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Drug discovery and development for metabolic diseases

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This Drug Discovery and Development for Metabolic Diseases meeting (IBC, 6–7 October 2003, Copenhagen, Denmark) focused mainly on obesity and diabetes, and provided a good overview of current developments in the obesity and diabetes drugs pipeline. Highlights included updates on new glucagon-like peptide-1 (GLP-1) derivatives, cannabinoid receptor-1 antagonists and the discovery of subtype thyroxine T3 receptor-specific analogs.

Stating the problem

Many speakers opened their talks with the gloomy statistics of the widening obesity epidemic, a disease that is characterized by a body mass index (BMI) of >30 kg/m^2. The number of people with morbid obesity (BMI>40), almost unheard of thirty years ago, has now reached >650 000 in the UK alone (John Wilding, University Hospital Liverpool; http://www.liv.ac.uk). Even among children, type II diabetes is now about as common as type I. Obesity complications include cancer, sleep apnea, depression, myocardial infarction, peripheral vascular disease, hypertension and, most commonly, type II diabetes. Part of the problem is that, from a BMI of 25 onwards, the risk for developing diabetes increases exponentially with an increasing BMI (which itself depends only linearly on weight), and that so many people today are becoming obese.

The pipeline

GLP-1 analogs and associated targets

GLP-1 is a peptide hormone that stimulates the secretion of insulin. One problem is that it is rapidly hydrolyzed by dipeptidyl peptidase IV (DPP-IV), a peptidase that circulates in blood plasma, and because of this, GLP-1 has an extremely short plasma half-life (1–2 minutes). Jens Juul Holst (University of Copenhagen; http://www.ku.dk/english) gave an excellent overview on the state-of-the-art in this area. An important proof-of-principle study [1] had shown that continuous infusion of GLP-1 in type II diabetic patients reduced plasma glucose and also resulted in a 2 kg weight loss. Therefore, the challenge is now to find a GLP-1 analogue that has better bioavailability. One of these is Exenatide/Exendin-4 from Amylin (http://www.amylin.com; the first part of a Phase III trial was recently finished). Twice-daily injection in patients improved plasma glucose levels, but also significantly reduced body weight by 3.4 kg over 24 weeks.

The second GLP-1 derivative is Albugon from Human Genome Sciences (http://www.hgsi.com), which is a fusion between GLP-1 (with a mutation that increases resistance against DDP-IV) and albumin. It has an impressive half-life of three days in monkeys.

Then there is DAC:GLP1 (CJC-1131) (ConjuChem; http://www.conjuchem.com), which is GLP-1 with an 'unnatural' D-alanine stereoisomer at position 8, and a linker with a chemically reactive group, so that the compound covalently binds albumin after injection. The half-life of DAC:GLP1 in humans is an impressive 10–12 days, and it has shown significant glucose-lowering effects up to six days after injection.

Lotte Jerre Knudsen (Novo Nordisk; http://www.novonordisk.com) presented NN2211 (Liraglutide), which is $GLP_{7\text{-}37}$ but with a C16-fatty acid tail attached to amino acid 26, and a C-terminal mutation. The 'tail' decreases the GLP-1 activity a little but, more importantly, the new GLP self-associates and binds to plasma albumin, resulting in a plasma half-life of over 10 h. Furthermore, the compound inhibited cytokine-mediated apoptosis of pancreatic β cells, and is currently in late phase II trials and is intended for once-daily injection.

David Holmes (Novartis; http://www.novartis.com) presented recent data on Novartis' DPP-IV inhibitor LAF237, which produced significant reduction in plasma glucose levels in a four week clinical study, on the basis of which Novartis intends to move into Phase III.

Cannabinoid receptor 1 antagonists

The cannabinoid receptor 1 is a promising target for antagonists and the treatment of obesity, with Sanofi (http://www.sanofi-synthelabous.com) leading the pack with a Phase III trial of SR141716 (Rimonabant) and whose results are eagerly awaited. Shawn Black (Pfizer; http://www.pfizer.com) described the development of assays with AM-251, a compound that is related to the Sanofi drug candidate. One of the effects of D9-THC (tetrahydrocannaboid), which is the active ingredient of marijuana and a cannabinoid receptor 1 and 2 agonist,

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is increased food intake, and Black's animal models confirmed that the antagonist has good efficacy in preventing obesity.

New targets

STADS: selective thyroid hormone agonists for treatment of dyslipidemia
Anders Berkenstam (Karo Bio AB; http://www.karobio.com) outlined the rationale for STADs. Thyroid hormone T3 lowers cholesterol and triglycerides, increases metabolic rate and induces weight loss, but it is not a popular drug because it also causes tachycardia and raises the metabolic rate to dangerous levels. Fortunately the 'good' effects are mediated by the TR-β receptor, whereas the 'bad' effects are mediated by the TR-α receptor. Now, three exciting papers this summer have demonstrated that it is possible to generate receptor subtype-specific agonists. KB-141 has only tenfold selectivity between the two TR receptors yet lowers cholesterol by half in monkeys without changing the heart rate. Berkenstam mentioned that the more recent compound KB74660 blocks the TR-β receptor at 35 nM with 15-fold selectivity over TR-α. TR-β–KB74660 co-crystals are now being analyzed to improve the agonists.

Peptide hormones PYY and oxyntomodulin

Peptide YY (PYY) is secreted in the intestinal tract following meals. Interestingly, obese patients have significantly lower plasma levels of endogenous PYY. Following tests in animals, a single PYY_{3-36} administration strongly reduced food consumption in human volunteers (33% over 24 h). Therefore, PYY appears to be an exciting drug candidate. A second protein, the glucagon derivative oxyntomodulin, reduced food intake in human volunteers as well, but unlike PYY, high (non-physiological) doses were required, and the effect was short-lived.

DG70 serine/threonine kinase inhibitors
Cord Dohrmann (DeveloGen AG; http://www.develogen.de) described how analyzing the triglyceride:glycogen ratios in >2000 different *Drosophila* knockouts had allowed him to identify an undisclosed serine/threonine kinase whose mammalian ortholog, DG70, might be a target for obesity. Mice that overexpress the gene eat 30% more than normal, are, on average, 30% overweight and suffer from insulin resistance and hyperglycemia. Knockout mice, by contrast, have reduced body weight. DevGen collaborated with EvoTec OAI to screen ~100 000 compounds against the kinase. The compound EDJ100015 was shown to inhibit fat accumulation in murine and human adipocytes at 25 μM.

Kir6.2/SUR2 K_{ATP} channel openers
Richard Carr (Novo Nordisk) addressed the problem of exhaustion of pancreatic insulin-producing β islet cells, a (another!) poorly understood process in type II diabetes. He proposed that Kir6.2/SUR1 K_{ATP} channel openers antagonize this process. His company's compound NN414 has, unlike a previously tested diazoxide, selectivity over heart and other muscular Kir6.2/SUR2 K_{ATP} channels that are of the A/B type. NN414 prevents apoptosis in human islet cells. He used a desert rat (*Psammomys obesus*) strain as an *in vivo* DIO (diet-induced obesity) model. These animals live off the desert in their natural habitat, and develop obesity when simply given standard rat food. This would seem an improvement over Marcus Schindler's rats at Boehringer Ingelheim, which become obese when fed on a diet of Mars bars. In as yet unpublished work, NN414 completely normalized plasma glucose and hemoglobin subtype A1c in the desert rats.

PTP1B inhibitors
Rob Hooft (Serono; http://www.serono.com) reviewed the target rationale for protein tyrosine phosphatase 1B (PTP1B), a tyrosine phosphatase that dephosphorylates and antagonizes the insulin receptor. Serono PTP1B inhibitors show dose-dependent oral activity in three animal models (postprandial hyperglycemia, fasting plasma glucose levels and an oral glucose tolerance test). In addition, several novel chemical series of Serono PTP1B inhibitors were disclosed for the first time. In mid-September, ISIS announced that its PTP1B antisense drug ISIS-113715 had shown efficacy in a Phase I trial, and that it was moving the compound into Phase II. This success validates the target for the first time in humans and will certainly stimulate the search for orally available PTP1B inhibitors as well.

Glucocorticoid receptor (GR) antagonists
Peer Jacobsen (Abbott; http://abbott.com) discussed glucocorticoid receptor (GR) antagonists as potential therapies for diabetes, based on observations that glucocorticoids stimulate hepatic gluconeogenesis. It had been noted that RU486 activates both the progesterone and glucocorticoid receptors. Therefore, Abbott synthesized A-348441, which consists of RU468 linked to cholic acid, which targets the liver. The compound lowers plasma glucose in ob/ob mice at 30–100 mg kg^{-1} and the compound has ~2.5-fold increased selectivity for GR over the progesterone receptor. However, concerns remain regarding the progesterone-like activity of the compound, which could ultimately limit its clinical use.

Future prospects and challenges

Drugs can act centrally (in the brain) or peripherally (e.g. target uncoupling protein-3). Centrally acting drugs might present risks, and obesity has been characterized 'as difficult to cure as cancer'. In spite of this, there are

now many studies that show that drugs can, in fact, alter human eating behavior and safely produce weight loss. As pointed out by Caroline Small (Imperial College, London; http://www.ic.ac.uk), many centrally acting drugs bind receptors in the arcuate nucleus, a part of the hypothalamus in the brain that is well conserved throughout evolution, and that plays a key role in feeding behavior. This arcuate nucleus conveniently has an incomplete blood–brain barrier, which greatly facilitates development of drugs that target this sensor.

Reference

1 Zander, M. *et al.* (2002) Additive glucose-lowering effects of glucagon-like peptide-1 and metformin in type 2 diabetes. *Diabetes Care* 359, 824–830

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