Lu et al.\textsuperscript{1} previously demonstrated that antagonist antibodies against the GIP receptor promote weight loss combined with GLP-1. They now elegantly developed a conjugate of GIPR antibodies and GLP-1 and show effective weight loss in obese non-human primates.

In the article “GIPR antagonist antibodies conjugated to GLP-1 peptide are bispecific molecules that decrease weight in obese mice and monkeys,”\textsuperscript{1} scientists from Amgen Research, a division of Amgen Inc., describe the development of a monoclonal antibody directed against the human and/or the murine GIP receptor conjugated with a GLP-1 peptide analog (stabilized against DPP-4).\textsuperscript{1} In mice and monkeys, these molecules reduce body weight and improve metabolic parameters. In addition, they have a long duration of action, consistent with their antibody backbone, suitable for at least weekly use. The findings are of great interest in view of the current development of pharmaceutical agents based on the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 receptor agonists (GLP-1RAs) were introduced for diabetes therapy in 2005 and are today used worldwide in the form of once-daily or once-weekly preparations. The GLP-1RAs have powerful antidiabetic effects in patients with diabetes and, in numerous clinical studies, have been found to improve glycemic control and have less serious side effects than other antidiabetic agents.\textsuperscript{2} They also reduced appetite by an action on brain centers regulating appetite and food intake, and one, liraglutide, has been approved for obesity.\textsuperscript{1} Most recently, a second-generation GLP-1RA, semaglutide, has shown surprisingly strong weight-reducing effects when used in a higher dose, resulting in weight losses of close to 20% of body weight.\textsuperscript{3} This is of great interest in view of the findings that weight losses of 15% and above can lead to diabetes remission in the majority of patients with diabetes.

So far, GIP has not been marketed as a drug, although it is a potent incretin hormone, powerfully stimulating insulin secretion during meal intake.\textsuperscript{4} Its insulinotropic discovery was discovered already in 1973, but subsequent research suggested that it also contributes to the development of body fat by enhancing deposition of fat in the adipose tissues (“the obesity hormone”). Indeed, mice with knockout of the GIP receptor or the GIP molecule develop resistance toward diet-induced obesity, and people with inactivating mutations of GIP receptor show reduced body weight. In addition, for unknown reasons, GIP loses most of its insulinotropic effect in diabetes patients and may be diabetogenic, because it retains a stimulatory effect on glucagon secretion.\textsuperscript{5}

Accordingly, various attempts have been made to antagonize the actions of GIP to prevent fat accumulation, and among the most successful so far is the development of monoclonal antibodies against the GIP receptor by Amgen Inc.\textsuperscript{5} These antibodies prevented weight gain in animal models, including non-human primates, and potentiated weight loss induced by GLP-1 RAs. The study by Lu and colleagues from Amgen, in which they combine a GIP antagonist with a GLP-1 agonist, represents a logical continuation.\textsuperscript{1}

During the last decade, several attempts have been made to combine two (or even three) biologically active peptides into one molecule. One of the first co-agonists in the diabetes/obesity field was a GIP/GLP-1 co-agonist.\textsuperscript{6} The chemists behind this molecule claimed that it inhibited body weight and have subsequently developed several such co-agonists and reported positive effects on body weight. However, the big surprise occurred when researchers from Eli Lilly in 2018 presented the new GIP/GLP-1 co-agonist tirzepatide. In published phase 2 studies,\textsuperscript{7} this molecule showed improved antidiabetic and anti-obesity effects even compared to the company’s own once-weekly GLP-1 agonist, dulaglutide. The company has now completed a large series of phase 3A registration studies with tirzepatide, and the results are remarkable. Not only does the compound provide weight losses that are comparable to those elicited by the once-weekly GLP-1 RA semaglutide, but the antidiabetic activity is such that about 50% of the patients treated with the co-agonist experience values of hemoglobin A1c (a long-term measure of glucose control) below 5.7%, a completely normal value.

Thus, we have a situation where combinations of a GLP-RA with GIP agonists, as well as with GIP antagonists, have beneficial metabolic effects and cause body weight losses beyond those elicited by either of the two components alone.

Biologically, the powerful effects of the co-agonists, both those based on GIP agonism and antagonism, suggest that the molecules affect the receptors in the body in hitherto unrecognized ways. The site with most pronounced expression of GIP and GLP-1 receptors is the insulin-producing β cells of the pancreatic islets. It has been demonstrated that tirzepatide
interacts with both of these receptors but also that post-receptor events of the GLP-1 receptor (β-arrestin recruitment and internalization) are significantly altered by the co-agonist compared to isolated GLP-1 agonists. With the GIP-antibody-GLP-1 conjugate described here, the authors report superior cAMP responses (both receptors activate Gzα and adenylylate cyclase) compared with single agonists, and the authors propose that the GIP and GLP-1 receptors form dimers upon stimulation (a controversial possibility, debated for years). However, experiments with animals with selective knockout of the GIP receptor in the β cells indicated that the molecule is not exerting its activity on body weight via the pancreas. GLP-1 alone clearly acts in the brain to inhibit food intake, but there is also expression of GIP receptors in the brain. Indeed, recent studies suggested that a set of hypothalamic neurons could be responsible for food intake inhibiting actions of GIP. In addition, certain hypothalamic cells may co-express receptors for both GIP and GLP-1. However, whether the large molecular size of the antibody conjugates prevents their access to the brain is unclear. In an attempt to understand the confusing findings, it has been proposed that desensitization, induced by GIP-mediated activation of its receptor and accompanied by receptor internalization, downregulates the GIP system to the extent that it mimics antagonism. However, internalization may also lead to continued cAMP formation, as the internalized complexes have been found to be able to continue signaling, and this mechanism was offered by Lu et al. to explain the efficacy of the anti-GIPR/ GLP-1 co-agonist.

Although the co-agonist showed efficacy in non-human primates, there is still a step to go before we can evaluate the GIP antagonists and the GIP agonists in human studies, where we already have the very convincing results with tirzepatide. Nevertheless, with the current study, the authors from Amgen Inc. have provided the scientific community with a stimulating input to the current debate regarding the role of GIP, GLP-1, and their combination in metabolic regulation.

DECLARATION OF INTERESTS

J.J.H. is a founder of Antag Therapeutics and a member of its scientific advisory board, a member of scientific advisory boards for NovoNordisk, and co-author of a patent regarding GIP antagonists.

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