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(54) Title: COMBINATION THERAPY FOR THE TREATMENT OF DIABETES

(57) Abstract: The present invention relates to compositions comprising an anti-obesity agent and an anti-diabetic agent useful for the treatment of diabetes, diabetes associated with obesity and diabetes-related disorders. The present invention further relates to methods of treating or preventing obesity, and obesity-related disorders, in a subject in need thereof by administering a composition of the present invention. The present invention further provides for pharmaceutical compositions, medicaments, and kits useful in carrying out these methods.

TITLE OF THE INVENTION

COMBINATION THERAPY FOR THE TREATMENT OF DIABETES

BACKGROUND OF THE INVENTION

Diabetes is caused by multiple factors and is most simply characterized by elevated levels of plasma glucose (hyperglycemia) in the fasting state. There are two generally recognized forms of diabetes: type 1 diabetes, or insulin-dependent diabetes mellitus (IDDM), in which patients produce little or no insulin, the hormone which regulates glucose utilization, and type 2 diabetes, or noninsulin-dependent diabetes mellitus (NIDDM), wherein patients produce insulin and even exhibit hyperinsulinemia (plasma insulin levels that are the same or even elevated in comparison with non-diabetic subjects), while at the same time demonstrating hyperglycemia. Type 1 diabetes is typically treated with exogenous insulin administered via injection. However, type 2 diabetics often develop "insulin resistance", such that the effect of insulin in stimulating glucose and lipid metabolism in the main insulin-sensitive tissues, namely, muscle, liver and adipose tissues, is diminished. Patients who are insulin resistant but not diabetic have elevated insulin levels that compensate for their insulin resistance, so that serum glucose levels are not elevated. In patients with NIDDM, the plasma insulin levels, even when they are elevated, are insufficient to overcome the pronounced insulin resistance, resulting in hyperglycemia.

Insulin resistance is primarily due to a receptor binding defect that is not yet completely understood. Resistance to insulin results in insufficient activation of glucose uptake, diminished oxidation of glucose and storage of glycogen in muscle, inadequate insulin repression of lipolysis in adipose tissue and inadequate glucose production and secretion by the liver.

The persistent or uncontrolled hyperglycemia that occurs in diabetics is associated with increased morbidity and premature mortality. Type 2 diabetics are at increased risk of developing cardiovascular complications, e.g., atherosclerosis, coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy and retinopathy.

Non-insulin dependent diabetes is also associated with cardiac hypertrophy, in particular left ventricular hypertrophy (Devereux, R. B., Circulation, 101:2271-2276 (2000)). Cardiac hypertrophy, such as left ventricular hypertrophy, is due to the response of the heart to chronic pressure or volume overload. Left ventricular hypertrophy (LVH) is characterized by thickening of the left ventricular wall, including increased left ventricular mass and increased left ventricular wall thickness, and is defined as a left ventricular mass index exceeding 131 g/m^2 of the body surface area in men, and 100 g/m^2 in women (Savage et al., The Framingham Study, Circulation, 75 (1 Pt 2): 26-33 (1987).

Left ventricular hypertrophy is independently associated with increased incidence of cardiovascular disease, such as congestive heart failure, ischaemic heart disease, cardiovascular and all-cause mortality, sudden death, and stroke. Regression of left ventricular hypertrophy has been associated

with a reduction in cardiovascular risk. It has also been found that the incidence of morbid events in patients with progression of left ventricular hypertrophy is greater than in patients with regression of left ventricular hypertrophy.

Current treatments for hypertrophy include non-pharmacological interventions, such as weight reduction, sodium restriction, and aerobic physical exercise can reduce left ventricular mass (Ghali, J.K. et al., American Journal of Geriatric Cardiology, 6:38-49 (1997).

Many patients who have insulin resistance but have not yet developed type 2 diabetes are also at a risk of developing metabolic syndrome, also referred to as syndrome X, insulin resistance syndrome, or plurimetabolic syndrome. The period of 5 to 10 years preceding the development of impaired glucose tolerance is associated with a number of hormonal imbalances, which give rise to an enlargement of visceral fat mass, hypertension, insulin resistance, and hyperlipidemia (Bjornstop, P., Current Topics in Diabetes Research, eds. Belfore, F., Bergman, R. N., and Molinath, G. M., Front Diabetes, Basel, Karger, 12:182-192 (1993)). Similarly, metabolic syndrome is characterized by insulin resistance, along with abdominal obesity, hyperinsulinemia, high blood pressure, low HDL and high VLDL. Although the causal relationship between the various components of metabolic syndrome remains to be confirmed, insulin resistance appears to play an important role (Requen, G.M., et al., N. Eng. J. Med. 334:374-381 (1996); Despres, J-P., et al., N. Engl. J. Med. 334:952-957 (1996); Wajchenberg, B. L., et al., Diabetes /Metabolism Rev. 10:19-29 (1994)). Metabolic syndrome patients, whether or not they develop overt diabetes mellitus, are at increased risk of developing the cardiovascular complications listed above. Associations have also been found between left ventricular hypertrophy and metabolic syndrome (Lind, L. et al., J Hypertens. 13:433-38 (1995).

Diabetes is treated with a variety of therapeutic agents including insulin sensitizers, such as PPARγ agonists, such as glitazones; biguanides; protein tyrosine phosphatase-1B inhibitors; dipeptidyl peptidase IV inhibitors; insulin; insulin mimetics; sulfonylureas; meglitinides; α-glucoside hydrolase inhibitors; and α-amylase inhibitors.

Increasing the plasma level of insulin by administration of sulfonylureas (e.g. tolbutamide and glipizide) or meglitinides, which stimulate the pancreatic β–cells to secrete more insulin, and/or by injection of insulin when sulfonylureas or meglitinides become ineffective, can result in insulin concentrations high enough to stimulate insulin-resistant tissues. However, dangerously low levels of plasma glucose can result, and increasing insulin resistance due to the even higher plasma insulin levels can occur. The biguanides increase insulin sensitivity resulting in some correction of hyperglycemia. Metformin monotherapy is often used for treating type 2 diabetic patients who are also obese and/or dyslipidemic. Lack of appropriate response to metformin is often followed by treatment with sulfonylureas, thiazolidinediones, insulin, or alpha glucosidase inhibitors. However, the two biguanides, phenformin and metformin, can also induce lactic acidosis and nausea/diarrhea, respectively. Alpha glucosidase inhibitors, such as acarbose, work by delaying absorption of glucose in the intestine. Alpha-

amylase inhibitors inhibit the enzymatic degradation of starch or glycogen into maltose, which also reduces the amounts of bioavailable sugars.

The glitazones, also known as thiazolidinediones (i.e. 5-benzylthiazolidine-2,4-diones), are a more recently described class of compounds with potential for a novel mode of action in ameliorating many symptoms of type 2 diabetes. These agents substantially increase insulin sensitivity in muscle, liver and adipose tissue in several animal models of type 2 diabetes resulting in partial or complete correction of the elevated plasma levels of glucose without occurrence of hypoglycemia. The glitazones that are currently marketed are agonists of the peroxisome proliferator activated receptor (PPAR) gamma subtype. PPAR-gamma agonism is generally believed to be responsible for the improved insulin sensitization that is observed with the glitazones. Newer PPAR agonists that are being developed for treatment of Type 2 diabetes and/or dyslipidemia are agonists of one or more of the PPAR alpha, gamma and delta subtypes.

However, treatment of diabetes with PPAR γ agonists has been associated with cardiac hypertrophy, or an increase in heart weight. Recent labeling revisions for Avandia® (rosiglitazone maleate), a PPAR γ agonist, indicate that patients may experience fluid accumulation and volume-related events such as edema and congestive heart failure. Cardiac hypertrophy related to PPAR γ agonist treatment is typically treated by withdrawing PPAR treatment.

Treatment of type 2 diabetes also typically includes physical exercise, weight control and dieting. While physical exercise and reductions in dietary intake of calories will dramatically improve the diabetic condition, compliance with this treatment is very poor because of well-entrenched sedentary lifestyles and excess food consumption, especially of foods containing high amounts of saturated fat. However, weight reduction and increased exercise are difficult for most people with diabetes.

Abnormal glucose homeostasis is also associated both directly and indirectly with obesity, hypertension and alterations in lipid, lipoprotein and apolipoprotein metabolism. Obesity increases the likelihood of insulin resistance, and increases the likelihood that the resulting insulin resistance will increase with increasing body weight. Therefore, therapeutic control of glucose homeostasis, lipid metabolism, obesity and hypertension are critically important in the clinical management and treatment of diabetes mellitus.

Obesity, which can be defined as a body weight more than 20% above the ideal body weight, is a major health concern in Western societies. It is estimated that about 97 million adults in the United States are overweight or obese. Obesity is the result of a positive energy balance, as a consequence of increased ratio of caloric intake to energy expenditure. The molecular factors regulating food intake and body weight balance are incompletely understood. [B. Staels et al., J. Biol. Chem. 270(27), 15958 (1995); F. Lonnquist et al., Nature Medicine 1(9), 950 (1995)]. Although the genetic and/or environmental factors leading to obesity are poorly understood, several genetic factors have been identified.

Epidemiological studies have shown that increasing degrees of overweight and obesity are important predictors of decreased life expectancy. Obesity causes or exacerbates many health problems, both independently and in association with other diseases. The medical problems associated with obesity, which can be serious and life-threatening, include type 2 diabetes mellitus, hypertension, elevated plasma insulin concentrations, insulin resistance, dyslipidemias, hyperlipidemia, endometrial, breast, prostate, kidney and colon cancer, osteoarthritis; respiratory complications, such as obstructive sleep apnea, gallstones, arterioscelerosis, heart disease, abnormal heart rhythms, and heart arrythmias (Kopelman, P.G., Nature 404, 635-643 (2000)). Obesity is also associated with metabolic syndrome, cardiac hypertrophy, in particular left ventricular hypertrophy, premature death, and with a significant increase in mortality and morbidity from stroke, myocardial infarction, congestive heart failure, coronary heart disease, and sudden death.

Abdominal obesity has been linked with a much higher risk of coronary artery disease, and with three of its major risk factors: high blood pressure, diabetes that starts in adulthood, and high levels of fats (lipids) in the blood. Losing weight dramatically reduces these risks. Abdominal obesity is further closely associated with glucose intolerance, hyperinsulinemia, hypertriglyceridemia, and other disorders associated with metabolic syndrome (syndrome X), such as raised high blood pressure, decreased levels of high density lipoproteins (HDL) and increased levels of very low density lipoproteins (VLDL) (Montague et al., Diabetes, 2000, 49: 883-888).

Obesity and obesity-related disorders, such as diabetes, are often treated by encouraging patients to lose weight by reducing their food intake or by increasing their exercise level, thereby increasing their energy output. A sustained weight loss of 5% to 10% of body weight has been shown to improve the co-morbidities associated with obesity, such as diabetes, and can lead to improvement of obesity-related disorders such as diabetes, left ventricular hypertrophy, osteoarthritis, and pulmonary and cardiac dysfunction.

Weight loss drugs used for the treatment of obesity include orlistat (Davidson, M.H. et al. (1999) JAMA 281:235-42), dexfenfluramine (Guy Grand, B. et al. (1989) Lancet 2:1142-5), sibutramine (Bray, G. A. et al. (1999) Obes. Res. &:189-98) and phentermine (Douglas, A. et al. (1983) Int. J. Obes. 7:591-5). However, the side effects of these drugs and anti-obesity agents may limit their use. Dexfenfluramine was withdrawn from the market because of suspected heart valvulopathy; orlistat is limited by gastrointestinal side effects; and the use of sibutramine is limited by its cardiovascular side effects which have led to reports of deaths and its withdrawal from the market in Italy.

There is a continuing need for new methods of treating diabetes, diabetes associated with obesity, and diabetes-related disorders. There is also a need for new methods of treating and preventing obesity and obesity related disorders, such as metabolic syndrome. There is currently no effective treatment for metabolic syndrome.

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