# Potential mechanisms for future anti-obesity drugs identified

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An interdisciplinary group of researchers at the University of Pennsylvania has, for the first time, identified the neurological and cellular signaling mechanisms that contribute to satiety — the sensation of feeling full — and the subsequent body-weight loss produced by drugs used to treat type 2 diabetes. More comprehensive knowledge of these mechanisms could form the basis for anti-obesity medications.

The group was led by Matthew Hayes of the School of Medicine's Psychiatry Department, Harvey Grill of the Psychology Department in the School of Arts and Sciences and Kendra Bence of the School of Veterinary Medicine's Animal Biology Department. Their research was aided by a team of postdoctoral and doctoral fellows, as well as technicians and undergraduate students at Penn.

The study was published in the March 2 edition of the journal *Cell Metabolism*.

While no pharmaceutical treatment for obesity currently exists, type 2 diabetes drugs targeting the hormone glucagon-like-peptide-1, or GLP-1, for insulin production may hold promise. These drugs were known to promote weight loss, simply as a result of patients eating less. Researchers, however, could not explain exactly what caused this change in behavior.

Naturally occurring GLP-1 is made in primarily two distinct locations in the body, the gut and the brain. Much of the previous research in this

area has focused on the former at the expense of the latter when attempting to identify the relevant population of GLP-1 receptors that may mediate the suppression in food intake by pharmaceutical GLP-1 drugs.

“Identifying both the site-of-action and mechanisms that accounts for the body weight loss of these GLP-1 drugs puts us one step closer to developing effective, FDA-approved, treatments for obesity,” Hayes said.

“Ignoring the brain is not the right strategy, as these drugs are certainly engaging multiple, distributed centers in the brain governing energy balance regulation,” Grill said.

The Penn group not only identified a necessary part of the brain which mediates the food intake suppression effect produced by these drugs, the nucleus tractus solitarius, or NTS, but also the cellular signaling pathways required for production of GLP-1’s satiety effects.

“GLP-1’s ability to alter these specific signaling pathways within the NTS of the brainstem may account for the suppression in food intake and body weight by altering the long-term neurochemistry and connectivity of this region of the brain with higher-order brain centers that also regulate energy balance,” Bence said.

Many researchers have tried to determine precisely how GLP-1 and other satiating signals work, especially since in obese individuals, the brain fails to correctly perceive and respond to naturally occurring energy balance signals from the body. This faulty signaling underscores the importance of pharmacological treatments, such as the long-acting GLP-1 drugs that are effective in engaging brain signaling to reduce excessive food intake and possibly obesity.

That the Penn researchers were able to demonstrate a potential neurochemical mechanism of weight loss for a class of drugs already used in the treatment of type 2 diabetes provides a missing piece of the puzzle for future FDA-approved anti-obesity drugs.

“If we can identify other chemical signals or hormones that act on the same pathways that we’ve shown here, then by combined action you have a coordinated, orchestrated symphony of weight suppression,” Hayes said.

Provided by University of Pennsylvania