

METHOD FOR REGULATING METABOLISM WITH DOPAMINE BETA HYDROXYLASE INHIBITORS

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FIELD OF THE INVENTION

This invention relates to methods for regulating or ameliorating lipid and glucose metabolism. This invention, further, relates to methods for reducing in a subject, a vertebrate animal (including a human), at least one of the following indices of metabolism: body fat stores, insulin resistance, hyperinsulinemia, hyperglycemia, hyperlipidemia, elevated blood lipoproteins (such as triglycerides and cholesterol including chylomicrons, VLDL and LDL), and/or increasing in the subject the plasma HDL, and, more generally, the improvement of metabolism disorders, especially those associated with obesity, atherosclerosis and Type II diabetes. The methods comprise administration or timed administration (i.e. administration at a predetermined time within a 24-hour period) of inhibitors of dopamine beta hydroxylase (DBH).

BACKGROUND OF THE INVENTION

Obesity and Lipid Metabolism Disorders—Body Fat Loss

In humans obesity can be defined as a body weight exceeding 20% of the desirable body weight for individuals of the same sex, height and frame (Salines, L. B., in *Endocrinology & Metabolism*, 2d Ed., McGraw-Hill, New York 1987, pp. 1203–1244; see also, R. H. Williams, *Textbook of Endocrinology*, 1974, pp. 904–916). In animals (including humans) obesity can additionally be defined by body weight patterns correlated with prolactin profiles given that members of a species that are young, lean and “healthy” (i.e., free of any disorders, not just metabolic disorders) have daily plasma prolactin level profiles that follow a regular pattern with little or no standard deviation. The “healthy” prolactin profile for humans (male and female) is depicted in FIG. 1.

Obesity, or excess fat deposits, correlates with and may trigger the onset of various lipid metabolism disorders, e.g. hypertension, Type II diabetes, atherosclerosis, etc.

Even in the absence of clinical obesity (according to the above definitions) the reduction of body fat stores (notably visceral fat stores) in humans, especially on a long-term or permanent basis, would be of significant benefit, both cosmetically and physiologically.

The reduction of body fat stores in domestic animals (including pets) especially on a long-term or permanent basis would also obviously be of considerable economic benefit to humans, particularly since farm animals supply, a major portion of a person's diet; and the animal fat may end up as de novo fat deposits in humans.

Whereas controlled diet and exercise can produce modest results in the reduction of body fat deposits, prior to the cumulative work of the present inventors (including the prior co-pending patent applications and issued U.S. patents referred to below), no truly effective or practical treatment had been found for controlling obesity or other lipid metabolism disorders that usually accompany obesity.

Elevated plasma concentrations of one or more of cholesterol- or triglyceride-carrying lipoproteins (such as

chylomicrons, very low density lipoproteins (VLDL) and low-density lipoproteins (LDL) are considered abnormal when they exceed a well-established normal limit, generally defined as the ninety-fifth percentile of a random population. Elevated levels of these substances have been positively correlated with atherosclerosis and increased risk of cardiac infarction (i.e. heart attack) which is the leading cause of death in the United States. Strong clinical evidence has been presented in which a reduction in plasma concentration of these substances correlates with a reduced risk of atherosclerosis (Noma, A., et al., *Atherosclerosis* 49:1, 1983; Illingworth, D. and Conner, W., in *Endocrinology & Metabolism*, McGraw-Hill, New York 1987). Thus, a significant amount of research has been devoted to finding treatment methods which reduce elevated levels of plasma cholesterol and triglycerides.

Another subset of the plasma lipoproteins found in vertebrates are high density lipoproteins, or HDL. HDL serve to remove free cholesterol from the plasma. A high HDL concentration as a percentage of total plasma cholesterol has been associated with a reduced risk of atherosclerosis and heart disease. Thus, HDL are known in the lay press as “good” cholesterol. Therefore, therapeutic strategies involve attempts both to reduce plasma LDL and VLDL content (that is, reduce total plasma cholesterol), and to increase the HDL fraction of total plasma cholesterol. Several lines of research have indicated that simply increasing HDL is of benefit even in the absence of reducing LDL or VLDL concentration (Bell, G. P. et al., *Atherosclerosis* 36:47–54, 1980; Fears, R., *Biochem. Pharmacol.* 33:219–228, 1984; Thompson, G., *Br Heart J.* 51:585–588, 1989; Blackburn, H., *N.E.J.M.* 309:426–428, 1983).

Current therapies for elevated lipid and lipoprotein values include a low fat diet and elimination of aggravating factors such as sedentary lifestyle. If the elevated lipid and lipoprotein levels are secondary (i.e. incident to e.g. a deficiency of lipoprotein lipase or LDL receptor, various endocrine pathologies, alcoholism, renal disorders, hepatic disorders) then control of the underlying disease is also central to treatment. Elevated blood lipid and lipoprotein levels are also treated with drugs, which usually alter the levels of particular components of the total plasma cholesterol, as well as reduce the total plasma lipid component. Among the most recently introduced drugs to treat such conditions is lovastatin (MEVACOR™) which selectively inhibits an enzyme involved in cholesterol production, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. This drug specifically reduces total cholesterol and can cause a modest (5–10%) increase in HDL concentrations. However, benefit from this therapy varies from subject to subject.

Moreover, use of the HMG-CoA enzyme inhibitor is sometimes accompanied by side effects such as liver-toxicity, renal myoglobinuria, renal shutdown, and lenticular opacity. The risk of such side effects necessitates close monitoring of the patients (e.g., monthly liver function tests are required).

Another drug prescribed against elevated cholesterol and triglycerides is clofibrate. The effectiveness of clofibrate also varies from subject to subject and its use is often accompanied by such side effects as nephrotic syndromes, myalgia, nausea and abdominal pain.

DIABETES

Diabetes, one of the most insidious of the major diseases, can strike suddenly or lie undiagnosed for years while attacking the blood vessels and nerves. Diabetics, as a group,