

## EFFECT OF GLYBURIDE ON CARBOHYDRATE METABOLISM IN THE LIVER

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**SUMMARY :** *Glyburide (Glibenclamide), one of the second-generation sulfonylureas, decreases glucose production and enhances insulin action in the liver. Available data suggests that glyburide : (1) enhances glycogen synthase; (2) inhibits glycogenolysis by phosphorylase a activity; (3) decreases gluconeogenesis and stimulates glycolysis by decreasing A - kinase activity, which results in increased fructose 2, 6-biphosphate, one of the key regulators of carbohydrate metabolism in the liver.*

*This review will focus on : The metabolic alterations responsible for increased hepatic glucose production in type II diabetes in vivo and in vitro demonstrating the metabolic effects of glyburide in type II diabetic liver.*

**Key Words :** *Glyburide, Carbohydrate Metabolism, Liver.*

Since Himsworth (18) established in 1936 that diabetes mellitus affects both patients who are insulin-sensitive and those who are insulin-resistant, much effort has been directed toward understanding the etiology of diabetes in these two groups. Currently there are two classifications of diabetes mellitus. Type I diabetes or insulin-dependent diabetes mellitus and Type II diabetes or non-insulin-dependent diabetes mellitus (25).

In type I diabetes the primary alteration resides in the pancreas and results in insulin deficiency, whereas in type II diabetes, multiple abnormalities are involved, including : (1) defects in insulin secretion; (2) peripheral (muscle and adipose tissue) insulin resistance; and (3) hepatic insulin resistance. Thus; Type II diabetes, which represents over 80 percent of all patients with diabetes mellitus, is a complex disorder in which the primary alteration is

still unknown. Moreover, type II diabetes is frequently accompanied by obesity, which in itself contributes to insulin resistance (7).

The liver appears to play a fundamental role in the development of fasting hyperglycemia in type II diabetes because of the well-documented increased hepatic glucose production that occurs with this disease (9).

Skeletal muscle plays the most important role in glucose disposal and thus insulin resistance in skeletal muscle explains the postprandial hyperglycemia of type II diabetes (9).

Oral hypoglycemic sulfonylureas have been used in the treatment of non-insulin-dependent diabetes (NIDDM) since 1955. Although a voluminous literature on the clinical use of these drugs has been presented over the last 40 years, many clinical

questions are still unresolved and major new insights into the mechanism and significance of this class of drugs have occurred just recently (19).

Glyburide; one of the second-generation sulfonylureas, provides an effective therapy for patients with type II diabetes. Glyburide normalizes blood glucose by increasing insulin secretion improving insulin action in the liver, decreasing hepatic glucose production (15). Insulin at a concentration of 10 mU/ml was unable to suppress glucagon's stimulation of glucose production or its activation of phosphorylase. However in the presence of glyburide it was able to decrease stimulated hepatic glucose production and phosphorylase activation by 40 and 50 % respectively. In the absence of insulin, glyburide was unable to suppress glucagon's glycogenolytic action on the liver rather than exerting an inhibitory effect directly. Glyburide is able to enhance the sensitivity of the perfused rat liver to insulin without altering maximal insulin responsiveness (13).

#### **Increase in Hepatic Glucose Production in Type II diabetes**

There is general agreement that increased hepatic glucose output, which might be caused by several metabolic alterations, plays a major role in the fasting hyperglycemia of type II diabetes (6, 12, 15, 26, 29, 30). Consoli et al (10) presented direct evidence from isotopic studies in humans that the increased hepatic glucose output of type II diabetes is brought about primarily by increased gluconeogenesis. The increased gluconeogenesis of type II diabetes in turn, is probably produced by several metabolic alterations. The fact that glycogenolysis appears to be more sensitive to inhibition by insulin than gluconeogenesis (4) in type II diabetes could explain the preferential increase in gluconeogenesis. Also, free fatty acids (FFA), which are chronically increased in type II diabetes, can activate key gluconeogenic enzymes (31). Baron et al (5), demonstrated also that the hyperglucagonemia present in type II diabetes, glycerol and alanine (the major gluconeogenic precursors), may contribute to increased glucose production by the liver.

#### **Decrease in Hepatic Glucose Production by Glyburide in Type II Diabetes**

Hypoglycemic effect of oral hypoglycemic agents in the initial phase of treatment is the result of acute stimulation of insulin secretion (27); du-

ring long term treatment, extrapancreatic effects are of greater importance. These extrapancreatic effects include suppression of hepatic glucose production and increased glucose utilization (16, 20).

In the patients with type I diabetes, the addition of glyburide did not improve glycemic control; however in patients with type II diabetes, glyburide produced a moderate improvement in glycemic control associated with increases in the c-peptide concentration (27).

Glyburide is generally thought to exert two major actions : stimulation of pancreatic insulin secretion and enhancement of insulin action in hepatic and extrahepatic tissues. Studies in patients with NIDDM indicate that the action of glyburide on the liver plays a central role in decreasing glucose. With short term therapy, glyburide decreases hepatic glucose production by elevating pancreatic insulin secretion. However this increase in pancreatic insulin secretion is not sustained as therapy is continued, suggesting that glyburide then acts directly on the liver. The mechanism for the improvement in hepatic glucose metabolism after long - term treatment is not known (24).

Initial studies suggested that its major site of action is the pancreas. After short-term glyburide therapy (1 day to two weeks), basal insulin levels are elevated and the insulin response to a meal is increased, leading to marked reductions in both preprandial and postprandial glycemia. After more prolonged therapy (6 months to two years) basal insulin levels and the insulin response to a meal are similar to, or only slightly greater than those observed before treatment. Nevertheless, the associated glucose levels remain markedly improved, suggesting that glyburide also acts at an extrapancreatic site (24).

The liver is a major site of insulin resistance in severely hypoglycemic patients with NIDDM was further supported by Campbell et al (8). They concluded that, in patients with NIDDM, the peripheral tissues and the liver were equally resistant to insulin action. They suggested, however, that elevated hepatic glucose production is the major cause of basal hyperglycemia in such patients. Hepatic insulin resistance and the consequent increase in hepatic glucose production are the main causes for the additional increase in fasting hyperglycemia in patients with NIDDM (24).

The exact site or sites of action of glyburide in the metabolic pathway (s) of carbohydrate metabolism in human liver have not yet been elucidated. However, animal models have provided evidence that glyburide may act at multiple sites in more than one metabolic pathway. Cultured rat hepatocytes and adipocytes were used by Davidson and Altan (2, 11) to study the direct effect of glyburide on liver and adipose carbohydrate metabolism. Glyburide significantly stimulated glycogen synthesis and glycogen synthase, and potentiated the action of insulin on glycogen synthesis. Also, Lenzen et al (21) demonstrated that glyburide enhances liver glucokinase. Therefore, the effects of glyburide on glycogen synthesis, phosphorylase a, and glucokinase result in increased glycogen synthesis, decreased glycogenolysis, and increased glucose utilization by the liver (3) suggesting a mechanism for the decreased glucose output by the liver.

The ability of glyburide to enhance insulin's activation of glycogen synthase could be due to an increase in the number or the affinity of insulin receptors. Prince and Olefsky (28) have reported that glyburide caused a small increase in the number of insulin receptors in human fibroblasts and inhibited insulin-induced down regulation of its receptor. However, Fleig et al (14) were unable to detect any alteration in insulin receptor number or affinity in hepatocytes treated with glyburide nor could affect insulin-induced down regulation of its receptor. Maloff and Lockwood (22) were also unable to detect any alteration in insulin receptor number or affinity in adipose tissue cultured with tolazamide. However, Altan et al (2) have reported that glyburide caused increase in the number of insulin receptors in cultured rat adipocytes. In addition, Altan et al. also demonstrated that the sulfonylurea glyburide is capable of exerting direct insulin-like and insulin-potentiating effects on non-pancreatic tissue glycogen synthase and glycogen synthesis (1, 2, 3).

Hatao et al (17) studied the effect of glyburide on fructose 2, 6-bisphosphate (Fru 2,6-P<sub>2</sub>) formation using isolated perfused rat liver. Glyburide stimulated fructose 2, 6-bisphosphate formation in a dose-dependent manner, with the maximal effect observed at 10<sup>-6</sup> M of Glyburide; a concentration that corresponds well with the blood levels of glyburide measured after administration of therapeutic oral doses of the drug.

This is probably the major mechanism by which glyburide inhibits gluconeogenesis and stimulates glycolysis, which in turn decreases hepatic glucose production and increases hepatic glucose utilization.

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