New drugs and developments in the research into diabetes treatment

In this science article, Mark Magas takes a look at current research and development in the treatment of diabetes, including ways of manufacturing and delivering insulin.

Diabetes mellitus and the various drugs used to treat it are often the subject of media coverage, perhaps notably and most recently with the withdrawal of rosiglitazone (PJ, 2 October 2010, p362). The loss of glucose control caused by diabetes is responsible for the deaths of millions of people worldwide each year and reduces the quality of life for many more. In the long term, diabetes causes secondary damage to a number of body organs, most notably the heart, which is the greatest cause of mortality.

As a result, the search continues for new drugs, as well as ways to manufacture and deliver insulin. This article explores some of the developments that are emerging onto the horizon.

SGLT2 inhibitors

Glucose is a valuable resource to the body and the kidney is designed to prevent it from being excreted. Most glucose reabsorption occurs by facilitated diffusion in the proximal tubules of the kidney via a carrier molecule called the sodium-glucose co-transporter-2 (SGLT2). Inhibiting this transporter would cause most of the glucose to be excreted instead of being reabsorbed and this would ultimately lower blood glucose levels.

This makes SGLT2 inhibitors a tantalising prospect since their effectiveness would be independent of insulin production or resistance; making SGLT2 inhibitors the first antidiabetic drugs that did not rely on the ability of a failing pancreas to produce insulin or insulin-resistant muscle cells to take in more glucose.

Dapagliflozin is an SGLT2 inhibitor that is currently undergoing phase III trials. Drugs like dapagliflozin, with a C-arylglucoside structure, are the most favoured since they have shown selectivity for the SGLT2 carrier molecule, are more potent, and resist hydrolysis, which makes them more orally stable.

Trials with dapagliflozin have shown that it is able to lower blood glucose and HbA1c successfully, but only modestly. This probably means that, if dapagliflozin becomes a licensed medicine, it will most likely be used as an add-on therapy. That said, any glucose lowering would be independent of failing insulin-related pathophysiological systems. Importantly, the drug also causes a decrease in body weight and waist circumference, demonstrating that it has the potential to provide additional benefits beyond simply lowering blood glucose.

Like any drug, SGLT2 inhibitors would not be without potential adverse effects. Any drug that acts as an SGLT2 inhibitor would have to be selective in its action. Non-selective inhibition of another subtype, the sodium-glucose co-transporter-1, would result in glucose-galactose malabsorption, causing dramatic water retention in the bowel leading to fatal diarrhoea and dehydration.

Since glucose would be present in above normal quantities in the urine, the possibility of an increased incidence of bacterial urine infections has been considered. But, since some people do not possess the gene that would allow them to make SGLT2s and these people do not get more urine infections than other members of the population, this seems unlikely.

However, it has recently come to light that dapagliflozin increases genital infections, such as candidiasis, by 3–8 per cent. This may be related to inadvertently creating favourable conditions for fungal growth, where a glucose solution is constantly coating the genital mucosa.

Normally, sodium travels into the endothelial cells along with glucose. When this mechanism is blocked, sodium is retained in the lumen along with the glucose. This might seem to suggest that sodium would become depleted from the body when being treated with SGLT2 inhibitors. Thankfully, this is not the case because there are other mechanisms for sodium reabsorption. Dapagliflozin seems to have no effect on blood sodium levels but, consequently, also has no effect on raised blood pressure, which is often related to the high sodium intake of a poor diet.

One area that needs to be examined is the effectiveness of SGLT2 inhibitors in those over 70 years of age. Although a small number of patients in one of the trials were 70–77 years of age, these patients were not grouped together in the study. As we age, the number of nephrons in the kidneys declines by up to 50 per cent and fewer nephrons may mean fewer SGLT2s. This may mean that SGLT2 inhibitors may differ in their effectiveness or adverse effects in this age group.

There are other possibilities. Developing irreversible SGLT2 inhibitors might result in a drug with greater blood glucose lowering
“Some companies are using genetic engineering to attach proteins to oil bodies in plant seeds and then developing low cost ways of extracting the protein from the seeds”

Potential than dapagliflozin and molecules are in the pipeline that alter gene expression, halting cellular production of SGLT2s by renal endothelial cells. 1

Glucokinase activators
Glucokinase has different roles in different cells. In muscle cells, glucokinase phosphorylates glucose to form glucose-6-phosphate for use as an energy source while, in the liver, it increases glycogen synthesis and reduces glycogenolysis. Finally, in the β-cells of the pancreas, glucokinase causes insulin release. 2

It is easy to see how a drug that activated glucokinase in any of these cells would prove useful in treating type-2 diabetes because it would increase glucose uptake in muscle cells, increase the amount of glucose being converted to glycogen and stimulate insulin release.

What makes this target appealing is that glucokinase is an enzyme that is not limited by any negative feedback mechanisms, meaning the action and activation of glucokinase is intrinsically linked to glucose levels alone. This effectively establishes glucokinase as an accurate glucose-sensing mechanism in the pancreas, which could be exploited by a glucokinase activator (GKA).

In order to fulfill its role, glucokinase exists in two forms: active and inactive. GKAs are thought to bind to an allosteric site on glucokinase (ie, a site other than, and separate from, the active site). This stabilises the glucokinase in its active form, lowering the concentration of glucose required for activation. 3 This does also mean that GKAs must be developed carefully so that they do not lock glucokinase permanently into its active form. If this happened, the glucose-sensing abilities of glucokinase would be lost, and severe and lethal hypoglycaemia may result. 4

Although a number of GKAs have reached trials, quite a few, such as piragliatin, have been withdrawn or discontinued at phase 1 or 2 trials. There is also some speculation that some GKAs may have a high affinity for the protein from the seeds and then developing low-cost ways of extracting the protein from the seeds. A Canadian-based company, SemBioSys, is developing a transgenic form of safflower to produce biosimilar human insulin. This method uses Agrobacterium to insert the DNA that carries the information necessary for the safflower to produce insulin into the plant genome, following much the same process as for genetically modified wheat, soybean and rapeseed. Once the safflower produces seeds, the oil bodies containing the insulin are extracted by a simple grinding, centrifugation and washing process. 5

SemiBioSys claims that, if its product and processes come to market, manufacturing insulin will become a cheaper and more productive venture than current bacterial methods. 6 Since the worldwide demand for insulin is increasing, this would seem to be a profitable and necessary prospect. However, genetically modified crops are very much at the forefront of environmental issues so any ventures using genetically modified field-grown insulin-producing safflower would have to address control and containment issues carefully.

New delivery methods
The ultimate goal of needle-free insulin has, as yet, proved elusive, with the most significant advance being improvement of insulin pumps. The greater flexibility that a pump offers has to be weighed against the increased cost of this delivery method and the danger of pump malfunction.

Inhaled insulin has been marketed, but the last product licensed in the UK, Exubera, was discontinued because it failed to gain wide acceptance among doctors and patients. This was possibly because it did not necessarily prevent the need for injections, the delivery system was bulky and insulin delivery could be variable in some situations alongside complexity of calculating the right dose.

Despite this, the concept of inhaled insulin is still being pursued and one product, Afrezza, is probably just one or two years away from being approved by the US Food and Drug Administration. Afrezza has been developed to reduce irritation to the lungs and provide better control over spikes in blood glucose after meals. Although this may not eliminate the need for injections, Afrezza may succeed where Exubera failed because, alongside a much smaller, neater delivery system, Afrezza uses an insulin monomer rather than a hexamer, giving it a short and possibly more predictable time to peak insulin levels. 7

Another approach has been to develop a system that delivers insulin through the skin without the use of a needle. InsuJet is now being used in The Netherlands and delivers a dose of insulin through the skin using a jet stream that is thinner than the bore of any needle, which has a number of benefits aside from appealing to the needle-phobic. Administration causes a smaller diameter trauma to the skin and the skin is damaged only once, on the way in, and not on the way out as it would be when using a needle. In addition, the distribution of the insulin within the subcutaneous layer is much greater, which means that absorption is likely to be quicker and possibly more predictable since the insulin comes into contact with a larger surface area of well perfused tissue. 8

Conclusion
These developments are all enticing, not least to those who cannot access appropriate treatment for their diabetes because of cost or those wishing to avoid the need for incessant painful injections. On the other hand, those opposed to the use of genetically modified crops will watch with concern, as will those charged with balancing tight drug budgets that might not stretch to new drugs or delivery methods.

The certainty is that, for these innovations to move closer to those with diabetes than the horizon, they must improve lives, reduce costs or both.

References
3. Efficacy and safety of dapagliflozin, added to therapy of patients with type 2 diabetes with inadequate glycaemic control in insulin. Available at: clinicaltrials.gov (accessed 18 February 2011).