News in focus

LISE AASERUD/NTB/ALAMY

Researchers adapted a peptide similar to the one used in the obesity drug Wegovy to elicit an even more potent weight-loss response in mice.

EXPERIMENTAL OBESITY DRUG PACKS DOUBLE PUNCH TO REDUCE WEIGHT

Test of weight-loss candidate in mice shows that there is still room for improvement in a burgeoning field.

By Asher Mullard

With obesity drugs now helping people to slim down, researchers are working to capitalize on their popularity by bulking up the weight-loss-drug pipeline. The latest contender takes a Trojan horse approach — hiding a small molecule in a gut-hormone-mimicking peptide that is already used in obesity drugs — to strike a double blow to the brain cells that control appetite.

The work, which demonstrated the effects of this drug candidate in mice and rats, was published on 15 May in *Nature*[1].

"It's a strong paper," says Daniel Drucker, an endocrinologist at Mount Sinai Hospital in Toronto, Canada, who helped to unravel the role of gut hormones such as GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide) in obesity. The blockbuster weight-loss drugs semaglutide (sold as Wegovy) and tirzepatide (Zepbound) act by mimicking these hormones, binding to their receptors on neurons in the brain that control hunger pangs. These drugs can help people to lose 15–20% of their body weight. And it could be possible to eke even more activity from these hormone mimics by fusing them with other drugs, the study suggests.

Trojan therapeutics

"Very high marks for the novelty" of the research, says Drucker, who was not involved in the study and is a consultant for the pharmaceutical industry. "Let's hope that we'll see some proof of concept in the clinic", when the approach is tested in humans.

The drug contender takes aim at both the

GLP-1 receptor and the NMDA receptor, an ion channel found on brain cells that was linked to obesity in 2015 (ref. 2). At the time, small molecules that blocked the NMDA receptor seemed like a non-starter for obesity drug developers, because this type of compound, which includes the 'party drug' and antidepressant ketamine, is associated with harmful side effects.

But Christoffer Clemmensen, a metabolism specialist at the University of Copenhagen, saw a path forwards. He speculated that it might be possible to sidestep the safety risks by fusing an NMDA-receptor blocker to a gut-hormone mimic that acts only on the neurons that regulate appetite.

To make this a reality, Clemmensen and his colleagues attached a peptide that looks like the GLP-1 hormone to a small molecule, dizocilpine (also called MK-801), that blocks the NMDA receptor. Dizocilpine was discovered in the 1980s by researchers at the US pharmaceutical firm Merck, based in Rahway, New Jersey, but was then abandoned. Clemmensen and the team saw that, in mice and rats, GLP-1-loving neurons in the brain took up this peptide–drug conjugate, and then cut the dizocilpine payload loose to block the NMDA receptor. (Some members of the team work at Novo Nordisk, which makes semaglutide, although Clemmensen says this was an academic collaboration and not a commercial one.)

"This is a really creative way to optimize for weight loss," says Darleen Sandoval, a physiologist at the University of Colorado in Aurora. "The big picture here is how far we have come in terms of being able to target the brain to treat obesity," adds Sandoval, who co-authored a commentary that accompanied the study in *Nature*[3].

Treating mice with dizocilpine alone caused side effects such as overheating and excess movement. The peptide–drug conjugate was safer, and it offered similar weight-loss benefits to treating mice with semaglutide alone. Where the conjugate shone was in mice predosed with semaglutide: once the animals reached a weight-loss plateau with that drug, giving them the conjugate as an add-on treatment drove their body mass down further.

"It is competitive with the current best therapies on the market," says Clemmensen. "Possibly, we can outperform these."

To the clinic

As a next step, Clemmensen and some colleagues have co-founded Ousia Pharma, based in Copenhagen, to advance a related drug candidate into clinical trials. This potential therapeutic, called OP-216, has the added benefit of also mimicking GIP in addition to GLP-1, Clemmensen says. "We could be in the clinic in 2025," he adds.

The success of the current crop of obesity drugs has set a high bar for next-generation therapeutics. But "there's definitely room for more drugs and targets", says Ruth Loos, an obesity geneticist at the University of Copenhagen who co-led the 2015 genetics study that linked the NMDA receptor to obesity[2]. Not everyone sheds weight using the currently available options. And gut-hormone mimics need to be taken continuously to maintain their effect.

Loos, who has also consulted for the pharmaceutical industry, was not involved in developing the latest peptide–drug conjugate, but hopes it will encourage others to look for innovative ways to treat obesity. Dozens of weight-loss drugs — many targeting GLP-1 and GIP — are already in the clinic, and drug developers are on the lookout for up-and-coming agents. The weight-loss drug market is forecast to be worth up to US$100 billion by 2030.

It's predicted that by 2035, more than half of adults worldwide will be obese. Treating them with obesity drugs could confer wider health advantages, such as cardiovascular and anti-inflammatory benefits. Trials of these drugs are also under way to treat kidney disease, Parkinson's and Alzheimer's diseases, and addiction-related behaviours such as drinking and smoking.

"Not all these trials are going to be successful," Drucker says. But enough might pan out to reshape the therapeutic landscape, he adds. "It's going to be fascinating to watch."

"When I started working on obesity in 2013, there was no interest in it," Clemmensen says. Right now, he adds, all the activity is a bit wild.

1. Petersen, J. *et al. Nature* https://doi.org/10.1038/s41586-024-07419-8 (2024).
2. Locke, A. E. *et al. Nature* **518**, 197–206 (2015).
3. Cook, T. M. & Sandoval, D. *Nature* https://doi.org/10.1038/d41586-024-01352-6 (2024).

'QUANTUM INTERNET' DEMO IN CITIES IS MOST ADVANCED YET

Experiments mark progress towards networks that could have revolutionary applications.

By Davide Castelvecchi

Three separate research groups have demonstrated quantum entanglement — in which two or more objects are linked so that they contain the same information even if they are far apart — over several kilometres of existing optical fibres in real urban areas. The feat is a key step towards a future quantum internet, a network that could allow information to be exchanged while encoded in quantum states.

"The step has now really been made out of the lab and into the field."

Together, the experiments are "the most advanced demonstrations so far" of the technology needed for a quantum internet, says physicist Tracy Northup at the University of Innsbruck in Austria. Each of the three research teams — based in the United States, China and the Netherlands — was able to connect parts of a network using photons in the optical-fibre-friendly infrared part of the spectrum, which is a "major milestone", says fellow Innsbruck physicist Simon Baier.

A quantum internet could enable any two users to establish almost unbreakable cryptographic keys to protect sensitive information. But full use of entanglement could do much more, such as connecting separate quantum computers into one larger, more powerful machine. The technology could also enable certain types of scientific experiment, for example by creating networks of optical telescopes that have the resolution of a single dish hundreds of kilometres wide.

Two of the studies[1,2] were published in *Nature* on 15 May. The third was described last month in a preprint posted on arXiv[3], which has not yet been peer reviewed.

Impractical environment

Many of the technical steps for building a quantum internet have been demonstrated in the laboratory over the past decade or so. And researchers have shown that they can produce entangled photons using lasers in direct line of sight of each other, either in separate ground locations or on the ground and in space.

But going from the lab to a city environment is "a different beast", says Ronald Hanson, a physicist who led the Dutch experiment[3] at the Delft University of Technology. To build a large-scale network, researchers agree that