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Common herbicides and fibrate drugs block nutrient-sensing 'taste' receptor found in gut and pancreas

Effects specific to humans, not revealed through testing on animal tissues

PHILADELPHIA (October 09, 2009) -- According to new research from the Monell Center and the Mount Sinai School of Medicine, certain common herbicides and lipid-lowering fibrate drugs act in humans to block T1R3, a nutrient-sensing taste receptor also present in intestine and pancreas.

Commonly used in agriculture and medicine, these chemical compounds were not previously known to act on the T1R3 receptor.

The T1R3 receptor is a critical component of both the sweet taste receptor and the umami (amino acid) taste receptor. First identified on the tongue, emerging evidence indicates that T1R3 and related taste receptors also are located on hormone-producing cells in the intestine and pancreas.

These internal taste receptors detect nutrients in the gut and trigger the release of hormones involved in the regulation of glucose homeostasis and energy metabolism.

"Compounds that either activate or block T1R3 receptors could have significant metabolic effects, potentially influencing diseases such as obesity, type II diabetes and metabolic syndrome," noted Monell geneticist and study leader Bedrich Mosinger, M.D., Ph.D.

In the study, published online in the *Journal of Medicinal Chemistry*, researchers tested the ability of two classes of chemical compounds to block the T1R3 receptor. The compounds – fibrates and phenoxy-herbicides – were selected based on their strong structural similarity to lactisole, a sweet taste inhibitor that exerts its taste effects by blocking T1R3.

Fibrates are a class of drugs frequently used to treat lipid disorders such as high blood cholesterol and triglycerides. Phenoxy-herbicides are used in agriculture to control broad-leaf weeds; the best known, 2,4-D, is one of the most extensively used herbicides worldwide.

Using an *in vitro* preparation, the researchers found that both classes of compounds potently blocked activation of the human sweet taste receptor, acting at micromolar concentrations to inhibit binding of sugars to the T1R3 component of the receptor.

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Additional testing revealed that the inhibitory effect of both fibrates and phenoxy-herbicides on the T1R3 receptor is specific to humans. That is, the ability of these compounds to block the receptor did not generalize across species to the rodent form of the receptor.

Mosinger commented on the implications of the findings and noted the importance of testing chemicals intended for human use on human tissues. “The metabolic consequences of short- and long-term exposures of humans to phenoxy-herbicides are unknown. This is because most safety tests were done using animals, which have T1R3 receptors that are insensitive to these compounds,” he said.

The ability of fibrate drugs to interact with T1R3 receptors also was previously unknown. The study findings suggest that these receptors might be an important pharmacological target of first-generation fibrates, such as clofibrate, which were believed to act on a different receptor to affect lipid metabolism. Newer fibrate drugs are more specific for the second receptor and interact less with the T1R3 receptor.

Mosinger points out that little is known about how T1R3 blockade affects hormone levels and metabolism. “Given the number of compounds used in agriculture, medicine and the food industry that may affect human T1R3 and related receptors, more work is needed to identify the health-related effects of exposure to these compounds,” he said.

Also contributing to the study were first author Emeline Maillet from the Department of Neuroscience at Mount Sinai School of Medicine and co-author Robert Margolskee of Monell.

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The Monell Chemical Senses Center is an independent nonprofit basic research institute based in Philadelphia, Pennsylvania. Monell advances scientific understanding of the mechanisms and functions of taste and smell to benefit human health and well-being. Using an interdisciplinary approach, scientists collaborate in the programmatic areas of sensation and perception; neuroscience and molecular biology; environmental and occupational health; nutrition and appetite; health and well-being; development, aging and regeneration; and chemical ecology and communication. For more information about Monell, visit www.monell.org.

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