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Review
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Future glucose-lowering drugs for type 2 diabetes

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Summary

The multivariable and progressive natural history of type 2 diabetes limits the effectiveness of available glucose-lowering drugs. Constraints imposed by comorbidities (notably cardiovascular disease and renal impairment) and the need to avoid hypoglycaemia, weight gain, and drug interactions further complicate the treatment process. These challenges have prompted the development of new formulations and delivery methods for existing drugs alongside research into novel pharmacological entities. Advances in incretin-based therapies include a miniature implantable osmotic pump to give continuous delivery of a glucagon-like peptide-1 receptor agonist for 6–12 months and once-weekly tablets of dipeptidyl peptidase-4 inhibitors. Hybrid molecules that combine the properties of selected incretins and other peptides are at early stages of development, and proof of concept has been shown for small non-peptide molecules to activate glucagon-like peptide-1 receptors. Additional sodium-glucose co-transporter inhibitors are progressing in development as well as possible new insulin-releasing biological agents and small-molecule inhibitors of glucagon action. Adiponectin receptor agonists, selective peroxisome proliferator-activated receptor modulators, cellular glucocorticoid inhibitors, and analogues of fibroblast growth factor 21 are being considered as potential new approaches to glucose lowering. Compounds that can enhance insulin receptor and post-receptor signalling cascades or directly promote selected pathways of glucose metabolism have suggested opportunities for future treatments. However, pharmacological interventions that are able to restore normal β-cell function and β-cell mass, normalise insulin action, and fully correct glucose homoeostasis are a distant vision.

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Introduction

A wealth of evidence from prospective and retrospective clinical studies supports the premise that early, effective, and sustained glycaemic control defers the onset of diabetes and reduces the severity of associated complications.[1–3] However, more than a third of all patients with diabetes do not achieve or maintain an appropriate glycaemic target.[1,4] Although this situation is attributed partly to late diagnosis of diabetes, delayed introduction or insufficient escalation of treatment, or poor patient adherence, more efficacious and durable treatments are needed. Type 2 diabetes is usually the product of various genetic susceptibilities and environmental factors that interact to create a highly heterogeneous and progressive pathological changes against which existing treatments have substantial limitations.[5] About half of all patients with type 2 diabetes require combinations of two or more differently acting non-insulin glucose-lowering drugs and about a third of patients will require insulin.[6] Moreover, the complications and comorbidities (eg, cardiovascular disease and renal impairment) that typically accompany advanced states of insulin resistance and pancreatic β-cell dysfunction restrict the choice of available treatments.

This update of a previous narrative Review in *The Lancet* in 2011[7] uses the same literature search procedure to carry the review forward to June, 2015. Emphasis is given to clinical studies of agents that are advanced in development and preclinical experimentation that explores potential new therapeutic mechanisms for diabetes. The main sites of action of present and possible future glucose-lowering treatments are summarised in figure 1 and key features of the modes of action of potential future therapies are summarised in table 1.[8]

Pancreatic β-cell function

Overview

Interventions with lasting efficacy are needed to prevent and reverse the progressive reduction in pancreatic β-cell function and β-cell mass in patients with type 2 diabetes.[9] Compounds acting at the level of the β cell currently under investigation include the small molecule insulin releasers, glucokinase activators, fatty acid receptor agonists, and imeglimin.

Small molecule insulin releasers

In addition to established initiators of insulin secretion (sulfonylureas and meglitinides), many compounds are known to improve β-cell function in vitro. These small molecule insulin releasers include succinate esters, imidazolines, selective phosphodiesterase inhibitors, α-2 adrenergic antagonists, and agents that close Kir6.2 potassium channels or open membrane calcium channels. However, the in-vivo effects of most of these compounds are too generalised to specifically target β cells and few have progressed in development.[10]

Glucokinase activators

Activators of the glucose phosphorylating enzyme, glucokinase, increase both insulin secretion and hepatic glucose metabolism (figure 2). Phase 2 and phase 3 studies in patients with type 2 diabetes have shown modest glucose-lowering for 4–6 months, but efficacy quickly reduces thereafter.[11] With stimulation of insulin secretion at low glucose concentrations, glucokinase activators are prone to cause hypoglycaemia. However, glucokinase is regulated differently in the liver to the β cell, and attention is now focused on the development of liver-selective glucokinase activators. Accumulation of hepatic triglycerides often occurs during protracted

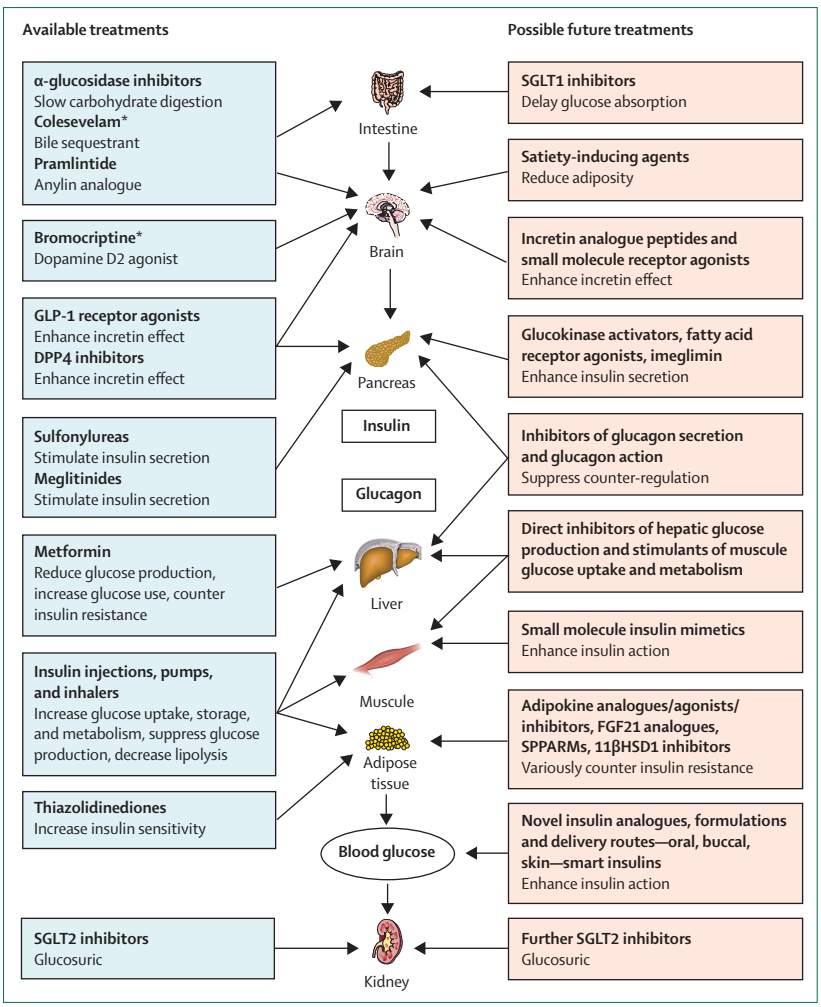

Figure 1: **Intervention sites for glucose-lowering, showing available treatments and possible new treatments**
GLP1=glucagon-like peptide-1. DPP4=dipeptidyl-peptidase-4. SGLT2=sodium-glucose co-transporter 2 (also known as SLC5A2). SGLT1=sodium-glucose co-transporter 1 (also known as SLC5A1). FGF21=fibroblast growth factor 21. SPPARM=selective peroxisome proliferator-activated receptor modulator. 11βHSD1=11β-hydroxysteroid dehydrogenase 1. *Not indicated for glucose-lowering in all countries.

glucokinase activation. This effect might be avoided with drugs that also enhance futile cycling in the liver, but long-term clinical efficacy remains to be established.[12,13]

Fatty acid receptor agonists

Several G-protein coupled receptors expressed by pancreatic β cells are activated by fatty acids leading to enhanced insulin secretion—eg, GPR40 (also known as FFAR1) and GPR119. As receptors (not transporters), they do not mediate cellular entry of their agonists so they do not invoke the detrimental effects of chronic excess fatty acids on the metabolism and survival of β cells.[9] GPR40 agonists increase insulin secretion by increasing cytosolic calcium. A promising GPR40 agonist (TAK-875) was discontinued because of hepatic side-effects, but other GPR40 agonists continue in development.[14]

GPR119 agonists activate adenylate cyclase, increasing cyclic adenosine monophosphate and potentiating nutrient-induced insulin secretion in a similar manner to glucagon-like peptide-1 (GLP1).[15] Both GPR40 and GPR119 are expressed by enteroendocrine pancreatic cells and other cells, K cells, L cells, and I cells, and synthetic agonists for these receptors can increase the secretion of glucose-dependent insulinotropic peptide (also known as gastric inhibitory polypeptide, GIP), GLP1, peptide YY (PYY), and cholecystokinin, potentially enhancing the incretin and satiety effects of these hormones. GPR40 and GPR119 receptors are also expressed by pancreatic α cells and agonists might increase glucagon secretion.[16]

Another long-chain fatty acid receptor, GPR120 (also known as FFAR4), expressed mainly by adipose tissue, promotes adipogenesis. Small molecule agonists of this receptor improve glucose homoeostasis by increasing insulin sensitivity and reducing ectopic fat in preclinical studies.[17]

Imeglimin

Imeglimin is a triazine derivative that enhances glucose-induced insulin secretion, especially the first phase, and improved glycaemic control during phase 2 studies in type 2 diabetes. It seems to change cellular energetics, in part through closure of mitochondrial permeability transition pores, which can also improve peripheral insulin sensitivity and reduce hepatic gluconeogenesis.[18]

Incretin-based therapies

Overview

Hormonal signals from the alimentary tract continue to provide important therapeutic templates for type 2 diabetes. The main incretin hormone, GLP1, has been successfully exploited in this respect by changing the molecule to avoid rapid inactivation by the enzyme dipeptidyl-peptidase-4 (DPP4) or by inhibiting DPP4.[4]

GLP1 receptor agonists

Injectable GLP1 receptor agonists (exenatide, liraglutide, lixisenatide, albiglutide, and dulaglutide) potentiate nutrient-induced insulin release, suppress excess glucagon secretion, delay gastric emptying, and exert satiety effects that assist with weight control. Although these agents have increased β-cell mass in animal studies,[19] this finding has yet to be clearly shown in human beings with type 2 diabetes. To avoid daily or weekly injections, a matchstick-sized subcutaneously implanted miniature osmotic pump has been developed for continuous delivery of up to 80 μg/day of exenatide. In an extended phase 2 study, implants delivering doses of 40 μg/day or more of this GLP1 receptor agonist for 48 weeks in patients with type 2 diabetes reduced HbA_{1c} (by 0·93–1·42%; 10–15 mmol/mol) from a baseline of about 8% (64 mmol/mol) and weight (by 3·0–4·2 kg) from a baseline of 93 kg. Initial dose-related nausea

	Mechanism of action	Glucose-lowering effect	Development status	Comments
Glucokinase activators	Increase glucokinase activity in pancreatic islets and liver	Increase insulin secretion and hepatic glucose uptake	Phase 3	Challenges of hypoglycaemia and durability
GPR40 (also known as FFAR1) and GPR119 agonists	Activates fatty acid receptors in pancreatic islets and gut	Increase insulin secretion and enteroendocrine L-cell incretin secretion	Phase 1–3	TAK-875 (GPR40 agonist) discontinued in phase 3
Imeglimin	Close mitochondrial transition pores	Increases insulin secretion and decreases gluconeogenesis	Phase 3	
Exenatide implantable osmotic pump	GLP1 receptor agonist	Mimics effects of GLP1	Phase 3	Active for 6–12 months
Oral and subcutaneous semaglutide	GLP1 receptor agonist	Mimic effects of GLP1	Phase 2–3	Oral drug has similar efficacy to subcutaneous injection
Non-peptide GLP1 receptor agonists	GLP1 receptor agonist	Mimic effects of GLP1	Preclinical	Proof of concept
Omarigliptin (once-weekly)	DPP4 inhibitor	Increase endogenous incretin action	Phase 3	Efficacy similar to sitagliptin
TGR5 (also known as GPBAR1) agonists	Stimulate bile acid receptors in ileum	Increase L-cell incretin secretion	Preclinical	Preliminary observations
Fixed-ratio combinations; GLP1 receptor agonists with insulin	GLP1 receptor agonist and basal insulin	Mimic effects of GLP1 and insulin at same time	Phase 3	Insulin degludec and liraglutide combination was recently approved and insulin glargine and lixisenatide combination is in development
Hybrid and chimeric designer peptides	Agonism or partial antagonism of selected peptides	Mimic effects of selected incretins and other peptides	Preclinical	Proof of concept
Glucagon receptor antagonists	Decrease glucagon action	Decrease hepatic glucose output	Preclinical to phase 2	Several drugs identified in preclinical studies, restricted clinical progression
Insulin receptor signalling potentiators	Prolong Tyr phosphorylation of insulin receptor B-subunit	Increase insulin action	Preclinical	Proof of concept—eg, PTP1B (also known as PTPN1) inhibitors and vanadium salts
SGLT1 and 2 inhibitors	Selectively decrease SGLT1 (also known as SLC5A1) and SGLT2 (also known as SLC5A2) activity in gut and kidney	Increase renal glucose elimination; delays gut glucose absorption; changes incretin secretion	Phase 2–3	Efficacy shown in initial clinical studies
Non-peptide adiponectin receptor agonists	Adiponectin R1/R2 agonists	Increase insulin action	Preclinical	Proof of concept
FGF21 analogues	FGF21 receptor agonists	Increase insulin sensitivity and improves lipid profile	Phase 1	Might act partly through adiponectin
GPR120 (also known as FFAR4)	Activates fatty acid receptors in adipose and other tissues	Increases insulin sensitivity and adipogenesis	Preclinical	Proof of concept
Selective peroxisome proliferator-activated receptor modulators	Selective peroxisome proliferator-activated receptor alpha, gamma, and delta agonists	Increase insulin sensitivity, adipogenesis or lipid profile, and islet β-cell viability	Phase 1–2	Opportunity to selectively enhance efficacy and reduce unwanted effects
11β hydroxysteroid dehydrogenase-1 inhibitors	Inhibit 11β hydroxysteroid dehydrogenase-1 conversion of cortisone to cortisol in liver and adipose tissue	Increase insulin sensitivity and improves lipid profile	Phase 1–2	Challenge to prevent compensatory rise in concentration of adrenocorticotropic hormone
Fructose-1,6 bisphosphatase inhibitors	Increase fructose-1,6 bisphosphatase activity	Decrease hepatic glucose output	Phase 2	Initial clinical studies show efficacy
Adenosine monophosphate kinase activators	Increase adenosine monophosphate kinase cellular effects on nutrient metabolism	Increase glucose uptake and metabolism	Preclinical	Proof of concept

This list is not comprehensive but shows the various mechanisms and stages of development represented in this Review.

Table 1: **List of some potential new glucose-lowering medications for type 2 diabetes**

(mostly transient) was reported by about a third of participants and antibodies were detected in up to 10% of patients but did not seem to impair efficacy of exenatide.[20] This therapy is in phase 3 of development.

Another approach to avoid injections is an oral tablet formulation of the GLP1 receptor agonist semaglutide. This peptide is in phase 3 trials, including one already completed trial (NCT02054897), as a once-weekly subcutaneous injection. The oral formulation is suggested to be equally effective.[21] Studies in mice have shown that GLP1 receptor agonists can also be delivered by bioencapsulation in chloroplasts.[22] Several non-peptide small molecule GLP1 receptor agonists have been characterised in preclinical studies, but clinical efficacy has yet to be reported.[23]

Dipeptidyl-peptidase-4 inhibitors

DPP4 inhibitors (eg, sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin) are once-daily (or twice-daily for vildagliptin) oral drugs that enhance the effects of

endogenous incretins by prolonging their circulating half-lives. Because the side-effects of these drugs have been minimal to-date, long-acting DPP4 inhibitors have been investigated.[24] In the most advanced stage of development, omarigliptin has shown similar efficacy and tolerability as sitagliptin in phase 3 clinical studies.[25]

TGR5 agonists

The bile acid sequestrant colesevelam, which is indicated for use as a glucose-lowering drug in some countries, raises the possibility that carriage of bile acids more distally along the ileum could activate the TGR5 (also known as GPBAR1) bile acid receptors on L cells and enhance GLP1 secretion. Preliminary studies are investigating whether poorly absorbed TGR5 agonists can act distally along the intestinal tract to enhance GLP1 secretion.[26]

Peptide combinations

A mix of two differently acting peptides in the same injection became a therapeutic reality with the introduction of IDegLira, a fixed-ratio combination of liraglutide with insulin degludec (ratio of 1·8 mg of liraglutide to 50 units of insulin degludec). This combination is titrated in a similar manner to insulin, and during a 1-year prospective randomised phase 3 trial[27] in patients who had insulin-naive type 2 diabetes, once-daily subcutaneous injection of IDegLira reduced HbA_{1c} by 1·84% (20·2 mmol/mol) compared with 1·40% (15·3 mmol/mol) for insulin degludec alone and 1·21% (13·2 mmol/mol) for liraglutide alone (each p<0·0001 versus IDegLira). The combination achieved this effect with a lower insulin dose (39 units) than insulin degludec alone (62 units; p<0·0001), and avoided weight gain in patients (p<0·0001 between each treatment group). Preliminary data from a phase 2 study indicate that a fixed-ratio combination of lixisenatide and insulin glargine (Lixilan: ratio 50 µg of lixisenatide to 100 units of glargine) has similar efficacy in patients who had insulin-naive type 2 diabetes.[28]

Preclinical and clinical studies have also explored the use of hybrid peptides in which two or more peptides are linked together to form a single molecule.[29] These hybrids have mostly included combinations of GLP1 with glucagon, GIP, or other intestinal peptides.[30] Hybrid molecules provide an opportunity to combine the effects of various peptides that affect blood glucose, lipids, satiety, energy expenditure, and adiposity, such as incretins, glucagon receptor agonists or antagonists, oxyntomodulin, PYY, obestatin, and ghrelin antagonists. These agents can be customised with a selection of desired sequences to construct chimeric molecules that exploit particular epitopes and enable new therapeutic portfolios in a single molecule.[31,32] For example, molecules with satiety-inducing, weight-lowering, and glucose-lowering properties might reproduce the metabolic effects of bariatric surgery.[7] Although substantial physicochemical constraints and potential immunological issues need to be addressed, multipurpose designer molecules offer a novel potential therapeutic prospect.

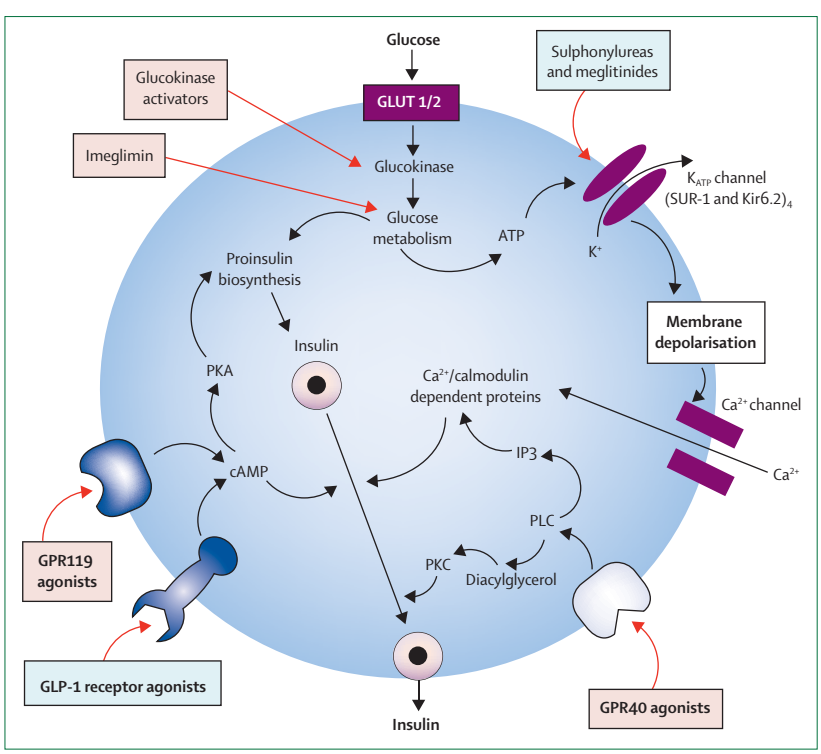

Figure 2: **Pancreatic β cell showing cellular mechanisms of insulin-releasing drugs[8]**
Blue boxes=approved drugs. Pink boxes=drugs under investigation. ATP=adenosine triphosphate. cAMP=cyclic adenosine monophosphate. GLUT=glucose transporter isoform. GLP1=glucagon-like peptide-1. GPR40=G-protein-coupled receptor 40 (also known as FFAR1). GPR119=G-protein-coupled receptor 119. IP3=inositol trisphosphate. PLC=phospholipase C. K_{ATP}=ATP-sensitive potassium channel. Kir=inwardly rectifying potassium channel. PKA=protein kinase A. PKC=protein kinase C. SUR=sulfonylurea receptor.

Glucagon secretion and action

Reduction of prandial (but not fasting) glucagon secretion by pancreatic α cells is an important action of GLP1 receptor agonists. Other inhibitors of glucagon secretion (eg, somatostatin analogues) have not been suitable for glucose-lowering in type 2 diabetes, mainly because of interference with the counter-regulatory response to hypoglycaemia, which is already defective in most patients.[10]

Despite many accounts in the medical literature of glucagon receptor antagonists over more than 20 years,[33] few have progressed beyond initial clinical trials.[34,35] Unwanted effects on liver function have been described with some glucagon receptor antagonists, and glucagon receptor antagonism could possibly cause compensatory hyperglucagonaemia and rebound hyperglycaemia if treatment is not maintained.

Insulin action

Insulin binds to the extracellular α subunits of the insulin receptor, changing their conformation. This effect in turn changes conformation of the β subunits

that extend into the cytosol, exposing tyrosine residues in the β subunits. Phosphorylation of these residues enables the β subunits to act as kinase enzymes, activating insulin receptor substrate (IRS) proteins that trigger the various post-receptor pathways responsible for the genomic and non-genomic actions of insulin. Thus, insulin resistance in patients with type 2 diabetes has many potential causes, many different presentations, and many possible sites for intervention (figure 3).[5,7–9] However, the rate-limiting defect is almost never identified and the potential benefits gained by circumventing any one defect might be off set by disturbances elsewhere in the insulin-receptor—effector pathways. Moreover, the various post-receptor signalling pathways of insulin action interact with, and are partly shared by, many other cellular signalling pathways, creating a challenge for any therapeutic intervention to act selectively on insulin action without interfering with other cellular control processes. In view of these constraints, much research into insulin resistance has, unsurprisingly, not yet yielded a new drug.

Because of the complexity of insulin receptor binding,[36] small (non-peptide) molecules are unlikely to be able to duplicate this act. However, a monoclonal antibody (XmetA) that exhibits high affinity binding to the insulin receptor at a different site to insulin initiated some of the effects of insulin in animal cells in vitro and improved glycaemic control in insulin resistant diabetic mice.[37] This finding suggests that conformational changes to the α subunit of the insulin receptor that differ from those induced by insulin binding could be exploited to produce conformational changes in the β subunit that will elicit therapeutically beneficial effects.

A fungal metabolite, demethylasterriquinone, which interacts directly with the cytosolic part of the insulin receptor β subunit, can initiate IRS-1-mediated post-receptor pathways without needing insulin binding. Although demethylasterriquinone is not suited to clinical development, the metabolite's ability to control the hyperglycaemia in diabetic animals suggests an opportunity exists for small molecules to mimic the actions of insulin.[38]

Various drugs have been reported to potentiate insulin-initiated tyrosine phosphorylation of the insulin receptor β subunit, or prevent its tyrosine dephosphorylation by phosphatases.[39] In particular, drugs directed against protein tyrosine phosphatase 1B and more general phosphatase inhibitors, such as vanadium salts, have successfully treated hyperglycaemic animals and shown efficacy in clinical trials, but none has proved sufficiently selective or free of side-effects to proceed into routine clinical use.[40,41]

Several intermediates within or activated by the post-receptor insulin signalling pathways exert a negative feedback by phosphorylating serine residues on the β subunit and IRS proteins (eg, protein kinase C-theta and the mammalian target of rapamycin). Attempts to interrupt this feedback have not been sufficiently selective. Provision of substrates for individual steps in the post-receptor pathways (eg, administration of the chiroinositol analogue pinitol enables signalling through phosphatidylinositol 3-kinase) is another approach under investigation.[10]

Sodium–glucose co-transporter inhibitors

Inhibitors of sodium–glucose co-transporters (eg, canagliflozin, dapagliflozin, and empagliflozin) are mainly directed against SGLT2 (also known as SLC5A2), which is located in the initial part of the proximal tubules and is responsible for reabsorption of about 90% of filtered glucose. Inhibition of SGLT2 causes excess glucose to be eliminated in the urine, which enables insulin-independent lowering of glucose, and lowering of bodyweight and blood pressure.[42] Several further SGLT2-selective inhibitors are advanced in development, all offering similar efficacy in clinical trials.[43]

Sotagliflozin strongly inhibits both SGLT2 and SGLT1 (also known as SLC5A1) and has also shown similar

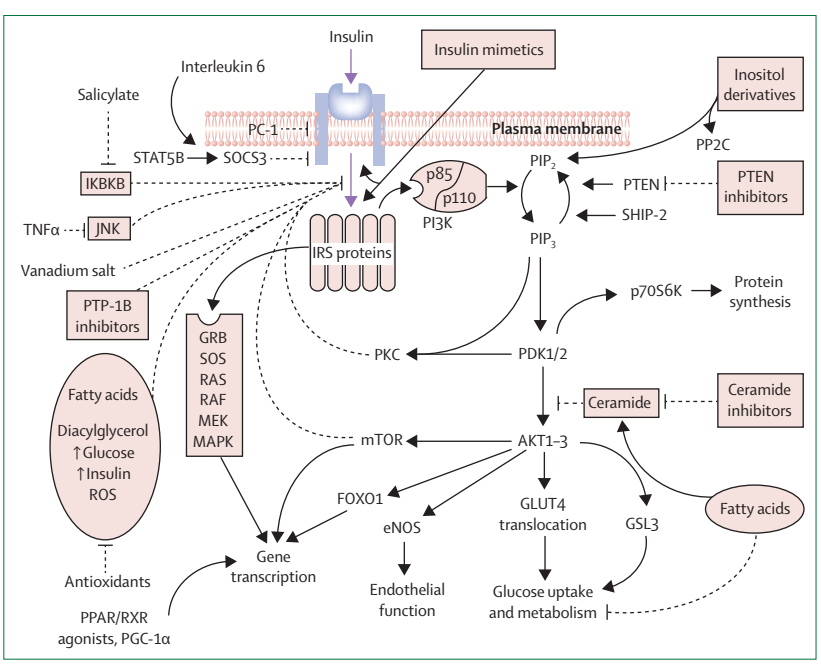

Figure 3: **Pathways of intracellular insulin signalling showing some of the potential sites for therapeutic intervention**[7,8]

Dotted lines=inhibition. Solid lines=activation. Some agents listed in this figure are not discussed in this up-date and the reader is referred to references 7 and 8. AKT=protein kinase B. AMPK=adenosine monophosphate-activated protein kinase. eNOS=endothelial nitric oxide synthase. FOXO1=forkhead box protein O1A. GLUT=glucose transporter isoform. GRB=growth factor receptor binding protein. GSK3=glycogen synthase kinase 3. IKBKB=inhibitor kappa-B kinase-β. IRS=insulin receptor substrate. JNK=c-Jun N-terminal kinase. MAPK=mitogen-activated protein kinase. MEK=mitogen-activated protein kinase kinase. mTOR=mammalian target of rapamycin. PC-1=glycoprotein-1. PDK=phosphoinositide-dependent protein kinase. PGC-1α=PPAR co-activator-1α (also known as PPARGC1A). PI3K=phosphatidylinositol 3-kinase. PIP_2=phosphatidylinositol-3,4-bisphosphate. PIP_3=phosphatidylinositol-3,4,5-trisphosphate. PKC=protein kinase C. PPAR=peroxisome proliferator-activated receptor. PP2C=protein phosphatase 2C. PTEN=phosphatase and tensin homologue. PTP-1B=protein tyrosine phosphatase-1B (also known as PTPN1). RAF=a serine–threonine protein kinase. RAS=a guanosine triphosphatase. ROS=reactive oxygen species. RXR=retinoid X receptor. SHIP-2=src homology-2-inositol phosphatase (also known as INPPL1). SOCS3=suppressor of cytokine signalling 3. SOS=SOS Ras/Rac guanine nucleotide exchange factor. STAT5B=signal transducer and activator of transcription 5B. TNFα=tumour necrosis factor α.

efficacy to other SGLT2 inhibitors in initial clinical studies.[44] SGLT1 mediates glucose absorption from the small intestine and contributes to the reabsorption of about 10% of filtered glucose by the kidney. Pharmacokinetic properties of this dual SGLT inhibitor suggest that it can defer intestinal glucose absorption more distally without causing malabsorption and might also increase the glucosuric effect. Sotagliflozin is now in phase 3 trials.[45] SGLT inhibitors that mainly inhibit SGLT1 are under investigation in phase 1.[46]

Adipokine-based treatments

In addition to facilitating weight loss through centrally mediated satiety and thermogenic effects, leptin exerts direct peripheral effects to improve insulin action and suppress glucagon. However, the glucose-lowering efficacy of leptin and leptin analogues was nominal during phase 3 trials in obese patients with type 2 diabetes, and benefits might only occur in individuals who are severely leptin deficient.[47]

Concentrations of another adipocyte hormone, adiponectin, are typically low in patients with type 2 diabetes, especially in the overweight, and adiponectin is known to exert several potentially beneficial effects including improved insulin sensitivity, improved endothelial function, and an anti-inflammatory effect.[48,49] Orally active small-molecule agonists of the adiponectin receptors, ADIPOR1 and ADIPOR2, have been shown to improve glycaemic control and prolong lifespan in insulin resistant diabetic animals, raising expectations for clinical studies.[48,49]

Preliminary data suggest that other treatments based on adipocyte hormones could be applied to type 2 diabetes. For example, resistin reduces insulin sensitivity, increases proinflammatory cytokines, and adversely affects vascular function, whereas immunoneutralisation of resistin has improved insulin sensitivity in rodents.[50] Increased concentrations of the retinol-binding protein 4 (RBP4), which transports plasma retinoids, have been detected early in the development of insulin resistance, and interventions that reduce RBP4 have increased insulin sensitivity in animals.[51]

Fibroblast growth factor 21 (FGF21) is a peptide secreted by adipose tissue, liver, and muscle, which promotes fatty acid oxidation and hepatic gluconeogenesis during starvation. Plasma concentrations of FGF21 are raised in obesity and type 2 diabetes, possibly due to FGF21 resistance, and preliminary animal and human studies suggest that administration of FGF21 analogues can improve the lipid profile, reduce insulin resistance, and assist glucose-lowering, partly through increased production of adiponectin.[52,53]

Selective peroxisome proliferator-activated receptor modulators

The nuclear peroxisome proliferator-activated receptor (PPAR) family offers a selection of potentially beneficial therapeutic effects but accompanying side-effects need to be minimised. PPARγ improves insulin sensitivity, glycaemic control, and various markers of vascular health while reducing inflammation, but also increases fluid retention and risk of heart failure, reduces bone mineral density, and often causes excessive adipogenesis.[54] PPARα improves the lipid profile, reduces inflammation, and seems to benefit microvascular complications, but might raise creatinine and risk of myopathological abnormalities,[54] whereas PPARδ counters weight gain through increased thermogenic energy expenditure, but long-term safety in man is not established.[54] Agents that selectively activate PPARγ and PPARα (dual PPARα/γ agonists, or glitazars), and triple PPAR agonists that also activate PPARδ (known as panPPARs) have not been introduced for routine clinical use due to side-effects.[54] Attention is directed to more selective PPAR modulators (SPPARMs) designed to capture desired effects and minimise unwanted effects.[55] For example, addition of a nonthiazolidinedione SPPARM, INT131, showed similar glucose-lowering efficacy to pioglitazone but with less oedema and less weight gain during a phase 2A, 24-week randomised double-blind study[56] in patients with type 2 diabetes receiving a sulfonylurea with or without metformin.

Inhibitors of 11β-hydroxysteroid dehydrogenase 1

Inhibitors of 11β-hydroxysteroid dehydrogenase 1 (11βHSD1) reduce the production of active cortisol from cortisone.[57] Such an inhibitor, INCB13739, improved insulin sensitivity, reduced HbA_{1c} by 0·6% (6 mmol/mol), improved the lipid profile and reduced bodyweight during a 12-week randomised phase 2 double blind placebo controlled study[58] in metformin-treated type 2 diabetes subjects. However, the efficacy achieved with 11βHSD1 inhibitors has been low and although these agents should theoretically restrict cortisol production within the liver and adipose tissue, a reduction of circulating cortisol can occur and cause a compensatory increase in adrenocorticotropic hormone.[59]

Agents that directly affect glucose production or metabolism

Many compounds have been shown to reduce blood glucose in diabetic animals by suppressing hepatic glucose production, but few have progressed in clinical development.[60] High risk of hypoglycaemia has been a limitation as noted with glucose-6-phosphatase inhibitors,[60] because these agents inhibit the last step in gluconeogenesis and glycogenolysis. The risk of hypoglycaemia might be lessened with inhibitors of fructose-1,6 bisphosphatase, which create a compensatory increase in glycogenolysis, and some phase 2 clinical studies are in progress.[61]

Activation of adenosine monophosphate-activated protein kinase (AMPK), which is one of the cellular

mechanisms of metformin and adiponectin, reduces blood glucose by increasing peripheral glucose uptake and increasing the metabolism of glucose and fatty acids. AMP is the main cellular activator of AMPK, and analogues of AMP are being explored as potential treatments.[62]

Epigenetics, genetics, and proteomics

The epigenetic approach is shown by sirtuins, which are nicotinamide-adenine-dinucleotide-dependent deacetylases and ADP ribosyltransferases that change gene transcription through chromatin silencing. Several small molecule sirtuin activators have produced effects similar to chronic caloric restriction in animal models. These effects include mitochondrial biogenesis and thermogenesis, glucose lowering, and improved vascular function, prompting continuing investigations into potential applications to treat obesity, diabetes, and cardiovascular disease.[63,64]

Genetic and proteomic studies continue to inform on the multivariable causes and pathogenesis of type 2 diabetes and identify specific treatment targets for a few patients, but for most patients these approaches have yet to inform the design of new drugs.[65–67]

Antiobesity drugs

Drugs approved for weight loss can assist glycaemic control in overweight and obese patients with type 2 diabetes. These products include the established intestinal lipase inhibitor orlistat and several newly approved satiety-inducing drugs, notably a high dose GLP1 receptor agonist (liraglutide), a 5HT2c serotonin receptor agonist (lorcaserin), a phentermine-topiramate combination, and a bupropion-naltrexone combination.[68–70] Further potential weight-lowering drugs, mostly based on intestinal satiety hormones, are in early development.[70]

Insulins

Advances in insulin treatment for patients with type 2 diabetes are beyond the remit of this Review, and have been reviewed recently.[71] Key developments for the immediate future include biosimilar insulins, notably biosimilar glargine and lispro, and the introduction of more concentrated U200–U500 formulations of existing insulins. Clinical assessment of an ultra-fast short-acting formulation of insulin aspart and a long-acting formulation of lispro are advancing in development. An inhaled insulin (afrezza) has received little use since its launch in the USA in 2015: a buccal spray insulin is now available in some countries, and closed-circuit insulin-glucagon pumps and other artificial pancreas devices are advancing in development. Delivery of insulin through skin patches or oral insulin formulations continue to be developed, and so-called smart insulins, which are activated or released from subcutaneous or circulating depots or skin patches in response to rising glucose concentrations, are giving encouraging results in preclinical studies.[72]

Safety issues

Safety is particularly relevant yet difficult to assess for glucose-lowering treatments in view of their long-term use in patients with comorbidities.[73] Cardiovascular risk is substantially raised in patients with type 2 diabetes and the US Food and Drug Administration (FDA) requires a meta-analysis of all cardiovascular events in phase 2 and 3 trials as part of any application for a new glucose-lowering treatment.[74,75] The FDA has also requested or encouraged extensive post-marketing randomised controlled cardiovascular safety studies with composite endpoints that include cardiovascular deaths and non-fatal myocardial infarction and stroke (table 2). The studies completed so far with saxagliptin (SAVOR-TIMI),[76] alogliptin (EXAMINE),[77] sitagliptin (TECOS),[78] and lixisenatide (ELIXA)[79] have reassuringly confirmed no adverse composite cardiovascular outcomes, and empagliflozin (EMPA-REG)[80] has reported a significant 14% reduction in its composite cardiovascular outcome.[80] During these studies other safety issues were being monitored including acute pancreatitis, bone fractures, infections, and cancers, and no significant increases in these adverse events have been reported to date. Although future drugs will ideally give positive outcomes in long-term cardiovascular safety trials, outcomes will vary with the numbers of different cardiovascular diseases, the duration of the study, and other variables across the different trial populations studied. Thus, the question arises as to whether heavy investment into large post-marketing cardiovascular outcome studies for new diabetes drugs could be compromising endeavours in innovative research.

	Drug	Start date	End date	Mean or median duration (years)	n	Primary endpoint
EXAMINE*	Alogliptin	2009	2014	1·5	5380	3-pt MACE
SAVOR-TIMI 53*	Saxagliptin	2010	2014	2·1	16 492	3-pt MACE
TECOS*	Sitagliptin	2008	2015	2·8	14 671	4-pt MACE
ELIXA*	Lixisenatide	2010	2015	~4·0	6075	4-pt MACE
EMPA-REG*	Empagliflozin	2010	2015	3·1	7020	3-pt MACE
LEADER	Liraglutide	2010	2016	~5·0	9340	3-pt MACE
CANVAS	Canagliflozin	2009	2017	~4·0	4407	3-pt MACE
EXSCEL	Exenatide QW	2010	2018	~5·5	14 000	3-pt MACE
CAROLINA	Linagliptin	2010	2018	~8·0	6000	4-pt MACE
CARMELINA	Linagliptin	2013	2018	~4·0	8300	4-pt MACE
DECLARE-TIMI 58	Dapagliflozin	2013	2019	~6·0	17 150	3-pt MACE
REWIND	Dulaglutide	2011	2019	~6·5	~9600	3-pt MACE
ACE	Acarbose	2009	?	~4·0	~700	3-pt MACE

MACE=major adverse cardiovascular event. 3 point MACE=composite of cardiovascular death and non-fatal myocardial infarction and stroke. 4 point MACE=3 point MACE plus hospitalisation for another specified cardiovascular event (eg, angina, heart failure). *Studies for which results have already been reported.

Table 2: **Post-marketing randomised cardiovascular safety studies for glucose-lowering drugs**

Search strategy and selection criteria

We searched MEDLINE, PubMed, and Google Scholar for original articles and reviews from January, 2011, to December, 2015, for full text papers in English on the treatment of hyperglycaemia. The main search terms were "hyperglycaemia", "diabetes", "obesity", "glucose lowering", "antidiabetes", "incretin" alone and with "therapy", "treatment", or "control".

Conclusion

Glycaemic control is crucial to the successful management of type 2 diabetes, but despite the variety of differently acting glucose-lowering drugs available, reversing the disease process and reinstatement of normal glucose homoeostasis is rarely possible. The need for multiple treatments has given rise to many new fixed-dose combinations of existing agents and further fixed-dose combinations are envisaged.[81] Innovative approaches with preclinical proof of concept include fatty acid receptor agonists and other novel interventions to promote β-cell function, chimeric designer peptides with pancreatic, satiety and thermogenic effects, small molecules to activate GLP1 receptors and potentiate insulin receptor β-subunit signalling, adipokine-based agents such as adiponectin receptor agonists, and AMPK activators. Many compounds have progressed into clinical studies and an analysis of ClinicalTrials.gov in February, 2014, has identified 180 trials registered for drugs to treat diabetes and its complications.[82] However, most of the drugs that are advanced in development are different formulations of existing drugs or new members of existing classes with modest pharmacokinetic modifications. Entirely new interventions to address the underlying aetiopathogenic lesions of type 2 diabetes remain elusive.

Contributors

All authors contributed to all aspects of this work.

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