METHOD FOR TREATMENT OF OBESITY USING PROLACTIN MODULATORS AND DIET

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Ser. No. 07/995,292 filed Dec. 22, 1992, U.S. Pat. No. 5,585,347, in turn a continuation-in-part of U.S. application Ser. No. 07/719,745 filed Jun. 24, 1991, U.S. Pat. No. 5,344,832, in turn a continuation-in-part of Ser. No. 463,327, filed Jan. 10, 1990, now abandoned, which is a continuation-in-part of Ser. No. 192,332 filed May 10, 1988, now abandoned, all by Anthony H. Cincotta and Albert H. Meier.

FIELD OF THE INVENTION

This invention relates to an improved method for the reduction in a subject, vertebrate animal or human, of weight and/or body fat stores. This method involves a reduction in caloric intake, in combination with the administration of a prolactin inhibitor.

In another aspect, this invention relates to an improved method for altering and/or resetting prolactin profiles of a vertebrate subject (including a human), by administering to such subjects a prolactin inhibitor in combination with restricting the caloric intake of the subject, thereby effecting an amelioration in abnormal metabolic indices of said subject.

Background of the Invention

The reduction of body weight and/or fat stores in man is of significant benefit, both cosmetically and physiologically. Whereas controlled diet and exercise can produce modest results in the reduction of weight and body fat deposits, these results are often unsatisfactory due to the substantial reduction in metabolic rate which accompanies a reduced calorie diet. Further, although a loss in body weight is seen with reduced caloric intake, this loss is often temporary and/or due to a reduction in lean body weight (as opposed to loss of fat). Various studies have shown that most calorie restriction diets result in weight loss approximately 40% of which is body fat lost and the remainder is lean body mass loss.

The reduction of body fat stores on a long term, or permanent basis in domestic animals is also obviously 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, with resulting adverse effects on health.

Obesity and insulin resistance, the latter of which is generally accompanied by hyperinsulinemia or hyperglycemia or both, are often associated conditions. No effective treatment has been found for controlling obesity-associated 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 defined by higher-than-normal levels of insulin (i.e., hyperinsulinemia) when accompanied by 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 vertebrate and particularly mammalian 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. The peak concentration of prolactin occurs at different times of day in lean and fat animals. The physiological responses to an increase in circulating prolactin (e.g., prolactin injections) include increases and decreases in body fat stores, dependent on the time of day of the prolactin increase. Prolactin was thus found to stimulate fattening only when injected at certain times of the day. Furthermore, the type of response to prolactin and the time at which this response is elicited was found to differ between lean animals and fat animals.

In our prior co-pending patent application Ser. No. 192,332 we have disclosed and claimed methods for regulating lipid metabolism disorders by administering prolactin (or both prolactin and a glucocorticosteroid ("GC")) into the bloodstream of an animal or human on a timed daily basis in an amount and for a period of time sufficient to modify and reset the neural phase oscillation of the prolactin daily rhythm which then increases insulin sensitivity. The prolactin (or prolactin and glucocorticosteroid) injections are timed to create a peak in the subject's daily prolactin (or both prolactin and glucocorticosteroid) level profile that coincides in time with the peak prolactin level (or prolactin and GC peaks, respectively) of a lean, insulin-sensitive human to increase insulin sensitivity and reduce body fat stores. Injections of the same agent(s) are timed towards the peak prolactin level time of an obese subject to achieve fat gain, if desired.

In our co-pending prior application Ser. No. 463,327 we have disclosed and claimed a method of modifying and resetting the neural phase oscillations of the brain which control both prolactin and GC in an obese animal (or human) by administering a dopamine agonist at a predetermined time of day such that the prolactin (and/or GC) peak(s) of the obese animal (or human) will be phase-shifted to occur at the time that it occurs (they occur) in a lean animal (or human) , with the result that at least one of body fat stores, body weight, hyperinsulinemia, or hyperglycemia will be reduced and/or insulin sensitivity will be increased.

In our co-pending prior application Ser. No. 719,745 we have disclosed and claimed enhanced methods for modifying and resetting the neural phase oscillations of the brain which control prolactin levels comprising both (a) administering to the subject a prolactin inhibitor (dopamine agonist) shortly after the time at which the normal prolactin profile peaks to reduce prolactin levels to the low "day" levels and (b) administering to the subject a prolactin stimulator at a time just before the prolactin level peaks in normal subjects with the objective of causing the subject's prolactin secretion profile to mimic in shape and time the profile of a lean human not suffering from one or more of the aforementioned metabolic disorders.

Ser. No. 719,745 also discloses and claims the further administration of a thyroid hormone to subjects that are being treated with the dopamine agonist and/or prolactin stimulator, especially to those subjects that are chronically or seasonally hypothyroid.

Our co-pending Ser. No. 995,292 discusses improved methods of detecting abnormal or aberrant prolactin level profiles of a subject, determining whether treatment is necessary, and if found necessary, methods of altering the