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Current strategies for the inhibition of hepatic glucose production in type 2 diabetes

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1. ABSTRACT

Diabetes is a complex disease involving multiple organs with dysregulation in glucose and lipid metabolism. Hepatic insulin insensitivity can contribute to elevated fasting glucose levels and impaired glucose tolerance in individuals with diabetes. Several currently available therapeutics address defects at the liver. Metformin inhibits glucose production, potentially through effects on AMPK. Thiazolidinediones activate PPAR-gamma and improve hepatic insulin sensitivity, primarily through indirect effects on lipid metabolism. Insulin analogs and secretagogues suppress glucose production and increase liver glucose utilization by both direct and indirect hepatic actions. Incretins, incretin mimetics, and dipeptidyl peptidase-4 inhibitors reduce postprandial hepatic glucose production by increasing insulin secretion and limiting glucagon release, as well as through possible direct effects on the liver. Pramlintide reduces the increase in plasma glucagon that occurs following a meal in individuals with diabetes, and may thereby suppress inappropriate stimulation of liver glucose production. Many other hepatic targets are being considered which may lead to alternative strategies for the treatment of diabetes. This review focuses on currently available therapeutics which target insulin resistance in the liver.

2. INTRODUCTION

Hyperglycemia in type 2 diabetes (T2D) results from insulin resistance coupled with impaired beta cell compensation. In the fasted state, the liver is the primary producer of endogenous glucose, whereas following feeding elevations in circulating glucose and insulin mediate a switch to hepatic glucose storage. Therefore, the liver plays a pivotal role in maintaining glucose homeostasis during both fasting and feeding, and defective hepatic insulin sensitivity in T2D results in impairments in fasting glucose levels and glucose tolerance.

After an overnight fast, glucose is produced in the liver by two processes: glycogenolysis, from available glycogen stores, and gluconeogenesis, which is fueled by lactate, glycerol, amino acids and pyruvate. Elevated basal hepatic glucose production in insulin resistant individuals leads to fasting hyperglycemia (1, 2) and is mainly accounted for by an increase in gluconeogenesis related to increased production of gluconeogenic precursors, elevated gluconeogenic enzyme activity, hyperglucagonemia and increased hepatic fatty acid oxidation (1). In the post-absorptive state, reduced suppression of hepatic glucose production and abnormal liver glucose clearance contribute to impaired glucose tolerance and postprandial hyperglycemia (3).

Thus, hyperglycemia associated with impairments in the regulation of fasting glucose production and glucose tolerance may be improved by therapeutics which target insulin resistance in the liver. While some drugs affect glucose metabolism through direct actions at the liver, others improve hepatic insulin resistance through indirect mechanisms. The purpose of this review is to discuss current strategies for the inhibition of hepatic glucose production in T2D.

3. METFORMIN

The biguanide metformin is the most common drug used in the treatment of T2D. It is generally accepted that metformin's primary therapeutic effect results from its action at the liver where it reduces glucose production (4, 5). In a recently published meta-analysis, based on 19 clinical studies, it was concluded that the drug enhances insulin's ability to inhibit hepatic glucose production without improving its ability to increase glucose uptake (6).

The question thus arises as to whether metformin decreases glucose production by inhibiting glycogenolysis or gluconeogenesis. Two studies carried out several years ago came to opposite conclusions with regard to this point. Metformin was shown to improve glycemic control in one case by suppressing gluconeogenesis (7) and in the other case by inhibiting glycogenolysis (8). In the study by Cusi *et al.* (7), 20 subjects with T2D and 8 control subjects were studied in a randomized double blind placebo controlled trial to determine the effect of 15 weeks of treatment with metformin (TID: 2.5 g/day). Subjects were studied in the basal state and during a euglycemic hyperinsulinemic (~40 μU/ml) clamp both before, and after, drug treatment. Glucose production was measured using [^{3}H]glucose and gluconeogenesis was assessed using [^{14}C]lactate. Metformin treatment reduced fasting hepatic glucose production from 12.9 ±0.7 to 11.0±0.5 μmol/kg/min (15%). It did not, however, enhance glucose disposal during hyperinsulinemia (10.9±0.9 vs. 11.0±0.65 μmol/kg/min) nor did it significantly enhance the suppression of hepatic glucose production brought about by the rise in insulin. In the fasting state, gluconeogenesis from lactate was not reduced, implying that the fall in hepatic glucose production was related to a decrease in glycogen breakdown.

In the study by Hundal *et al.* (8), seven T2D subjects and seven control subjects were assessed before and after treatment with metformin (TID; total dose ~ 2.5g) for 3 months. Glucose production was measured using [6,6-$^{2}H_2$]glucose while the rate of net hepatic glycogenolysis was estimated using ^{13}C NMR. Gluconeogenesis was also directly measured using the deuterated water ($^{2}H_2O$) technique. Metformin reduced fasting glucose production by 24% and at the same time reduced gluconeogenesis by 36% (^{13}C NMR) or 33% ($^{2}H_2O$), depending on the approach used to measure it. This was enough to explain virtually all of the decrease in hepatic glucose production. The authors thus concluded that inhibition of gluconeogenesis explains the ability of metformin to decrease fasting hepatic glucose production.

Although these two studies agree on the drugs' ability to reduce fasting glucose production, they differ with regard to their conclusion on the way in which this comes about. The duration of treatment, the drug dose, the subjects' BMI and age, and their glycosylated hemoglobin levels were similar in both studies. It is possible that concurrent or pre-existing medications may have caused a difference in the response to drug, but it seems more likely that the different approaches used to measure gluconeogenesis led to different conclusions. Interestingly, Stumvoll *et al.* (9) used the [^{14}C]lactate approach in an earlier study and concluded that an alteration in gluconeogenesis explains metformin's effect, while Christiansen *et al.* (10) used the mass isotopomer distribution analysis (MIDA) approach to measure gluconeogenesis and concluded that the drug worked by inhibiting glycogenolysis. Given these conflicting data, the process by which metformin decreases glucose production in the human remains controversial.

There is an abundance of *in vitro* data (11-14) and rodent data (15-17) which also indicate that metformin can reduce hepatic glucose output, and in general they support a role for an effect of the drug on gluconeogenesis. A variety of hepatic gluconeogenic targets have been identified including glucose-6-phosphatase (G6Pase) (16), fructose-1,6-bisphosphatase (F16BPase) (17) and phosphoenolpyruvate carboxykinase (PEPCK) (14). Recently many of the beneficial effects of metformin have been attributed to its ability to activate AMP-activated protein kinase (AMPK), and to thereby bring about allosteric changes in various enzymes (14), as well as effects on gene transcription (14). Most recently, the involvement of the orphan nuclear receptor SHP has been proposed (12). In general, AMPK activation is associated with an inhibition of gluconeogenesis (14) rather than glycogenolysis. It should be noted, however, that in a recent study AICAR, an adenosine analog activator of AMPK, was shown to stimulate glycogen synthase, raising the possibility that changes in glycogenolysis might still be involved in metformin action (18). Thus, while the *in vitro* rodent data support the concept that the drug primarily alters gluconeogenesis, this is in part because few studies have focused on glycogenolysis. In one study that did assess glycogenolysis, metformin was in fact shown to have an acute inhibitory effect on glycogenolysis in the dog (19).

One of the difficulties in assessing the action of metformin on glucose production *in vivo* is separating its acute effect from the chronic effects which result from the overall improvement in the metabolic state of the T2D patient treated with the drug. A recently published study examined the effects of metformin treatment in T2D patients in whom oral drugs were washed out (20). Subjects received the drug BID at 2 g/d and were studied before and after 4 months of treatment. A hyperinsulinemic euglycemic clamp was used to increase insulin by a modest amount in the presence of a fixed basal glucose concentration. Glucose production was measured using [^{3}H]glucose, and gluconeogenesis and glycogenolysis were measured using $^{2}H_2O$. Fasting glucose production and

utilization were not altered by drug treatment, although the fasting plasma insulin level was reduced by ~20% (even in the presence of increased plasma glucagon), suggesting an improvement in insulin sensitivity. On the other hand, the ability of a small increase in arterial insulin to inhibit glucose production was not altered by metformin treatment. Likewise, the declines in gluconeogenesis and glycogenolysis caused by the rise in insulin were not altered by the drug. Interpretation of the data from this study is, however, complicated by the fact that insulin was infused via a peripheral vein at the same time that somatostatin inhibited endogenous insulin secretion (as confirmed by very low C-peptide levels). As a result, the hepatic sinusoidal insulin levels were undoubtedly below basal during the glucose clamp. This means that the reduction in glucose production was secondary to the extra-hepatic effects of insulin. In addition, the rise in arterial insulin was greater post-treatment (Δ81 pmol/L) than pretreatment (Δ49 pmol/L), further complicating data interpretation. Finally, the inhibition of hepatic glucose production, gluconeogenesis, and glycogenolysis were so extensive (65%, 70% and 70%, respectively) prior to treatment that there was little room for improvement post-treatment. Thus, although the results of this study do not support an effect of metformin on the liver, the experimental design prevents a definitive conclusion. In a similar study by Tikkainen *et al.* (21) carried out four years earlier, four months of metformin treatment in previously untreated T2D patients was shown to be associated with an enhanced ability of insulin to inhibit glucose production. It should be noted that the glucose levels in the latter study were clamped at 8 mM rather than 5 mM, and that insulin secretion was not inhibited by somatostatin.

In summary, there is no doubt that metformin improves glycemic control in patients with T2D. The majority of data support the concept that the drug inhibits glucose production by the liver. The effect on hepatic glucose production is small but the glycemic gain is significant. *In vitro* data and results from studies in rodents support a predominant role for gluconeogenic inhibition in explaining the metformin induced decline in hepatic glucose production. Data in the human, however, are controversial. The cellular mechanisms by which metformin works are also not clearly understood, but more recent data suggests an involvement of AMPK, a molecule which is thought to act as a fuel sensor. Regardless of the mechanisms by which metformin works, it is a good option for treatment of individuals with T2D.

4. THIAZOLIDINEDIONES

Thiazolidinediones (TZDs) are high affinity agonists for the nuclear peroxisome proliferator-activated receptor gamma (PPAR-γ), which improve glucose homeostasis and whole-body insulin sensitivity via multiple actions (22, 23). The antidiabetic effects of TZDs were first described in the 1980's and two TZDs, pioglitazone and rosiglitazone, have been available for the treatment of T2D in the US and Europe for almost a decade.

While some studies have not demonstrated an effect of TZD treatment on hepatic glucose production, a review of 23 clinical studies revealed that PPAR-γ agonists potentiate insulin-stimulated glucose disposal over a wide range of insulin concentrations, while also improving the sensitivity of hepatic glucose production to insulin and increasing fasting glucose clearance (6). In this systematic review, when glucose production was adjusted for the prevailing plasma insulin concentration, TZDs, as well as metformin, decreased an index of glucose production (rate of glucose production per unit of circulating insulin) by ~20%. In this analysis, TZDs also improved non-hepatic insulin sensitivity, whereas metformin did not.

The beneficial effects of TZDs on insulin action are primarily mediated through PPAR-γ, a member of the nuclear receptor superfamily (24, 25), which acts as a lipid-activated transcription factor in the regulation of genes that control lipid and glucose metabolism (26). PPAR-γ plays an essential role in adipocyte differentiation and lipogenesis (27, 28) and is weakly activated by fatty acids and eicosanoids, components of oxidized low density lipoproteins (LDL), and nitrolinoleic acid (26). A highly specific natural ligand for PPAR-γ has not been identified and indeed may not exist; instead, PPAR-γ may act as a physiologic lipid sensor which is activated by the combined concentration of weakly binding activators (26).

PPAR-γ is expressed predominantly in adipose tissue and to a much lesser extent in muscle and the liver (29, 30). The effects of TZD treatment on hepatic insulin sensitivity appear to be primarily indirect, through PPAR-γ mediated changes in adipose gene expression, although in liver specific PPAR-γ knockout mice insulin resistance was associated with elevated basal endogenous glucose production (31), suggesting that TZDs may also have direct effects on the organ. On the other hand, mice lacking PPAR-γ in adipose did not respond to the insulin-sensitizing effects of TZDs (32, 33), highlighting the importance of PPAR-γ's effect in fat. The mechanisms by which TZDs mediate improved insulin action include altered body composition, reduced free fatty acid (FFA) levels, decreased intramyocellular and intrahepatocellular triglyceride (TG) content, decreased production / actions of circulating proinflammatory proteins and altered expression of metabolically important genes in adipose, liver and muscle (26, 34-36).

Visceral adiposity is associated with hepatic insulin resistance in nondiabetic and T2D subjects (37, 38). TZD treatment has been demonstrated to improve this condition through adipocyte remodeling such that lipids are redistributed from insulin-resistant, lipolytic visceral fat depots into subcutaneous fat (39-42). In several studies, fat redistribution following TZD treatment in T2D subjects was associated with a 50% reduction in hepatic fat and improvements in hepatic insulin sensitivity, including greater insulin-mediated suppression of endogenous glucose production and augmented splanchnic glucose uptake (42, 43).

Obesity associated increases in circulating FFAs and hepatic TG storage correlate with reduced insulin mediated glucose uptake and production at the liver (34, 44, 45). Recently, intrahepatic TG content in obese subjects

was shown to be the best predictor of insulin action in liver, skeletal muscle and adipose tissue (46). In addition to dietary intake, hepatic TG accumulation is affected by *de novo* lipogenesis, fatty acid beta oxidation and very low density lipoprotein (VLDL) export. PPAR-γ affects these processes in multiple ways. First, it mediates the partitioning of lipids into adipocytes, away from the circulation and tissues including the liver. This occurs as FFA uptake by fat is augmented through increased expression of lipoprotein lipase (47), fatty acid transport protein (48), fatty acid translocase (49) and oxidized LDL receptor 1 (50). In addition, TZDs promote recycling instead of export of intracellular FFAs by increasing adipose expression of PEPCK (enabling gluconeogenic precursors to form the glycerol backbone required for TG synthesis) (28), glycerol kinase (enabling the direct synthesis of glycerol-3-phosphate from glycerol) (51) and glycerol transporter aquaporin (52). Finally, FFA oxidation is increased through the induction of the coactivator PGC-1a, which promotes mitochondrial biogenesis (53). These cumulative effects result in increased FFA flux into adipose tissue and decreased TG accumulation in the liver (41, 43), improving hepatic insulin sensitivity (54, 55). In addition, TZDs increase arachidonic acid content in TGs, which is associated with increased insulin sensitivity (56).

TZDs also improve hepatic insulin sensitivity by inducing the expression of the insulin-sensitizing factor, adiponectin (57). Adiponectin is produced by adipose tissue, is reduced in obesity (58) and T2D (59), and has direct insulin sensitizing actions on the liver (60). It exists in the serum and intracellularly in multiple complexes, including high-molecular weight (HMW) multimers, which have the predominant action in the liver (60). The adiponectin promoter contains a functional PPAR-γ response element (61, 62) and production of adiponectin is increased by TZD treatment in humans (21, 63-65). Importantly, TZD treatment preferentially increases the formation, secretion and amount of circulating HMW adiponectin (66). In one study, patients with T2D treated with a TZD for 21 days showed a strong correlation between the percent increase in HMW adiponectin and percent decrease in endogenous glucose production, and these rapid treatment effects occurred prior to confounding effects on plasma glucose and FFA levels (65). The observed early hepatic response was the result of improved suppression of endogenous glucose production by insulin and occurred when arterial plasma insulin concentrations were clamped at 50 but not 400 μU/ml, presumably because at the higher dose insulin's effect on the liver was saturated. Greater suppression of glucose production with TZD treatment was also observed at low (42) but not higher (42, 67, 68) insulin clamp levels after longer periods of treatment (8 to 16 weeks).

The TZD mediated adiponectin effect on the liver appears to be brought about in part by increased hepatic fatty acid oxidation through activation of PPAR-α (69), another member of the PPAR family. In the liver, PPAR-α promotes FFA oxidation, high density lipoprotein synthesis, and TG hydrolysis (70). Treatment with adiponectin *in vitro* resulted in increased activity of acyl-CoA oxidase, carnitine palmitoyl transferase-1 and fatty acid binding protein, leading to increased fatty acid oxidation (71). In addition, TZDs ameliorate the negative effects of TNF-α on adiponectin expression (62). Part of the insulin sensitizing action of adiponectin may involve the activation of AMPK, which results in inhibition of acetyl CoA carboxylase and subsequent increased fatty acid beta oxidation (72). Adiponectin has also been shown to reduce glucose production in the liver by inhibition of PEPCK and G6Pase expression (73).

PPAR-γ activation also ameliorates the effects of insulin resistance associated with inflammation by decreasing the expression of proinflammatory cytokines and a wide variety of other insulin desensitizing molecules, such as resistin, TNF-α, PAI-1, IL-6, IL-1β, retinol-binding protein-4, inducible nitric oxide synthase, matrix metallo-proteinase-9, scavenger receptor-A, NF-κB, and superoxides (34, 74-76). In addition, expression of 11β-hydroxysteriod dehydrogenase-1 (11β-HSD1), which elevates intracellular cortisol levels, is reduced by PPAR-γ activation (77). Cortisol antagonizes the effects of insulin and promotes hepatic glucose production, and since the rate of hepatic cortisol production approaches that of all other endogenous sources (78, 79), inhibition of 11β-HSD1 may represent an important part of the TZD effect on the liver.

In summary, TZDs increase insulin sensitivity in the liver through the activation of PPAR-γ, which mediates a variety of effects, especially in adipose tissue. Effects of TZD treatment on patients with T2D include alterations in the site of fat deposition, decreases in circulating FFA levels and intrahepatic TG accumulation, and altered expression of adipokines such as adiponectin, resistin and TNF-α. Beneficial effects at the liver appear to relate to greater suppression of glucose production and increased glucose utilization.

5. INSULIN ANALOGS AND SECRETAGOGUES

It is clear that insulin is a critical regulator of hepatic glucose production (80). It brings about its effects on the liver by both direct and indirect means. The direct effect results from the interaction of the hormone with its hepatic receptor and involves the classic Akt signaling cascade (81). The indirect effects of insulin include an action on fat, muscle, the alpha cell and the brain (82, 83). In adipose tissue, insulin inhibits lipolysis and in turn decreases the supply of glycerol and FFA reaching the liver. Glycerol is a gluconeogenic substrate, while FFA provide energy and exert control over gluconeogenic / glycolytic flux, in part via an action on 6-phosphofructo-1-kinase (PFK-1) (84-86). In muscle, insulin stimulates protein synthesis and glucose uptake, thereby again regulating the flow of gluconeogenic precursors (amino acids and lactate) to the liver. In the alpha cell, insulin inhibits glucagon secretion, which in turn lowers hepatic glucose production (87). More recently, it has been demonstrated in rodents that insulin can reduce glucose output by the liver through an action in the hypothalamus (88). To date this has not been confirmed in man.

In a study carried out in the dog (89), there was a very similar fall in glucose production (60-75%) seen in response to a modest rise in plasma insulin (~14 μU/ml) brought about selectively at the liver (i.e. the insulin level was basal in the rest of the body), or in the periphery (i.e. the liver insulin level was basal). Since insulin is secreted into the portal vein, the levels of the hormone that normally exist in the hepatic sinusoid are about three-fold that in the artery. One would predict, therefore, that in the normal individual the direct effects of insulin would be dominant. This was shown to be the case in a study by Edgerton *et al.* (90) where during a pancreatic clamp in dogs the route of insulin delivery was switched from the portal vein to a leg vein. The insulin levels in arterial blood doubled (i.e. doubling insulin's indirect effects), while its level in the hepatic sinusoid fell by ~50% (i.e. halving insulin's direct effect). As a result of these changes, glucose production rose significantly and hyperglycemia resulted, showing that the change in insulin at the liver was more important than its change in the periphery.

Normally, the sensitivity of the liver to insulin is extremely high. In fact, a doubling of basal insulin secretion will markedly decrease hepatic glucose output (80%), while a tripling will cause the liver to stop producing glucose altogether (80). In the individual with T2D this sensitivity is impaired. If this impairment is accompanied by beta cell failure these patients often require insulin treatment to control their diabetes. The individual with type 1 diabetes is, of course, dependent on insulin administration for control of glucose homeostasis. Over the past several decades a variety of long acting (glargine, detemir) and short acting (lispro, aspart, glulisine) insulin analogs have been developed which have improved the ability of the patient to manage their blood sugar. However, all of these preparations must be delivered by subcutaneous injection, resulting in an abnormal ratio between peripheral and portal vein insulin concentrations. In order to adequately control the blood sugar, insulin levels in arterial blood must be higher than appropriate to compensate for relative hypoinsulinemia in the hepatic sinusoids. This is thought to contribute to the weight gain, hypoglycemia, and possibly macrovascular disease associated with insulin treatment. Ideally, one would like an insulin molecule that could be given orally (thereby increasing the portal to arterial insulin ratio) or one with preferential sensitivity for the liver. The latter could be given peripherally, but would act as if it had been given intraportally.

Sulphonylureas have been intensely used in the treatment of diabetes for nearly 50 years (5). They lower blood glucose by stimulating the release of insulin from pancreatic beta cells following the binding of an ATP-dependent K^+ channel (KATP) on the cell membrane. First (acetohexamide, chlorpropamide, tolbutamide, tolazamide), second (glipizide, gliclazide, glibenclamide, gliquidone) and third (glimepiride) generation sulphonylureas have been developed. More recently, meglitinide insulin secretagogues, which target first phase insulin release (nateglinide, repaglinide, mitiglinide), have become available. They bind to a beta cell KATP channel in a similar manner to sulfonylureas, but at a separate binding site. Compared to sulfonylureas, meglitinides have a faster onset and peak, with a shorter duration, thus they are generally taken just before meals and have reduced potential for hypoglycemia.

Insulin secretagogues cause the release of endogenous insulin and in doing so bring about a normal distribution of insulin between the liver and the peripheral tissues and regulate glucose production as described above for insulin. For a review related to the insulin secretagogues, see the article by Krentz and Bailey (5).

6. INCRETINS, INCRETIN MIMETICS AND DIPEPTIDYL PEPTIDASE-4 INHIBITORS

Glucagon-like peptide-1 (GLP-1) is a gut derived incretin peptide which is released following the ingestion of food, stimulating insulin secretion in a glucose dependent manner (91). GLP-1 also suppresses glucagon secretion and appetite, delays gastric emptying and may help maintain beta cell mass (91). GLP-1 is rapidly degraded by dipeptidyl peptidase-4 (DPP4), therefore DPP4 resistant GLP-1 analogs (liraglutide) and incretin mimetics (exenatide) as well as inhibitors of DPP4 (sitagliptin, vildagliptin) are, or might soon, be available (92).

With ~80% of hepatic blood supplied by the hepatic portal vein, GLP-1 levels are significantly greater at the liver than in the periphery (93). Mixed results suggest that at best, minimal levels of the classical GLP-1 receptor are present in the liver (94, 95), but it has been shown that radiolabeled GLP-1 binds to hepatic membranes (96). Thus, there is potential for direct regulation of the liver by GLP-1 with resulting in changes in glucose production and utilization (96, 97).

While it is clear that hepatic glucose production and uptake can be regulated indirectly by GLP-1 through its effect on pancreatic hormone levels, there is evidence that GLP-1 can exert a direct effect on the liver as well (93, 98). In humans, a peripheral infusion of GLP-1 that created a physiologic increase in plasma GLP-1 levels, suppressed glucose production under euglycemic clamp conditions with pancreatic hormones clamped at basal levels (99). In dogs, when physiological or pharmacological increases in plasma GLP-1 were brought about under hyperglycemic-hyperinsulinemic clamp conditions, there was a modest increase in net hepatic glucose uptake (93, 98, 100). This effect occurred whether GLP-1 was administered intraportally or via the hepatic artery (93, 98), suggesting that GLP-1 was mediating this effect directly by activating its receptors at the liver. This effect was small and required high physiological levels of the peptide.

In an *in vitro* study, GLP-1 increased glucose incorporation into glycogen in hepatocytes due to increased glycogen synthase and decreased glycogen phosphorylase activity (101). Changes in enzyme activation were the result of cAMP-independent signaling via PI-3 kinase / PKB pathways (102). This is in agreement with the inhibition of glucagon-induced glycogenolysis by GLP-1

(103). When GLP-1 levels were elevated in the brain of mice, insulin mediated hepatic glucose uptake and conversation into glycogen was favored over nonhepatic glucose uptake (104). These results indicate that GLP-1 may enhance glucose uptake and storage in the liver by both direct and indirect mechanisms.

In addition to possible direct hepatic effects, elevated GLP-1 or incretin mimetic levels inhibit endogenous glucose production by increasing insulin and decreasing glucagon secretion. Glucagon is inappropriately elevated following a meal in T2D patients (105-107) and is therefore considered a component of liver insulin resistance. In recent studies, vildagliptin (108, 109) and exenatide (110) suppressed endogenous glucose production by increasing the insulin to glucagon ratio.

In summary, incretins, incretin mimetics and DPP4 inhibitors suppress hepatic glucose production by increasing the plasma insulin to glucagon ratio. In addition, some evidence suggests that signaling through the GLP-1 receptor in the liver may mediate direct inhibitory effects.

7. PRAMLINTIDE

Amylin, sometimes referred to as islet amyloid polypeptide when produced endogenously, is a peptide secreted by the pancreatic beta cell. Amylin is co-localized and co-secreted with insulin (111). Primary gluco-regulatory effects of the peptide are decreased food intake and slowed gastric emptying, both resulting in a decrease in the rate of nutrient entry in the body (112). Pramlintide, a relatively new adjunct treatment for type 1 and 2 diabetic patients who use insulin, is a stable analogue of human amylin.

Earlier studies suggested that amylin increases hepatic glucose production (113-116). This effect was observed with supraphysiologic circulating levels of amylin achieved after exogenous administration and appears to result from increased muscle glycogenolysis, which in turn increases circulating lactate levels and fuels gluconeogenesis in the liver (116-118). There is no evidence for a direct effect of amylin on endogenous glucose production in hepatocytes, perfused liver, or *in vivo* in humans (119).

It has been shown that in patients with either type 1 or type 2 diabetes, pramlintide infusion decreases postprandial glycemia (120-122), and it is speculated that a third mechanism, suppression of postprandial glucagon levels (123, 124), is a key contributing factor alongside the slowing of gastric emptying (125). The decrease in postprandial glucagon levels may be a consequence of the effect on gastric emptying, which leads to lower circulating levels of amino acids during the postprandial period, rather than a direct effect on the pancreatic alpha cell (112). However, euglycemic clamp studies conducted in rodents suggest that there may be an effect to suppress glucagon independent of gastric emptying, where arginine-induced glucagon release was suppressed by amylin (126). Of note, the inhibitory effect of amylin on glucagon secretion is absent in the setting of hypoglycemia (127, 128). At present, studies clarifying this issue have not been performed in humans (129), but it appears that while amylin reduces postprandial glucagon levels, it does not affect glucagon action at the liver (130, 131). Lastly, studies of glucagon secretion in isolated islets and in the perfused pancreas (132) show no amylin effect, suggesting that the effect on the alpha cell is not directly mediated.

In summary, since glucagon is inappropriately elevated in T2D (105-107), it has been suggested that amylin may reduce excessive endogenous glucose production during the postprandial period through the reversal of hyperglucagonemia (123, 124, 133). However, it remains unclear what accounts for the significant reductions in postprandial glucose levels observed in T2D patients treated with pramlintide (120, 121) since studies in the rat employing pharmacologic concentrations of amylin have suggested stimulation of glucose production by amylin (113-115), whereas improved glycemia in humans is associated with reduced glucagon levels (123) as well as slowed gastric emptying (125).

8. POTENTIAL HEPATIC TARGETS

The rate at which the liver produces glucose during fasting, and the degree to which it switches to glucose clearance following a meal, are determinants of circulating glucose concentrations. Therefore, enzymes and hormones controlling pathways involved in hepatic glucose production and uptake represent potential targets for the treatment of T2D. These have been reviewed previously (134, 135) and include inhibition of glucagon binding or signaling (glucagon receptor antagonists, compounds that interfere with the coupling between the glucagon receptor and activation of adenyl cyclase), inhibitors of intrahepatic cortisol binding or production (hepatic selective glucocorticoid receptor antagonists, 11β-HSD-1 inhibitors) enzyme inhibitors of gluconeogenesis (G6Pase, F16BPase, the bisphosphatase activity of 6-phosphofructo-2-kinase / fructose-2,6-bisphosphatase [PFK-2 / F26BPase]), PEPCK) and glycogenolysis (G6Pase, glycogen phosphorylase), and activators of glucose uptake (glucokinase) storage (glycogen synthase) and oxidation (PFK-1, pyruvate kinase, or the kinase activity of PFK-2 / F26BPase). Modulators of these pathways are in various stages of development and it remains unclear which may prove therapeutically viable.

9. SUMMARY

Dysregulation of hepatic glucose metabolism in the diabetic state leads to elevated basal endogenous glucose production with fasting hyperglycemia, as well as impaired postprandial suppression of glucose production and reduced liver glucose clearance. Several of the currently available therapeutics target hepatic dysfunction, directly or indirectly. Although mechanisms of action are frequently not fully understood, the health benefits of improved hepatic glucose metabolism are clear.

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Abbreviations: T2D: type 2 diabetes; ^2H_2O: deuterated water; MIDA: mass isotopomer distribution analysis; G6Pase: glucose-6-phosphatase; F16BPase: fructose-1,6-bisphosphatase; PEPCK: phosphoenolpyruvate carboxykinase; AMPK: AMP-activated protein kinase; TZD: thiazolidinedione; PPAR-γ: peroxisome proliferator-activated receptor gamma; LDL: low density lipoprotein;

FFA: free fatty acid; TG: triglyceride; VLDL: very low density lipoprotein; HMW: high molecular weight; 11β-HSD1: 11β-hydroxysteriod dehydrogenase-1; PFK-1: 6-phosphofructo-1-kinase; KATP: ATP-dependent K^+ channel; GLP-1: glucagon-like peptide-1; DPP4: dipeptidyl peptidase-4; PFK-2: 6-phosphofructo-2-kinase; F26BPase: fructose-2,6-bisphosphatase

Key Words: Hepatic Glucose Production, Diabetes, Metformin, Thiazolidinediones, Insulin, Incretins, Dipeptidyl Peptidase-4 Inhibitors, Pramlintide, Review

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