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Review Article

NOVEL MULTI ACTION THERAPY APPROACHES OF GLUCOKINASE ACTIVATOR TO TREAT TYPE 2 DIABETES

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ABSTRACT

Glucokinase enzyme is a member of the hexokinase family that are responsible for the phosphorylation of glucose to glucose-6-phosphate for further utilization in cells. The enzyme play vital role in glucose homeostasis. Phosphorylation of glucose by glucokinase in the liver promotes glycogen synthesis, while in the β-cell it results in insulin release. Activators of glucokinase increase the sensitivity of the enzyme to glucose, leading to increased insulin secretion and liver glycogen synthesis and a decrease in liver glucose output. Thus, small molecule glucokinase activators have been demonstrated to be effective glucose-lowering agents in animal models of type 2 diabetes and have advanced into clinical studies.

Keywords: Diabetes mellitus, Glucokinase activator, Glucokinase regulatory protein, Anti-hyperglycemic agents

1. INTRODUCTION

Diabetes mellitus is one of the common metabolic disorders with micro-and macro vascular complications that results in significant morbidity and mortality. It is considered as one of the five leading causes of death in the world [1, 2]. According to the International Diabetes Federation, diabetes affected approximately 425 million people in 2017, and this number is expected to rise to 629 million by 2045. The increasing prevalence of diabetes is driven by a variety of factors, including diet, urbanization, and obesity. Type 2 diabetes mellitus (T2DM) is the predominant form of the disease and constitutes the majority of adult cases worldwide [3]. T2DM is typically characterized by hyperglycemia, insulin resistance, abnormally elevated hepatic glucose production, and inadequate glucose-stimulated insulin secretion (GSIS) from pancreatic β-cells [4]. Insufficient blood glucose control increases the risk of vascular complications such as coronary artery disease, peripheral arterial disease, stroke, nephropathy, neuropathy, and retinopathy [5]. Although various oral anti-hyperglycemic agents are available, monotherapy or combination regimens are frequently inadequate for maintaining blood glucose levels in the long term. Furthermore, many of these agents exhibit side effects such as hypoglycemia, weight gain, gastrointestinal side effects, and genitourinary infection [6, 7]. Once patients lose approximately half of their pancreatic β-cells, [8] type 2 diabetes develops as a consequence of insufficient insulin release from the pancreas to compensate for insulin resistance developed in the liver [9, 10] and muscle [11, 12]. It is believed that pancreatic β-cell loss in humans is irreversible, [13] although further damage may be delayed by diet, weight loss and exercise [14, 15]. Inasmuch as control of blood glucose concentrations, as measured by glycosylated hemoglobin (A1C), has been correlated with a decreased risk of micro vascular complications [16, 17] control of blood glucose concentration is a primary goal of therapy [18]. Diabetes also is a prominent risk factor for serious cardiovascular events [19-21]. The increased prevalence of diabetes is driven by a variety of factors including population growth, changing diets, urbanization, sedentary lifestyles and the growing epidemic of obesity. The disease itself is characterized by elevated fasting plasma glucose, insulin resistance, dysregulated hepatic glucose production and impaired glucose-stimulated insulin secretion (GSIS). Left uncontrolled, the hyperglycemia associated with T2DM can lead to a variety of micro- and macro vascular complications. Although several classes of therapies for glycemic control are available for clinical use, there still remains a significant need for novel therapies offering improved efficacy, durability and safety to help patients achieve and maintain effective glycemic control. Among the potential novel treatments currently in clinical development, activators of the glucokinase (GK) enzyme

represent a promising approach for helping patients achieve improved glucose control [22, 23]. Therefore, an unmet need exists for more effective therapies offering improved efficacy and safety for the management of diabetes.

Glucokinase (hexokinase IV) is a monomeric enzyme that catalyzes the ATP-dependent conversion of glucose to glucose 6-phosphate, the first and rate-limiting step of glycolysis in the liver and pancreas [24, 25]. GCK was first discovered in the early 1960's, and shortly thereafter it became the subject of intense study due to its unique sigmoidal kinetic response to glucose and its essential role in glucose metabolism [26-28]. Although it shares extensive sequence identity with the three other human hexokinase isozymes, GCK is considered the body's primary glucose sensor because small fluctuations in its activity alter the threshold for glucose stimulated insulin secretion (GSIS) from pancreatic b-cells [29-31]. GCK's midpoint of glucose responsiveness (*K*0.5) is ~30-fold lower than that of homologous isozymes (7 mM for GCK vs. ~0.2 mM for hexokinases I-III) and this value closely matches physiological, circulatory glucose concentrations. Unlike the other hexokinases, GCK is not susceptible to feedback inhibition by physiological concentrations of its product glucose 6-phosphate [32]. In humans, GCK is primarily produced in pancreatic β-cells and liver hepatoparenchymal cells. Within pancreatic β-cells, GCK acts to maintain glucose homeostasis by governing the rate of insulin secretion, while in the liver GCK participates in glycogen synthesis [33]. The importance of precise control over GCK activity in both tissues is emphasized by several disease phenotypes that result from mutations in the human *gck* locus. Maturity onset diabetes of the young type 2 and the more serious permanent neonatal diabetes mellitus (PNDM) are caused by heterozygous inactivating *gck* mutations. By contrast, gain-of-function, activating *gck* mutations produce persistent hyperinsulinemic hypoglycemia of infancy, the severity of which directly correlates with the level of enzyme activation [34-36]. GK demonstrates relatively low substrate binding affinity (S0.5 ~ 8 mM), positive substrate cooperativity and lack of product inhibition [37]. The sensitivity of GK activity to substrate concentration over the physiologically relevant glucose range enables the enzyme to function as a glycemic sensor and metabolic regulator in the pancreas, liver, ventromedial hypothalamus and the gastrointestinal tract. In the pancreas, GK serves as a 'glucostat' controlling the threshold for GSIS in b-cells [38]. In islets from subjects with type 2 diabetes, this threshold for GSIS is inappropriately attenuated requiring higher glucose concentrations to trigger insulin secretion, thereby contributing to hyperglycemia. This impairment in glucose sensing has been postulated to be due, in part, to impaired activity of pancreatic GK [39]. In the liver, GK activity is the rate-determining step for glucose uptake and helps to regulate hepatic glucose production [40]. Interestingly, in hepatocytes, but not other cell types, the activity of GK is regulated through an interaction with the glucokinase regulatory protein (GKRP) [41]. During periods of low glucose, GKRP binds the inactive conformation of GK and sequesters the enzyme to the nucleus. As intracellular glucose concentrations rise, GK dissociates from GKRP and enters the cytoplasm where it can bind and phosphorylate glucose. Significant progress in the understanding of the molecular basis for the activity of GKRP has been achieved with the publication of crystal structures of GKRP and the GK-GKRP complex along with studies of the binding and translocation of the complex [42-45]. Recent data suggest that this GKGKRP interaction may also be influenced by hormonal regulation through the action of glucagon [46]. During the progression of diabetes, patients experience abnormally elevated hepatic glucose production coupled with reduced capacity for hepatic glucose uptake and glycogen synthesis, which is attributable, in part, to reduced hepatic GK activity [47, 48]. Although available data are limited, one study found that T2DM patients lose up to 50% of their hepatic GK activity during the progression of this disease, potentially contributing to reduced hepatic glycogen synthesis and improper regulation of hepatic glucose output [49]. Potentially related to the loss of hepatic GK activity during diabetes, preclinical studies have shown that Zucker diabetic rats experience impaired GKRP regulation of GK, which also contributes to the dysregulation of hepatic glucose metabolism [50]. GK is additionally found in glucose-sensing neurons of the ventromedial hypothalamus where it helps regulate the counter regulatory response to hypoglycemia [51]. Finally, the enzyme is also expressed in the endocrine K and L cells of the gut as well as certain pituitary cells where its functions are less well characterized but may be involved in nutrient sensing [52-53].

2. THE ROLE OF GK IN GLUCOSE HOMEOSTASIS

GK is selectively expressed in a restricted number of cell types most notably the pancreatic β -cells and liver parenchymal cells (hepatocytes) where its function has been most extensively characterised. GK is encoded by a single gene whose expression is driven by tissue selective promoters in the liver and pancreas. Liver and pancreatic GK differ only in the amino acid sequence at the extreme amino terminus and these tissue isoforms appear enzymatically and kinetically identical [54]. The pancreatic isoform of GK is also expressed outside the pancreas in discrete populations of cells in the gut and brain; hence this isoform is also referred to as the neuroendocrine isoform [55, 56]. However, the role of GK that is expressed in neuronal cells and in gut entero-endocrine cells remains a subject of ongoing investigation that is revisited later in this review. GK catalyses the phosphorylation of glucose to glucose 6-phosphate. In both the pancreatic β -cell and the hepatocyte, glucose is transported into the cell by a high capacity, low affinity glucose transporter, GLUT2. Consequently, the intracellular glucose concentration matches that of plasma glucose. GK is therefore the rate-limiting step for glucose uptake and metabolism in these cells [57, 58].

GK is often referred to as the 'glucose sensor' as it directly relates the rate of β -cell glucose-dependent insulin secretion and the rate of hepatocyte glucose metabolism to the ambient blood glucose level [59]. The sigmoidal kinetics of GK makes it ideally suited for this role. GK displays positive cooperativity for glucose phosphorylation with a half maximum velocity reached at a substrate concentration (S 0.5) of ~ 7.5 mM. Consequently, GK activity is acutely sensitive to changes in blood glucose within the physiological range of 5 -10 mM. In contrast, if GK displayed non-cooperative Michaelis Menten kinetics its activity would show a greatly reduced fluctuation over the physiological glucose range [60]. GK is sometimes referred to as hexokinase IV, or hexokinase D, to reflect the fact that three other homologous hexokinases exist in mammals. Hexokinases I, II and III are expressed more ubiquitously than GK. These hexokinases do not serve as glucose sensors as the enzymes have Michaelis Menten substrate phosphorylation kinetics with Km values ranging from 0.02 mM to 1 mM glucose; well below the physiological glucose range. It is the high affinity, low capacity, glucose transporters which are coexpressed with hexokinases I, II and III, which determine the rate of glucose metabolism.

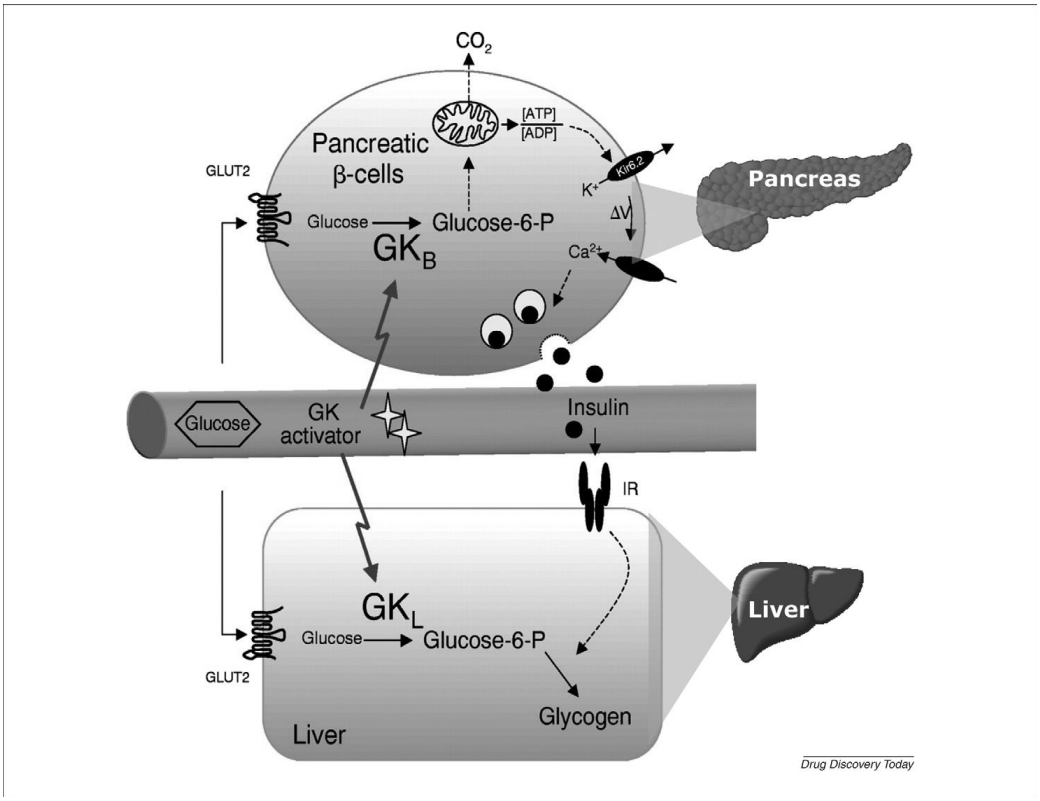

Fig. 1: The mechanism of glucokinase in pancreas and liver

The fundamental importance of GK in maintaining glucose homeostasis is explained by its role in the liver and pancreas [61]. These two tissues, either directly or indirectly, determine the ambient blood glucose levels throughout the day [62]. In the postprandial period blood glucose levels are high. Consequently, hepatic GK activity is high and this catalyses glucose phosphorylation and its incorporation into hepatic glycogen stores. Simultaneously, the high GK activity acts to reduce hepatic glucose output (HGO) through the suppression of hepatic glycogenolysis and gluconeogenesis. In the postprandial period increased pancreatic β -cell GK activity mediates the observed glucose stimulated insulin secretion. Elevated insulin levels also act to promote hepatic glycogen synthesis and suppress HGO. Additionally, insulin promotes the peripheral disposal of glucose into muscle and fat. Therefore, the net effect of postprandial glucose stimulated increases in hepatic and pancreatic GK activity is to return blood glucose level to its normal fasted level. Once this fasted glucose level is reached the concomitant reduction in hepatic and pancreatic GK activities leads to a suppression of insulin secretion and an increase in hepatic glucose output. This catabolic state then maintains the fasted blood glucose level until the next meal is consumed [63-65].

3. SMALL MOLECULES AS GLUCOKINASE ACTIVATORS

The allosteric pocket of GK, which is the binding site for GK activators (GKAs), is about 20Å remote from the glucose binding. It has been shown that the glucose-lowering effect of recently discovered GKAs is due to binding to this pocket. Many of these GK activators have been shown [66-70] to have potent antihyperglycemic actions in rodents, by increasing pancreatic insulin secretion and by enhancing hepatic glucose metabolism. It is worthy of mention that a bifunctional enzyme, 6-phosphofructo-2-kinase/ fructose-2,6-bisphosphatase (6PF2K/F26P2ase), was found to be an activator of GK [71], although it remains to be clarified whether this is an endogenous activator of GK that acts by a similar mechanism to GKAs. Subsequently, many structurally diverse small molecule activators of GK have been reported [72]. These GK activators (GKAs) have been shown to effectively lower blood glucose in a variety of diabetic animal models, and multiple candidates have advanced into Phase I and II clinical studies where they have been found to effectively lower both fasting and postprandial glucose in both healthy volunteers and T2DM patients [73]. However, despite the promising efficacy of this mechanism, there has been significant attrition in the clinical development of GKAs driven by narrow therapeutic indexes against hypoglycemia as well as concerns around durability of efficacy and chemotype-related safety issues [74]. The importance of GCK in glucose metabolism and disease has stimulated much interest from the pharmaceutical industry to develop activators of the enzyme [75-76].

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