THERAPEUTIC PROCESS FOR THE TREATMENT OF THE PATHOLOGIES OF TYPE II DIABETES

RELATED APPLICATIONS

This is a continuation of application Ser. No. 08/465,818, filed Jun. 6, 1995, now U.S. Pat. No. 5,866,584, which is a continuation of Ser. No. 08/158,153, filed Nov. 24, 1993, now U.S. Pat. No. 5,468,755, which is a continuation of Ser. No. 07/813,135, filed Dec. 23, 1991, now abandoned, which is a continuation-in-part of application Ser. No. 07/463,327, filed Jan. 10, 1990, (now abandoned), which is a continuation-in-part of Ser. No. 07/192,332, filed May 10, 1988, now abandoned. Each of these prior applications is hereby incorporated herein by reference, in its entirety.

1. FIELD OF THE INVENTION

This invention relates to a process for the reduction in vertebrates, animals or humans, of body fat stores, and reduction of insulin resistance, hyperinsulinemia, which is often associated with insulin resistance, and hyperglycemia, or reduction of plasma glucose. In particular, it relates to timed administrations of a dopamine agonist, by oral, sublingual or parenternal administration, to reduce and control over an extended period high insulin resistance which, with obesity and hyperinsulinemia or hyperglycemia, or both, are pathologies characteristic of the onset of noninsulin dependent, or Type II diabetes.

2. BACKGROUND

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, are far more often afflicted with blindness, heart disease, stroke, kidney disease, hearing loss, gangrene and impotence. One third of all visits to physicians are occasioned by this disease and its complications, and diabetes and its complications are a leading cause of death in this country.

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 metabolized in the liver to CO_2 and H_2O (50%); to glycogen (5%), and to fat (30–40%), which is stored in fat depots. Fatty acids are circulated, returned to the liver and metabolized to ketone bodies for utilization by the tissues. The fatty acids are also metabolized by other organs, fat formation being 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 Type I diabetes the pancreas produces little or no insulin, and insulin must be injected daily for the survival of the diabetic. In Type II diabetes the pancreas produces insulin, but the amount of insulin is insufficient, or less than fully effective due to cellular resistance, or both. In either form there are widespread abnormalities, but 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 (increased hepatic glucogenesis). There is therefore an extracellular glucose excess and an intracellular glucose deficiency which has been called "starvation in the midst of plenty". There is also a decrease in the entry of amino acids into muscle and an increase in lipolysis. Thus, these result, as a consequence of the diabetic condition, in elevated levels of glucose in the blood, and prolonged high blood sugar which is indicative of a condition which will cause blood vessel and nerve damage. Obesity, or excess fat deposits, is often associated with increasing cellular resistance to insulin which precedes the onset of frank diabetes. Prior to the onset of diabetes, the pancreas of the obese are taxed to produce additional insulin; but eventually, perhaps over several years, insulin productivity falls and diabetes results.

The reduction of body fat stores on a long term, or permanent basis in domestic animals would obviously be of considerable economic benefit to man, particularly since animals supply a major portion of man's diet; and the animal fat may end up as de novo fat deposits in man. The reduction of body fat stores in man likewise would be of significant benefit, cosmetically and physiologically. Indeed, obesity, and insulin resistance, the latter of which is generally accompanied by hyperinsulinemia or hyperglycemia, or both, are hallmarks of Type II diabetes. Controlled diet and exercise can produce modest results in the reduction of body fat deposits. Unfortunately however no effective treatment has been found until now for controlling either hyperinsulinemia, or insulin resistance. Hyperinsulinemia is a higher-than-normal level of insulin in the blood. Insulin resistance can be defined as a state in which a normal amount of insulin produces a subnormal biologic response. In insulin-treated patients with diabetes, insulin resistance is considered to be present whenever the therapeutic dose of insulin exceeds the secretory rate of insulin in normal persons. Insulin resistance is also found in the setting defined by higher-than-normal levels of insulin—i.e., hyperinsulinemia—when there is present normal or elevated levels of blood glucose. Despite decades of research on these serious health problems, the etiology of obesity and insulin resistance is unknown.

The principal unit of biological time measurement, the circadian or daily rhythm, is present at all levels of organization. Daily rhythms have been reported for many hormones inclusive of the adrenal steroids, e.g., the glucocorticosteroids, notably cortisol, and prolactin, a hormone secreted by the pituitary. In an early article, discussing the state-of-the-art at that time, it is reported that "Athough correlations have been made between hormone rhythms and other rhythms, there is little direct evidence that the time of the daily presence or peaklevel of hormones has important physiological relevance." See *Temporal Synergism of Prolactin and Adrenal Steroids* by Albert H. Meier, General and Comparative Endocrinology, Supplement 3, 1972 Copyright 1972 by Academic Press, Inc. The article then describes avian physiological responses to prolactin injections given over daily periods. These responses include increases and decreases in body fat stores, dependent on the time of day of the injection and season, the season being a determinant of normal high body weight and consequent high fat stores or low body weight and consequent low fat stores within the animal. Prolactin was thus found to stimulate fattening only when injected at certain times of the day, and the time of the response to prolactin was found to differ between lean animals and fat animals. In an article titled *Circadian and Seasonal Variation of Plasma Insulin and Cortisol Concentations in the Syrian Hamster, Mesocricetus Auratus* by Christopher J. de Souza and Albert H. Meier, Chronobiology International, Vol. 4, No. 2, pp 141–151, 1987, there is reported a study of circadian variations of plasma insulin and cortisol concentrations in scotosensitive and scotore-