particles.

"To ease experiments, many studies are performed on gels prepared by mixing purified mucin solids, isolated from cell cultures or animals, with buffers. This process, in turn, can alter mucus, including its chemical and barrier properties, in ways that no longer reflect physiological mucus function," Lai says. "The most direct way to study the barrier properties of physiological mucus would be to utilize fresh, undiluted and minimally perturbed mucus secretions directly from humans or animals, but there are exceedingly few studies that attempt to do so."

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