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Promising antiobesity drug fails to produce clinically meaningful weight loss

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A drug designed to target a powerful hunger-stimulating factor that has long been considered a prime target for antiobesity therapy failed to produce clinically meaningful weight loss in obese people in a long-term clinical trial. People taking the drug known as MK-0557 for a year consistently lost about three pounds more than those taking a placebo, researchers reported in the October issue of the journal *Cell Metabolism*, published by Cell Press.

The results, which are the culmination of a 10 year program of study, suggest MK-0557 alone will not provide a useful weapon in the fight against obesity. The possibility remains, however, that the treatment could potentially play a role in future combination therapies, according to the research team that includes Steven Heymsfield and Ngozi Erondu of Merck & Co., Inc. Heymsfield said that combination therapies were among the possibilities being considered by scientists conducting obesity research.

"The current findings add to a growing sense that you will have to try a lot of different targets or get an even better understanding of the scientific underpinnings in order to unwire the food intake system with some combination of drugs," Heymsfield said. "Finding safe and effective antiobesity drugs is not unlike the challenge and complexity of sending the space shuttle into orbit."

MK-0557 blocks brain receptors that respond to the hunger factor called neuropeptide Y (NPY). NPY, whose role in driving appetite Heymsfield

likens to an accelerator in a car, is one in a chain of players in the hunger pathway that includes the fat hormone leptin. Leptin hormone sends signals to the brain about the level of energy stores available, information that is then used to gauge metabolism and appetite.

Scientists discovered NPY more than two decades ago, making it one of the first identified appetite stimulants, but it was only after the discovery of leptin in 1994 that the neuropeptide's key role and potential as a drug target was fully appreciated, Heymsfield explained. After screening numerous compounds for their safety and ability to specifically bind NPY receptors, MK-0557 emerged as the "survivor," he added.

In the current study, the researchers first conducted a unique imaging study designed to directly reveal the number of human NPY receptors bound by MK-0557 after people took the drug at various doses. Using this method, they found that it only takes a small amount--1 mg per day--for almost complete occupancy of the "NPY5R" receptor.

A 12 week proof-of-concept and dosing study including 547 participants taking either a placebo or the drug at doses ranging from 0.2–25 mg/day supported the imaging study's findings, the researchers reported. MK-0557 was found to be well tolerated and to induce modest weight loss in obese individuals. The amount of weight loss and proportion of receptors bound by the drug reached a plateau at doses greater than 1 mg.

The results led the researchers to proceed with a year long clinical trial including 1661 patients randomized into placebo or 1 mg MK-0557 groups, in order to test whether the drug would support continued weight loss.

Of the 832 participants who successfully completed the trial, those in the placebo group lost an average of about 4 pounds, while those taking

MK-0557 lost about 7.5 pounds. While the weight loss difference between groups was found to be statistically significant, the results "strongly suggest that a highly selective NPY5R antagonist" on its own is insufficient treatment for curbing obesity, Heymsfield reported.

The findings in some ways mirror earlier studies that looked to leptin as a "magic bullet" for weight loss therapy, Heymsfield said.

"Most obesity was found to be insensitive to leptin," he said. "It appears the same is true for the NPY5R pathway. When you hit this receptor as a single target, it doesn't generally appear to change energy balance profoundly."

"The studies now described provide novel insight into the use of the NPY5R as a sole target for the development of antiobesity drug therapy," the researchers concluded. "However, other chronic diseases, such as high blood pressure or diabetes, commonly require two or even three drugs to achieve optimal therapeutic response."

It is generally accepted that significant and robust weight-loss efficacy may require a multipronged pharmaceutical solution, they said. Based on the modest degree of weight loss observed after 52 weeks of treatment, drugs such as MK-0557 targeting single receptors would ideally be used with other agents that combined have synergistic weight loss effects.

Source: Cell Press