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(54) Title: METHOD OF REGULATING GLUCOSE METABOLISM, AND REAGENTS RELATED THERETO

(57) Abstract

The present invention provides methods and compositions for modification and regulation of glucose and lipid metabolism, generally to reduce insulin resistance, hyperglycemia, hyperinsulinemia,obesity, hyperlipidemia, hyperlipoprotein–emia (such as chylomicrons, VLDL and LDL), and to regulate body fat and more generally lipid stores, and, more generally, for the improvement of metabolism disorders, especially those associated with diabetes, obesityand/or atherosclerosis.

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Method of Regulating Glucose Metabolism, and Reagents Related Thereto

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Background of the Invention

Diabetes adversely affects the way the body uses sugars and starches which, during digestion, are converted into glucose. Insulin, a hormone produced by the pancreas, makes the glucose available to the body's cells for energy. In muscle, adipose (fat) and connective tissues, insulin facilitates the entry of glucose into the cells by an action on the cell membranes. The ingested glucose is normally converted in the liver to CO_2 and H_2O (50%); to glycogen (5%); and to fat (30-40%), the latter being stored in fat depots. Fatty acids from the adipose tissues are circulated, returned to the liver for re-synthesis of triacylglycerol and metabolized to ketone bodies for utilization by the tissues. The fatty acids are also metabolized by other organs. Fat formation is a major pathway for carbohydrate utilization.

The net effect of insulin is to promote the storage and use of carbohydrates, protein and fat. Insulin deficiency is a common and serious pathologic condition in man. In insulin-dependent (IDDM or Type I) diabetes the pancreas produces little or no insulin, and insulin must be injected daily for the survival of the diabetic. In noninsulin-dependent (NIDDM or Type II) diabetes the pancreas retains the ability to produce insulin and in fact may produce higher than normal amounts of insulin, but the amount of insulin is relatively insufficient, or less than fully effective, due to cellular resistance to insulin.

Diabetes mellitus (DM) is a major chronic illness found in humans with many consequences. Some complications arising from long-standing diabetes are blindness, kidney failure, and limb amputations. Insulin-dependent diabetes mellitus (IDDM) accounts for 10 to 15% of all cases of diabetes mellitus. The action of IDDM is to cause hyperglycemia (elevated blood glucose concentration) and a tendency towards diabetic ketoacidosis (DKA). Currently treatment requires chronic administration of insulin. Non-insulin dependent diabetes mellitus (NIDDM) is marked by hyperglycemia that is not linked with DKA. Sporadic or persistent incidence of hyperglycemia can be controlled by administering insulin. Uncontrolled hyperglycemia can damage the cells of the pancreas which produce insulin (the β-islet cells) and in the long term create greater insulin deficiencies. Currently, oral sulfonylureas and insulin are the only two therapeutic agents

available in the United States. for treatment of Diabetes mellitus. Both agents have the potential for producing hypoglycemia as a side effect, reducing the blood glucose concentration to dangerous levels. There is no generally applicable and consistently effective means of maintaining an essentially normal fluctuation in glucose levels in DM. The resultant treatment attempts to minimize the risks of hypoglycemia while keeping the glucose levels below a target value. The drug regimen is combined with control of dietary intake of carbohydrates to keep glucose levels in control.

In either form of diabetes there are widespread abnormalities. In most NIDDM subjects, the fundamental defects to which the abnormalities can be traced are (1) a reduced entry of glucose into various "peripheral" tissues and (2) an increased liberation of glucose into the circulation from the liver. There is therefore an extracellular glucose excess and an intracellular glucose deficiency. There is also a decrease in the entry of amino acids into muscle and an increase in lipolysis. Hyperlipoproteinemia is also a complication of diabetes. The cumulative effect of these diabetes-associated abnormalities is severe blood vessel and nerve damage.

Endocrine secretions of pancreatic islets are regulated by complex control mechanisms driven not only by blood-borne metabolites such as glucose, amino acids, and catecholamines, but also by local paracrine influences. Indeed, pancreatic α- and β-cells are critically dependent on hormonal signals generating cyclic AMP (cAMP) as a synergistic messenger for nutrient-induced hormone release. The major pancreatic islet hormones, glucagon, insulin and somatostatin, interact with specific pancreatic cell types to modulate the secretory response. Although insulin secretion is predominantly controlled by blood glucose levels, somatostatin inhibits glucose-mediated insulin secretion.

The human hormone glucagon is a polypeptide hormone produced in pancreatic A-cells. The hormone belongs to a multi-gene family of structurally related peptides that include secretin, gastric inhibitory peptide, vasoactive intestinal peptide and glicentin. These peptides variously regulate carbohydrate metabolism, gastrointestinal motility and secretory processing. However, the principal recognized actions of pancreatic glucagon are to promote hepatic glycogenolysis and glyconeogenesis, resulting in an elevation of blood sugar levels. In this regard, the actions of glucagon are counter regulatory to those of insulin and may contribute to the hyperglycemia that accompanies Diabetes mellitus (Lund et al. (1982) PNAS, 79:345-349).

Preproglucagon, the zymogen form of glucagon, is translated from a 360 base pair gene and is processed to form proglucagon (Lund, et al., supra). Patzelt, et al. (Nature, 282:260-266 (1979)) demonstrated that proglucagon is further processed into glucagon and

a second peptide. Later experiments demonstrated that proglucagon is cleaved carboxyl to Lys-Arg or Arg-Arg residues (Lund et al., supra; and Bell et al. (1983) Nature 302:716-718). Bell et al. also discovered that proglucagon contained three discrete and highly homologous peptide regions which were designated glucagon, glucagon-like peptide 1 (GLP-1), and glucagon-like peptide 2 (GLP-2). GLP-1 has attracted increasing attention as a humoral stimulus of insulin secretion. In humans, this 29-amino acid peptide, cleaved from proglucagon by cells of the intestinal mucosa, is released into the circulation after nutrient intake (Holst et al. (1987) FEBS Lett 211:169; Orskov et al. (1987) Diabetologia 30:874; Conlon J (1988) Diabetologia 31:563).

GLP-1 has been found to be a glucose-dependent insulinotropic agent (Gutniak et al. (1992) N. Engl. J. Bled. 326:1316-1322). GLP-1 is now known to stimulate insulin secretion (insulinotropic action) causing glucose uptake by cells which decreases serum glucose levels (see, e.g., Mojsov, S., Int. J. Peptide Protein Research, 40:333-343 (1992)). For instance, it has been shown to be a potent insulin secretagogue in experimental models and when infused into humans (Gutniak et al., supra; Mojsov et al. (1988) J Clin Invest 79:616; Schmidt et al. (1985) Diabetologia 28:704; and Kreymann et al. (1987) Lancet 2:1300). Thus, GLP-1 is a candidate for the role of an "incretin", having augmentary effects on glucose-mediated insulin release.

It is also noted that numerous GLP-1 analogs have been demonstrated which demonstrate insulinotropic action are known in the art. These variants and analogs include, for example, GLP-1(7-36), Gln_9-GLP-1(7-37), D-Gln_9-GLP-1(7-37), acetyl-Lys_9-GLP-1(7-37), Thr_{16}-Lys_{18}-GLP-1(7-37), and Lys_{18}-GLP-1(7-37). Derivatives of GLP-1 include, for example, acid addition salts, carboxylate salts, lower alkyl esters, and amides (see, e.g., WO91/11457).

Objects of the Invention

It is one object of this invention to provide improved methods for reducing in animal subjects (including humans) in need of such treatment at least one of insulin resistance, hyperinsulinemia, and hyperglycemia and abating Type II diabetes. Another object is to provide improved methods for reducing at least one of body fat stores, hyperlipidemia, hyperlipoproteinemia, and for abating atherosclerosis. It is another object of this invention to provide methods for interfering with glucose and/or lipid metabolism in a manner beneficial to the host.

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