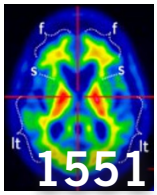


PET adoption:
Imaging agents aid trials of new Alzheimer's drugs

Shared interest:
The rise of biotech-capable shared lab facilities

Year in review:
The highs and lows of biomedical R&D in 2013

Drugs with dual-hormone action gain attention in diabetes field

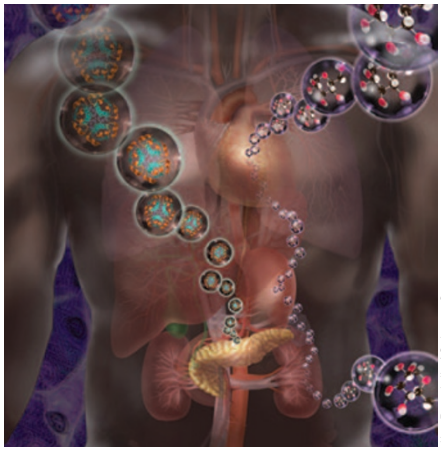
Engineered peptide drugs that simultaneously target two hormone receptors have historically attracted interest among scientists hoping to create new treatments for diabetes. Now, many in the field seem buoyed by new data from a class of diabetes medicines designed to mimic gastrointestinal hormones called incretins, which stimulate insulin release from pancreatic beta cells.

The 'incretin mimetics' currently on the market modulate only one receptor. For example, Byetta (exenatide) from California's Amylin Pharmaceuticals and Victoza (liraglutide) from Denmark's Novo Nordisk trigger the glucagon-like peptide-1 receptor (GLP-1). To adequately control blood glucose, these drugs are often used at high doses, commonly causing vomiting and nausea. Long-term effects could include increased risk for pancreatitis, pancreatic cancer and thyroid cancer.

The problem is that GLP-1 receptors aren't confined just to the gut. They're also found in other tissues, especially the thyroid, pancreas, meninges, kidney and bone. In March, the US Food and Drug Administration began reviewing research linking GLP-1 agonists to increased risk of pancreatitis and precancerous cellular changes associated with pancreatic cancer. And this September, France's Sanofi withdrew a new drug application in the US for its once-daily injectable GLP-1 agonist lixisenatide, although not because of any safety concerns but rather to avoid releasing data that could compromise an ongoing clinical trial.

According to drug developers, drugs that target two receptors simultaneously could provide a solution by more closely approximating the normal physiology lost when type 2 diabetes develops. The hope is to use these drugs at lower doses, decreasing the likelihood for adverse reactions.

In addition to GLP-1, another endogenous gut hormone is glucose-dependent insulinotropic peptide (GIP), which stimulates postprandial insulin release. Activity of GLP-1 and GIP is thought by some to be impaired in type 2 diabetes. A paper published in late October detailed the effects in humans of a new compound—originally called MAR701 by Indiana's Marcadia Biotech, which contributed to early development of the compound—that binds and triggers receptors for both GLP-1 and GIP[1]. It offered data from a phase 2 trial done in collaboration with Roche, the Swiss drug giant, that included 53 patients with inadequately controlled type 2 diabetes.



Jim Dowdalls / Science Source

Dual fuel: Two-hormone drugs help treat diabetes.

The trial found a dose-dependent decrease in hemoglobin A1C (HbA1c) in the experimental group, ranging from a decrease of 0.53% to as much as a 1.11% drop; by comparison, the placebo group had an average drop of 0.16%. No participants experienced vomiting, a common side effect of incretin mimetics on the market, and few had nausea. The study also reported that this type of dual agonist lowers blood glucose levels and weight more effectively than single agonists in animal models.

Incredible incretin?

According to study author Matthias Tschöp, scientific director of the Helmholtz Diabetes Center in Munich, the pace of research on engineered peptides for dual-agonist incretin-based therapy has picked up in recent years. Tschöp and his collaborator Richard DiMarchi, a chemist at the University of Indiana in Bloomington, have worked previously on a GLP-1 and glucagon receptor co-agonist, in collaboration with New Jersey–based Merck, and a GLP-1 and estrogen receptor co-agonist, the latter of which showed potential for reversing the metabolic syndrome in rodents[2].

Other researchers are in hot pursuit of similar drugs. Scientists at Amylin Pharmaceuticals, which was acquired last year by New York's Bristol-Myers Squibb, are working on peptide hybrids made of an analog of Byetta linked to davalintide, which mimics amylin, a hormone released from pancreatic beta cells that helps regulate blood glucose levels after a meal[3]. "The exendin-amylin mimetic peptide hybrids . . . improve glucose tolerance and reduce HbA1c levels in diabetic rodents, coupled with body weight loss that is greater than that achieved by the parent peptides," says Soumitra Ghosh, senior director of research programs and collaborations at Amylin.

Researchers at the University of Copenhagen and the University of Alberta, in Canada, in collaboration with Denmark's Zealand Pharma and Germany's Boehringer Ingelheim, are working on a single molecule that mimics the gut hormone oxyntmodulin, an endogenous peptide hormone with dual GLP-1 and glucagon receptor agonist activity[4]. The team is in competition with Merck, which has explored oxyntmodulin mimetics, including one called DualAg[5].

Some teams are even looking into triple-receptor agonists. Nigel Irwin, a pharmacologist at the Diabetes Research Group at the University of Ulster in Ireland, works with a group focused on preclinical drug discovery of novel peptides for treating metabolic disease and obesity. Irwin's team published results in late October showing that a hybrid triple agonist, combining the effects of GLP-1, GIP and glucagon, decreased body weight and significantly improved glucose tolerance and insulin sensitivity in mice fed high-fat diets, as compared to conventional antidiabetic agents[6]. "We also believe that concurrent activation of three receptors will minimize any potential side effects that can occur through over stimulation of a single regulatory peptide receptor," Irwin explains.

Veronica Hackethal

Corrected after print 7 January 2014.

1. Finan, B. *et al. Sci. Transl. Med.* **5**, 209ra151 (2013).
2. Finan, B. *et al. Nat. Med.* **18**, 1847–1856 (2012).
3. Tan, T.M. *et al. Diabetes* **62**, 1131–1138 (2013).
4. Axelsen, L.N. *et al. Br. J. Pharmacol.* **165**, 2736–2748 (2012).
5. Pocai, A. *et al. Diabetes* **58**, 2258–2266 (2009).
6. Gault, V.A., Bhat, V.K., Irwin, N. & Flatt, P.R. *J. Biol. Chem.* doi:10.1074/jbc.M113.512046 (2013).

Correction

The December 2013 news story "Drugs with dual-hormone action gain attention in diabetes field" (*Nat. Med.* **19**, 1549, 2013) incorrectly stated that Sanofi withdrew its US application for the diabetes drug lixisenatide owing to concerns over cardiovascular safety. As Sanofi announced in September, the application was actually withdrawn to avoid public disclosure of early interim data that could potentially compromise the integrity of an ongoing clinical trial. The error has been corrected in the HTML and PDF versions of the article.