Researchers identify universal bitter blocker that could help patients take their life-saving medicines as prescribed

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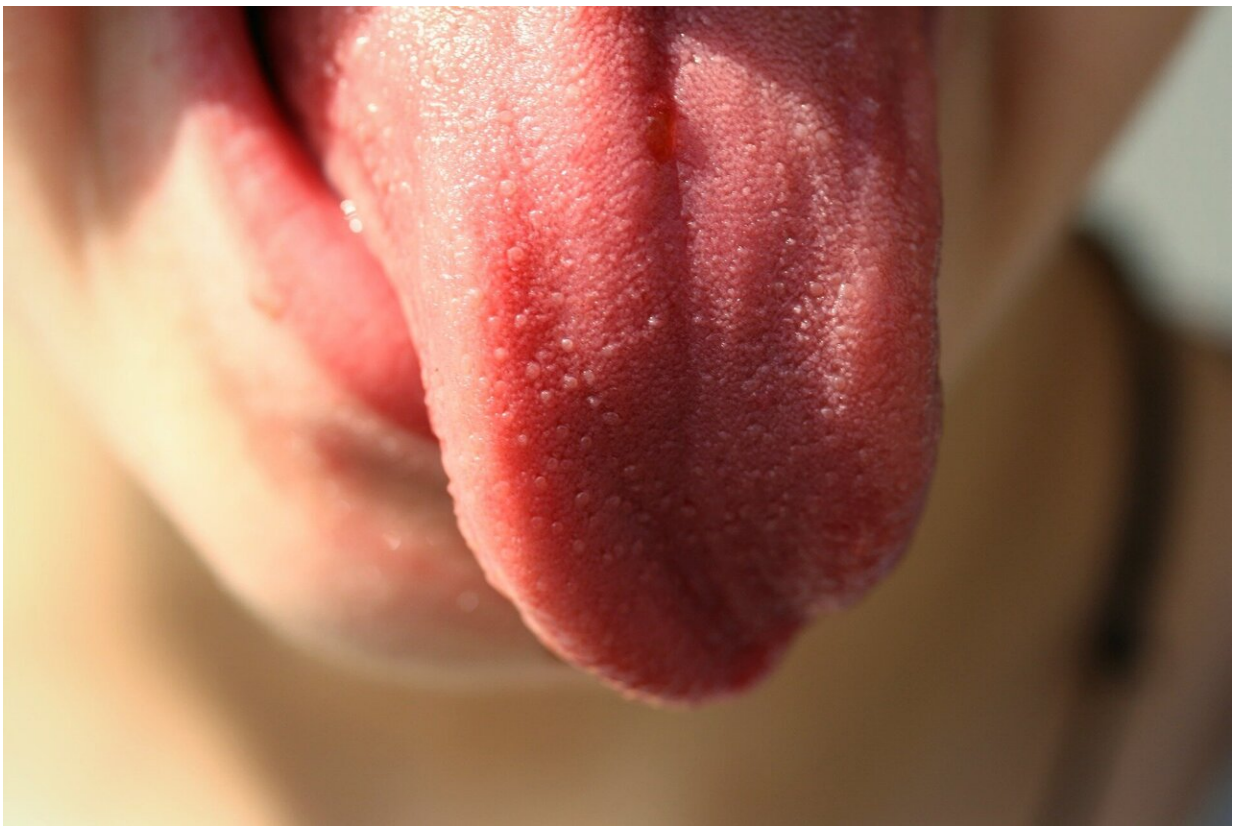

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Many people, especially children and the elderly, have difficulty swallowing pills. Liquid forms of many medicines taste extremely bitter

and are often rejected. Put simply, strong bitterness is the main reason why people all over the world, especially children, avoid taking their medicines, putting their health and sometimes their lives at risk.

Now, a group of scientists at the Monell Chemical Senses Center has identified the first temporary, universal taste blocker that works in people. Their findings appear in the *British Journal of Pharmacology.*

"Remarkably, and unlike our experience with blockers of bitter taste receptors, the taste-nerve blocker we tested worked for every subject and every bitter compound we tested," said first author Linda J. Flammer, Ph.D., Monell Senior Research Associate and Director of the Corporate Partners Program. "I have never seen this before."

Until now, efforts to block bitterness in foods and medicines have focused on finding blockers for bitter taste receptors on the tongue. Because different medications activate distinct sets of bitter taste receptors, targeting specific receptors may only suppress bitterness for certain, but not all, bitter-tasting compounds.

"There is a clear need to develop bitter blockers that are able to suppress the bitterness of many medications," said co-author Carol Christensen, Ph.D., Monell Alumnus Faculty Member. "Although humans have 25 different bitter receptors, our ongoing research suggests only a handful of bitter receptors may be responsible for most of the bitterness of medicines."

Taste cells in the mouth that express the TAS2R family of taste receptors are stimulated by sweet, bitter, and savory compounds, and transmit signals to nerve fibers by releasing adenosine triphosphate (ATP), a cell's main source of energy. In turn, ATP activates a receptor called P2X2/P2X3 on the receiving nerve cells. These nerves send information to the brain about the taste of foods and medications.

The team used an inhibitor of P2X2/P2X3 receptors, called AF-353, to block taste-nerve transmission and reduce the bitterness signal caused by medications and other taste compounds. Several blockers of P2X2/P2X3 receptors have been identified, with some tested in clinical trials to treat chronic cough; however, a side effect in these trials was taste disturbance. The Monell team capitalized on the "side effect" of these compounds to create an oral treatment that enhances the palatability of medicines.

A key finding of the study is that rinsing the mouth with AF-353 significantly reduced the bitterness of two important medicines that treat common chronic diseases: Praziquantel for parasites and Tenofovir Alafenamide (TAF) for hepatitis B and HIV.

"AF-353 is the first universal bitter taste blocker that has been identified," said Monell Faculty Member Peihua Jiang, Ph.D.. "In addition to bitter taste, it also affects savory, salt, sweet, and sour tastes. However, AF-353 only blocks taste. Other oral sensations like the tingle from carbonation were not affected."

The team conducted both human sensory taste testing and mouse behavioral experiments to determine the breadth, strength, and duration of the blocking effects. The results of the human and rodent studies were similar in the breadth and duration of AF-353's action.

The topical application of AF-353 directly into the mouth may improve compliance of many important medications, especially those that are life-saving for children in developing countries. "In people, the blocking effect lasted 60 to 90 minutes, when their taste was restored to normal," said Flammer.

"We are now looking for taste blockers that act faster and allow taste to return to normal sooner," said Jiang.

Along with Flammer, Jiang, and Christensen, the co-authors are Hillary Ellis, Natasha Rivers, Lauren Caronia, Misgana Y. Ghidewon, Paul A. S. Breslin, and Michael G. Tordoff, all from Monell. Breslin is also a faculty member of Rutgers University. Ghidewon is a student at the University of Pennsylvania.

More information: Linda J. Flammer et al, Topical application of a P2X2/P2X3 purine receptor inhibitor suppresses the bitter taste of medicines and other taste qualities, *British Journal of Pharmacology* (2024). DOI: 10.1111/bph.16411

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