Innovative glucose therapies in diabetes care

Neil Munro

ARTICLE POINTS

1 Further understanding of the fundamental concepts in the pathophysiology of diabetes remains crucial to the development of improved therapies.

2 Therapeutic developments have been made in various areas, including oral glucose-lowering agents, new insulins, continuous subcutaneous insulin infusion, continuous subcutaneous glucose monitoring, inhaled insulin and islet cell transplantation.

3 New approaches in the near future will focus on incretin mimetics, amylinomimetics and therapies involving the peroxisome proliferator-activated receptor.

4 Translating theoretical therapeutic concepts into real clinical gain remains difficult.

KEY WORDS

- Glucose
- Insulin
- Transplantation
- Incretins
- Hormones

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Introduction

In the face of a diabetes epidemic worldwide, researchers continue to seek new treatments for this complex condition. This article highlights some of the key therapeutic developments in improving glycaemic control – including glucose-lowering agents, new insulins, continuous subcutaneous insulin infusion, and inhaled insulins. In addition, it outlines new approaches to glucose-lowering that are in the early stages of development and may become important in the near future.

Deeper understanding of fundamental concepts in the pathophysiology of diabetes remains crucial to the development of improved therapies. Much interest continues to be shown by clinicians and pharmaceutical companies alike. Whilst it is impossible to comprehensively cover all therapeutic developments in glucose lowering, this article describes some of those that currently impact on diabetes care as well as exploring interesting developments for the future.

Oral glucose-lowering agents

UKPDS (1998) established metformin as the first line agent of choice in nearly all people with type 2 diabetes. The benefit to overweight patients was particularly evident. Longer-acting preparations should be available in the near future.

Ward and Law (2003) proposed that the taking of a 'polypill' (statin, thiazide diuretic, β-blocking agent, angiotensin converting enzyme inhibitor, folic acid and aspirin) would reduce cardiovascular disease by more than 80% in everyone with existing cardiovascular disease above the age of 55. For people with type 2 diabetes additional drugs will be required to counter the deleterious effects of their condition, including anti-obesity agents, drugs to treat neuropathies, drugs to help erectile dysfunction, and anti-depressant therapies. With compliance becoming a very real problem, a number of combination products are available, or being developed at this time:

- metformin and glibenclamide
- metformin and glipizide
- metformin and rosiglitazone
- metformin and pioglitazone
- rosiglitazone and glimepiride.

The thiazolidinediones have become increasingly established as appropriate interventions early in type 2 diabetes. Their role in prevention of development of type 2 diabetes in those with impaired glucose tolerance is currently being studied. Adjuvant effects of blood pressure lowering have been reported (Bennett et al, 2004) and could potentially provide a useful additional means of achieving treatment targets recommended by the British Hypertension Society (Williams et al, 2004): <130/80 mmHg (<140/80 mmHg audit standard).

Newer insulins

The introduction of newer synthetic analogues of insulin, such as insulin glargine, has enabled many people with diabetes to achieve reasonable glycaemic control with reduced risk of hypoglycaemia (Yki-Jarvinen et al, 2000). Glargine is a very long-acting insulin analogue with a 'peakless' profile (Owens et al, 2001). This complements the earlier availability of reliably absorbed rapid-acting insulin analogues, such as insulin lispro and insulin aspart, allowing users more flexibility in timing of injections and meals (Vajo and Duckworth, 2000).

Another long-acting insulin analogue, insulin detemir, is due to be launched shortly. It is claimed that insulin detemir reduces the risk of nocturnal hypoglycaemic episodes by 34% compared with NPH (Standl, 2002). Preliminary work has also demonstrated no weight gain with detemir as opposed to NPH in 6 and 12 month studies (Vague et al, 2003). Given once or twice daily, detemir offers an alternative long-acting analogue to glargine – already well established in clinical practice.

Continuous subcutaneous insulin infusion (CSII)

According to the National Institute for Clinical Excellence (NICE, 2003): 'continuous subcutaneous insulin infusion (CSII or "insulin pump therapy") is recommended as an option for people with type 1 diabetes provided that:

- multiple-dose insulin (MDI) therapy (including, where appropriate, the use of insulin glargine) has failed; and
- those receiving the treatment have the commitment and competence to use the therapy effectively (*Figure 1*).

People for whom MDI therapy has failed are considered to be those for whom it has been impossible to maintain a HbA_{1c} level no greater than 7.5% (or 6.5% in the presence of microalbuminuria or adverse features of the metabolic syndrome) without disabling hypoglycaemia occurring, despite a high level of self care of their diabetes'.

'Disabling hypoglycaemia', for the purposes of this guidance, means the repeated and unpredictable occurrence of hypoglycaemia requiring third-party assistance that results in continuing anxiety about recurrence and has a significant adverse effect on quality of life.

NICE guidelines further stipulate that 'CSII therapy should be initiated only by a trained specialist team, which should normally comprise a physician with a specialist interest in insulin pump therapy, a diabetes specialist nurse and a dietitian. All those starting CSII therapy should be provided with specific training and ongoing support from a specialist team'.

Availability of pumps is dependent on local arrangements both at acute trust and primary care trust level.

Home glucose monitoring

Consensus guidelines produced by a multidisciplinary group on blood glucose self-monitoring in type 1 and type 2 diabetes have recently been published (Owens et al, 2004).

Continuous subcutaneous glucose monitoring

Besides self-monitoring, a clearer picture of glucose profiles over a prolonged period of time can be obtained. Continuous subcutaneous glucose monitoring utilising the Minimed device is being increasingly used in research and clinical practice (Cheyne et al, 2002). Recordings taken over a 72-hour period can provide useful insight into daily fluctuations in blood glucose levels (Gross et al, 2000).

Islet cell transplantation

In June 2000, researchers in Edmonton published preliminary findings of their islet cell transplantation programme (Shapiro et al, 2000). Seven patients with type 1 diabetes and a history of severe hypoglycaemia and metabolic instability underwent islet cell transplantation. In addition they received glucocorticoid-free immunosuppression with sirolimus, tacrolimus and daclisumab. Islet cells were obtained from donor pancreases and transplanted by percutaneous transhepatic portal embolisation.

All trial subjects maintained insulin

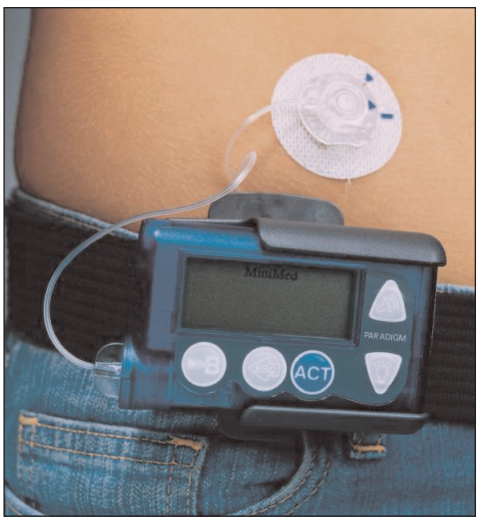

Figure 1. CSII therapy is an option for patients as long as multiple-dose insulin therapy has failed and they have the ability and commitment to use it actively.

PAGE POINTS

1 The long-acting insulin analogue glargine complements previously available rapid-acting analogues such as insulin lispro and insulin aspart.

2 Continuous subcutaneous insulin infusion therapy is an option for patients in whom multiple-dose insulin therapy has failed and who have the ability and commitment to use it effectively.

3 A clear picture of glucose profiles over a prolonged period of time can be obtained with continuous subcutaneous glucose monitoring.

PAGE POINTS

1 Remarkable progress has occurred in the field of islet cell transplantation during the last three years, with dramatic improvements in outcomes after clinical operations.

2 Inhalation of insulin has attracted interest over a number of years. Several inhaled insulin products are currently being developed.

3 The phenomenon whereby glucose taken orally stimulates insulin secretion much more than when it is infused intravenously so as to result in similar blood glucose concentrations is known as the 'incretin effect'.

4 Incretin mimetics is one therapeutic area that will be developed in the near future.

5 As potential therapeutic agents, incretin hormones (such as GLP-1 and GIP) show considerable promise.

independence (mean duration 11.9 months) at the time this work was published. Since the Edmonton transplantation research trial began, 48 patients have undergone 92 islet infusions in Canada. Remarkable progress has been made in the last three years, with dramatic improvements in outcomes after clinical islet transplantation (Shapiro et al, 2003).

In January 2003 it was reported that 84% of patients remained insulin independent one year post transplantation and 89% of patients were producing insulin three years into the programme. Previously, less than 10% of transplants had been successful. Over 200 patients have received islet transplants worldwide using the 'Edmonton' protocol or variations thereof.

Subsequent work using stem cell technology is actively being undertaken by researchers in several centres in the hope of overcoming the technological limitations of harvesting living islet cells and extending transplant programmes more widely.

Inhaled insulins

Inhalation of insulin has attracted interest over a number of years. Several inhaled insulin products are currently being developed. These include:

- Aerodose inhaler (Aerogen Inc, CA, USA): liquid insulin delivered by a device the size of a mobile phone;
- Exubera (Pfizer and Aventis in collaboration with Nektar Therapeutics): phase 3 development is complete. Additional studies are being undertaken to determine long-term pulmonary safety profile;
- Qdose (MicroDose Technologies Inc and Quadrant Drug Delivery Ltd, Nottingham, UK): in Phase I development;
- Rapidmist (Generex Biotechnology Corporation): an oral spray whereby insulin is delivered by pressurised inhaler and absorbed through the buccal mucosa.

There are several questions to be answered in connection with inhaled insulins, including:

- whether it is possible to administer accurate dosages;
- whether these devices can be used in all age groups and in those with physical disabilities or impaired lung function;
- concerns about the local pulmonary effects of high doses of inhaled insulin required to achieve normoglycaemia.

Developments in the near future

Incretin mimetics

Glucose taken orally stimulates insulin secretion much more than when it is infused intravenously so as to result in similar blood glucose concentrations (Visboll and Hollst, 2004). Known as the 'incretin effect', ingestion of carbohydrate results in the release of substances from the intestinal mucosa that enhance insulin secretion beyond that attributable solely to absorbed glucose (McIntyre and Holdsworth, 1965).

Two intestinal insulin-stimulating hormones, glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP) are thought to be responsible for 50–70% of the insulin response to glucose. In type 2 diabetes, secretion of GIP is normal but its action is impaired, whereas secretion of GLP-1 is reduced. Treatment with GLP-1 or its analogues produces near-normal glycaemia and may compensate for impaired secretion of endogenous GLP-1 and the impaired action of GIP.

As potential therapeutic agents incretin hormones show considerable promise. Besides its glucose-normalising effect (which is dependent on substrate presence in the intestine), GLP-1 has a number of other actions (*Figure* 2), including:

- insulin secretion (potentiates glucose induced insulin; secretion enhances all steps of insulin biosynthesis; up regulates insulin gene expression; up regulates gene expression essential for β-cell function (glucokinase, glucose transporter 2 [GLUT 2], etc); mitotic for β-cells; promotes differentiation of duct progenitor cells to β-cells and inhibits apoptosis of β-cells)
- inhibition of glucagon secretion
- inhibition of gastrointestinal secretion and motility
- inhibition of appetite and food intake.

Initial agents were very short-acting. The

incretin hormones are rapidly metabolised by dipeptidyl-peptidase IV (DPP-IV).

Currently several DPP-IV resistant and long-acting analogues of GLP-1 are being developed for clinical practice (Hollst, 2002). Early results over a 5-month period of treatment with the GLP-1 receptor activator, exendin-4, have included improvements in blood glucose concentrations, HbA_{1c} and weight loss (Baron et al, 2003). Delivered by a subcutaneous injection, it remains to be seen how this product may fare in the clinical arena.

Amylinomimetics

Pramlintide is a synthetic version of the human hormone, amylin. It is the first member of a new class of therapeutic medications known as amylinomimetic agents, or amylin receptor agonists. Amylinomimetic agents mimic the actions of the hormone amylin and have demonstrated activity in blood glucose regulation. Amylin is secreted from β-cells. In normal physiology, amylin complements the actions of insulin, and these two hormones work with glucagon to maintain normal glucose concentrations. Along with insulin, amylin concentrations normally increase and glucagon levels decrease after meals.

In people with type 1 diabetes, and those with type 2 diabetes who are insulin requiring, insulin and amylin concentrations are extremely low or undetectable and do not increase after meals, and conversely, glucagon levels tend to rise after meals. These hormonal abnormalities contribute significantly to the disturbance of glucose metabolism in the context of a meal. Addition of pramlintide has been shown to lower HbA_{1c} without weight gain in this group of patients. It is currently being marketed in the US.

PPARα and PPARγ

Thiazolidinediones activate peroxisome proliferator-activated receptor-γ (PPARγ). This specific nuclear hormone receptor is found mainly in adipose tissue but also in vascular smooth muscle, skeletal muscle, the heart and the kidney. The activated PPARγ complex alters the promoter region of specific genes regulating glucose and lipid metabolism. This mirrors the effect of insulin on adipocytes, i.e. enhanced expression of genes encoding glucokinase and lipoprotein lipase. Although increased expression of insulin sensitising genes is thought to be the primary mechanism of action, the thiazolidinediones are also believed to exert their action by lowering triglycerides and NFAs (non-fatty acids), increasing hepatic glucose disposal, increasing GLUT 4 (glucose transporter 4) production, correcting TNFα (tumour necrosis factor alpha) overproduction and altering leptin gene expression. Much recent interest has been shown in combining action of PPARγ with PPARα, which have been shown to reduce triglycerides. Fibrates are activators of PPARα.

Future possibilities

Potential agents currently being examined include the trace elements vanudin, molybdate, tungstate and selenium. Greater understanding of the insulin signalling chain has led to the development of non-peptide insulin receptor activators and sensitisers (early insulin signalling enhancers). The plant extract pinitol (from *Bougainvillea*) has been found to lower plasma glucose and is being investigated. Adinopectin acts on the vascular wall to decrease atherosclerosis. It reduces inflammatory endothelial markers including TNFα, free fatty acids and oxidative stress,

PAGE POINTS

1 Besides its glucose normalising effect, GLP-1 stimulates insulin secretion; inhibits glucagon secretion, gastrointestinal secretion and motility; and inhibits appetite.

2 Currently several DPP-IV resistant and long-acting analogues of GLP-1 are being developed for clinical practice.

3 Pramlintide is a synthetic version of the human hormone, amylin. It is the first member of a new class of therapeutic medications known as amylinomimetic agents.

4 Much recent interest has been shown in combining action of PPARα with PPARγ, which have been shown to reduce triglycerides.

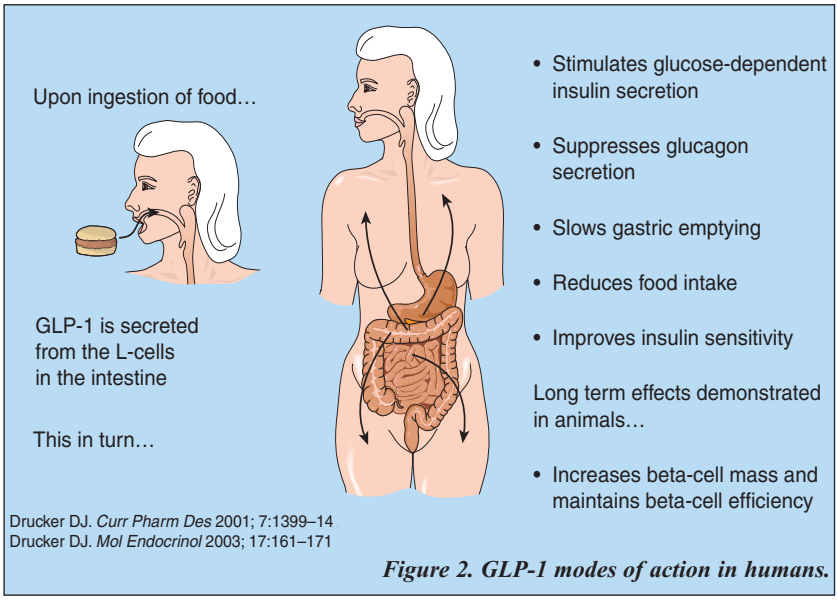

Figure 2. GLP-1 modes of action in humans.

decreases hepatic glucose production and increases glucose uptake in muscle. Other agents attracting attention include glucagon receptor antagonists, and inhibitors of glycogen phophorylation, gluconeogenesis and glycogen 6 phosphatase (G6P).

Conclusion

There are many potential areas of development in the management of glucose control in diabetes. Translating theoretical therapeutic concepts into real clinical gain, however, remains difficult. Nevertheless the need to improve our understanding of pathophysiological processes that underpin metabolic disturbances seen in diabetes remains central to achieving a long term solution to this most disabling chronic disease. ■

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