'Trojan Horse' weight loss drug found to be more effective than available therapies

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In a study published in *Nature*, Christoffer Clemmensen and colleagues demonstrate a new use of the weight loss hormone GLP-1. GLP-1 can be used as a "Trojan Horse" to smuggle a specific molecule into the brain of mice, where it successfully affects the plasticity of the brain and results in weight loss.

"I consider the drugs available on the market today as the first generation of weight-loss drugs. Now we have developed a new type of weight-loss drug that affects the plasticity of the brain and appears to be highly effective," says Clemmensen, from the Novo Nordisk Foundation Center for Basic Metabolic Research at the University of Copenhagen and senior author of the study.

"The effect of GLP-1 combined with these molecules is very strong. In some cases, the mice lose twice as much weight as mice treated with GLP-1 only."

This means that future patients can potentially achieve the same effect with a lower dosage. Moreover, the new drug may be an alternative to those who do not respond well to existing weight-loss drugs.

"Our studies in mice show side effects similar to those experienced by patients treated with the weight loss drugs available on the market today, including nausea. But because the drug is so effective, we may be able to lower the dosage and thus mitigate some of the side effects in the future—though we still don't know how humans respond to the drug," Clemmensen says.

Testing of the new weight loss drug is still in the so-called preclinical phase, which is based on studies with cells and on experimental animals. The next step is clinical trials with human participants.

"We already know that GLP-1-based drugs can lead to weight loss. The molecule that we have attached to GLP-1 affects the so-called glutamatergic neurotransmitter system, and in fact, other studies with human participants suggest that this family of compounds has significant weight loss potential. What is interesting here is the effect we get when we combine these two compounds into a single drug," Clemmensen says.

The drug must undergo three phases of clinical trials on human participants. According to Clemmensen, it can therefore take eight years before the drug could be available on the market.

The brain defends excessive body weight

Clemmensen and colleagues developed an interest in molecules that are used to treat chronic depression and Alzheimer's disease.

The molecules block a receptor protein called the NMDA receptor, which play a key role in long-term changes in brain connections and have received scientific attention within fields of learning and memory. Drugs targeting these receptors will strengthen and/or weaken specific nerve connections.

"This family of molecules can have a permanent effect on the brain. Studies have demonstrated that even a relative infrequent treatment can lead to persistent changes to the brain pathologies. We also see molecular signatures of neuroplasticity in our work, but in this case in the context of weight loss," he explains.

The human body has evolved to protect a certain body weight and fat mass. From an evolutionary perspective, this has probably been to our advantage, as it means that we have been able to survive periods of food scarcity. Today, food scarcity is not a problem in large parts of the world, where an increasing part of the population suffers from obesity.

"Today, more than one billion people worldwide have a BMI of 30 or more. This makes it increasingly relevant to develop drugs to aid this disease, and which can help the organism to sustain a lower weight. This topic is something we invest a lot of energy in researching," says Clemmensen.

A Trojan Horse smuggles small molecule modulators of neuroplasticity into appetite-regulating neurons

We know that drugs based on the intestinal hormone GLP-1 effectively target the part of the brain that is key to weight loss, namely the appetite control center.

"What is spectacular—on a cellular level—about this new drug is the fact that it combines GLP-1 and molecules that block the NMDA receptor. It exploits GLP-1 as a Trojan Horse to smuggle these small molecules exclusively into the neurons that affect appetite control. Without GLP-1, the molecules that target the NMDA receptor would affect the entire brain and thus be non-specific," says Postdoc Jonas Petersen from the Clemmensen Group, who is the first author on the study and the chemist who synthesized the molecules.

Non-specific drugs are often associated with severe side effects, which has previously been seen in drugs for treating different neurobiological conditions.

"A lot of brain disorders are difficult to treat, because the drugs need to cross the so-called blood-brain barrier. Whereas large molecules like peptides and proteins generally have difficulties accessing the brain, many small molecules have unlimited access to the entire brain. We have used the GLP-1 peptide's specific access to the appetite control center in the brain to deliver one of these otherwise non-specific substances to this

region only," Clemmensen says.

"In this study, we have focused on obesity and weight loss, but in fact this is a completely new approach for delivering drugs to specific parts of the brain. So, I hope our research can pave the way for a whole new class of drugs for treating conditions like neurodegenerative diseases or psychiatric disorders."

Clemmensen, along with postdoc Jonas Petersen and a former scientist from the University of Copenhagen (Anders Klein), have co-founded of the biotech company Ousia Pharma, which is a spinout company from the University of Copenhagen. The company is continuing to develop the medical concept presented in this study for the treatment of severe obesity.

More information: Jonas Petersen et al, GLP-1-directed NMDA receptor antagonism for obesity treatment, *Nature* (2024). DOI: 10.1038/s41586-024-07419-8

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