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REVIEW

Something old, something new and something very old: drugs for treating type 2 diabetes

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Diabetes mellitus belongs to the most rapidly increasing diseases worldwide. Approximately 90–95% of these patients suffer from type 2 diabetes mellitus, which is characterized by peripheral insulin resistance and the progressive loss of beta-cell function and mass. Considering the complications of this chronic disease, a reliable anti-diabetic treatment is indispensable. An ideal oral anti-diabetic drug should not only correct glucose homeostasis but also preserve or even augment beta-cell function and mass, ameliorate the subclinical inflammation present under insulin-resistant conditions and prevent the macro- and microvascular consequences of diabetes in order to reduce the mortality. Despite the many anti-diabetic drugs already in use, there is an ongoing research for additional drugs, guided by different concepts of the pathogenesis of type 2 diabetes. This review will briefly summarize current oral anti-diabetic drugs. In addition, emerging strategies for the treatment of diabetes will be described, among them the inhibition of glucagon action and anti-inflammatory drugs. Their suitability as 'ideal anti-diabetic drugs' will be discussed.

Abbreviations

11β-HSD, 11β-hydroxysteroid dehydrogenase; AICAR, 5-aminoimidazole-4-carboxamide riboside; AMPK, adenosine monophosphate (AMP)-dependent kinase; CRTC, cAMP-regulated transcriptional co-activator; DPP 4, dipeptidylpeptidase 4; GLP-1, glucagon-like peptide-1; GPR40/FFAR1, G-protein coupled receptor/free fatty acid receptor 1; IKKβ, IκB kinase β; OCT, organic cationic transporter; SGLT, sodium-glucose transporter; UKPDS, United Kingdom Prospective Diabetes Study; WAT, white adipose tissue

Pathogenesis of type 2 diabetes mellitus

Diabetes mellitus belongs to the most rapidly increasing diseases worldwide. Among the consequences of diabetes are micro- and macrovascular complications such as retinopathy and nephropathy leading to blindness and renal insufficiency, respectively, and cardiovascular and cerebrovascular diseases (Alberti and Zimmet, 1998; Stratton *et al.*, 2000). Indeed, more than 60% of type 2 diabetics die of myocardial infarction or stroke (Giorgino *et al.*, 2013). In general, two forms of diabetes mellitus are distinguished: type 1 diabetes is caused by the autoimmune destruction of the insulin-producing beta-cells in early childhood and resulting in an absolute lack of insulin (American Diabetes Association, 2004). For the development of type 2 diabetes, obesity caused by the chronic imbalance between calorie intake and energy expenditure is the major risk factor (American Diabetes Association, 2004; Lazar, 2005). The excess of nutrients is stored mainly in the white adipose tissue (WAT), the liver and the skeletal muscle. However, under conditions of chronic over-nutrition, their storage capacity is eventually exceeded and mitochondrial dysfunction, oxidative stress, endothelial

reticulum stress and abnormal post-translational modification of intracellular proteins ensue. The cellular stress activates diverse signalling pathways, including the JNKs and the IκB kinase β (IKKβ), which, in turn, inhibit insulin signalling pathways and trigger inflammation within the WAT and other tissues (Donath and Shoelson, 2011; Lumeng and Saltiel, 2011; Odegaard and Chawla, 2013). This subacute inflammation within the metabolic tissues leads to increased secretion of pro-inflammatory cytokines, which reinforces inflammatory signals and decreases the secretion of protective factors such as adiponectin (Hotamisligil *et al.*, 1995; Hotta *et al.*, 2000; Donath and Shoelson, 2011; Lumeng and Saltiel, 2011; Odegaard and Chawla, 2013). Furthermore, mainly via inhibitory serine/threonine phosphorylation of the insulin receptor substrate 1, some pro-inflammatory cytokines inhibit insulin signalling, thereby escalating insulin resistance (Tamemoto *et al.*, 1994; Aguirre *et al.*, 2000; Hirosumi *et al.*, 2002; Ueki *et al.*, 2004; Werner *et al.*, 2004). In this scenario, insulin resistance might be considered protective as it prevents the further excess uptake of nutrients and the deterioration of the cells within the metabolic tissues (Lumeng and Saltiel, 2011; Saltiel, 2012; Odegaard and Chawla, 2013). Deregulated nutrient uptake itself can activate inflammation by various mechanisms (Pal *et al.*, 2012; Tremaroli and Backhed, 2012; Odegaard and Chawla, 2013). Thus, obesity-induced insulin resistance contributing to the low-grade inflammation of metabolic tissues and the low-grade inflammation contributing to insulin resistance perpetuate each other. To compensate for the increased insulin demand under conditions of insulin resistance, beta-cell hypertrophy and hyperplasia develops, leading to hyperinsulinaemia (Butler *et al.*, 2003; Rhodes, 2005). It should be noted that most of the obese, insulin-resistant humans do not become diabetic, implying additional mechanisms for the pathogenesis of type 2 diabetes mellitus. Indeed, dysfunction of the beta-cells with regard to insulin secretion and biosynthesis and a reduction of beta-cell mass were demonstrated in patients suffering from type 2 diabetes or impaired glucose tolerance (Butler *et al.*, 2003; Kahn *et al.*, 2009; Marchetti *et al.*, 2012; Weir and Bonner-Weir, 2013) (Figure 1). Hence, the targets of an optimal anti-diabetic therapy are the attenuation of the inflammation of metabolic tissues and insulin resistance and the restoration or at least the amelioration of beta-cell function and mass to ultimately prevent the development of micro- and macrovascular complications.

Something old: current drugs for treating type 2 diabetes mellitus

The current drugs for treating type 2 diabetes mellitus can be roughly distinguished into those acting directly on beta-cells and those that do not. Sulfonylureas such as glibenclamide, tolbutamide and glimepiride have been in use since the 1950s. By inhibition of the ATP-dependent potassium channel (K_{ATP}, $K^{IR}6.2$; channel nomenclature follows Alexander *et al.*, 2013a) favouring membrane depolarization and subsequent calcium influx through the voltage-dependent L-type calcium channel ($Ca_v1.x$), they directly stimulate insulin secretion from the beta-cells. Increased insulin levels reduce blood glucose concentration but lead to weight gain, a most undesired effect in the typical obese type 2 diabetic. Another important adverse effect is hypoglycaemia. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated a significant reduction of microvascular complications after long-term treatment with glibenclamide (UKPDS 33) (UKPDS Group, 1998). In two observational studies, a higher risk for myocardial infarction and for mortality was found in patients treated with glibenclamide in comparison to treatment with glimepiride and gliclazide (Monami *et al.*, 2006; Thisted *et al.*, 2006). Another observational study found a higher incidence of cardiac events under glibenclamide in comparison to gliclazide only in patients with previously known ischaemic heart disease (Monami *et al.*, 2007).

In addition to glucose, glucagon-like peptide-1 (GLP-1) secreted from the intestinal L-cells in response to meal ingestion is another important insulin secretagogue (Doyle and Egan, 2001). The short plasma half-life of GLP-1 of 2 min due to cleavage by dipeptidylpeptidase 4 (DPP 4; nomenclature follows Alexander *et al.*, 2013b) makes the substitution of GLP-1 itself unsuitable. Therefore, s.c. injectable GLP-1 analogues with a mutated (i.e. exenatide) or a masked DPP 4 cleavage site (i.e. liraglutide) or orally available DPP 4 inhibitors (the gliptins sitagliptin, vildagliptin, saxagliptin) raising the endogenous GLP-1 levels are used. GLP-1 analogues and the gliptins have attracted much attention in the past years. As GLP-1 potentiates insulin secretion only in the presence of elevated glucose levels, the possibility of hypoglycaemic events is rather low. In rodents and in humans, GLP-1 has been shown to improve beta-cell function and increase beta-cell mass (Xu *et al.*, 1999; Skoglund *et al.*, 2000; Stoffers *et al.*, 2000; Sonoda *et al.*, 2008; Butler *et al.*, 2013a). In addition, GLP-1 promotes satiety, slows down gastric emptying, inhibits the secretion of the glucogenic hormone glucagon from α-cells and results in weight loss (Thornberry and Gallwitz, 2009; Pabreja *et al.*, 2014). However, recent reports have raised concerns about the safety profile of the GLP-1 receptor agonists and the DPP 4 inhibitors. In rodents, treatment with the long-acting GLP-1 receptor agonist exendin resulted in acinar cell death and inflammation and in accelerated metaplasia and lesion formation of pancreatic intraepithelial neoplasia (Nachnani *et al.*, 2010; Gier *et al.*, 2012). In humans, GLP-1-based therapy leads to increased proliferation and dysplasia within the exocrine pancreas (Butler *et al.*, 2013a) and a meta-analysis revealed an association between GLP-1 therapy and increased risk for hospitalization for acute pancreatitis (Singh *et al.*, 2013). In contrast, two recent studies evaluating the cardiovascular safety of saxagliptin and alogliptin, respectively, reported no increase in the incidence of pancreatitis; a slightly increased risk of heart failure was observed in the saxagliptin group (Scirica *et al.*, 2013; White *et al.*, 2013). It remains to be seen whether the undoubted benefits of GLP-1-based therapy outweigh its potential risks (Gallwitz *et al.*, 2012; Butler *et al.*, 2013b; Nauck, 2013).

As a result of the UKPDS (UKPDS Group, 1998), the biguanide metformin experienced a revival of its use and is now the first-choice anti-diabetic drug. A rare but potentially lethal effect is lactic acidosis, with an incidence of 4.3 cases in 100 000 patient-years (Salpeter *et al.*, 2010). Still, there are

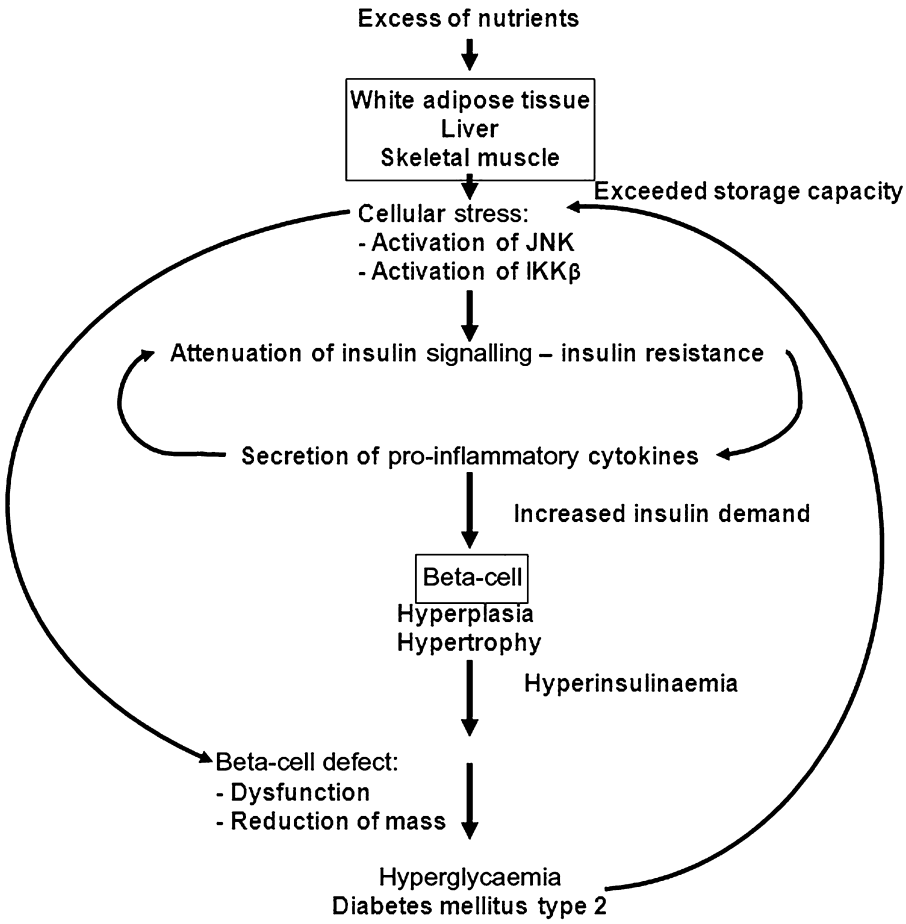

Figure 1

Pathogenesis of type 2 diabetes mellitus. Excess of nutrients is stored in the WAT, liver and skeletal muscle. When their storage capacity is exceeded, cellular stress leads to the activation of JNK and IKKβ, which, in turn, attenuates insulin signalling. Peripheral insulin resistance leads to secretion of pro-inflammatory cytokines mainly from macrophages migrated into the WAT. Pro-inflammatory cytokine signalling further aggravates insulin resistance. To compensate for the increased insulin demand, beta-cells hypertrophy and become hyperplastic, leading to hyperinsulinaemia. In addition, beta-cells themselves are exposed to cellular stress promoting beta-cell dysfunction and loss of beta-cells, and finally resulting in hyperglycaemia. The elevated blood glucose levels reinforce cellular stress.

several contraindications for metformin use, including cardiovascular, renal, hepatic and pulmonary diseases. In the case of metformin, the beneficial effects clearly outweigh its potential risks: metformin was shown to prevent cardiovascular mortality and disease (UKPDS 34, 1998) and might reduce cancer incidence (Evans *et al.*, 2005; Libby *et al.*, 2009; Noto *et al.*, 2012; van Staa *et al.*, 2012). In male mice, long-term treatment with metformin extended their lifespan (Martin-Montalvo *et al.*, 2013). In pre-diabetic humans, both lifestyle intervention and metformin reduced the incidence of diabetes, but lifestyle intervention was more effective (Knowler *et al.*, 2002). Metformin lowers blood glucose levels mainly through inhibition of hepatic gluconeogenesis; enhanced glucose uptake into the skeletal muscle has also been described. Metformin is weight neutral (Viollet *et al.*, 2012; Rena *et al.*, 2013). Although metformin has been in use since the 1950s, its molecular mechanisms are still not completely understood: inhibition of complex I in the mitochondrial electron transport chain, resulting in energy depletion with increased ADP/ATP and AMP/ATP ratios and activation of the AMP-dependent kinase (AMPK), a central cellular energy sensor and regulator of energy homeostasis have been proposed (Hardie *et al.*, 2012; Logie *et al.*, 2012; Hardie, 2013; Rena *et al.*, 2013). Consistent with this, infusion of the direct activator of AMPK, 5-aminoimidazole-4-carboxamide riboside (AICAR) decreased hepatic glucose output, thus lowering blood glucose levels in type 2 diabetic patients (Boon *et al.*, 2008). Shaw *et al.* (2005) suggested that AMPK-induced inhibition of the cAMP-regulated transcriptional co-activator (CRTC) 2 prevents the expression of gluconeogenic genes in hepatocytes, consistent with the findings that CRTC2 plays a pivotal role in hepatic glucose output under fasting conditions (Koo *et al.*, 2005). However, metformin still exerted hypoglycaemic effects in mice lacking AMPK in the liver, suggesting that AMPK – and transcription-independent mechanisms – confer metformin-caused reduction of hepatic gluconeogenesis (Foretz *et al.*, 2010). Another AMPK-independent mechanism of metformin action was proposed

by Miller *et al*. (2013), showing that metformin attenuated glucagon-induced hepatic gluconeogenesis, by indirectly inhibiting the adenylate cyclase. Metformin is a hydrophilic base and is transported via organic cationic transporters (OCT) 1 and 2 into the liver, the gut and the kidney (Graham *et al*., 2011; Viollet and Foretz, 2013; transporter nomenclature follows Alexander *et al*., 2013c). In OCT1-deficient mice, hepatic metformin concentration was decreased and the drug no longer reduced fasting blood glucose levels, suggesting that OCT1 is important for hepatic metformin action (Shu *et al*., 2007).

From a pathophysiological point of view, the thiazolidinediones have a very favourable pattern of action: they enhance insulin sensitivity of skeletal muscle and liver, inhibit hepatic gluconeogenesis and are anti-inflammatory in various organs. However, fluid retention with associated peripheral oedema due to altered renal sodium and water reabsorption, the higher rate of fractures due to decreased bone formation and increased bone resorption, and the weight gain, in part, due to increased food intake and to increased adipogenesis greatly diminished the widespread use of rosiglitazone and pioglitazone (Ahmadian *et al*., 2013). Whereas pioglitazone was suggested to exert modest protective effects on the CVS (Dormandy *et al*., 2005; Lincoff *et al*., 2007), rosiglitazone has been associated with an increased risk of myocardial infarction (Nissen and Wolski, 2007; 2010), resulting in the withdrawal of this drug. However, rosiglitazone's increased risk of myocardial infarction remains a matter of debate, whereas an increased risk for heart failure is well documented for the thiazolidinediones (Home *et al*., 2009; Kaul and Diamond, 2011; Winterstein, 2011). In addition, increased incidence of bladder cancer has been reported for pioglitazone (Zhu *et al*., 2012). Thiazolidinediones are agonists of the PPARγ (NR1C; nomenclature follows Alexander *et al*., 2013d), a nuclear receptor that forms permissive heterodimers with retinoid X receptors (RXR, NR2B; Ahmadian *et al*., 2013). Specific endogenous PPARγ ligands are still elusive, but some fatty acids and their derivatives can bind and activate this nuclear receptor (Ahmadian *et al*., 2013). In addition to ligand binding, PPARγ activity is regulated by post-translational modifications, among them phosphorylation by distinct kinases, acetylation, sumoylation and ubiquitination (Ahmadian *et al*., 2013), thereby expanding the cell- or tissue-specific modulation of this nuclear receptor. To prevent the adverse effects of thiazolidinediones, but retaining the desired effects, in analogy to the selective oestrogen receptor modulators, selective PPAR modulators might be promising new anti-diabetic drugs (Bhalla *et al*., 2011; Choi *et al*., 2011; Weidner *et al*., 2012; 2013; Cheon, 2013). Dual PPARγ/α agonists represent an approach to combine the glucose-lowering effects of the PPARγ agonists with the lipid-lowering effects of the PPARα agonists (like the fibrates) to effectively manage glycaemic control and improve cardiovascular outcome in type 2 diabetic patients. Several dual agonists, called glitazars, have been developed with promising effects on lowering HbA1c and plasma lipid levels (Henry *et al*., 2009; Rosenson *et al*., 2012; Wilding, 2012). However, due to diverse safety concerns, the further development and in the case of aliglitazar phase 3 clinical trials were stopped (Rosenson *et al*., 2012; Wilding, 2012) (media release from Roche, http://www.roche.com/de/media/media.release/medcor-2013-07-10.htm). Whereas the glucose-lowering effect of thiazolidinediones is due to many actions, dapagliflozin exerts its effect through inhibition of the sodium-glucose transporter 2 (SGLT2) in the proximal tubule of the kidney, thus preventing glucose reabsorption. The SGLT2 is a low-affinity, high-capacity transporter, reabsorbing most of the glucose in the urine. Its inhibition cannot result in hypoglycaemia because a fraction of the remaining glucose is reabsorbed by the SGLT1, a high-affinity, low-capacity transporter that is expressed in the more distal part of the renal tubular system (Tahrani *et al*., 2011).

Something new: potential drug targets and drugs

Given the epidemic dimensions of obesity and diabetes worldwide, it is not surprising that many more potential drug targets are currently under investigation. TAK-875, an agonist of the G-protein coupled receptor/free fatty acid receptor 1 (GPR40/FFAR1) highly expressed on beta-cells, is one example for a novel anti-diabetic drug (Yashiro *et al*., 2012). In isolated rat and human islets, TAK-875, by binding to its receptor, increased the intracellular calcium concentration and activated PKC, thereby potentiating glucose-stimulated insulin secretion (Yashiro *et al*., 2012). A phase 2 trial revealed that the glucose-lowering effects of TAK-875 and the sulfonylurea glimepiride are comparable, but less hypoglycaemic events occurred in the group treated with TAK-875. However, weight gain was similar in both patient groups treated either with glimepiride or with TAK-875 (Burant *et al*., 2012). The long-term effects of this novel drug-like protection or maintenance of beta-cell mass or the prevention of cardiovascular complications remain to be seen.

Another potential drug target within the beta-cell, but not exclusively there, is the activation of the glucokinase. In beta-cells, glucokinase acts as a glucose sensor and by phosphorylation of glucose triggers glucose oxidation, insulin biosynthesis and insulin secretion. In hepatocytes, this enzyme enhances glycolysis, glycogen synthesis and lipogenesis (Matschinsky *et al*., 2011; Matschinsky, 2013). Thus, activators of glucokinase effectively lower blood glucose levels by increased beta-cell insulin release and decreased hepatic glucose output. Heterozygous inactivating mutations of glucokinase cause maturity-onset diabetes of the young characterized by mild fasting hyperglycaemia; homozygous inactivating mutations result in permanent neonatal diabetes mellitus, demonstrating the importance of this enzyme for glucose homeostasis (Osbak *et al*., 2009). However, in a recent phase 2 trial, type 2 diabetic patients treated with the glucokinase activator MK0941 developed hyperlipidaemia and vascular hypertension, besides hypoglycaemic events. Furthermore, after 3–4 months of treatment, the drug failed (Meininger *et al*., 2011; Matschinsky, 2013). Two structurally distinct glucokinase activators induced hepatic steatosis in normoglycaemic and diabetic rodents (De Ceuninck *et al*., 2013). Hence, the long-term activation of glucokinase might not be beneficial at all (Rees and Gloyn, 2013).

Glucagon is another quite intriguing target for the therapy of diabetes. This peptide hormone is secreted from

the pancreatic α-cells in response to mixed meal nutrients, amino acids and hypoglycaemia. Glucagon secretion and biosynthesis is inhibited by insulin and probably other factors, secreted by the neighbouring beta-cells (Philippe, 1989; Grzeskowiak *et al.*, 2000; Gromada *et al.*, 2007; Kawamori *et al.*, 2009; D'Alessio, 2011; Unger and Cherrington, 2012). Glucagon binds to its G_s-protein coupled receptor (see Alexander *et al.*, 2013e) on hepatocytes, thus stimulating gluconeogenesis and enhancing glucose output. Hence, glucagon, elevating fasting glucose levels, can be considered as a functional antagonist of insulin, decreasing postprandial glucose levels. The relevance for targeting glucagon receptors or α-cells to interfere with the pathogenesis of diabetes has long been neglected (D'Alessio, 2011; Unger and Cherrington, 2012). Glucagon levels are enhanced in poorly controlled type 1 and type 2 diabetes, and some type 2 diabetic patients with at least moderately controlled glucose levels show fasting hyperglucagonaemia (Reaven *et al.*, 1987; D'Alessio, 2011). Dysfunction of the α-cells might contribute to the pathogenesis of type 2 diabetes: in diabetic patients, α-cell response to hyperglycaemia is blunted and glucagon secretion is enhanced by physiological stimuli to a greater extent than in non-diabetics (Unger, 1985). In addition, the α-cell itself might become insulin resistant, failing to reduce glucagon biosynthesis and secretion in response to insulin (Gonzalez *et al.*, 2008; Kawamori *et al.*, 2009). Hence, blocking glucagon action is a suitable target for treating type 2 diabetes mellitus. Glucagon-receptor knockout mice and treatment of several animal models with antibodies against glucagon or antisense oligonucleotides against the glucagon receptor support this notion (Gelling *et al.*, 2003; Liang *et al.*, 2004; Sorensen *et al.*, 2006a,b; Conarello *et al.*, 2007; D'Alessio, 2011; Tahrani *et al.*, 2011). However, α-cell hyperplasia with elevated glucagon and GLP-1 levels, and hepatic steatosis have been observed in animal models (Gelling *et al.*, 2003; Conarello *et al.*, 2007; D'Alessio, 2011; Tahrani *et al.*, 2011). It should be noted that already drugs exist that interfere with glucagon action: GLP-1 analogues and DPP 4 inhibitors reduce α-cell glucagon secretion (Thornberry and Gallwitz, 2009; Pabreja *et al.*, 2014); metformin seems to inhibit hepatic glucagon action by indirectly inhibiting the adenylate cyclase of the G_s-coupled glucagon receptor (Miller *et al.*, 2013).

Guided by the observation that an excess of glucocorticoids (Cushing's syndrome) shows similarities to the metabolic syndrome with obesity, insulin resistance and diabetes, decreasing local concentrations of hydrocortisone (cortisol) has become another alternative for the treatment of type 2 diabetes. Cortisol, produced and secreted from the adrenal glands, induces hyperglycaemia by promoting hepatic gluconeogenesis and glycogenolysis. In the presence of NADPH, 11β-hydroxysteroid dehydrogenase 1 (11β-HSD 1) converts the inactive cortisone to the active cortisol. This enzyme is mainly expressed in liver and the adipose tissue. The 11β-HSD 2 is mainly expressed in tissues that also express the mineralocorticoid receptor such as the kidney and oxidizes cortisol to cortisone, thus allowing aldosterone to bind to its receptor (Tahrani *et al.*, 2011; Anagnostis *et al.*, 2013). Mice deficient in 11β-HSD 1 or treated with specific 11β-HSD 1 inhibitors show improved glucose tolerance, reduced insulin resistance and decreases in body weight (Morgan *et al.*, 2009; Tahrani *et al.*, 2011; Anagnostis *et al.*, 2013). The effects seem to be mainly due to the inhibition of the adipose tissue enzyme (Lavery *et al.*, 2012). In type 2 diabetic patients treated for 12 weeks with INCB13739 in addition to metformin therapy, reduced HbA1c levels (by 0.6%) and fasting glucose levels were observed (Tahrani *et al.*, 2011; Anagnostis *et al.*, 2013). Other 11β-HSD 1 inhibitors tested in diabetic patients had negligible effects on glucose metabolism (Anagnostis *et al.*, 2013).

Taking into account the inflammatory nature of diabetes, immune-modulating therapies may be another option for the treatment of type 2 diabetes mellitus (Donath and Shoelson, 2011; Lumeng and Saltiel, 2011). The pro-inflammatory cytokine IL-1β seems to initiate the migration of macrophages to the inflamed adipose tissue and islets (Brooks-Worrell *et al.*, 2012). Furthermore, IL-1β is secreted from the beta-cells themselves in hyperglycaemia, inhibits insulin gene transcription and induces beta-cell apoptosis (Maedler *et al.*, 2002; Oetjen *et al.*, 2007). Hence, attenuating this cytokine's effect represents a promising target. In a double-blind trial, type 2 diabetic patients were randomized to placebo or to treatment with the recombinant human IL-1-receptor antagonist anakinra administered once daily s.c. for 13 weeks. Treatment with anakinra lowered HbA1c by 0.46% and reduced the markers of systemic inflammation (Larsen *et al.*, 2007). In a 39 week follow-up study, the anti-inflammatory effect of anakinra was still present, whereas the improvement in HbA1c levels was no longer detectable (Larsen *et al.*, 2009). Other IL-1β neutralizing antibodies are currently investigated in clinical trials (Brooks-Worrell *et al.*, 2012). TNF-α is secreted from the adipose tissue in the pre-diabetic state and is elevated in obesity, insulin resistance and type 2 diabetes (Hotamisligil *et al.*, 1993; Plomgaard *et al.*, 2007). A recent study demonstrated that treatment of obese, insulin-resistant patients with the recombinant TNF-α receptor 2 etanercept for 6 months improved fasting glucose levels (Stanley *et al.*, 2011). These findings suggest that targeting the chronic, low-grade inflammation might provide a useful drug target. In fact, the glucose-lowering effect of a well-known anti-inflammatory drug was described already more than 100 years ago (Ebstein, 1876).

Something very old: salicylic acid for the treatment of type 2 diabetes

In 1876, a report by Ebstein was published, describing the attenuation of classical diabetic symptoms (polyuria, polydipsia and elevated glucose concentration of the urine) in two middle-aged patients receiving salicylic acid natron. Without knowing the pathogenesis of diabetes or the pharmacodynamics of salicylic acid, Ebstein proposed that this drug might be used to treat diabetes (Ebstein, 1876). This report was long forgotten. However, with the realization of insulin resistance and diabetes as a chronic inflammatory process, salicylate as an anti-inflammatory drug was re-evaluated. Indeed, in type 2 diabetic patients, treatment with high-dose acetylsalicylic acid (approximately 7 $g \cdot day^{-1}$) reduced fasting glucose levels and hepatic glucose output, and improved insulin-stimulated peripheral glucose uptake

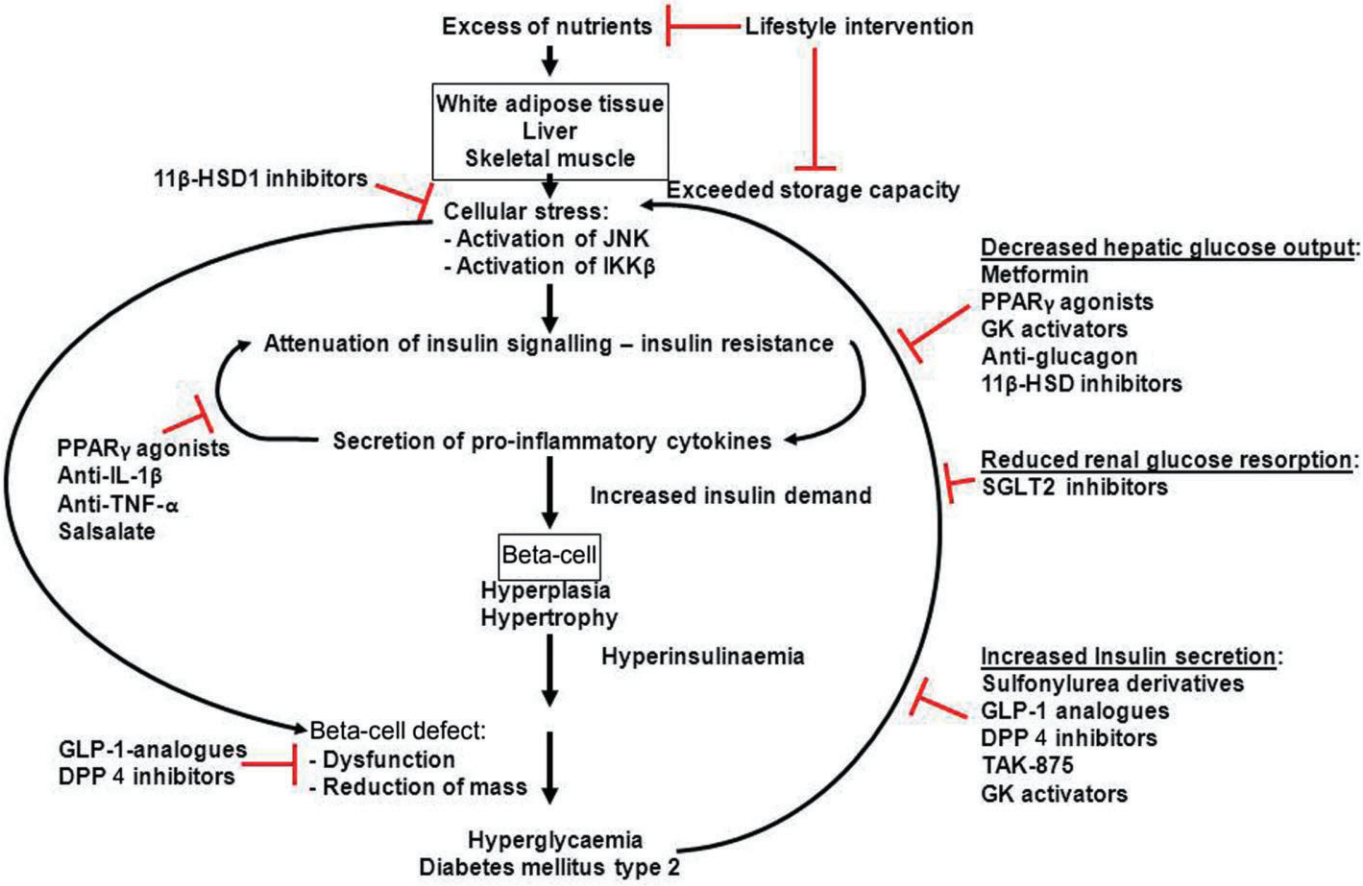

Figure 2
Action of old and new drugs against type 2 diabetes.

(Hundal *et al.*, 2002). Salicylates inhibit COX and therefore prostanoid synthesis (Higgs *et al.*, 1984). In addition, they inhibit IKKβ, crucial for the activation of the pro-inflammatory transcription factor complex NF-κB (Yuan *et al.*, 2001). As salicylates still confer anti-inflammatory actions in mice deficient in COX-2 or in a component of the NF-κB complex, other mechanisms must apply (Cronstein *et al.*, 1999; Hawley *et al.*, 2012). The finding that in AMPK-deficient mice the effects of salicylate, such as increased fat utilization and the decrease of plasma fatty acids, were lost indicates that AMPK might be a target of salicylate action. Indeed, salicylate was shown to directly bind and activate this kinase (Hawley *et al.*, 2012). In addition, down-regulation of 11β-HSD 1 in adipose tissue by salicylate, thereby reducing intra-adipose glucocorticoid levels and improving insulin sensitivity, was reported (Nixon *et al.*, 2012). Irrespective of its mechanism of action, salicylates were used in clinical trials. To reduce the adverse effects of acetylsalicylic acid (aspirin), such as its anti-thrombotic action and irritation of the gastrointestinal tract, the dimer of salicylic acid, salsalate, was used. Salsalate is only marketed in the US. In patients with newly diagnosed type 2 diabetes, 12 week salsalate treatment (3 g day^{-1}) reduced fasting glucose and HbA1c (Faghihimani *et al.*, 2013). In a randomized double-blind trial, patients with type 2 diabetes were treated for 48 weeks either with salsalate or placebo as 'add on' to their usual anti-diabetic therapy. In the salsalate treatment group, glycaemia improved concomitantly, with a reduction in the already existing diabetes medication. In addition, a reduction of inflammation estimated by lower circulating leukocyte, neutrophil and lymphocyte counts was observed (Goldfine *et al.*, 2013b). The findings that in the same group body weight, plasma low-density lipoprotein cholesterol levels and urinary albumin levels increased warrants, however, further evaluation of salsalate (Goldfine *et al.*, 2010; 2013b). In patients at risk for diabetes (insulin resistance, impaired fasting glucose or impaired glucose tolerance), salsalate lowered fasting glucose levels and inhibited adipose tissue NF-κB activity without changing peripheral insulin resistance (Goldfine *et al.*, 2013a). The explanation for this unexpected finding might be that salsalate through activation of AMPK reduced hepatic glucose output (Hawley *et al.*, 2012).

Conclusion and outlook

Considering the new concepts of the pathogenesis of type 2 diabetes, attenuation of cellular stress in the metabolic tissues thereby preventing insulin resistance and low-grade inflammation and protection of beta-cell function and mass are

desirable goals in the treatment of this chronic progressive disease (Figure 1). Clearly, lifestyle intervention to balance nutrient intake and consumption, thus avoiding obesity is the best way to reach these goals (Figure 2), but the nearly pandemic dimensions of obesity argue against the realization of this approach. There is a broad range of oral anti-diabetic drugs, but none of them can cover all the needs in diabetes therapy, and for the new drugs (and the very old drug salsalate), long-term data on the prevention of macrovascular complications and drug safety are lacking. As it is the decompensation of beta-cell function and the loss of beta-cell mass that result in diabetes, protecting beta-cells against the beta-cell toxic signals present under insulin-resistant and subacute inflammatory conditions is supposed to prevent or at least slow the onset of clinically apparent diabetes. To date, this has only been shown for the GLP-1 analogues and the DPP 4 inhibitors, whose safety profile remains a matter of debate. Hence, to achieve the maintenance of beta-cell function and mass, the identification of new drug targets within the beta-cell and the subsequent development of drugs provide an additional and much needed strategy to treat diabetes mellitus.

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Conflict of interest

The authors declare to have no conflict of interest.

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