Study: The science behind bodily secretions

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The salivary gland secretes saliva that helps us chew and swallow the food we eat. The pancreas secretes digestive juices that enable our bodies to break down the fat, protein, and carbohydrates in the food. Secretions like these are important in countless activities that keep our bodies running day and night. A study published today in the journal *Science Signaling* uncovers a previously mysterious process that makes these secretions possible.

At the heart of the new study is calcium, which is present in all of our cells and is a gatekeeper of sorts: an increase in calcium in our cells opens up "gates" or "channels" that are required for the production and secretion of fluids like saliva. If calcium doesn't increase inside cells the gates won't open, a problem that occurs in diseases like Sjögren's syndrome. Sjögren's patients experience dry mouth due to a lack of saliva and have difficulty chewing, swallowing, and speaking, which severely hampers quality of life.

For the past 15 years David I. Yule, Ph.D., professor in the department of Pharmacology and Physiology at the University of Rochester School of Medicine and Dentistry has studied calcium's role in Sjögren's and other disorders in which calcium and secretions are disrupted, like acute pancreatitis. In the new study he answers an important question that has stumped scientists for years: what does it take for a particularly important calcium channel to open and start these processes?

Scientists have known that the presence of a protein called the IP3 receptor is necessary to increase calcium and generate channels in many,

if not all cells, but the IP3 receptor is complex. One channel is created from four identical units in the IP3 receptor, and it was not known how many of the individual units had to be engaged for the channel to work.

Using advanced molecular engineering and gene editing techniques driven by Kamil Alzayady, Ph.D., research assistant professor in the Yule lab, they discovered that, without exception, all four parts must be activated (turned on) for calcium to increase in a cell and start processes like fluid secretion. Yule believes this feature ensures that the calcium channel only opens under strict conditions that result in secretions, avoiding harmful events that would occur if the channel could open more easily. (Paradoxically, too much calcium is also bad and can lead to processes that kill cells, so it is no surprise that cells keep tight control over calcium levels.)

"This elegant study by Drs. Alzayady and Yule uses a very clever approach to definitively answer a long standing question in the calcium signaling and secretion fields," said Robert T. Dirksen, Ph.D., the Lewis Pratt Ross Professor and Chair of the department of Pharmacology and Physiology at the University of Rochester School of Medicine and Dentistry. "The results have broad implications not only for how calcium is controlled in cells, but also for understanding various human secretory disorders that range from dry mouth to pancreatitis."

"Our hope is that better knowledge of the mechanisms that control the flow of calcium in and out of cells will advance research on new treatments for many diseases, including Sjögren's," said Yule, who is also a professor in the Center for Oral Biology and the department of Medicine, Gastroenterology/Hepatology. Currently, there are no effective treatments for Sjögren's and the accompanying dry mouth, which causes oral infections, cavities, and a loss of teeth.

Ongoing research in Yule's lab is aimed at using the same molecular

engineering and gene editing technologies to investigate how genetic diseases affecting the IP3 protein result in brain and immune system disorders.

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