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Invited Review

Treatment of type 2 diabetes: future approaches

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Introduction or background: Type 2 diabetes, which accounts for ~90% of all diabetes, is a heterogeneous and progressive disease with a variety of causative and potentiating factors. The hyperglycaemia of type 2 diabetes is often inadequately controlled, hence the need for a wider selection of glucose-lowering treatments.

Sources of data: Medline, PubMed, Web of Science and Google Scholar.

Areas of agreement: Early, effective and sustained control of blood glucose defers the onset and reduces the severity of microvascular and neuropathic complications of type 2 diabetes and helps to reduce the risk of cardiovascular (CV) complications.

Areas of controversy: Newer glucose-lowering agents require extensive long-term studies to confirm CV safety. The positioning of newer agents within therapeutic algorithms varies.

Growing points: In addition to their glucose-lowering efficacy, some new glucose-lowering agents may act independently to reduce CV and renal complications.

Areas timely for developing research: Studies of potential new glucose-lowering agents offer the opportunity to safely improve glycaemic control with prolonged efficacy and greater opportunity for therapeutic individualisation.

Key words: type 2 diabetes, /glucose-lowering agents, /glycaemic control

Introduction

Type 2 diabetes mellitus (T2DM) accounts for ~90% of the 425 million people with diagnosed diabetes worldwide, and is projected to increase to ~629 million by 2045.[1] All treatment guidelines emphasise the benefits of early, effective and sustained control of blood glucose in order to delay the onset and reduce the severity of complications. Given the variable and progressive nature of type 2 diabetes, most guidelines favour an individualised approach to treatment underpinned throughout with lifestyle measures, notably diet, exercise, body weight control and healthy living advice.[2–5] When lifestyle measures alone are unable to achieve or sustain the desired glycaemic control, pharmacological therapies are introduced, and two or more glucose-lowering agents (including fixed-dose oral combinations and insulin) with different modes of action may be required as the disease progresses (Table 1).[6] Despite the variety of available glucose-lowering agents, many patients do not attain or maintain adequate glycaemic control, emphasising the need for further therapeutic options.[4,7] This review considers examples of preclinical studies that illustrate potential new pharmacological approaches to glycaemic control and agents advancing in clinical development that utilise new modes of action or delivery.

Selecting pharmacological targets for type 2 diabetes

The hyperglycaemia of type 2 diabetes typically emerges when insulin sensitivity deteriorates (insulin resistance) and pancreatic β-cells are unable to provide sufficient insulin (Fig. 1). The glucotoxic effects of persistent hyperglycaemia precipitate and accentuate the characteristic microvascular complications of type 2 diabetes, notably a deterioration in renal function and detrimental changes to the retina as well as development of neuropathic problems. The combined effects of gluco-lipotoxicity, insulin resistance and other pathogenic factors such as hypertension, dyslipidaemia and hypercoagulation contribute to the increased long-term cardiovascular (CV) risks associated with type 2 diabetes. This mandates a management strategy that addresses the hyperglycaemia alongside other aspects of risk.[5,8]

Early intervention with stringent dietary measures and certain bariatric procedures can achieve protracted remission of hyperglycaemia in some type 2 diabetes patients, usually associated with weight reduction.[9,10] However, the vast majority of patients will eventually require pharmacological therapy that is escalated as the disease advances.[2–5] Insulin resistance and insulin insufficiency are obvious pharmacological targets to address the hyperglycaemia, but many other defects that contribute to the disease process are also potential sites for intervention. The multiplicity of defects in type 2 diabetes requires future agents to have new modes of action which permit their use in a complementary manner with existing agents to enhance efficacy.[11]

Practical considerations

Responsiveness of an individual to a given agent is not readily predicted because efficacy requires corrective adjustments across several tissues and organ systems: thus, even with the emerging assistance of pharmacogenomics, the matching of patient and treatment retains a degree of uncertainty. Given that a glucose-lowering agent may be required for decades, long-term safety is paramount. The convenience of administration, tolerability and cost will substantially influence accessibility and adherence. Positioning of a new medicine within a treatment algorithm is invariably problematic: initial caution often defers use of a new medicine until established agents have been exhausted, irrespective of the ideal placement against disease pathophysiology.[6,11]

Avoiding hypoglycaemia is very important, and the ability to prevent weight gain, assist weight loss and offer additional advantages such as reduced CV risk are valuable features, indicating why metformin is widely preferred as initial pharmacological therapy.[6] Assessing durability of effectiveness of an agent inevitably requires longer than pre-approval trials, but will be apposite when finalising the position of an agent within an algorithm. Agents with pharmacokinetic properties suited to use with co-morbidities

Table 1 Blood glucose-lowering agents currently approved for use in the UK*

Class with examples	Dose range, mg/day (unless stated)	(a) Glucose-lowering efficacy† (b) Hypo risk† (c) Weight†	Mode of action	Cautions, limitations and additional benefits
Oral				
Biguanide				
Metformin (IR, SR/XR formulations)	500–3000	(a) High efficacy (b) Low hypo risk (c) Weight neutral	Counter insulin resistance ↓ Hepatic glucose output ↑ Glucose uptake and cycling	Check renal function. Interrupt if using contrast media. Avoid in renal or liver impairment, or any hypoxaemic state and history of lactic acidosis. Rare risk of lactic acidosis. Glucose-independent effects to reduce CV risk.
Sulfonylureas				
Glibenclamide	2.5–20	(a) High efficacy (b) Moderate hypo risk (c) Weight gain	Initiate and potentiate insulin secretion (effect lasts 6–24 h depending on agent and dose)	Initial efficacy may wear-off after 6–12 months in some patients. Avoid in renal or liver impairment depending on agent. Note risk of hypoglycemia.
*Gliclazide**	40–320			
*Gliclazide MR**	30–100			
Glimepiride	1–6			
Glipizide	2.5–20			
Tolbutamide	500–3000			
Meglitinides				
Nateglinide	60–540	(a) Intermediate efficacy (b) Moderate hypo risk (c) Weight gain	Initiate and potentiate insulin secretion (rapid effect, typically lasts <6 h)	Avoid in liver impairment. Take with main meals.
Repaglinide	0.5–16			
DPP-4 inhibitors				
Alogliptin	6.25–25	(a) Intermediate-high efficacy (b) Low hypo risk (c) Weight neutral	Prolong circulating half-lives of some incretin hormones such as GLP-1	Discontinue if acute pancreatitis. Dose adjustment in renal impairment except linagliptin.
Linagliptin	5			
Saxagliptin	2.5–5			
Sitagliptin	25–100			
Vildagliptin	50–100			
Thiazolidinedione				
Pioglitazone	15–45	(a) High efficacy (b) Low hypo risk (c) Weight gain	↑ Insulin sensitivity mainly via activation of PPARγ	Slow onset of action, risk of oedema. Increased risk of heart failure and bone fractures. Check liver enzymes and CV risk.
SGLT2 inhibitors				
Canagliflozin	100–300	(a) Intermediate-high efficacy (b) Low hypo risk (c) Weight reduction	Inhibit renal SGLT2 to eliminate glucose via the urine.	Check for adequate renal function and hydration. Glucosuric effect: risk of genital and urinary infections. Can reduce blood pressure: evidence of reduced CV risk.
Dapagliflozin	5–10			
Empagliflozin	10–25			

Continued

Table 1 *Continued*

Class with examples	Dose range, mg/day (unless stated)	(a) Glucose-lowering efficacy[†] (b) Hypo risk[†] (c) Weight[†]	Mode of action	Cautions, limitations and additional benefits
Alpha-glucosidase inhibitors				
Acarbose	50–600	(a) Intermediate efficacy (b) Low hypo risk (c) Weight neutral	Slow carbohydrate digestion by competitive inhibition of intestinal glucosidases	Avoid if gastrointestinal disorders. Side effect of flatulence.
Subcutaneous injection				
GLP-1 receptor agonists				
Dulaglutide	0.75–1.5 QW	(a) High efficacy (b) Low hypo risk (c) Weight reduction	Activate GLP-1 receptors to potentiate prandial insulin secretion, ↓ prandial glucagon secretion, delay gastric emptying and exert satiety effect	Initial nausea, titrate as appropriate. Avoid in severe renal impairment. Discontinue if acute pancreatitis. Can reduce blood pressure: evidence of reduced CV risk.
Exenatide BD	5–10 µg BD			
Exenatide QW	2 QW			
Liraglutide	0.6–1.8 OD			
Lixisenatide	10–20 µg OD			
Insulin				
Ultra-rapid acting: *Fiasp*	For basal sc injections usually start at 0.1 or 0.2 units/kg body weight daily (i.e. 10 or 20 units per day for a person weighing 100 kg). Titrate up dose to achieve target glycaemic control. For MDI give ~30–50% as basal, and remainder divided between meals	(a) Very high efficacy (b) High hypo risk (c) Weight gain	↓ hepatic glucose output ↑ peripheral glucose uptake ↑ glucose metabolism ↓ lipolysis ↑ lipogenesis ↑ protein anabolism	Select regimen consistent with patient lifestyle and needs. Glucose monitoring required. Appropriate lifestyle adjustments. Note high risk of hypoglycemia.
Rapid-acting: *Aspart, Glulisine, Lispro*				
Short-acting: *Actrapid, Humulin S, Insuman Rapid*				
Intermediate: *Insulatard, Humulin I*				
Long-acting: *Degludec, Detemir, Glargine*				
Biphasic (pre-mixed): *Humalog, Humulin M3, Novomix*				

BD, twice daily; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; MDI, multiple daily insulin injections; OD, once daily; PPARγ, peroxisome proliferator-activated receptor-gamma; QW, once weekly; SGLT, sodium–glucose co-transporter; ↑ increase; ↓ decrease.

*Some agents are not available in all countries, e.g. gliclazide is not available in the USA. Some agents have different names and formulations in other countries, e.g. glibenclamide is available as micronized glyburide in the USA, and formulations of glipizide may vary between countries. Additional agents have indications as glucose-lowering agents outside of Europe, e.g. colesevelam (bile sequestrant), bromocriptine (dopamine D2 receptor agonist) and pramlintide (amylin analogue taken as subcutaneous injections before meals) have an indication for diabetes in the USA, and additional α-glucosidase inhibitors (miglitol and voglibose) and the GLP-1 receptor agonist albiglutide are available in some countries outside of the UK. Rosiglitazone is available in some countries outside of Europe. Dosages may vary between countries, e.g. a maximum recommended dose of metformin is 3000 mg/day in Europe and 2550 mg/day in the USA. Exclusions, precautions and monitoring may also vary (e.g. extent of renal impairment to contraindicate metformin varies between countries; TZDs are excluded for New York Heart Association (NYHA) categories I–IV in Europe but III–IV in the USA). Fixed-dose combinations of several oral agents are widely available, e.g. single tablet combinations of metformin with a DPP-4 inhibitor or SGLT2 inhibitor, and fixed-ratio combinations of a GLP-1 receptor agonist with insulin have recently been introduced. Pre-mixed insulins are identified with the proportion of the shorter-acting component first in Europe but second in the USA. Prescribers are encouraged to check national and local formulary directives.

[†]Based on ADA/EASD position statement.[2]

This table is based on and updated from reference.[11]

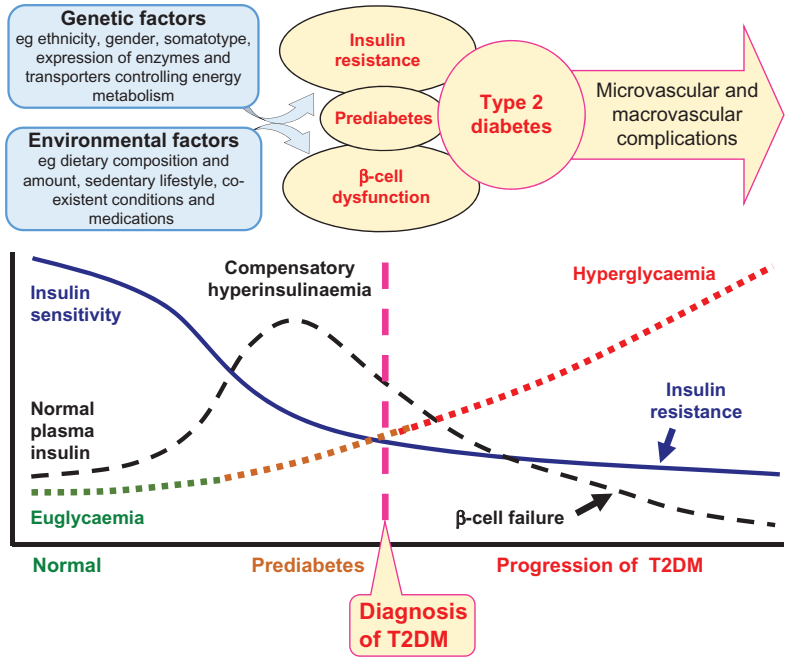

Fig. 1 Typical sequence of insulin resistance and pancreatic β-cell dysfunction during the development and progression of hyperglycaemia in type 2 diabetes. Initiation of the disease process mostly involves interactions of environmental factors with genetic factors to disrupt the control of nutrient homoeostasis. A family history of diabetes or prior gestational diabetes indicates particular susceptibility, which may be compounded by obesity, a sedentary lifestyle and conditions or medicines that disturb metabolic control such as acromegaly or prolonged use of glucocorticoids. During the prodromal period insulin sensitivity deteriorates (insulin resistance) and this is compensated by increased insulin secretion (compensatory hyperinsulinaemia). 'Stressed' pancreatic β-cells lose their ability to respond promptly to a prandial rise in blood glucose: their normal secretory rhythmicity becomes disrupted and there is incomplete conversion of proinsulin to insulin, resulting in the secretion of more proinsulin which is less biologically active than insulin. If raised insulin concentrations become insufficient to compensate for the insulin resistance, blood glucose concentrations rise, leading to a condition of 'prediabetes'. This is characterised by elevated postprandial glycaemia, often coupled with elevated basal glycaemia, but below the thresholds for a diagnosis of diabetes. Prediabetes can be defined by impaired glucose tolerance (IGT) with or without impaired fasting glucose (IFG). The detrimental effects of raised blood glucose concentrations are aggravated by accompanying disturbances of lipid metabolism, increased production of pro-inflammatory cytokines from expanded adipose depots, alterations to the microbiome and adjustments to the autonomic control of nutrient metabolism. A decline of insulin-secretory function escalates the prediabetic hyperglycaemia into a state of type 2 diabetes, and the hyperglycaemia becomes progressively worse with advancing β-cell failure. Throughout this process, adverse changes to other gluco-regulatory factors become increasingly apparent, notably impaired postprandial suppression of glucagon secretion and reduced activity of incretin hormones such as glucagon-like peptide-1 (GLP-1).

such as impaired kidney or liver function, cardiorespiratory conditions or in the elderly or frail are always helpful.

Developing a new agent may take more than a decade and involve detailed preclinical assessment of many compounds to select very few for Phase 1 clinical evaluation. Confirmation of efficacy and initial safety in Phase 2 clinical trials allow progression into an extensive Phase 3 programme of clinical trials. These should demonstrate therapeutic utility,

benefit-risk and marketability involving at least 2500 (typically many more) patients of whom at least 1500 will be exposed to the agent for ≥1 year. Development costs are difficult to determine as they include compounds investigated and discarded along the way, but the cost to completion of Phase 3 is expected to exceed US$ 1 billion, and an average cost was recently estimated at US$ 2.6 billion.[6]

Regulatory requirements for cardiovascular safety

In view of the high CV risk of type 2 diabetes and concerns over the CV safety of some glucose-lowering therapies, notably rosiglitazone (no longer available in Europe), the Food and Drug Administration in the USA specified in 2008 that new glucose-lowering agents needed to demonstrate specific margins of CV safety to gain marketing approval, and provide confirmatory evidence with post-marketing outcome trials if required.[12] In 2012, the European Medicines Agency also requested more extensive evidence to demonstrate no increase in adverse CV events with glucose-lowering agents.[13] This has prompted a proliferation of large clinical trials to monitor CV events in type 2 diabetes patients receiving glucose-lowering agents. To-date, these trials have reassuringly demonstrated that recently approved glucose-lowering agents do not increase the risk of a composite of major adverse cardiac events (including CV death, non-fatal MI and stroke) in patients at high risk of a CV event, and some agents have shown significant CV benefits.[14] Several agents have reduced systolic blood pressure and reduced progression of renal conditions more than may be attributed to improved glycaemic control. Other advantages such as weight reduction have been confirmed and useful information on a range of safety parameters has emerged. Overall, this has generated an expectation for future glucose-lowering agents to offer benefits beyond glucose-lowering alone.

Insulin secretion enhancers

Dysfunction and declining numbers of pancreatic β-cells underlie reduced insulin secretion in type 2 diabetes. Currently available sulfonylureas and meglitinides can 'initiate' insulin secretion—even at low glucose concentrations—hence, the risk of hypoglycaemia. In contrast, incretin-based therapies, namely dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists 'potentiate' nutrient-induced insulin secretion—hence, little or no effect at low glucose concentrations and low risk of hypoglycaemia.[6] However, an important unmet need is to address the declining number of β-cells in type 2 diabetes. GLP-1 receptor agonists, peroxisome proliferator-activated receptor-γ (PPARγ) agonists and gastrin can increase β-cell mass *in vitro* and when administered during early development of non-insulin-dependent diabetes in rodents. The durable efficacy of GLP-1 receptor agonists raises the possibility that these agents might help to preserve β-cell mass in human type 2 diabetes, but current and imminent agents have not been shown to regenerate β-cell mass after the β-cell mass has already become depleted.[15]

Insulin release is enhanced by many compounds that generate ATP, inhibit K^+ATP channels, raise cytosolic calcium, activate imidazoline receptors, suppress α_2-adrenergic receptors, increase cyclic AMP or alter other intracellular regulators of insulin exocytosis. However, most of these compounds have not been suited to therapeutic development due to an inability to target them specifically at the pancreatic β-cells and exclude unwanted effects on other cell types.[16] Current interest is focussed on imeglimin, fatty acid receptor agonists and glucokinase activators.

Imeglimin, now in Phase 3, is a tetrahydrotriazine which closes mitochondrial permeability transition pores, facilitating ATP synthesis, reducing oxidative stress and decreasing hyperglycaemia-induced apoptosis. Pancreatic β-cells are particularly responsive to this agent, and studies in type 2 diabetes patients have noted partial restoration of glucose-induced insulin secretion, especially the immediate (first) phase, together with some improvement of insulin sensitivity and reduced hepatic glucose production.[17]

Pancreatic β-cells express the G-protein-coupled fatty acid receptors GPR40 (FFAR1) and GPR119: activation of these receptors by fatty acids increases insulin secretion via phospholipase C and adenylate cyclase, respectively. Small molecule agonists of these receptors

have shown glucose-lowering efficacy in type 2 diabetes but their most studied member, the GPR40 agonist TAK-875, was discontinued due to hepatic side effects.[18] GPR40 and GPR119 are also expressed by several entero-endocrine cells including L-cells which produce GLP-1, peptide YY (PYY) and oxyntomodulin. Thus, agonists for these receptors could augment insulin secretion via an increased incretin effect, a direct effect on the β-cells and a strong satiety effect. Also, activation of GPR40 receptors on pancreatic α-cells can reduce glucagon secretion.[18–20]

Glucokinase activators can initiate and potentiate insulin secretion at any glucose concentration, but trials in type 2 diabetes indicate that efficacy soon wains as β-cells adapt by reducing glucose sensitivity. It has proved difficult to develop a mechanism that 'switches off' at low glucose to avoid hypoglycaemia.[21] Glucokinase in liver is regulated differently to pancreatic β-cells, but whilst increased hepatic glucokinase reduces hyperglycaemia the resulting increase in hepatic glycogenesis and lipogenesis may be an encumbrance to normal liver function.[22]

Glucagon-like peptide-1 receptor agonists

GLP-1 receptor agonists potentiate nutrient-induced insulin secretion and suppress glucagon secretion at raised (but not low) glucose concentrations—hence, minimal risk of hypoglycaemia. They also delay gastric emptying and usually enable weight reduction via a centrally-mediated satiety effect that can off-set the weight gain associated with raised insulin concentrations. GLP-1 receptor agonists may also reduce CV risk and renal complications.[23] Current GLP-1 receptor agonists have modified molecular structures and formulations to extend their half-life by protecting against rapid inactivation by the enzyme DPP-4. Initial nausea in some patients, cost and the need to inject these agents remains a hindrance to their wider adoption.

To avoid injections the GLP-1 receptor agonist, semaglutide, which is advanced in development as a once weekly subcutaneous injection, is now being formulated into a tablet with the absorption enhancer sodium hydroxybenzoylamino-caprylate (SNAC) to facilitate absorption across the gastric epithelium. SNAC appears to protect the peptide from proteolytic degradation by raising the pH around the peptide and assisting transcellular absorption. Oral semaglutide should be taken in the morning on an empty stomach and food should be avoided for ~90 min to allow adequate absorption of the drug. Clinical trials have shown the oral and injectable formulations of semaglutide to be similarly effective in controlling blood glucose and body weight.[24]

For the long-term, it is possible that orally active non-peptide GLP-1 receptor agonists will be developed. Several such agonists have shown glucose-lowering and weight-lowering efficacy in preclinical studies.[25] These agonists may act allosterically at a separate location to the peptide-binding epitope. This modifies the conformation and signalling activity of the GLP-1 receptors, offering the potential to increase receptor binding of endogenous GLP-1 or exogenous peptide GLP-1 receptor agonists.[26] Whether the profile of metabolic and other effects generated in this way will exactly replicate native GLP-1 remains to be seen.

Continuous release of the GLP-1 receptor agonist exenatide from a subcutaneously implanted miniature osmotic pump (ITCA 650) has provided therapeutic concentrations of exenatide that maintain glucose-lowering efficacy for up to 2 years.[27,28] The matchstick-sized device is implanted as a minor procedure, remains intact and is removed or replaced as required. Storing the peptide with retained biological integrity for 2 years at body temperature is a notable feature of this technology. Continuous release of a GLP-1 receptor agonist from an implanted depot should obviate issues of non-adherence.

A different type of depot, with proof of concept from preclinical studies, is a subcutaneously injected co-formulation of a DPP-4 resistant GLP-1 analogue linked with the soluble fusion protein elastin-like-polypeptide (ELP). The ELP forms a gel at body temperature which holds a reservoir of the GLP-1 analogue that can be released by local proteases.[29]

Fixed-ratio injectable combinations

GLP-1 receptor agonists act particularly to reduce postprandial hyperglycaemia whereas basal insulin targets

mainly basal hyperglycaemia: thus, the actions of these two types of agents are complementary. Advances in the formulation of peptide mixtures have facilitated 'fixed-ratio' combinations of a GLP-1 receptor agonist with a basal insulin in the same subcutaneous injection. Such a combination of liraglutide with insulin degludec (IDegLira) confers greater blood glucose-lowering at a lower dose of insulin and with less weight gain and no increased risk of hypoglycaemia compared with degludec alone.[30] A 'fixed-ratio' combination of lixisenatide with insulin glargine offers similar efficacy.[31]

Future complementary combinations of peptides may be anticipated if additional therapeutic peptides with glucose-lowering and/or weight-lowering properties become available. Several gastrointestinal hormones provide templates for new therapeutic peptides such as oxyntomodulin and PYY which exert satiety effects. Glucagon can also increase satiety as well as energy expenditure, but glucagon would need to be paired with a peptide that is able to counter its hyperglycaemic effect. Glucose-dependent insulinotropic peptide (GIP) (enhances insulin secretion), gastrin (can improve β-cell mass), and ghrelin antagonists (reduce hunger) are further examples of the many peptides that can affect gluco-regulation and might be considered as therapeutic templates.[32]

Hybrid and chimeric peptides

The prospect of single injections containing mixtures of two complementary peptides has prompted the development of hybrid molecules in which two complete peptide molecules, or their active amino acid sequences, are linked together to form a single molecule.[33] For example, GLP-1 has been linked with gastrin to improve glycaemic control, weight control and β-cell mass: GLP-1 has also been linked with glucagon to improve energy expenditure, satiety and weight loss.[34,35]

An extension of this approach is the development of chimeric molecules. An example of a dual-action chimeric peptide is an intermixed sequence of GLP-1 and GIP, giving strong insulin releasing properties, which improved glycaemic control during studies in obese-diabetic rodent models, monkeys and type 2 diabetic patients.[36] Triple-action chimeric peptides have also been produced to interact with receptors for GLP-1, GIP and glucagon, and these have improved glycaemic control, suppressed food intake, reduced body weight and increased energy expenditure in rodent models.[37] Thus, it is possible to create chimeric peptides with bespoke properties to exert desired effects via selected target receptors. However, significant physico-chemical challenges as well as immunogenicity, acute reactions, antibody production and adaptive responses of receptors must be considered for this approach.[32]

Other entero-pancreatic mechanisms

DPP-4 inhibitors are well-established glucose-lowering agents that act mainly by preventing the breakdown of endogenous incretins.[38] Until recently, these agents have been available as once-daily tablets, but some long-acting once-weekly versions (e.g. omarigliptin and trelagliptin) are now available in some countries.[39]

Agonists of the TGR5 (GP-BAR1) bile acid receptor have recently been considered as possible stimulants of GLP-1 secretion. Interest was raised by the bile acid sequestrant colesevelam, which has an indication for glucose-lowering in type 2 diabetes in the USA. Preliminary evidence suggests that bile acids carried distally along the intestinal tract might activate TGR5 receptors (expressed by intestinal L-cells) to stimulate GLP-1 secretion.[40] However, TGR5 receptors are mostly sited in the basolateral membranes of L-cells, so activation from the luminal side is likely to be limited.[41]

Glucagon secretion and action

Reducing hyperglucagonaemia can reduce hyperglycaemia in type 2 diabetes: for example, the glucose-lowering efficacy of GLP-1 receptor agonists is attributable in part to suppression of prandial glucagon secretion. Small molecules that inhibit glucagon secretion have proved difficult to target specifically against pancreatic α-cells, and have interrupted the glucagon response to low blood glucose (which is not interrupted with GLP-1 receptor agonists).[16] Many studies have evaluated the inhibition of glucagon

action with peptide and non-peptide glucagon receptor antagonists and glucagon receptor antisense oligonucleotides. However, impeding glucagon action leads to increased plasma glucagon concentrations with a rapid rebound hyperglycaemia if treatment is stopped. Inhibiting glucagon action may also produce unwanted effects on the liver, so this theoretically logical approach to the treatment of hyperglycaemia remains problematic.[42,43]

Sodium–glucose co-transporter inhibitors

SGLT2 in the renal proximal tubules is responsible for reabsorption of most of the glucose filtered by the kidney, and SGLT1 in the brush border of enterocytes is responsible for the intestinal absorption of glucose. Inhibitors of SGLT2 eliminate excess glucose via the urine, reducing blood glucose and assisting weight loss in an insulin independent manner. This glucosuric mechanism creates an osmotic diuresis which, by analogy with other forms of diuresis, contributes to a lowering of blood pressure and reduced CV risk.[44] Inhibition of SGLT2 may also increase delivery of sodium around the loop of Henle to the macula densa where it will promote tubulo-glomerular feedback to constrict afferent glomerular vessels and reduce intraglomerular pressure. This should help to protect against advancement of diabetic renal disease.

New SGLT2 inhibitors are advanced in development as well as a dual SGLT1/2 inhibitor. The dual inhibitor defers glucose absorption more distally along the intestinal tract, but does not prevent complete glucose absorption within the small intestine as the dual inhibitor is absorbed and degraded during transit along the gut.[44,45] If the plasma concentration of a dual inhibitor is sufficient to impede SGLT1 in the kidney, this might increase the glucosuric effect.

Tissue selective and smart insulins

Many type 2 diabetes patients eventually require insulin therapy, usually as basal insulin in conjunction with metformin and other glucose-lowering agents. Research continues apace into different methods of insulin delivery such as buccal, oral, inhaled and transdermal. Also, there is development of new insulin analogues, reformulations of insulins to alter absorption rate and various pump technologies integrated with glucose monitoring. These topics are too extensive to review here, and are considered in detail elsewhere[46] but the targeting of insulin to particular tissues and the development of non-cellular glucose-responsive insulins are briefly considered here because they offer interesting therapeutic concepts for the long-term future.

A limitation of subcutaneously injected insulin is that it does not mimic the physiological release of insulin from the pancreas into the portal system, which exposes the liver to higher insulin concentrations than the periphery. To increase the proportion of insulin in contact with liver cells, insulin analogues have been linked to various carriers including graded sizes of polyethylene glycol. This gives easier access across the fenestrated sinusoidal endothelium in the liver than tighter endothelia in the periphery.[47] Although one such preparation has not been progressed after extensive development, the concept of hepato-selective insulins remains therapeutically enticing.

Considerable advances continue to be made with closed-loop insulin delivery systems that link glucose monitoring technologies to insulin pump devices that automatically metre-out the required amount of insulin. The same general principle has been applied to the development of glucose-responsive 'smart' insulins that are released from an implanted or circulating depot by a direct chemical reaction with glucose. For example, polymers that contain boronic acid derivatives become deformed when two boronates are cross-linked by glucose. Such polymers can be incorporated into hydrogels containing insulin, so that the insulin is 'squeezed out' in proportion to the interactions with glucose. Another approach is to link insulin to the boronic acid derivatives and to displace the insulin with glucose.[48,49] Proof of principle has been demonstrated in diabetic mice with insulin analogues linked to boronic acid derivatives: these achieved more effective glycaemic control than unlinked analogues.[50] Other approaches at preliminary stages of development are using implanted insulin depots or transcellular insulin patches that contain glucose oxidase to monitor

glucose levels. Products of the reaction between glucose and glucose oxidase alter the structure of polymers thereby determining the release of insulin from the depot in a glucose-dependent manner.[51–53]

Insulin action enhancers

Insulin resistance is an early and enduring feature of most presentations of type 2 diabetes, usually involving multiple signalling defects from the insulin receptor through post-receptor pathways to biological effectors of insulin action within the cell.[54] The complex manner in which insulin binds and activates its receptor has proved difficult to mimic.[55] Studies with a monoclonal antibody have established that it is possible for interaction with the insulin receptor at different sites to insulin and still create conformational changes that will initiate some of the intracellular effects of insulin.[56] Also, the fungal metabolite chaetochromin A has been shown to interact with an extracellular region of the insulin receptor independently of insulin binding. This initiates insulin action independently of insulin as well as potentiating the action of insulin.[57] These studies provide proof of concept that a small orally-delivered molecule can at least partially mimic and potentiate the glucose-lowering effects of insulin.

Several small molecules such as the fungal metabolite, demethylasterriquinone, interact with the intracellular region of the insulin receptor to activate receptor signalling and lower blood glucose without insulin binding.[58] Other substances can potentiate insulin action after insulin has bound to the receptor (but do not initiate insulin action independently). These include agents that inhibit tyrosine phosphatases which prolong insulin-induced tyrosine phosphorylation and kinase activity of the intracellular region of the insulin receptor.[59,60] Vanadium compounds are notably effective as glucose-lowering phosphatase inhibitors but their therapeutic application is compromised by 'off-target' effects.[61]

Various compounds improve insulin action and lower blood glucose in diabetic animals through effects on post-receptor insulin signalling intermediates, but these have yet to generate viable therapeutic agent.[16] Examples include inhibitors of intermediates that exert negative feedbacks along the post-receptor signalling chain such as some isoforms of protein kinase C. Further examples are supplements of substrates for post-receptor intermediates such as methyl-chiroinositol (pinitol) which increases signalling by phosphatidylinositol 3-kinase.[16,60]

Adipokines

Adipose tissue is a source of many peptides and other substances that influence gluco-regulation. These adipokines provide potential therapeutic templates.[32] For example, leptin facilitates weight loss through satiety and thermogenic effects whilst enhancing insulin action and suppressing glucagon. Unfortunately, the body quickly develops resistance to therapeutic concentrations of leptin and its analogues which has precluded long-term use.[62] Another promising peptide is adiponectin which can potentiate insulin action and may improve vascular parameters and reduce inflammation. Small molecule agonists of the adiponectin receptors AdipoR1 and AdipoR2 have been reported to improve insulin sensitivity and lower blood glucose in preclinical studies.[63] Other adipocyte peptides that improve insulin action such as omentin and visfatin, or peptides that impede insulin action such as resistin, retinol-binding protein-4 and the pro-inflammatory adipokines tumour necrosis factor alpha and interleukin-6 may provide therapeutic targets for type 2 diabetes.[32]

Fibroblast growth factor-21 (FGF21) is secreted by adipose tissue, liver and muscle, and FGF21 analogues can lower blood glucose and improve insulin sensitivity in type 2 diabetes. However, it is unclear whether patients become resistant to FGF21, or if some of the effects of FGF21 are mediated via increased adiponectin secretion.[64,65]

Vitamins and minerals

Deficiencies of several vitamins and minerals are commonplace in type 2 diabetes, and supplements that reinstate normal levels (not large excesses) can often benefit glycaemic control. Correcting deficiencies in vitamins D (cholecalciferol), C (ascorbic acid), E (α-tocopherol), β-carotene, B_1 (thiamine) and H (biotin) as well as the minerals magnesium, chromium and

zinc have all been reported to assist glucose-lowering in type 2 diabetes: the effects are generally modest but worthwhile. The effects of lithium are variable as lithium can improve insulin sensitivity but may also decrease insulin secretion. The potential value of vanadium to increase insulin action has been considered above and there is evidence from preclinical studies that selenium, molybdenum, tungsten, mercury and cadmium can improve glucose metabolism, but attendant dangers of toxicity are well recognised.[16]

Other putative glucose-lowering therapies

Selective peroxisome proliferator-activated receptor modulators

Various thiazolidinedione and non-thiazolidinedione molecules have been designed to selectively modify the activity of peroxisome proliferator-activated receptors (PPARs).[66,67] These include PPARγ agonists which enhance insulin sensitivity and improve glycaemic control. However, molecules must be designed to minimise unwanted side effects such as excess adiposity, bone resorption, fluid retention and risk of heart failure.[62] Studies have also been undertaken with dual agonists that activate PPARγ and PPARα (known as glitazars)—designed to accentuate lipid-lowering and anti-inflammatory effects as well as PPARδ agonists and selective triple PPARα/γ/δ agonists (pan PPARs)—designed to assist energy expenditure and weight loss.[68]

Hydroxysteroid dehydrogenase-1 inhibitors

Inhibiting the enzyme 11β-hydroxysteroid dehydrogenase-1 prevents conversion of cortisone back to active cortisol in the liver and adipose tissue. Although this has improved insulin sensitivity, glycaemic control and weight control in type 2 diabetes patients, there has been sufficient reduction of circulating cortisol to cause a compensatory increase in ACTH.[69]

Adenosine monophosphate-activated protein kinase activators

Adenosine monophosphate-activated protein kinase (AMPK) is activated when energy levels are depleted: this enhances the uptake and oxidation of glucose and fatty acids to restore ATP production while decreasing gluconeogenesis and lipogenesis. Several compounds, notably analogues of AMP such as AICAR (5-amino-imidazole-4-carboxamide-1-B-D-ribofuranoside) can activate AMPK and lower blood glucose in animal models and possibly also reduce tumour formation. Metformin, PPARγ agonists and adiponectin receptor agonists activate AMPK and several novel agents that activate AMPK are under investigation as potential glucose-lowering agents.[70,71]

Glucose production and metabolism

Among the agents reported to suppress hepatic gluconeogenesis and/or glycogenolysis, studies with inhibitors of glucose 6-phosphatase and fructose 1,6-bisphosphatase have confirmed strong blood glucose-lowering activity.[60,72] However, the challenge here is to ensure that counter-regulatory glucose output is not compromised in times of hypoglycaemia. Many compounds that directly stimulate peripheral glucose uptake and metabolism can lower blood glucose, but limited potency and adverse side effects have generally mitigated against therapeutic development.[16]

Sirtuins

Sirtuins are nicotinamide-adenine-dinucleotide-dependent histone deacetylases and ADP-ribosyltransferases which exert epigenetic effects to modify the transcription of genes that increase mitochondrial biogenesis and energy expenditure, and alter nutrient metabolism similarly to caloric restriction.[73] They have been shown to protect against weight gain and diabetes in animal models and their suitability for therapeutic purposes is under investigation.

Microbiome modulators

Although dietary fibre can reduce prandial glucose excursions, unpalatability and gastrointestinal discomfort have moderated enthusiasm for fibre supplements such as guar gum, celluloses and brans. However, prebiotic and probiotic supplements which selectively alter the gut microbiome and modify the formation of bio-active products such

as short-chain fatty acids are being considered.[74,75] Faecal transplants to achieve the same effects are also being studied.

Conclusion

This review has evaluated the different modes of action of potential new glucose-lowering agents in preclinical, early clinical and advanced clinical stages of development (Fig. 2). The broad range of agents under investigation is warranted by the diversity of pathophysiological disturbances in type 2 diabetes and the anticipated benefits of addressing several targets simultaneously. Attention is directed to orally active GLP-1 receptor agonists, fixed-ratio injectable combinations of insulin with other peptides, and the construction of hybrid and chimeric peptides to interact with several target receptors from a single administration. Future opportunities for SGLT1/2 inhibitors and prospects for tissue selective insulins, glucose-dependent ('smart') insulins, novel insulin releasers and glucagon receptor antagonists have also been assessed. Additional awareness is directed to proof of principle studies with putative adipokine-based therapies including adiponectin receptor agonists, orally active insulin mimetics and agents to directly alter cellular energy metabolism.

Not included within this review are the non-pharmacological approaches such as adjustments to dietary nutrient composition, insulin-secreting cell implants, bariatric surgery and agents primarily designed to suppress appetite and reduce adiposity. These will all contribute to the future management of type 2 diabetes which will continue to recognise the combined impact of pharmacological and non-pharmacological

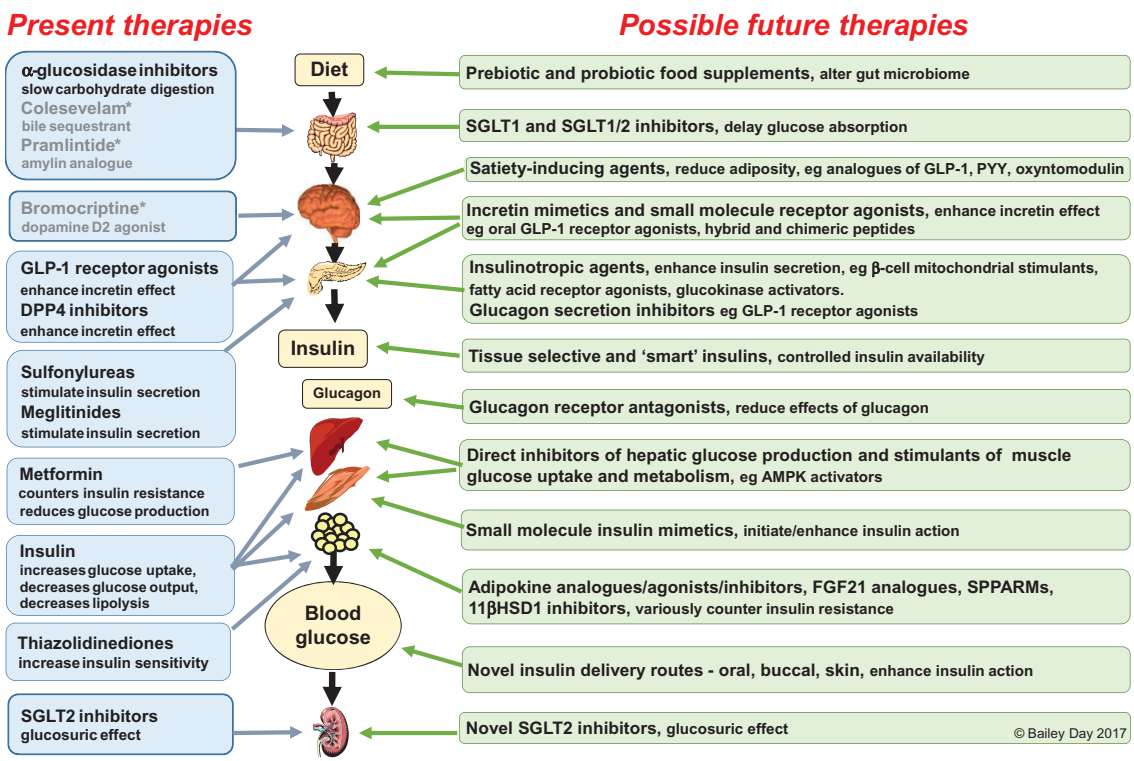

Fig. 2 Summary of possible future therapies showing main sites and modes of action in comparison to present therapies. 11βHSD1, 11β-hydroxysteroid dehydrogenase-1; AMPK, adenosine monophosphate-activated protein kinase; DPP-4, dipeptidyl peptidase-4; FGF21, fibroblast growth factor-21; GLP-1, glucagon-like peptide-1; PYY, peptide YY; SGLT, sodium–glucose co-transporter; SPPARM, selective peroxisome proliferator-activated receptor modulator. *Not indicated for glucose-lowering in the UK. Updated from reference.[11]

interventions to safely achieve early and sustained glycaemic control alongside further measures to minimise CV and other risks.

Conflict of interest statement

The authors have no potential conflicts of interest.

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