

News Summary

P3-374: Experimental drug TTP2515 helps rats lose weight

An experimental drug targets a brain pathway that regulates body weight in humans, and it reduces food intake and obesity in rodents, according to a new study funded by the National Institutes of Health. The results will be presented Friday at The Endocrine Society's 91st Annual Meeting in Washington, D.C.

“The potential obesity treatment works in animals by blocking an inhibitor of the brain melanocortin system, a brain pathway that plays a critical role in regulating body weight in animals and humans,” said lead author Sharon Wardlaw, MD, professor of medicine at Columbia University College of Physicians & Surgeons, New York City. “It can also blunt some of the hormonal changes that occur after weight loss and contribute to weight regain.”

The experimental oral drug, TTP2515, developed by TransTech Pharma in High Point, N.C., was designed to inhibit a protein in the body called agouti-related protein (AGRP), Wardlaw said. This protein increases in the brain during calorie restriction and stimulates food intake and reduces the ability to burn calories. When given as an infusion in animals, AGRP disrupts the brain melanocortin system. This increases food intake, body weight and body fat and is accompanied by increased levels of insulin and the fat hormone leptin. Leptin and insulin, at normal levels, act in the brain to curb appetite and maintain body weight. However, in obesity, resistance develops to the abnormally high levels of insulin and leptin. Also, this protein suppresses thyroid hormone levels similar to what occurs during fasting.

When AGRP is blocked, receptors activate in the brain melanocortin system. These activated brain melanocortin receptors (MC4R) then regulate food intake and energy expenditure. During fasting or caloric restriction AGRP increases in the brain and is responsible for some of the hormonal responses caused by weight loss. Inhibition of AGRP could reverse some of these hormonal responses, Wardlaw said.

In the first experiment by Wardlaw and colleagues, male rats received brain infusions of AGRP or saline for 1 week. The animals were randomly assigned to receive either TTP2515 or water orally during the infusions. AGRP increased food intake and weight gain in the rats that did not get TTP2515, but TTP2515 in the other rats blunted both changes. TTP2515 also lessened increases in body fat and improved levels of leptin, insulin and thyroid hormones.

In another experiment, male mice with food-induced obesity received water or TTP2515 orally for 3 weeks. TTP2515 reduced food intake and weight gain. Magnetic resonance imaging (MRI) showed that the loss in body weight in the TTP25-treated group was due to a selective reduction in fat mass. Leptin and insulin levels tended to be lower and thyroid hormone levels were higher with treatment. These data suggest TTP2515 can reduce obesity, Wardlaw said.

“The drug could be studied in humans,” she said. “It is possible that TTP2515 or a similar agent could one day serve as a treatment of obesity and to help prevent people from regaining the weight they lost.”

Several study co-authors are employees of TransTech Pharma, which supplied the study drug.

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