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REVIEW

Novel and emerging diabetes mellitus drug therapies for the type 2 diabetes patient

Charmaine D Rochester, Oluwaranti Akiyode

Charmaine D Rochester, Department of Pharmacy Practice and Science, University of Maryland School of Pharmacy, Baltimore, MD 21201, United States
Oluwaranti Akiyode, Department of Pharmacy Practice and Science, Howard University College of Pharmacy, Washington, DC 20059, United States
Author contributions: Both Rochester CD and Akiyode O contributed to the conception of the document, drafting the outline, reviewing research articles and the writing of the paper; the drug classes were divided between the two authors; both Rochester CD and Akiyode O reviewed the final paper for grammar, clarity, consistency and accuracy; they revised the document critically to ensure important intellectual content; both authors would give final approval of the version to be published.
Correspondence to: Charmaine D Rochester, PharmD, CDE, BCPS, BCACP, Associate Professor, Department of Pharmacy Practice and Science, University of Maryland School of Pharmacy, 20 North Pine Street, Baltimore, MD 21201, United States. crochest@rx.umaryland.edu
Telephone: +1-410-7064336 Fax: +1-410-7065906
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Abstract

Type 2 diabetes mellitus is a metabolic disorder of deranged fat, protein and carbohydrate metabolism resulting in hyperglycemia as a result of insulin resistance and inadequate insulin secretion. Although a wide variety of diabetes therapies is available, yet limited efficacy, adverse effects, cost, contraindications, renal dosage adjustments, inflexible dosing schedules and weight gain significantly limit their use. In addition, many patients in the United States fail to meet the therapeutic HbA1c goal of < 7% set by the American Diabetes Association. As such new and emerging diabetes therapies with different mechanisms of action hope to address some of these drawbacks to improve the patient with type 2 diabetes. This article reviews new and emerging classes, including the sodium-glucose cotransporter-2 inhibitors, 11β-Hydroxysteroid dehydrogenase type 1 inhibitors, glycogen phosphorylase inhibitors; protein tyrosine phosphatase 1B inhibitors, G Protein-Coupled receptor agonists and glucokinase activators. These emerging diabetes agents hold the promise of providing benefit of glucose lowering, weight reduction, low hypoglycemia risk, improve insulin sensitivity, pancreatic β cell preservation, and oral formulation availability. However, further studies are needed to evaluate their safety profile, cardiovascular effects, and efficacy durability in order to determine their role in type 2 diabetes management.

Key words: Type 2 diabetes mellitus; Sodium dependent glucose co-transporter 2 inhibitors; 11β-Hydroxysteroid dehydrogenase type 1 inhibitors; Glycogen phosphorylase inhibitors; Protein tyrosine phosphatase 1B inhibitors; G protein-coupled receptor agonists; Glucokinase activators

Core tip: Type 2 diabetes mellitus is a metabolic disorder of deranged fat, protein and carbohydrate metabolism resulting in hyperglycemia. Limited efficacy, adverse effects, cost, contraindications, renal dosage adjustments, inflexible dosing schedules and weight gain significantly limit the use of currently available anti-hyperglycemic agents. In the past, drug researchers targeted defects of pancreatic β-cell failure and insulin resistance, but more recent attention has shifted to other contributing factors. This article reviews new and emerging diabetes classes, including the sodium-glucose cotransporter-2 inhibitors, 11β-Hydroxysteroid dehydrogenase type 1 inhibitors, glycogen phosphorylase inhibitors, protein tyrosine phosphatase 1B inhibitors, G protein-coupled receptor agonists, and glucokinase activators.

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INTRODUCTION

Type 2 diabetes mellitus is a metabolic disorder of deranged fat, protein and carbohydrate metabolism resulting in hyperglycemia from insulin resistance and inadequate insulin secretion, which can cause complications of nephropathy, retinopathy, neuropathy, and cardiovascular disorders[1,2].

Diabetes mellitus is an epidemic in the United States and the world. According to the International Diabetes Federation's 2013 statistics, 382 million people worldwide have diabetes, which is estimated to increase to 592 million by 2035[3]. The Centers for Disease Control and Prevention estimates 79 million Americans have pre-diabetes and approximately 26 million have diabetes mellitus of which seven million of these are still undiagnosed[4].

Despite a wide variety of available food and drug association (FDA) approved oral and injectable diabetes therapies, limited efficacy, adverse effects, cost, contraindications, renal dosage adjustments, inflexible dosing schedules and weight gain significantly limit their use[5,6].

In addition, less than 50% of patients with type 2 diabetes in the United States achieve the HbA1c goal of < 7% set by the American Diabetes Association[7].

Currently available oral agent classes include sulfonylureas, meglitinides, biguanide, α-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, dopamine agonist, bile acid sequestrant, thiazolidinediones and their combinations. Injectable agents include insulin, amylin analogue and incretin mimetics.

In the past, drug researchers and manufacturers targeted the primary pathophysiologic defects in type 2 diabetes of pancreatic β-cell failure and insulin resistance, but more recent attention has shifted to other contributing factors including increased glucose reabsorption by the kidneys, and the contributing effects to hyperglycemia by glucagon, glucocorticoid, glycogen, 11β-Hydroxysteroid dehydrogenase-2 and others. As such new and emerging diabetes therapies with new mechanisms of action hope to address these contributing pathophysiologic defects and offer new approaches in order for the patient to achieve therapeutic goals[1,6]. Table 1 lists the new and emerging drug therapy and approaches[8].

An ideal antihyperglycemic agent will be a safe, tolerable, efficacious, cost effective oral agent with a flexible dosage schedule providing clinically significant weight loss with cardiovascular and mortality benefits. This article reviews several new classes of antihyperglycemic agents, including the sodium-glucose cotransporter-2 inhibitors (which are furthest along in development); 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD-1) inhibitors, glycogen phosphorylase inhibitors, protein tyrosine phosphatase 1B inhibitors, G Protein-Coupled receptor agonists and glucokinase (GK) activators.

SODIUM DEPENDENT GLUCOSE CO-TRANSPORTER 2 INHIBITORS

Kidney and sodium dependent glucose co-transporter 2 transporters

Glucose homeostasis involves the liver, pancreas and the kidney[9]. Glucose transporter proteins (GLUT) and sodium-dependent glucose co-transporters (SGLT) are responsible for glucose transportation across the plasma membrane into cells[10].

Over the course of 24 h, the kidney filters 180 g of glucose while only 500 mg is excreted in the urine, and the rest is reabsorbed as it flows from the glomerulus to the proximal convoluted tubules then to the bloodstream[10]. GLUTs and SGLTs are involved in this glucose reabsorption and active transportation of glucose across cell membranes against concentration gradients[10,11].

SGLT-1 is responsible for 10% of glucose uptake and is expressed in the heart, skeletal muscle, gastrointestinal tract, liver, lung and the S3 segment of the proximal tubule of the kidney, while SGLT-2 is responsible for 90% of glucose uptake and is expressed in the S1 segment of the proximal tubule of the kidneys[11,12].

In addition to the reabsorption of approximately 99% of glucose, recent studies show the kidney takes up lactate, glutamine, glycerol, and alanine and converts them to glucose by the process of gluconephrogenesis, which can account for about 20% of all glucose released into the circulation and nearly 90% of the glucose released by the kidney[13].

The SGLT-2 inhibitors inhibit SGLT-2, which increases renal excretion of glucose thus reducing glucose in the plasma. Due to the minimal glucose uptake by SGLT-1 and the important roles of SGLT-2 in glucose reabsorption, several researchers and manufacturers have turned their attention to SGLT-2 inhibitors for treating hyperglycemia[14-16]. There are several SGLT-2 inhibitors in varying phases of studies including dapagliflozin, empagliflozin, ipragliflozin, ertugliflozin, luseogliflozin, tofogliflozin and LX4211[6,17].

The FDA approved canagliflozin (Invokana®) to treat type 2 diabetes based on the agreement that post marketing studies will be completed for evaluating cardiovascular outcomes, malignancies, severe pancreatitis, hypersensitivity and photosensitivity reactions; liver abnormalities, adverse events during pregnancy, bone safety, and two pediatric studies under the Pediatric Research Equity Act CR[18].

Dapagliflozin was approved in Europe, Australia, Brazil, Mexico and New Zealand as Forxiga®, but the FDA initially delayed its approval as there were concerns of increased breast and bladder cancer in patients taking the drug compared to placebo[19].

In January 2014, the FDA approved dapagliflozin as Farxiga® with six postmarketing studies including a

Table 1 Emerging classes of medications and approaches[8]

SGLT inhibitors
11β-HSD-1 inhibitors
GKA
AMPK agonists
SIRT activators
PTP-1B inhibitors
GCGR antagonists
GR antagonists
Novel insulin sensitizers
GPR119 agonists
Other drugs augmenting GLP-1 secretion: GPR40, G-protein coupled bile acid receptor (TGR5) agonists
Acyl-CoA: DGAT1 inhibitors
FGF-21-receptor agonists
Ranolazine
Other glucometabolic approaches
Other metabolic approaches
Anti-inflammatory approaches
Induction of immune tolerance
Pancreatic beta cell protection and regeneration
Pancreatic islet cell transplantation
Various antidiabetic approaches

SGLT: Sodium-dependent glucose co-transporter; 11beta-HSD-1: 11beta-hydroxysteroid dehydrogenase type 1; GKA: Glucokinase activators; AMPK: Adenosine monophosphate activated protein kinase; SIRT: Sirtuin; PTP-1B: Protein tyrosine phosphatase-1B; GCGR: Glucagon receptor; GR: Glucocorticoid receptor; GPR119: G-protein coupled receptor 119; GLP-1: Glucagon like peptide-1; Acyl-CoA: Acyl-coenzymeA; DGAT1: Diacylglycerol acyltransferase1; FGF-21: Fibroblast growth factor-21.

cardiovascular outcomes trial (CVOT) to evaluate the cardiovascular risk in patients with high cardiovascular disease risk and the evaluation of bladder cancer risk in patients enrolled in the CVOT[20].

Although there are several SGLT-2 inhibitors in varying phases of development, canagliflozin and dapagliflozin will be presented here due to availability of human safety and efficacy data.

Canagliflozin (invokana®) clinical trials

Wilding *et al*[14] designed a randomized, double-blind, placebo-controlled, phase 3, multicenter, 52-wk study to evaluate the safety and efficacy of canagliflozin added to metformin plus sulphonylurea in patients with type 2 diabetes.

The trial, called CANagliflozin Treatment And Trial Analysis-Metformin plus SUIphonylurea, included patients if they were 18-80 years with type 2 diabetes, who were stable on maximum or near maximum dosages of metformin and sulfonylureas with an A1c $\geqslant$ 7% and $\leqslant$ 10.5%[14].

The primary efficacy endpoint was A1c change from baseline to 26 wk. The secondary end points included change in baseline A1c at 52-wk, change in baseline in fasting plasma glucose (FPG), systolic blood pressure (BP), percent change in body weight, triglycerides, and high density lipoprotein (HDL) cholesterol, and percent patients reaching A1c 7%[14]. The investigators evaluated safety by observing adverse event reports, vital signs and laboratory tests[14]. Patients were randomized to receive either 100 mg or 300 mg canagliflozin or placebo in addition to their metformin and sulphonylurea therapies[14].

Results of the study show that 381 (81%) of 469 patients, who were randomized to the study, completed the 52-wk study. By week 26, the A1c was significantly reduced in the canagliflozin 100 mg and 300 mg study arm to -0.85% and 1.06% which was statistically significant compared to baseline and the A1c was sustained over the entire 52 wk study period[14]. Results are presented in Table 2[14]. FPG was significantly improved at 26 wk and 52 wk with both canagliflozin 100 mg and 300 mg compared to placebo. Canagliflozin significantly reduced weight but there were no significant changes with systolic blood pressure, pulse or cholesterol parameters[14].

Safety profile and adverse events: Although investigators reported that adverse effects were higher with canagliflozin than placebo, they were comparable across the treatment groups. Patients on canagliflozin had higher rates of genital mycotic infections compared to placebo, which were described as mild to moderate in severity[14]. Patients who developed a mycotic infection, especially women, had a prior history of genital mycotic infections compared to those women who received canagliflozin and did not have adverse effects[14]. Genital mycotic infections were treated without interrupting canagliflozin therapy[14].

Canagliflozin compared to sitagliptin

Canagliflozin has been shown to be non-inferior to sitagliptin and in another analysis superior to sitagliptin with regard to lowering of A1c[16].

In a randomized, double-blind, active-control, multicenter, phase three, 52-wk study, Schernthaner evaluated the efficacy and safety of canagliflozin 300 mg compared with sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes mellitus inadequately controlled with metformin and a sulfonylurea[16].

The inclusion criteria were similar to the previously described study, and patients were randomized to receive either 300 mg canagliflozin or 100 mg sitagliptin[16]. The primary efficacy endpoint was A1c change from baseline to 52 wk while the secondary endpoints were similar to the previously described study[16].

Results of the study show that 464 (61%) of 755 patients, who were randomized to receive either canagliflozin 300 mg or sitagliptin 100 mg daily, completed the study. Most of the withdrawals were observed in the sitagliptin therapy arm of the trial due to the lack of glycemic rescue therapy[16]. Canagliflozin demonstrated both noninferiority and in another analysis, showed superiority to sitagliptin 100 mg in reducing A1c (-1.03% and -0.66%, respectively). There were greater reductions with canagliflozin *vs* sitagliptin in FPG, body weight, and systolic BP. More patients on canagliflozin compared with sitagliptin achieved A1c < 7.0%, and A1c < 6.5% at week 52, though the authors did not confirm statistical significance[16]. Results are presented in Table 3[16].

Table 2 Results of phase 3, CANagliflozin treatment and trial analysis-metformin plus SUIphonylurea, *n* = 469[14]

Parameters	Canagliflozin 100 mg	Canagliflozin 300 mg	Placebo	Comments
A1c (%) week 26	-0.85	-1.06	-0.13	$P < 0.001$
A1c (%) week 52	-0.74	-0.96	-0.01	$P < 0.001$
% Patients with A1c < 7% week 26	43.2	56.6	18.0	$P < 0.001$
% Patients with A1c < 7% week 52	39.4	52.6	18.7	$P < 0.001$
FPG (mg/dL) week 26	-21.6	-34.2	-	$P < 0.001$
FPG (mg/dL) week 52	-28.8	-37.8	-	$P < 0.001$
Weight	-1.10	-1.7	-	$P < 0.001$
Change in systolic blood pressure (mmHg)	-2.20	-1.6	-	Non significant
Change in pulse (beats/min)	0.90	-1.2	-0.4	Non significant

A1c: Hemoglobin A1c; FPG: Fasting plasma glucose.

Table 3 Results of canagliflozin compared with sitagliptin for patients with type 2 diabetes: (*n* = 755)[16]

Parameters	Canagliflozin 300 mg	Sitagliptin 100 mg	Comments
A1c (%) week 52	-1.03	-0.66	Non inferiority to sitagliptin (upper limit of the 95%CI < 0.3%) and superiority to sitagliptin (upper limit of the 95%CI < 0.0%)
Percent (%) of patients with A1c < 7% at week 52	47.6	35.3	Not significant
Percent (%) of patients with A1c < 6.5% at week 52	22.5	18.9	Not significant
FPG (mg/dL) week 26	-29.9	-5.9	$P < 0.001$
Weight (kg)	-2.3	-0.1	$P < 0.001$
Change in systolic blood pressure (mmHg)	-5.1	0.9	$P < 0.001$
Change in diastolic blood pressure (mmHg)	-3.0	-0.3	Not significant

A1c: Hemoglobin A1c; FPG: Fasting plasma glucose.

Safety profile and adverse events: There were no differences in adverse effects, hypoglycemia or discontinuation of therapy between treatment groups. Nevertheless, canagliflozin had higher rates of genital mycotic infections (vulvovaginitis in females and balanitis in males) compared to sitagliptin[16]. In other studies, canagliflozin is implicated in urinary tract infections, hypoglycemia and gastrointestinal upset when used alone or in combination with other antihyperglycemic therapy[21].

Canagliflozin was associated with a dose dependent increase in serum creatinine, decrease in estimated glomerular filtration rate, renal impairment, and acute failure in patients especially those with moderate renal impairment and hypovolemia[22].

Canagliflozin 100-300 mg is recommended for patients with creatinine clearance > 60 mL/min per 1.73 m^2 and canagliflozin 100-mg is recommended for patients with creatinine clearance of 45-60 mL/min per 1.73m^2[22]. Canagliflozin is not recommended in patients with creatinine clearance of 30-44 mL/min per 1.73 m^2, and it is contraindicated in patients with creatinine clearance of < 30 mL/min per 1.73m^2[22]. Clinicians should assess patients' renal functions when initiating therapy and for long term drug monitoring. This agent will be a safe and efficacious addition to a dual therapy regimen such as metformin and sulfonylurea based on this study[16].

DAPAGLIFLOZIN AS MONOTHERAPY

List *et al*[23] designed a prospective, dose ranging 12-wk, randomized parallel-group, double-blind, placebo-controlled study to evaluate the safety and efficacy of dapagliflozin. The primary objective was to compare the mean change from baseline A1c in type 2, treatment-naïve adult patients (age 18-79) with A1c ≥ 7% and ≤ 10%[23].

Patients were randomly assigned to one of five once-daily dapagliflozin doses (2.5, 5, 10, 20 or 50 mg), metformin XR (750 mg force titration to 1500 mg) or placebo. Investigators also evaluated changes in FPG, weight, and adverse effects[23].

Results of the study show that 348 (89%) of 389, who were randomized to the study completed the study at week 12[23]. At the end of the study, dapagliflozin had statistically significant mean dose-dependent reduction of A1c from -0.55% to -0.90% when compared with placebo -0.18% but not with metformin of -0.73%[23]. Dapagliflozin also had significant reduction in FPG of -16 to -31 mg/dL compared to 6 mg/dL with placebo and -18 mg/dL with metformin[23]. Dapagliflozin caused a weight loss change of -1.3 to 2 kg[23]. In this trial, dapagliflozin did not demonstrate any renal function changes[23]. The percentage of patients achieving A1c < 7% was 40%-59% for the dapagliflozin group *vs* 32% for placebo and 54% for metformin[23]. Hypoglycemia was reported in 6%-10% of patients treated with dapagliflozin but this was not dose related, compared to 4% of placebo patients and 9% of metformin-treated patients[23].

Dapagliflozin in combination with metformin

Henry *et al*[24] conducted two randomized, double-blind,

Table 4 Dapagliflozin in combination with metformin[24]

Parameters	Study 1			Study 2		
	DAPA 5 ± MET	DAPA 5 ± PBO	MET ± PBO	DAPA 10 ± MET	DAPA 10 ± PBO	MET ± PBO
A1c at 24 wk (%)						
Baseline (*n*)	9.21 (185)	9.14 (196)	9.14 (195)	9.1 (202)	9.03 (216)	9.03 (203)
A1c (%) at 24 wk (baseline change)	7.13 (-2.05)	7.96 (-1.19)	7.79 (-1.35)	7.1 (-1.98)	7.59 (-1.45)	7.6 (-1.44)
DAPA ± MET *vs* DAPA	-0.86 (-1.11, -0.62)			-0.53 (-0.74, -0.32)		
P value	< 0.0001			< 0.0001		
DAPA ± MET *vs* MET	-0.70 (-0.94, -0.45)			-0.43 (-0.75, -0.33)		
P value	< 0.0001			< 0.0001		
Patients with A1c < 7% at 24 wk						
n (%)	96/185 (52.4%)	46/196 (22.5%)	68/195 (34.6%)	92/202 (46.6%)	69/216 (31.7%)	72/203 (35.2%)
DAPA ± MET *vs* DAPA	29.9	22.5		14.9		
P value	< 0.0001			0.0012		
DAPA ± MET *vs* MET	17.8			11.3		
P value	< 0.0001			0.0165		
Plasma glucose at 24 wk (mg/dL)						
Baseline FPG (mg/dL)	193.14 (*n* = 192)	190.62 (*n* = 203)	196.56 (*n* = 200)	189.36 (*n* = 209)	197.28 (*n* = 216)	189.72 (*n* = 207)
FPG after 24 wk (baseline change)	132.3 (-61.02)	150.3 (-41.94)	161.1 (-33.48)	130.86 (-60.3)	147.6 (-46.44)	156.42 (-34.74)
DAPA ± MET *vs* DAPA	-19.08			-13.86		
P value	< 0.0001			< 0.0001		
DAPA ± MET *vs* MET	-27.54			-25.56		
P value	< 0.0001			< 0.0001		
Total body weight at 24 wk (kg)						
Baseline weight (*n*)	84.24 (192)	86.20 (203)	85.75 (200)	88.56 (209)	88.53 (219)	87.24 (208)
Change from baseline	-2.66 (-3.14, -2.19)	-2.61 (-3.07, -2.15)	-1.29 (-1.76, -0.82)	-3.33 (-3.80, -2.86)	-2.73 (-3.19, -2.27)	-1.36 (-1.83, -0.89)

DAPA: Dapagliflozin; MET: Metformin; PBO: Placebo; FPG: Fasting plasma glucose; A1c: Hemoglobin A1c.

three-arm 24-wk trials to compare the combination of dapagliflozin plus metformin *vs* dapagliflozin monotherapy and metformin monotherapy to determine if the combination would be an advantage for treatment naïve type 2 diabetes patients with high baseline A1c.

Study 1 compared dapagliflozin 5 mg in combination with metformin XR, dapagliflozin 5 mg in combination with placebo, and metformin XR plus placebo. Study 2 compared dapagliflozin 10 mg in combination with metformin XR, dapagliflozin 10 mg in combination with placebo, and metformin XR plus placebo[24].

Eligible patients had a baseline A1c 7.5%-12%, and the primary endpoint was a change in A1c from baseline while the investigators also evaluated the change in FPG and weight as secondary endpoints[24].

Results show that in both trials, the combination of dapagliflozin and metformin resulted in significantly lower reductions in A1c compared with either metformin or dapagliflozin monotherapy[24]. Results of the study are presented in Table 4[24]. The combination therapy was statistically superior to monotherapy in reduction of FPG and was more effective than metformin for weight reduction. Dapagliflozin 10 mg was non-inferior to metformin in reducing A1c in study 2[24].

Safety profile and adverse events: Adverse effects of mild to moderate cases of genital infection of vulvovaginitis and balanitis and urinary tract infections were reported and treated without discontinuing the study[24]. There were no major hypoglycemic events reported. Diarrhea was more common in patients on combination therapy with metformin than with dapagliflozin therapy alone[24].

Summary of SGLT-2 inhibitors: Canagliflozin and dapagliflozin have been shown to lower renal threshold for glucose in a dose dependent fashion by increasing urinary glucose excretion through SGLT-2 inhibition, which leads to clinical significant reduction in A1c, FPG, and body weight[14,24]. The reduction in renal threshold is above the threshold for hypoglycemia demonstrating this agent has a low risk of hypoglycemia[17]. The SGLT-2 inhibitors can be used with any other agent whether in a treatment naïve patient or a patient with a long history of type 2 diabetes[22,23,25]. Both therapies are safe and tolerable, but clinicians need to observe for genital infections, which can be easily treated without discontinuation of therapy.

METABOLIC APPROACHES TO THERAPY

11β-HSD-1 inhibitors

High levels of glucocorticoids have been associated with hyperglycemia, insulin resistance, dyslipidemia and visceral obesity[4]. 11β-HSD is an enzyme, presenting as two distinct isoenzymes: 11β-HSD-1 and 11β-HSD-2. 11β-HSD-1 is found in the liver and adipose tissue and converts inactive cortisone to active cortisol while 11β-HSD-2 is found primarily in the kidneys and colon and it inactivates glucocorticoids by converting active cortisol to inactive cortisone[4,26].

It has been suggested that the increased glucocorticoid activity in the white adipose tissue by 11β-HSD-1 is a key player in the development of visceral obesity, insu-

Table 5 Efficacy assessment of INCB13739 in combination with metformin[30]

	Placebo	5 mg	15 mg	50 mg	100 mg	200 mg
Baseline A1c (%)	8.3 ± 1	8.2 ± 1	8.3 ± 1	8.3 ± 1	8.2 ± 1	8.2 ± 1
LS mean change A1c (%) from baseline	0.09 ± 1	-0.21 ± 1[b,e]	-0.11 ± 1	-0.09 ± 2	-0.38 ± 1[a,e]	0.47 ± 1[d,h]
A1c > 8% (*n*)	-0.10 ± 0.2 (23)	-0.39 ± 0.2[e] (23)	-0.24 ± 0.2 (18)	-0.65 ± 0.3[b,e] (11)	-0.72 ± 0.2[a,e] (16)	0.65 ± 0.2 (19)
A1c (%) for BMI > 30 mg/m^2 (*n*)	0.17 ± 0.1 (29)	-0.24 ± 0.2[b,f] (23)	-0.10 ± 0.2 (26)	-0.25 ± 0.2[b] (18)	-0.36 ± 0.2[a] (26)	-0.76 ± 0.2[d,h] (18)
Baseline FPG (mg/dL)	179 ± 51	172 ± 41	175 ± 44	178 ± 53	170 ± 64	165 ± 41
LS mean change from baseline (mg/dL)	12.6 ± 6.1	6 ± 6.3	2.3 ± 6.4	-4.7 ± 7.2[b]	-1.6 ± 6.1[b]	-11.5 ± 6.2[d,f]
Weight (kg)	-0.2 ± 0.3	-0.5 ± 0.38	-0.6 ± 0.4[e]	0 ± 0.4	-1.1 ± 0.3[b,e]	-0.9 ± 0.3[h]
HOMA-IR	0.25 ± 0.4	-0.29 ± 0.4	0.33 ± 0.4	-0.42 ± 0.5	0.51 ± 0.4	-1.06 ± 0.4[a,e]

Data are placebo adjusted least-squares (LS) mean change from baseline: mean ± SE. [a]$P < 0.05$, [b]$P < 0.01$, [d]$P < 0.01$, active *vs* Placebo, [e]$P < 0.05$, [f]$P < 0.01$, [h]$P < 0.01$, week 12 *vs* baseline. A1c: Hemoglobin A1c; FPG: Fasting plasma glucose; LS: Least squares; BMI: Body mass index; HOMA-IR: Homeostatic model assessment-insulin resistance.

lin resistance, diabetes, type 2 diabetes, dyslipidemia and hypertension in mice[27]. Increased levels of 11β-HSD-1 in adipose tissue produce a metabolic syndrome in mice while 11β-HSD-1 deficiency or inhibition has beneficial metabolic effects on liver metabolism[27].

In humans, researchers discover that though patients with glucocorticoid excess develop central obesity, yet the circulating glucocorticoid levels are normal. The metabolic syndrome resembles Cushing's syndrome, but without the elevated circulating glucocorticoid levels. Researchers suggest that it is the increased activity of 11β-HSD-1 in humans, which is metabolizing cortisol from cortisone within adipose tissue that may play a major role in the pathophysiology of obesity[28]. Inhibition of this enzyme may potentially decrease weight and blood glucose.

Non selective 11β-HSD-1 inhibitors

Older non-selective 11β-HSD-1 inhibitors such as liquorice and its active metabolite glycyrrhizic and glycyrrhetinic acids inhibit both 11β-HSD-1 and 11β-HSD-2 enzymes[29].

Ingesting liquorice and glycyrrhizic or glycyrrhetinic acids have been shown to produce a type of "mineralocorticoid excess" syndrome, hypertension encephalopathy, and hypokalemic paralysis[29]. It can also cause weight loss, sodium retention, potassium loss, and hypertension through the inhibition of 11β-HSD-2[29].

Carbenoxolone, a non-selective 11β-HSD-1 inhibitor and product of liquorice reduces glucose concentrations and increases weight loss; inhibits hepatic triglyceride production, inhibits lipolysis, and increase HDL-C levels, but also causes sodium retention, potassium loss, and hypertension by inhibiting 11β-HSD-2[29].

Vitamin A enriched diets also decrease fat and improve insulin sensitivity in animals and humans as it may inhibit 11β-HSD-1 and mRNA[29]. These non-selective agents were evaluated in small trials with short durations[29].

Several 11β-HSD-1 inhibitors have been developed and are being tested for patients with obesity and diabetes, including INCB013739, MK0916, PF915275, AMG221 produced by a variety of manufacturers. Results from INCB013739 clinical studies show that 11β-HSD-1 inhibitors when administered to patients with type 2 diabetes for 2 wk prevented the conversion of oral cortisone to cortisol, decreased hepatic gluconeogenesis, decreased fasting plasma glucose and low density lipoprotein cholesterol[30].

Clinical trial of INCB13739 (a 11β-HSD-1 inhibitor)

Rosenstock *et al*[30] evaluated the efficacy and safety of the agent INCB13739 (an 11β-HSD-1 inhibitor) for patients with type 2 diabetes, who were inadequately controlled on a mean dosage of 1.5 g daily of metformin therapy.

The study was a double-blind, placebo-controlled parallel study conducted with 302 type 2 diabetes mellitus patients on metformin therapy with an A1c of 7% to 11%[30]. Patients received one of five dosages (5, 15, 50, 100 or 200 mg) of INCB13739 or placebo once daily for 12 wk in addition to metformin. The primary end point was a change in A1c at the end of 12 wk. Investigators also reviewed FPG, lipids, weight loss, and adverse events[16,30]. Patients had a mean duration of type 2 diabetes of 6.2 years with baseline body mass index of 32.4 kg/m^2, A1c 8.3% and FPG 173 mg/dL[30].

Results of the study show that 228 of 302 (75%) patients completed the study[30]. At the end of the study, INCB13739 resulted in a dose dependent reduction in A1c of -0.38% and -0.47% in the 100 mg and 200 mg groups respectively[30]. However, it was noted that there were more significant A1c changes in obese patients on the higher dosages[30]. In addition, those with A1c > 8% had more significant decrease in A1c which was dosage dependent[30]. Results of the study are presented in Table 5[30]. The investigators reported that at the end of 12 wk, 25% of patients who were randomized to the 100 mg and 200 mg therapy groups achieved an A1c < 7% compared to 9.5% of placebo patients[30]. FPG decreased in a dose and time dependent fashion in the 100-200 mg treatment groups while there was significant weight loss in the 15, 100 and 200 mg groups[30]. The investigators reported that this study group had generally controlled blood pressure and plasma lipids at baseline but there was a modest dose dependent decrease in total cholesterol -7 mg/dL ($P_{trend} = 0.026$) from baseline in the 200 mg group[30]. There was no significant difference with HDL cholesterol[30].

Safety profile and adverse events: The therapy was well

tolerated and adverse events were similar across all treatment groups[30]. There were no serious events reported except for cardiac arrest unrelated to study therapy and there were no hypoglycemia reported. The most common adverse event in four patients was nausea in the 200 mg group but this resolved during continuation of therapy[30].

It was noted that there was also a dose dependent statistically significant reduction in Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) suggesting an insulin sensitizing mechanism of action in the 200 mg group[30]. The authors concluded that in patients with type 2 diabetes inadequately controlled with metformin, INCB13739 added to metformin significantly improved A1C, FPG and HOMA-IR[30]. INCB13739 also decreased weight though it did not affect the waist to hip ratio[30].

Summary: 11β-HSD-1 is increased in the adipose tissues of obese patients and those with the metabolic syndrome. 11β-HSD-1 inhibitors may be a viable option for these patients since it converts inactive cortisol to active cortisol in target tissues, which inhibits pancreatic beta cell insulin production, and prevents peripheral glucose uptake promoting weight loss, and decrease in blood glucose[30]. Researchers and clinicians have questions with regard to effects on the immune system, duration and timing of therapy, the long term effects of weight and lipids, glycemic control, insulin action, atherosclerotic plaque formation and cardiovascular risk[30]. The reduction in A1c was moderate but further studies will answer many of these questions to determine the safety and efficacy of 11β-HSD-1 inhibitors.

Glycogen phosphorylase inhibitors

The liver contributes to glucose production by both gluconeogenesis (glucose synthesis) and glycogenolysis (glycogen breakdown)[31]. Type 2 diabetes is characterized by excessive glucose production and inadequate suppression of hepatic gluconeogenesis postprandially[31].

Except for metformin, the production of gluconeogenesis inhibitors has yielded disappointing results with an increase in compensatory hepatic glycogenolysis, which maintains excessive hepatic glucose production[31,32]. Researchers hypothesized that glycogenolysis inhibition can improve blood glucose control by observing patients with hepatic glycogen storage disease experience intermittent hypoglycemia[31]. Glycogen phosphorylase is an enzyme that catalyzes the breakdown of glycogen to glucose-1-phosphate in the liver and tissues that demand high energy[33].

Hepatic glycogenolysis has a major role in the regulation of plasma glucose levels in diabetic mice, and suggests that glycogen phosphorylase inhibitors may be useful in the treatment of type 2 diabetes[31]. Further studies will elucidate if this is so.

Two types of glycogen phosphorylase inhibitors exist[31]. One is a glucose analog, which binds near the active site of the enzyme, and the other is caffeine and other heteroaromatic analogs which bind at the purine inhibitory site (I-site). The I-site is a target for therapy as compounds which bind at this inhibitory site are more potent in the presence of high glucose concentrations[31]. Researchers hypothesized that the inhibitory activity can be regulated by blood glucose concentrations and the inhibitory activity can decrease as normal blood glucose is achieved, which would decrease the risk of hypoglycemia[31].

CP-91149-a glycogen phosphorylase inhibitor in animal studies: CP-91149 was identified as a potent inhibitor of hepatic glucose production in *in vivo* studies in diabetic ob/ob mice[31]. CP-91149 exhibited rapid dose dependent decreases in plasma glucose concentrations (36-120 mg/dL) at 10, 25, and 50 mg/kg doses ($P < 0.001$) without producing hypoglycemia. Hypoglycemia was defined as glucose < 60 mg/dL for CP91149 in this study[31]. Administration of CP-91149 to normoglycemia non diabetic mice at 25-100 mg/dL did not affect glucose lowering. The glucose lowering of CP91149 was accompanied by an inhibition of hepatic glycogen breakdown in the diabetic ob/ob mice[31].

CP-316819-a glycogen phosphorylase inhibitor: CP-316819 is an analogue of CP-91149, which binds to the inhibitor site of glycogen phosphorylase to prevent its transformation to a more active form of the enzyme[33].

One of the concerns was that this analogue does not demonstrate hepatic specificity, so potentially affecting skeletal tissues and having possible deleterious effects to patients who exercise[33]. In a study by Baker, CP-316819 reduced glycogen phosphorylation activation in rat skeletal muscle at rest and maximal contraction, which produced a modest reduction in muscle lactate production[33]. According to the researcher, the study demonstrated that the concern related to potential negative effects of glycogen phosphorylase inhibition on quality of life due to impaired muscle function are unfounded[33].

Summary of glycogen phosphorylase inhibitors

These findings support the possible use of the glycogen phosphorylase inhibitors as a possible addition to the treatment of patients with type 2 diabetes. Further studies are needed to evaluate the effects of glycogen phosphorylase inhibition after chronic oral dosages and under a variety of exercise activities[33].

PROTEIN TYROSINE PHOSPHATASE 1B INHIBITORS

Type 2 diabetes and obesity are both characterized by insulin and leptin resistance[34,35].

Insulin resistance is found in tissues important for glucose homeostasis such as the liver, fat, central nervous system and muscle[34]. Leptin suppresses food intake and increases energy expenditure, but its levels are elevated in obesity demonstrating leptin resistance. Protein tyrosine phosphatases play a major role in leptin resistance by suppressing leptin signaling[36].

Protein tyrosine phosphatase 1B (PTP-1B) is an enzyme that removes phosphate from tyrosine residues in protein such as insulin receptors, so it is described as a negative regulator for insulin and leptin, by dephosphorylating phosphorylated tyrosine residues from the insulin receptor[34]. PTP-1B activity is increased in insulin resistance and obese patients[34].

Summary

Diabetes mice treat with specific PTP-1B inhibitors exhibited normalized BG control, improved insulin sensitivity, and modulated fat storage, and lipogenesis in adipose tissue[34]. Therefore these inhibitors have emerged as a potential oral agent that can provide a strategy for the treatment of type 2 diabetes and obesity and may work best in patients with beta cell function that releases insulin[35].

Further studies will elucidate if these agents can also be a potential addition to the armamentarium of oral diabetes agents affecting both obesity and the metabolic syndrome.

G-PROTEIN-COUPLED RECEPTOR 119 AGONISTS

A dysfunction in pancreatic β cell leading to decreased insulin secretion is a major abnormality in type 2 diabetes mellitus[37]. The pharmacotherapy approach of stimulating insulin release in a glucose-dependent manner using G-protein-coupled receptor has been investigated[38]. Specifically, G-protein-coupled receptor 119 (GPR119) is largely distributed in pancreatic islet cells, somewhat in the gastrointestinal tract, and found to be involved in glucose metabolism[39-41].

GPR119 may be stimulated by endogenous ligands or synthetic compounds resulting in an elevated cyclic adenosine monophosphate[42]. Studies have shown that stimulation of GPR119 yields glucose-dependent insulin release from the pancreatic β cells, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide secretions from intestinal cells[42]. Thus, pharmacological agents that target GPR119 results in glucose reduction with low hypoglycemia risk, body weight loss, and potential for pancreatic β cell preservation[42]. These characteristics are very similar to the commercially available GLP-1 agonists, however the studied GPR119 agents may be orally administered. Several GPR119 molecules (GSK1292263, MBX-2982, PSN-821, AR231453, AR-7947) have been studied in preclinical and/or early clinical trials with poor outcomes due to loss of pharmacological effect or minimal glycemic lowering effect[42]. Furthermore, GPR119 agonists have also been considered in combination with DPP-4 inhibitors in an attempt to enhance the GLP-1 effects[42].

Summary

GPR119 agonists have strong potential to meet the needs of patients with type 2 diabetes because of their relative safety profile, lack of weight gain, oral formulation, and possible β cell preservation effect. However, there have been challenges to their development due to potential tachyphylaxis and low anti-hyperglycemia efficacy.

GK ACTIVATORS

GK is a key enzyme in the hexokinase family that facilitates glucose homeostasis *via* glucose phosphorylation and metabolism mainly in the pancreatic β cells and hepatocytes[43-45]. GK functions as a glucose sensor in pancreatic β cells, thereby stimulating glucose-stimulated insulin secretion and regulating glucose metabolism within the liver, including gluconeogenesis, glycolysis, glycogen synthesis, glucose oxidation, lipogenesis, urea, and uric acid production[43,45-48].

Since the initial development of small molecules known as GK activators (GKAs) that bind to an allosteric site of the enzyme in 2003, more than 150 patents have been established[49-51]. Preclinical and clinical phase trials of GKAs have demonstrated glucose lowering effect in both animal and humans[52]. This novel class of anti-diabetic agents holds promise particularly because both mechanistic actions of GK are impaired in type 2 diabetes[53]. However, there are concerns about potential side effects including hyperlipidemia, hypoglycemia, and fatty liver that may limit the development of GKAs[54]. For example, a small Phase I clinical trial involving the GKA piragliatin was discontinued in type 2 diabetes patients with unrevealed rationale[55].

Another GKA molecule, MK0941 was evaluated in a 54-wk Phase Ⅱ trial in type 2 diabetes patients, but was discontinued because of observed hyperlipidemia, vascular hypertension and early therapy failure[56].

Summary of GKA

GKAs offer a unique pharmacotherapeutics approach to type 2 diabetes management and have demonstrated useful potential in glycemic management. However, further development is needed to address the potential side effects observed in clinical trials. Additional advancements may include modifications of the GKAs structures and activities to minimize hypoglycemia, hyperlipidemia, fatty liver, and vascular hypertension[44].

CONCLUSION

The management of type 2 diabetes present many treatment challenges, but new and emerging drug therapies are a welcome addition to complement the current agents. The SGLT-2 inhibitors have shown significant benefits as monotherapy and in combination with available agents like metformin, sulphonylurea and insulin therapy. The selective 11β-HSD-1 inhibitor is another class of possibly safe and efficacious agent that lowers fasting blood glucose, A1c and weight, although the A1c lowering was modest. The glycogen phosphorylase inhibitors appear to show rapid and safe blood glucose decreases in mice without the risk of hypoglycemia. Hope-

fully similar results translate into human studies. PTP-1B is still in clinical trials and may show significant decrease in weight and glucose levels in insulin and leptin resistant patients. Mice studies show positive results of normalized blood glucose control, improved insulin sensitivity and improvements in lipogenesis. The GPR119 agonists have strong potential for meeting the needs of type 2 diabetes patients because of their safety profile, lack of weight gain and possible beta cell preservation effect. However, the GK inhibitors may have some potential problems as agents so far have been discontinued due to dyslipidemia, vascular hypertension and early therapy failure. Prescribers and pharmacists may have to recognize that these new agents may not be first line agents due to costs, monitoring parameters, modest reductions of A1c, and lack of cardiovascular disease data. Further studies will help to more clearly define these new and emerging anti-hyperglycemia agents' roles in therapy.

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