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Study suggests that medication could improve gastric bypass results

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New findings about the mechanisms involved - or not involved - in the effects of the most common form of bariatric surgery suggest that combining surgery with a specific type of medication could augment the benefits of the procedure. In a report that has been published online in the journal *Endocrinology*, Massachusetts General Hospital (MGH) investigators report that the effects of Roux-en-Y gastric bypass (RYGB) do not utilize neurologic pathways controlled by the serotonin 2C receptor. Since that receptor is a proven target for the FDA-approved anti-obesity drug lorcaserin, the findings imply that the two methods could have complementary effects, producing even more weight loss than achieved with either one alone.

"This is the first reported example of a rational, mechanism-based strategy for combining bariatric surgery with medication to treat obesity," says Lee Kaplan, MD, PhD, director of the Obesity, Metabolism and Nutrition Institute at MGH and senior author of the report. "Our finding that not all potential weight-loss-activating pathways are engaged after surgery suggests that those unengaged pathways could be good targets for complementary therapies to improve surgical outcomes."

Also founding director of the MGH Weight Center, Kaplan has led several studies in recent years investigating the mechanisms behind the effects of RYBG and other surgical procedures designed to combat obesity. In a 2012 study his team found that activity of the melanocortin-4 receptor (MC4R), which was already known to regulate

energy balance and body weight, was essential for the weight-loss effects of RYGB. Since stimulation of serotonin receptors is known to suppress food consumption and reduce weight and since serotonin 2C receptors are located on neurons known to activate MC4R, the research team investigated whether they were involved with the MC4R-controlled pathway required for the benefits of RYGB.

In a series of experiments with two groups of mice raised on a high-fat diet - one in which expression of the serotonin 2C receptor was blocked - the researchers found that, in contrast to MC4R, the presence of serotonin 2C receptors was not required for the beneficial effects of RYGB, including reduced food intake and weight loss. Adding treatment with fenfluramine, a drug that broadly increases serotonin signaling, to RYGB increased the beneficial effects, while treatment with topiramate, an antiseizure medication also approved to treat obesity, failed to improve the effects of RYGB - findings that indicate topiramate operates through mechanisms that overlap with those of surgery and are different from those activated by drugs that target serotonin-controlled pathways.

Fenfluramine was once approved to treat obesity, both alone and in combination with the drug phentermine, but was subsequently withdrawn from the market because of cardiovascular side-effects related to its broad stimulation of all serotonin receptors. Because lorcaserin, one of the few currently approved anti-obesity medications, selectively stimulates the serotonin 2C receptor, it avoids the main harmful effects of fenfluramine. Lorcaserin was not available in a form appropriate for treating mice, so the research team tested a different drug that selectively targets the serotonin 2C receptor and found that it too improved the results of RYGB - further reducing food intake and increasing weight loss - which demonstrated that weight loss mechanisms not utilized by surgery are good targets for complementing and extending the beneficial effects of surgery.

"Finding that functioning serotonin 2C receptors are not required for the effects of RYGB was surprising, since serotonin 2C receptor signaling appears central to weight regulation and is closely tied to the function of MC4R," says Jill Carmody, PhD, of the Obesity, Metabolism and Nutrition Institute, lead author of the study. "While further defining the pathways through which RYGB works should aid in the development of less-invasive treatments that mimic the therapeutic benefits of surgery, pathways not utilized by surgery would seem to be promising targets for drugs that enhance the benefits of surgery. And since not all patients respond well to RYGB, there is a strong need to augment the effects of these operations."

An associate professor of Medicine at Harvard Medical School, Kaplan adds that future studies should identify additional weight-regulating pathways not engaged by bariatric surgery that could be potential treatment targets. A clinical trial adding lorcaserin therapy to RYGB would be a logical follow-up to the current study's results, he notes.

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